Memory Consolidation in Ageing and Neurodegeneration

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Research into the neuroanatomical bases of long-term memory has consistently implicated medial temporal lobe structures, namely the hippocampus, to play a critical role in the consolidation of newly acquired episodic memory (memory of specific events in a person's life) for long-term storage. The work described in this thesis investigates consolidation of anterograde episodic memory using recognition and source (contextual) behavioural tasks with the addition of extensive neuroimaging techniques to better understand the role of medial temporal lobe structures when this process is intact and when it is impaired. We examined intact consolidation and the cognitive effect of healthy ageing in a sample of young and elderly participants, and impaired consolidation in early stage Alzheimer's disease (AD) and semantic dementia (SD) patients, who show contrasting atrophy in the medial temporal lobe region.

Building on previous studies, functional neuroimaging revealed the posterior region of the left hippocampus is crucial for intact long-term consolidation of memories that have a contextual component. Diffusion tensor imaging further revealed greater white matter integrity in the fornix and cingulate, two subcortical structures responsible for efferent and afferent communication with the hippocampus, respectively, also predicted successful consolidation. Behaviourally, cognitive changes associated with healthy ageing showed decreased recognition and source memory retrieval after extended delays, but the same pattern of performance change over time was observed in young and elderly participants. In amnesic patients, AD showed a significant dissociation in the pattern of source memory performance over time compared to controls while in SD this was only observed for recognition memory. Considering atrophy in early stage AD is often reported to be confined to the hippocampus, these results are consistent with the multiple trace model of long-term consolidation.

The critical role of the hippocampus and adjacent subcortical structures along the Papez memory circuit in long-term consolidation of anterograde episodic memory is consistent with our findings. In addition, our results from additional testing of a single SD patient found the memory impairment appears to leave implicit long-term memory retrieval intact. The theoretical and clinical implications of these findings for human long-term memory will be discussed.

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Publications Arising From This Thesis

Papers

Tu, S., Mioshi, E., Savage, S., Hodges, J. R., & Hornberger, M. Dissociation of explicit and implicit long-term memory consolidation in semantic dementia: A case study. ***Neurocase***. (in press)

Tu, S., & Hornberger, M. Posterior Hippocampal and Fornix Contributions to Long-Term Memory Consolidation of Contextual Memory. (in preparation)

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Tu, S., & Hornberger, M. (2012). Posterior Hippocampal and Fornix Contributions to Long-Term Memory Consolidation of Contextual Memory. ***18th Annual Meeting of the Organisation for Human Brain Mapping***, 10-14 June, 2012, Beijing, China. p. 195.

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Table of Contents

List of Tables

Page No.

List of Figures

Page No.

Abbreviations

ACE-R	Addenbrooke’s Cognitive Examination Revised
AD	Alzheimer's Disease
BOLD	Blood-Oxygen-Level-Dependent
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
FEAT	FMRI Expert Analysis Tool
fMRI	Functional Magnetic Resonance Imaging
FMRIB	Functional MRI of the Brain
FOV	Field of View
FSL	FMRIB Software Library
GLM	General Linear Model
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
MTT	Multiple Trace Theory
PFC	Prefrontal Cortex
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
ROI	Regions of Interest

SCT	Standard Consolidation Theory
SD	Semantic Dementia
TBSS	Tract-Based Spatial Statistics
TE	Echo Time
TR	Repetition Time
URL	Uniform Resource Locator
VBM	Voxel-Based Morphometry
XML	Extensible Markup Language

Chapter 1. Introduction

Memory serves as storage of information from past experiences in our lives, able to be retained and recalled. Our behaviour and how we respond to everyday events and social interaction is largely dictated by knowledge gained from experience. Healthy memory function is therefore critical to define who we are and for our quality of life. As a result, the study of memory, including its nature and organisation as well as the neural systems underpinning this process, occupies a central position in the field of cognitive neuroscience.

Theories of human memory propose that memory is not a unitary function, but in fact represents a number of separate but interacting systems (Schacter & Tulving, 1982). The broadest distinction in memory processes is that of working memory, memory held in brief consciousness, and long-term memory, retrieved memories dating years back (James, 1890). Within the literature there has been, and still remains, considerable controversy over the neural organisation of long-term memory. The most debatable feature involves the role of medial temporal lobe (MTL) structures, specifically the interaction between the hippocampus and neocortical regions, in the long-term consolidation and retrieval of memory.

The work carried out in this thesis investigated anterograde long-term consolidation with a prospective experimental design to closely examine the rate at which newly learnt information is retained over days, weeks and months. Long-term memory consolidation was assessed in healthy young and elderly participants as well as Alzheimer's disease (AD) and semantic dementia (SD) patients, who show distinct atrophy in MTL structures critical for memory. Behavioural data is complemented with structural and functional magnetic resonance imaging (fMRI) as well as diffusion tensor imaging (DTI) to identify underlying neural substrates involved in long-term memory consolidation processes.

Memory Systems

Memory is these days not seen as a unitary system, as it comprises many different and dissociable functions. This is reflected in the literature where considerable debate exists regarding the cognitive and neural organisation of memory systems (Aggleton & Brown, 1999; Schacter & Tulving, 1994; Squire, 1992).

Declarative vs. non-declarative memory

An influential view put forward by Squire (1992) highlighted clear distinctions between declarative and procedural memory (Fig. 1.1). Declarative memory refers to our store of facts and experiences which can be consciously 'declared' or explicitly stated. In contrast, procedural memory encompasses cognitive or behavioural abilities dependent on skill based learning. Evidence for this dissociation has mainly been derived from amnesic patients, most notably patient HM. Patient HM underwent surgery for bilateral resection of the medial temporal lobe, which structural MRI has confirmed affected the entorhinal cortex and hippocampal complex (dentate gyrus, hippocampus and subiculum) (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997). Corkin (1968) demonstrated that despite having no recollection, HM was able to acquire new motor skills on mirror tracing, rotary pursuit and tacking tasks. Similarly, an amnesic patient reported by Stefanacci and colleagues (2000), EP, whom also suffered bilateral MTL damage, formed a habit of moving directly to the testing table following months of repeated home visits despite having no recollection of who the tester was or that he had seen them before. These findings clearly support the notion of separate declarative vs. non-declarative memory systems, which have specific neural correlates, in particular the hippocampal complex for declarative memory.

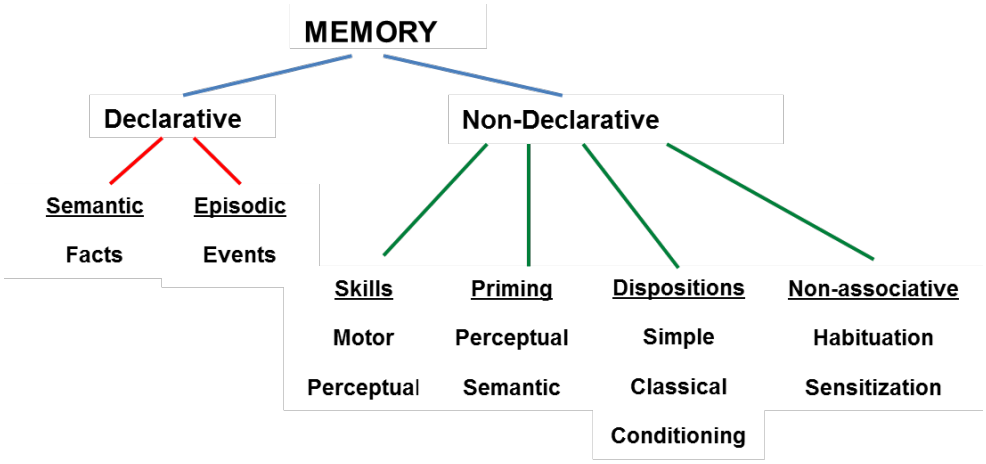


Figure 1.1. Taxonomy of long-term memory, Squire (1992).

Declarative memory is further divided into episodic and semantic memory processes (Squire, 1992). Tulving (1972), in one of the earliest and most influential models of declarative memory systems, proposed that semantic memory, our store of conceptual knowledge of the world, represented only one kind of memory and a separate, but interacting, system also existed to store context specific representations of events, which he labelled as episodic memory. He likened these two types of memory to sensory and perceptual processes, such that both work in conjunction with each other to allow normal cognitive functioning, but are in fact separate and dissociable systems. More explicitly, he defines both types of memory as follows:

Episodic Memory: a type of memory specialised in the acquisition, storage and retrieval of events or episodes linked to specific temporal-spatial context. Perceptual events that occur are stored such that its temporal-spatial relationship to existing episodic memories is maintained. Autobiographical memory, i.e. memories of one's past, is a clear example of episodic memory, where recall is often likened to conscious mental time travel to re-experience a past event (Tulving, 1999).

Semantic Memory: the system responsible for the storage of multi-modal conceptual knowledge of the world. Its function is essentially that of a mental thesaurus, maintaining an organised store of knowledge, including words, objects, places and people, as well as any relationships and categorical distinction that exist between them (Tulving, 1972). In contrast to episodic memory, semantic memory does not require encoding of contextual information, such as when or where the information was learnt.

The dissociation of semantic and episodic memory is generally accepted. However, the interaction between these memory systems is still unclear. For example, whether intact episodic memory is contingent upon semantic memory (Hodges & Graham 2001; Squire, 1987; Tulving, 1984)? This theoretical issue is, however, beyond the scope of this thesis and we will only be discussing episodic memory from here on.

Episodic memory is currently one of the most investigated memory processes, as its spatial-temporal context retrieval makes it very relevant for an understanding of our everyday memory. Various forms of episodic memory are investigated, including source memory, navigational memory, item memory and autobiographical memory. Nearly all of the forms investigate episodic memory on an anterograde basis, i.e. newly learnt/encoded information is assessed for recall or recognition. Only few episodic memory forms, such as autobiographical memory, investigate its retrograde aspects, i.e. recall or recognition of information learnt prior to the experiment. Regardless of the form of episodic memory, most of these investigations are centred around MTL regions, and in particular the hippocampus, and its function across a range of processes (for a review see Small, Schobel, Buxton, Witter, & Barnes, 2011). Nevertheless, functional neuroimaging has shown that many other regions are included in episodic memory processing, with parietal and frontal regions also being activated in episodic memory processes. The role of these regions and their interaction with the medial temporal lobe are still disputed (Simons & Spiers, 2003; Wagner, Shannon, Kahn, & Buckner, 2006).

A surprising fact for most anterograde episodic memory experiments is that the delay between when information is encoded and retrieved is relatively short and rarely exceeds a 1 hour delay. Thus, most episodic memory experiments measure immediate memory retrieval and do not consider how memory gets strengthened or consolidated in the brain over longer periods. By contrast, retrograde memory experiments specifically investigate how information has been consolidated but offer little control over the information learnt, which varies across participants and normally relates to memories years back. Thus, there is a clear gap between current knowledge of anterograde and retrograde consolidation processes. In the following section we will define memory consolidation more explicitly, before reviewing current theories and existing data.

Memory Consolidation

Memory consolidation refers to the formation or transformation of new memories for long-term storage and can be defined as the progressive post-acquisition stabilisation of fresh memories, which are prone to interference from distracting stimuli, injury or toxins (Dudai, 2004). This concept was introduced in the literature by a series of German studies by Muller and Pilzecker (1900) who observed that participant performance improved after a short delay of a few minutes, but if presented with distracting stimuli during this post-training interval performance would be impaired. This effect of time dependent stabilisation of memory has since been replicated in countless studies involving both humans and a variety of animals (Wixted, 2004).

In the modern domain of memory research, the term consolidation refers to two processes, synaptic and system level consolidation. Synaptic consolidation is a rapid process that occurs within minutes of training and concerns changes observed in neuronal synaptic activity associated with increased gene expression and protein synthesis in animals (Wixted, 2004). By contrast, system level consolidation is a slow process taking days, weeks, months, and involves the reorganisation of neural circuits or systems involved in the encoding, storage and retrieval of memories. In humans evidence of system consolidation stems largely from the amnesic literature and concerns the temporally graded retrograde amnesia observed, where remote memory is spared relative to recent memory and vice versa (Dudai, 2004). This effect is predominantly observed in amnesic patients with damage to the medial temporal lobes and hippocampal complex (Squire, Clark & Knowlton, 2001) and has been replicated in animals with selective lesions to the hippocampus (Clark, Broadbent, Zola, & Squire, 2002). In this thesis, the term consolidation will always refer to system level consolidation.

Within the memory literature there is currently considerable debate over the cognitive and neural organisation of long term memory consolidation, in particular, how new memory traces are encoded and distributed over time and the role of neural structures, namely the hippocampus and temporal neocortex, in this process. We discuss the two most influential theories proposed.

Standard Consolidation Theory

The standard model of consolidation (SCT) is the most widely accepted and longstanding cognitive model for long term memory. This theory was formulated in the 1950's based on the earliest reported cases of medial temporal lobe resection resulting in retrograde amnesia (Scoville & Milner, 1957; Milner, 2005), which has since been reported often in the literature (Hassabis, Kumaran, Vann, & Maguire, 2007; Maguire, Nannery, & Spiers, 2006; Marlsen-Wilson & Teuber, 1975; Press, Amaral & Squire, 1989; Rempel-Clower, Zola-Morgan, Squire, & Amaral, 1996; Rosenbaum et al., 2008; Squire & Bayley, 2007; Zola-Morgan, Squire & Amaral, 1986). Essentially, the theory posits that the formation of durable long term memory from transient short term memory is a time dependent process (Hebb, 1949). Initially, the newly encoded components of a memory trace are represented in distributed neocortical areas and are linked together by the hippocampus. With consolidation, these components undergo neural reorganisation and form permanent connections within the neocortical circuit, such that retrieval becomes independent of the hippocampus (Alvarez & Squire, 1994; Smith & Squire, 2009). Furthermore these consolidated memories retain the same features as when they were represented initially in the hippocampus, and are identical to the originally acquired memory (Winocur, 2010).

Support for this theory has mainly been derived from lesion studies. In humans, the pattern of temporally graded retrograde amnesia observed in amnesic patients with selective damage to the hippocampus, where remote memory is spared relative to more recent memory, has been interpreted to demonstrate the hippocampal complex plays a time-limited role in long-term memory consolidation. For example, patient HM despite being severely amnesic was still able to recollect old autobiographical memories and also performed within the normal range for immediate recall (Corkin, 2002). This implies that his impairments in episodic memory are not in acquisition or storage, but rather in consolidating the newly acquired information (Dudai, 2004). Furthermore, selective lesions to the hippocampal complex or entorhinal cortex has been demonstrated in laboratory animals, including mice, rabbits and monkeys, to produce the same pattern of temporally graded amnesia seen in amnesic patients (Cho, Beracochea, & Jaffard, 1993; Clark et al., 2002; Kim & Fabselow, 1992; Kubie, Sutherland, & Muller, 1999; Tse et al., 2007; Winocur, 1990; Zola-Morgan & Squire 1990). Studies of functional brain imaging have also shown temporally graded decreases in activity with successful memory retrieval in the hippocampus in humans (Takashima et al., 2006) and mice (Bontempi et al., 1999).

Certainly, SCT provides an excellent explanation for how recently acquired premorbid memories are forgotten more readily than remote ones, as a result of damage to the hippocampus, i.e. recent memories have not yet had a chance to be consolidated and retrieval remains dependent on a functioning hippocampus, but older memories that have been consolidated are not affected. However, an issue that needs to be raised is the duration of time required for memories to be consolidated. If we use the case of H.M, initial autobiographical evaluations suggested memory impairment affected the preceding two years prior to injury (Scoville & Milner, 1957) while subsequent studies increased the interval to two decades (Corkin, 2002). In fact a recent review article by Sutherland, Sparks and Lehman (2010) highlighted that the trend of increasing precision in measuring retrograde amnesia has steadily increased the length of pre-injury interval from which memories are lost. This trend seems to suggest that there is no temporal gradient for the memory impairment. Rather damage to the hippocampus has affected retrieval of episodic memory regardless of age. Certainly, from a practical standpoint, it also seems improbable that consolidation has not occurred after years let alone decades.

As a result, while the phenomenon of temporally graded retrograde amnesia is the most influential support for SCT, there appears to be an equal number of reports of non-graded retrograde amnesia in the literature (for a review see Winocur, Moscovitch & Bontempi, 2010), leading to the formulation of an alternative cognitive model the multiple trace theory.

Multiple Trace Theory

The second influential cognitive model of long-term memory is multiple trace theory (MTT), first posited by Nadel and Moscovitch (1997). In MTT, it is argued that the hippocampal complex acts as a permanent indexer for the neocortical elements constituting a memory and that, upon reinstatement, multiple traces of the memory will be represented in the hippocampal complex (Nadel & Moscovitch, 1998). In regard to the temporally graded amnesia (greater impairment of remote relative to recent memory) observed in lesion studies, MTT suggests that every time a memory is reinstated, a new trace of the memory is formed in the hippocampus. Thus older memories have more traces distributed across a larger area of the hippocampus and is therefore less affected by lesions. According to MTT, not only is the hippocampus essential for registering episodic memories, but it is always needed for their recall (Winocur & Moscovitch, 2011).

Support for this theory has mainly arisen from observation of variations in retrograde amnesia seen across dementia patients. In particular, that retrograde amnesia is not always reported to be temporally graded (Moscovitch & Nadel, 1999; Winocur & Moscovitch, 2011). As we mentioned earlier, one of the key assumptions of SCT is that it is a time-dependent process (Hebb, 1949), such that initial retention and retrieval is dependent on the hippocampus but over time becomes reliant on neocortical structures. In the human amnesic literature, it is clear that when both extra-hippocampal structures in the media temporal lobe and the hippocampus proper are damaged temporally graded retrograde amnesia is observed. However, when lesions are restricted to the MTL, including the hippocampus proper, both temporally graded and ungraded amnesia have been reported (Clark, Broadbent & Squire, 2005a; Clark, Broadbent & Squire, 2005b; Winocur, Moscovitch, & Bontempi, 2010; Winocur & Moscovitch, 2011). Functional imaging studies of autobiographical memory in healthy adults, have also found activation in the hippocampus regardless of memory age (Piolino et al., 2004; Rekkas & Constable, 2005; Soderlund, Moscovitch, Kumar, Mandic, & Levine, 2012; Steinvorth, Corkin, & Halgren, 2006; Viard et al., 2007).

In order to resolve these conflicting results, MTT proposes a transformation hypothesis (Winocur, Moscovitch, & Bontempi, 2010), whereby the consolidation process produces two types of the originally encoded memory.

Context-specific type: identical to the original memory and dependent on the hippocampus for retrieval.

Non-contextual schematic type: a schema of the event consisting of only semantic information and independent of the hippocampus for retrieval.

This transformation hypothesis is one of the core components of MTT and accommodates for the varying degrees of retrograde amnesia reported in the amnesic patient literature. Essentially the initial memory trace, which retains all the features of an episodic memory, is still present and retrieval is dependent on the hippocampus. However, over time and with reinstatement, a schematic version is also developed in the neocortex which retains the essential features and meaning of the original memory, but few of its contextual details (Winocur, 2011). While it has not been explicitly stated how this transformation occurs, it is proposed that both types of memory exist and can be accessed concurrently (Winocur, Moscovitch & Bontempi, 2010). Furthermore, retrieval of one or the other is impaired disproportionately depending on damage to the hippocampus or neocortex. Accordingly, we

would expect to see patients with hippocampal damage to show greater impairment in recalling contextual memory, compared to semantic memory, and vice versa for patients with neocortical damage.

While both theories have found support from different studies in the literature, the bulk of previous experiments examined retrograde memory.

Retrograde Long-Term Memory

Much of the earliest studies of memory disorder originated from accounts of patients suffering from amnesic syndromes following damage to the hippocampus as a result of surgery, viral infection, or grievous injury, such as HM and EP mentioned above. These patients suffered from severe anterograde amnesia and were unable to form new long-term memories as well as a temporally graded retrograde amnesia, i.e. more intact remote relative to recent memory obtained prior to the condition.

A trend reported by several case studies of retrograde amnesic patients found greater impairment in retrieving relatively recent memories than remote memories (Press, Amaral & Squire, 1989; Rempel-Clower et al., 1996; Scoville & Milner, 1957; Squire & Bayley, 2007; Zola-Morgan, Squire & Amaral, 1986), which built the basis for the SCT consolidation model. Furthermore, the extent of the impairment varied depending on the locus of temporal lobe damage (Hodges, 1995) with evidence suggesting extensive damage to cortical regions resulted in greater remote memory impairment (Mayes, 2000).

The scarcity of hippocampal lesion patients have made studies of consolidation processes difficult and bases the evidence on single cases, while group studies are rarely feasible. Therefore, studies have increasingly employed other patients groups which can serve as human lesion models of medial temporal lobe dysfunction, especially epilepsy and neurodegenerative patients. Two groups of neurodegenerative patients that have been particularly investigated in regard to memory consolidation are: Alzheimer's disease (AD) and Semantic dementia (SD). Patients with Alzheimer's disease show a progressive loss of pre-morbidly acquired and new memories in the early stages of the disease (Hodges, 1998). Pathology in AD originates in MTL regions (Braak & Braak, 1998) and spreads to inferior lateral temporal, inferior parietal, prefrontal and lateral occipital cortices, as the disease progresses (Weiner et al., 2011). Semantic dementia is a neurodegenerative disease primarily characterized by a progressive and selective loss of multi-modal conceptual semantic

knowledge of the world (Adlam, Patterson, & Hodges, 2009). The pathology in SD originates in the anterior temporal lobes, mainly neocortical atrophy with relative sparing of the hippocampus, in the early stages of the disease (Hodges & Patterson, 2007). Thus, AD and SD patients show complementary atrophy, with the hippocampus being mainly affected in AD and the extra-hippocampal temporal lobe cortex being affected in SD.

Not surprisingly, therefore, studies of retrograde autobiographical memory in AD and SD have reported different retrograde temporal memory gradients in both patient groups (Graham & Hodges, 1997; Press, Amaral, & Squire, 1989; Scoville & Milner, 1957; Zola-Morgan, Squire & Amaral, 1986). For example, Graham and Hodges (1997) assessed the extent of retrograde memory impairment in AD and SD patients, as well as age-matched controls on the Autobiographical Memory Interview (Kopelman, Wilson, & Baddeley, 1989). Participant responses were categorised into three time periods, childhood, early adulthood and recent (past 5 years). Their study replicated that of early amnesic case studies showing a temporal gradient for retrograde memory impairment in AD, where recall of remote memory was significantly better than recall of recent memory (Fig. 1.2). SD patients also showed temporally graded memory impairment. However, their recall of recent events was significantly better than remote events (Fig. 1.2), i.e. a reverse temporal gradient. MRI comparing AD and SD atrophy revealed selective asymmetric hippocampal atrophy in the former and focal left inferolateral temporal lobe atrophy, with relative sparing of the hippocampus, in the latter. Numerous studies have replicated the pattern of preserved recent autobiographical memory relative to remote memory in SD (Graham, Kropelnicki, Goldman, & Hodges, 2003; Hou, Miller, & Kramer, 2005; Nestor, Graham, Bozeat, Simons, & Hodges, 2002; Snowden, Griffiths, & Neary, 1996). Their intact recent memory has been interpreted to reflect intact functioning of the hippocampus, while impaired remote memory results from damage to the integrity of the temporal neocortex (Hodges, Patterson, Oxbury, & Funnell, 1992; Hodges, Patterson, & Tyler, 1994; Kapur, Ellison, Smith, McLellan, & Burrows, 1992; Squire, 1992). This pattern of results, however, is still debated as other studies have failed to observe a temporal gradient in autobiographical memory performance in SD patients, instead reporting preserved recent and remote memory in the early stages of the disease (McKinnon, Black, Miller, Moscovitch, & Levine, 2006; Moss, Kopelman, Cappalletti, De Mornay Davies, & Jaldow, 2003; Westmacott, Leach, Freedman, & Moscovitch, 2001). It is still not clear why this discrepancy of results has been observed. However, it could be attributed to

different assessment methods of autobiographical memory, as well as employment of patients in different disease stages.

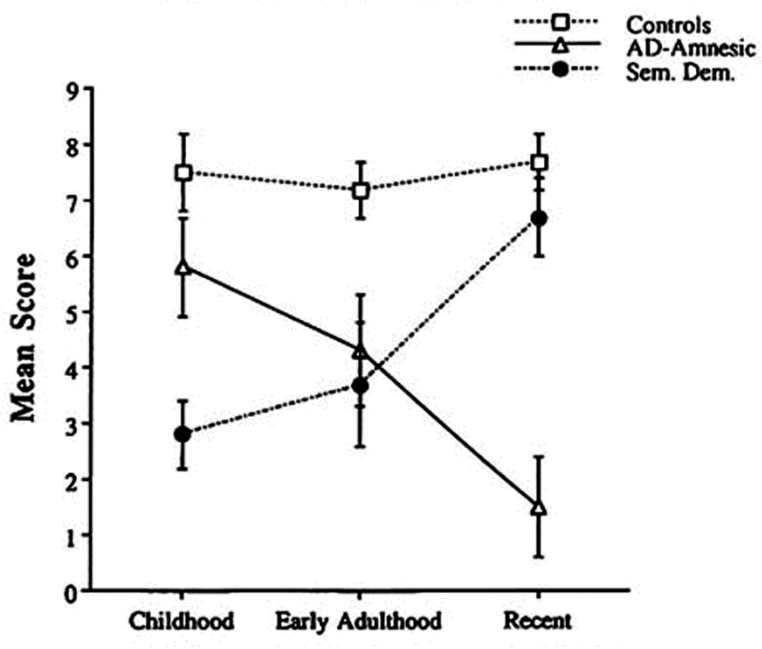


Figure 1.2. Dissociation of episodic memory impairment in SD and AD patients on the Autobiographical Memory Interview, Graham & Hodges (1997).

Still, these contrasting behavioural results in these dementia syndromes and their affected neural regions highlight how changes in MTL structures appear to be critical for the consolidation of long-term episodic memory, a fact that is also supported by numerous functional imaging studies. The majority of fMRI studies in healthy adults, again employing retrograde memory tasks, have consistently found activation in the hippocampus during the retrieval of autobiographical memory (Soderlund et al., 2012). Further, some studies have found hippocampal involvement regardless of memory age (Piolino et al., 2004; Rekkas & Constable, 2005; Steinvorth, Corkin, & Halgren, 2006; Viard et al., 2007), while others have found bilateral divergence in hippocampal activation for remote memory (Maguire & Frith, 2003), and also differences in activation along the anterior-posterior plane of the hippocampus (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Rekkas & Constable, 2005; Soderlund et al., 2012). The hippocampus, however, is not the only critical structure involved in long-term memory retrieval. Extra-hippocampal structures in the MTL, including

the parahippocampus, retrosplenial cortex and fornix, as well as frontal lobe are all believed to be functionally connected to the hippocampus during memory retrieval. Furthermore, Viard and colleagues (2007) examined autobiographical memory retrieval across the entire lifetime in a sample of elderly healthy participants and identified a network (left hippocampus, left superior frontal gyrus, bilateral precuneus and posterior cingulate gyrus) to be commonly active for all time periods.

Anterograde Long-Term Memory

In contrast to retrograde memory consolidation, no studies have explored long-term anterograde memory consolidation in humans (i.e. retention of newly acquired memories following experimental manipulation). As outlined above, most studies on anterograde episodic memory have testing delays of 1 hr or less with very few studies investigating 24 hr delays. Scarcer still are studies on consolidation of anterograde episodic memory in patients with MTL dysfunction and the associated memory impairments. Consequently, there is a gap between consolidation processes after memories have been freshly laid down and memories that have been consolidated for many years, such as in retrograde memory tests. Furthermore, it is unclear whether similar behavioural patterns and neural correlates are observed in anterograde long-term memory consolidation.

Anterograde episodic memory studies with short delays have typically employed recognition and source monitoring based tasks, with recognition only requiring yes/no judgments on presented items (e.g. “Yes, I have learnt this item before”), while source memory requiring participants to place the item in spatial-temporal context (e.g. “Yes, this item was on the right side of the screen”). In the literature there is evidence of a neuroanatomical dissociation between simple item recognition and contextual recall, with contextual retrieval relying on the hippocampus while recognition depends on extra-hippocampal regions of the MTL such as the perirhinal cortex (Eichenbaum, Yonelinas, & Ranganath, 2007; Yu, Johnson, & Rugg, 2012). However, it has been argued that this disparity is a result of differences in memory strength resulting in differential hippocampal activity (Wixted & Squire, 2011; Yu, Johnson & Rugg, 2011). Functional neuroimaging studies in young healthy participants have shown that various brain regions are activated during both types of conditions, including MTL, parietal and prefrontal cortices (Rajah, Languay, & Valiguette, 2010). In addition, when young and elderly cohorts have been compared, age-related differences in the left/right PFC activation have been observed (Rajah,

Ames, & D'Esposito, 2008). Based on Tulving's original statement that episodic memory should be defined as being able to retrieve information in a spatial-temporal context, source memory should reveal a more 'pure' episodic memory correlate than recognition memory, though this is still disputed. This indicates retrieval of remote anterograde episodic memories has the same pattern of activation as studies of retrograde autobiographical memory.

To our knowledge, only very few studies have investigated the long-term anterograde consolidation of memory, For example, Mendelsohn and colleagues (2010) recruited 18 young healthy participants to watch a 45 minute documentary film then tested them one week later in an MRI scanner using factual and fictitious statements of details in the movie. Functional analysis found significant activity during retrieval of factual statements in bilateral hippocampi and left parahippocampal gyrus MTL structures as well as widespread prefrontal lobe activity. Similarly, anterograde studies that examined the consolidation process per se have found that the hippocampus shows significant activity for both recent and remote memory retrieval (Takashima et al., 2006; Takashima et al., 2009). Takashima and colleagues (2009) trained 27 young healthy participants on two sets of face-location associations spaced 24 hrs apart. After training on the second set of stimuli, they received a cued-recall test in the MRI. Visual stimuli trained on the first day were considered remote and second day was recent. Functional analyses contrasting correct remote and recent responses found increased activity with consolidation in the left posterior parietal cortex extending to motor areas as well as bilateral inferior frontal gyrus. Interestingly though, decreased activity with consolidation was observed bilaterally in the posterior tail of the hippocampus, which would suggest a transfer of activity from the hippocampus to neocortex, similar to the standard consolidation theory.

Long-term anterograde studies in patients with memory impairment are rare and have mostly aimed at investigating potential rehabilitation techniques to re-learn lost information. In the dementia literature we found three studies that have examined long-term re-learning in SD patients. Two studies by Graham and colleagues (1999), and Snowden and Neary (2002) have shown retention of newly learnt information in SD patients 6 weeks and 6 months post-training, respectively. Graham and colleagues (1999) demonstrated that daily rehearsal of word lists over 2 weeks could improve performance on category fluency tasks in their patient to the same level as controls, but once daily practice ceased performance dropped rapidly. Snowden and Neary (2002) examined picture naming in two SD patients and found additional contextual information provided during training improved long-term memory

retention. More recently, Dewar and colleagues (2009) examined semantic learning on a series of famous people tasks in semantically impaired patients, one of whom was diagnosed with SD. Critically, the SD patient performed near ceiling on all tasks 2 weeks post-training. Together these studies indicate that while learning processes are intact in these patients they are unable to consolidate newly acquired information into long-term memory as a result of atrophy associated with the disease.

From the literature we can see that the neural organisation of long-term memory remains unclear on the role of hippocampal and extra-hippocampal structures in the MTL. While these structures appear to be critical for long-term consolidation their function and dependence over time is debated. The literature contains a considerable number of studies which have examined retrograde episodic memory in dementia patients. However, some potential pitfalls of assessing autobiographical memory in this manner is difficulty in controlling for level of vividness, personal detail and emotional detail associated with the retrieved memories, which can have significant impacts on pattern of long-term behavioural performance and MTL activation (Svoboda, McKinnon, & Levine, 2006).

It becomes obvious that anterograde long-term memory in functional neuroimaging and patient populations remains relatively unstudied and leaves a critical gap in our understanding of how memories become consolidated prospectively. Therefore, the current thesis set out to explore the behavioural and neural correlates of long-term anterograde memory consolidation. The experiments carried out in this thesis addressed three key aims:

1. To investigate anterograde long-term memory performance for item and contextual memory information in healthy and patient cohorts.
2. To investigate the neural correlates of those anterograde consolidation process.
3. To contrast declarative and non-declarative long-term consolidation

To address these aims, we conducted 3 experiments, which will be described in the subsequent chapters. Experiment 1 was a functional neuroimaging study employing fMRI in healthy young and elderly participants, while participants' anterograde memory was tracked over a 4 week period. The second experiment used the same paradigm as experiment 1 but employed a small group of AD and SD patients. Finally, the last experiment explored long-term declarative and non-declarative consolidation in a SD case study.

Chapter 2. General Methods

This chapter outlines all the stimuli and methodology used to carry out the experiments in this study. Experiments 1 and 2 employed visual test stimuli while experiment 3 utilised verbal stimuli to assess long-term episodic memory consolidation. For the visual stimuli, all testing was administered online via WebExp experimental software (http://www.webexp.info), which we modified to accommodate large scale participant testing. All neuroimaging analyses were performed using toolboxes from the Functional MRI of the Brain (FMRIB) Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl) (Woolrich et al., 2009; Smith et al., 2004): functional MRI (fMRI) analysis was conducted using the FMRI Expert Analysis Tool (FEAT) toolbox, diffusion tensor imaging (DTI) analysis was conducted using the Tract-Based Spatial Statistics (TBSS) toolbox, and structural voxel-based morphomtery (VBM) analysis was conducted using the VBM toolbox. Behavioural analyses were carried out using SPSS Statistics version 20.

Visual Episodic Memory Task (Experiments 1 & 2)

A large database of 325 high quality images depicting common everyday objects was created from online sources for testing. The word frequency of each object was calculated using the MRC Psycholinguistic Database (http://www.psych.rl.ac.uk) and images were allocated into 13 stimuli sets (A, B, C, D, E, F, G, H, I, J, K, L, M), each containing 25 images. Stimulus sets were matched for total word frequency, as a proxy measure of object familiarity, to ensure that each set had a relatively similar level of difficulty for participants to encode. All images were presented with a plain white background (Fig. 2.1) on a computer screen. In experiments 1 & 2, the aim was to assess consolidation of long-term anterograde episodic memory. At the start of the experiments, each participant was randomly allocated a target set (A, B, C, D, E, F, G, H, I, J, K, L, M) of images to encode during training. Participants were asked to explicitly encode the images, by remembering them to the best of their ability.

Figure 2.1. Example of the objects used for visual stimuli.

The training phase was conducted using E-Prime 2.0 (Fig. 2.2) and consisted of two phases, encoding and test. At the start of the encoding phase participants were given written instructions: a) to remember each object shown and b) what side of the screen each object was presented on. The 25 target images were then presented in a random order and remained on screen for 3 seconds each, followed by a 1 second fixation cross, resulting in an inter-stimulus interval (ISI) of 4 seconds. Crucially, objects were presented randomly across trials on the left and right side of the screen. Thirteen of the encoded objects were presented on the left side of the screen, while the remaining twelve were presented on the right side of the screen. Once this phase was completed written instructions appeared onscreen explaining the test phase. During the test phase participants are shown, in randomised order, all 25 images from the encoded object set, as well as 25 novel objects in the middle of the screen. Participants had to decide whether each object had been shown during encoding or not and if it was encoded whether it was shown on the left or right side of the screen. Together, the encoding and test phases equated one training run. Training was repeated until participants scored $\geq$ 90% for both recognition (old/new) and source (L/R) responses on the test phase for two consecutive training runs. Importantly, a different set of novel images was used in the test phase on each run to avoid confounding target images with previously seen foils. A maximum of 5 training runs were conducted per participant and if criterion was not reached they were ineligible to participate in the study.

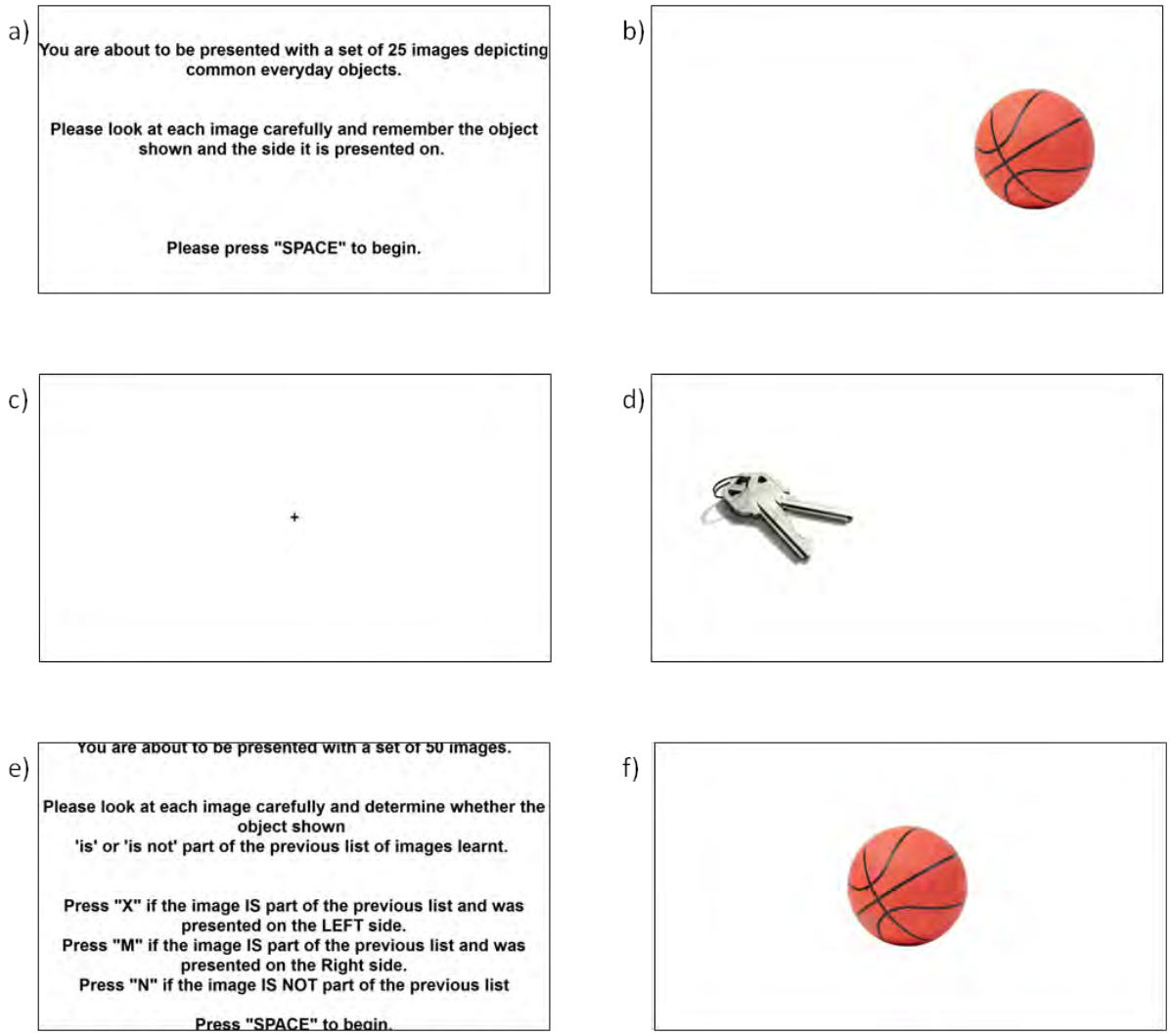


Figure 2.2. Sample E-Prime training run, encoding phase (a, b, c, d): encoding instructions (a), objects are presented on either the right (b) or left (d) of the screen and separated by a fixation point (c); test phase (e, f): test instructions (e), all objects are shown in the middle (f) of the screen.

All post-training assessments consisted of only the test phase and were conducted online via WebExp. Assessments were carried out 1 hr, 24 hrs, 1 wk, 2 wks and 4 wks post-training (Fig. 2.3). It is important to note, the target images were mixed with a previously unseen set of novel images for each test. MRI scans were taken immediately after training and 4 weeks later to compare functional and structural differences. To assess patterns of functional activity, participants performed an immediate post-training test (baseline assessment) and the final assessment (4 week delay) in the MRI scanner.

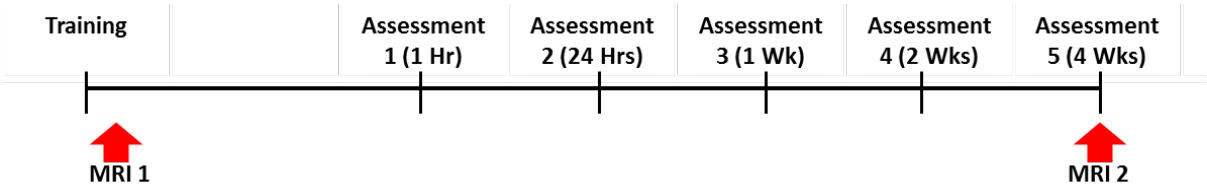


Figure 2.3. Timeline of visual episodic memory task assessments and MRI scans.

Online Assessment

Post-training assessments of the visual episodic memory task (Fig. 2.3) were all conducted over the internet through WebExp Experimental Software, with the exception of those given during the MRI scans. At the start of the study, all participants were given an information pack on the study that included online assessment dates along with URL links for each test that were unique to each participant. A reminder email was sent to each participant the day before they were scheduled to do a test and a phone call was made if they had not attempted the test by 3pm on the day.

WebExp is a Java based program using extensible markup language (XML) as the description language. There are two parts to the software: the server and the client. The server is an application which runs on a web server hosting the experiments. It allows different clients, running through participant internet browsers, to access the experimental paradigms hosted on the server and saves completed results. Essentially, experiments hosted on WebExp are a series of webpages where user responses as well as the timing to make the response can be recorded. Experimental paradigms must be designed in the form of a webpage and written in XML format. One of the main benefits of having a Java based application is that it is platform-independent, such that any browser with Java installed can access the experiment regardless of whether they are using Windows, Linux, Unix or MacOS operating systems.

In our study, we configured WebExp to deliver the test phase of the visual episodic memory task on the Neuroscience Research Australia web server. One of the downfalls of WebExp is the lack of an inbuilt redirect function, which makes large scale participant testing on experimental paradigms with many alternate versions difficult. To get around this we created personalised uniform resource locator (URL) links that redirected each participant to their designated set of test images. To accommodate the testing of participants with minimal computer skills and cognitively impaired patients, the layout was made as simple and clear as

possible (Fig. 2.4). On the first page participants were required to enter their name and age to proceed with the test. These details were checked during scoring of the results file to confirm the correct participant had taken the designated test. Next participants are shown instructions asking them to determine whether the objects shown are new or part of the target list and if so what side it was presented on. Each test consisted of 50 images (25 target objects, 25 novel objects).

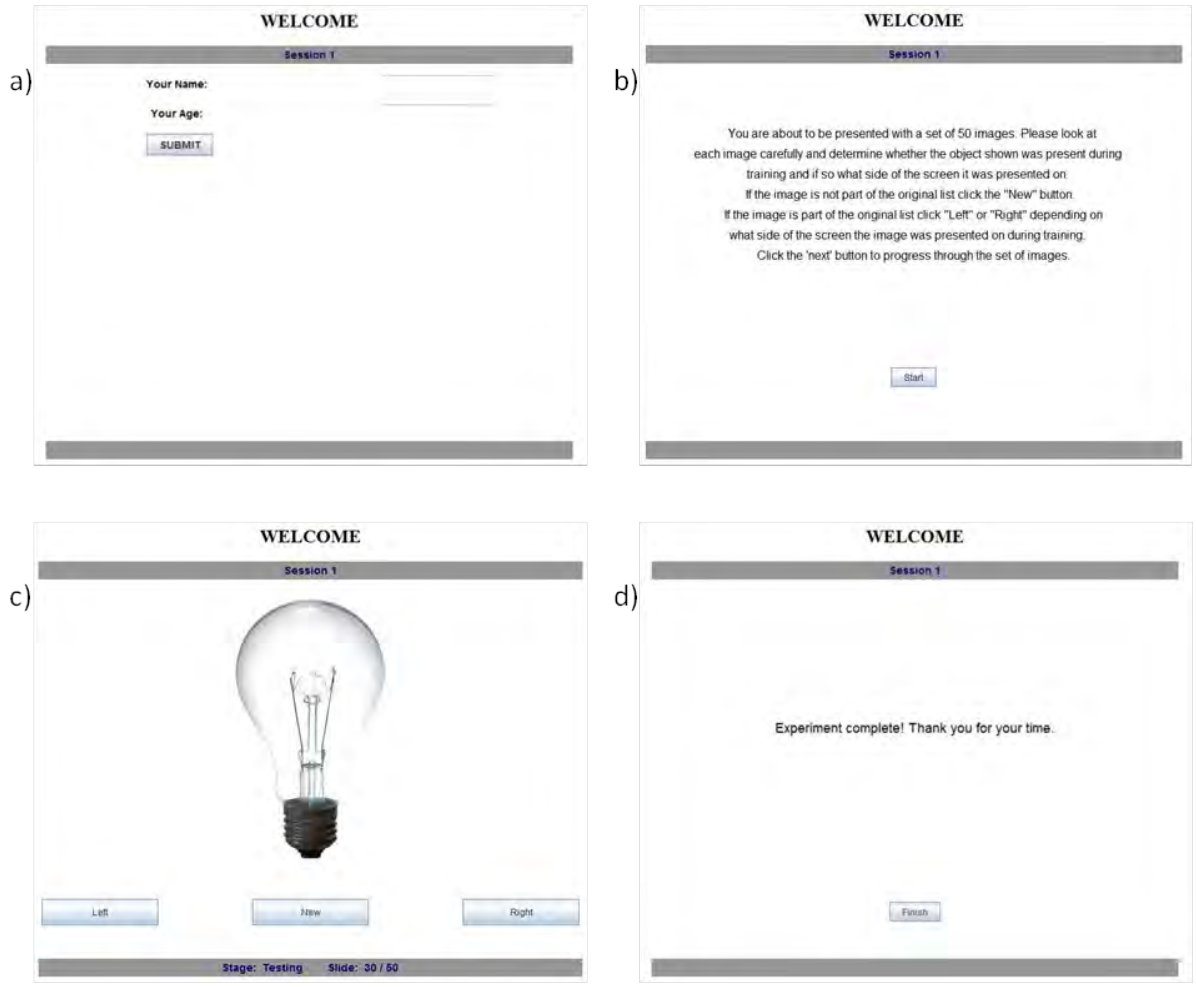


Figure 2.4. Example of online visual episodic memory task: (a) login page, (b) instructions, (c) visual stimuli with response buttons, (d) completion page.

The order the images are presented in is randomized on each run. Across different versions and sessions of the online assessment, only the sets of images used differ. Upon completion of each test, a result file is generated on the web server with the user's responses.

Verbal Episodic Memory Task (Experiment 3)

The verbal task used in experiment 3 is an adapted version of the word-stem completion test (Schott, Richardson-Klavehn, Heinze, & Duzel, 2002). Previous studies have found this task to be effective in assessing implicit and explicit memory in both healthy participants and amnesic patients (Schott et al., 2006).

Participants were shown a list of 15 high-frequency words (Appendix 1), on a computer screen and asked to explicitly recall the list without delay. This was repeated until participants were able to accurately recall the entire list on two consecutive occasions. At test, 30 three letter word stems were presented and participants were asked to verbally complete them with a word from the study list, but if they could not, use the first word that came to mind. Afterwards, they were required to state whether the word they used was part of the study list or not with an old/new response. Critically, of the 30 word stems presented at test, only 15 could be completed with words from the study list.

The order of word stem presentation was pseudo-randomised and 3 test sets (A, B, C) were established (Appendix 1). Testing occurred immediately following training (A) and after a 2 (B), 4 (C), and 8 (A) week delay.

Neuroimaging

Imaging Acquisition

All participants underwent the same imaging protocol with whole-brain T1, T2 and DTI-weighted images being acquired using a 3T Philips MRI scanner with standard quadrature head coil (8 channels).

The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix = 256x256, 200 slices, 1x1 mm^2 in-plane resolution, slice thickness: 1 mm, echo time (TE)/ repetition time (TR) = 2.6/5.8 ms.

The T2-weighted sequences were acquired as follows: echo-planar imaging sequence, matrix size = 128, 40 axial slices, slice thickness: 3.5 mm, ascending slice acquisition, TE/TR = 30/3000 ms, 80° flip angle, slice gap: 0 mm, field of view (FOV): 240x240x140 mm.

The DTI-weighted sequences were acquired as follows: 32 gradient direction diffusion tensor imaging sequence, matrix = 96x96, 55 horizontal slices, slice thickness: 2.5

mm, TR/TE/TI = 8400/68/90 ms, b-value = 1000 s/mm^2, end resolution: 2.5x2.5x2.5 mm^3, FOV: 240x240 mm, repeated 2 times. Two DTI sequences were acquired for each participant, which were in a first step then averaged. All scans were then visually checked for field inhomogeneity distortions and corrected for eddy current distortions. The diffusion tensor models were then fitted at each voxel via the FMRIB's Diffusion Toolbox in FSL (http://www.fmrib.ox.ac.uk/fsl/fdt/index.html), resulting in maps of three eigenvalues (L1, L2 and L3) which allowed calculation of fractional anisotropy (FA) maps for each subject.

Imaging Analysis

VBM Analysis

3D T1-weighted sequences were analysed with the VBM toolbox using a voxel-based morphometry approach (Ashburner & Friston, 2000; Good et al., 2001; Smith et al., 2004). First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (Zhang, Brady, & Smith, 2001) from brain extracted images. The resulting grey matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI 152) using the nonlinear registration tool FMRIB's Non-Linear Image Registration Tool (Andersson, Jenkins, & Smith, 2007), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The registered partial volume maps were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM or full-width half maximum: 8 mm). Finally, a voxel wise general linear model (GLM) was applied and permutation-based non-parametric testing was used to form clusters with the Threshold-Free Cluster Enhancement method (Smith & Nichols, 2009), tested for significance at $p < 0.05$, corrected for multiple comparisons via Family-wise Error correction across space.

fMRI Analysis

3D T2-weighted sequences were analysed using the FEAT toolbox. Results were analysed on a subject-by-subject basis then combined for group analysis. First-level analysis was performed on each participant's scan prior to any group analysis. First, motion correction was applied using MCFLIRT (motion correction using FMRIB's linear image registration tool), an inbuilt linear registration tool applying rigid-body transformations. Brain extraction was then applied using the Brain Extraction Tool to create a brain mask from the first volume in

the fMRI data. Spatial smoothing (5 mm) was carried out on each volume of the fMRI data separately, to reduce noise without reducing valid activation. Highpass temporal filtering was applied to use a local fit of a straight line (Gaussian weighted within the line) to remove low frequency artefacts. GLM statistical models were created using the onset times and duration of responses made during the visual memory task conducted during the scan to measure the haemodynamic response function of each participant. To achieve a better fit for our data, temporal filtering and adding a temporal derivative was also applied to the model. Cluster thresholding was made, such that each cluster's estimated significance level is compared with the cluster probability threshold. Clusters reported have significance at $p < 0.05$, corrected for multiple comparisons across family-wise error correction space. Finally, the participant's fMRI low resolution image was spatially normalized and registered to the MNI 152 standardised image for higher level group analysis, along with statistical results derived from first level analysis.

Peak percentage signal-change within regions of interest (ROI) was calculated using the FEAT-query toolbox. After registering participant scans in MNI 152 standard space, ROI masks were created from the Harvard-Oxford Subcortical Structural Atlas to calculate the number of significant voxels within this mask. The peak voxel was identified and used to extrapolate the percentage signal-change for each participant.

DTI Analysis

The Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) toolbox was used to perform a skeleton-based analysis of white matter FA. Results were analysed on a subject-by-subject basis then combined for group analysis. FA maps of each individual was eddy current corrected and co-registered using FNIRT nonlinear registration (Andersson, Jenkinson, & Smith, 2007) to the MNI standard space using the FMRIB58_FA template, which is available as part of the FSL software package. The template was sub-sampled at 2x2x2 mm^3 due to the coarse resolution of native DTI data (i.e. 2.5x2.5x2.5 mm^3). After image registration, FA maps were averaged to produce a group mean FA image. A skeletonization algorithm (Smith et al., 2006) was applied to the group mean FA image to define a group template of the lines of maximum FA, assumed to correspond to centres of white matter tracts. FA values for each individual subject were then projected onto this group template skeleton. Clusters were tested using permutation-based non-parametric testing as described for the VBM analysis. Clusters

reported have significance at $p < 0.05$, corrected for multiple comparisons across via family-wise error correction space.

Behavioural Analysis

Statistical analyses of performance on all behavioural experimental tasks were performed using SPSS Statistics version 20. Correct item recognition and contextual source scores were calculated for each participant. Mean values and standard error were calculated for each participant group. Mean based repeated measures ANOVA analysis was performed for tests across different delays and between participant groups. P-value < 0.05 was considered statistically significant.

Chapter 3. Memory Consolidation in Healthy Ageing

Experiment 1. Memory Consolidation for Visual Stimuli

In the first experiment, long-term anterograde episodic memory was investigated in a sample of young and elderly healthy participants. We examined participants' ability to accurately retrieve item recognition and contextual source information of learnt stimuli over a period of four weeks. Previous functional imaging studies have implicated MTL structures, including the hippocampus and parahippocampus, and prefrontal cortex (PFC) structures for immediate recognition and contextual retrieval (Rajah, Ames, & D'Esposito, 2008; Rajah, Languay, & Valiquette, 2010). Studies of healthy young participants, employing a delay of 24 hours, found decreased hippocampal activity with consolidation (Takashima et al., 2006; Takashima et al., 2009). However, it is currently not clear whether such changes are also observed over longer consolidation delays. In addition, it is currently unknown whether there are behavioural and neural changes that differ across age groups, as all previous studies have only investigated young participants. Immediate retrieval studies in ageing suggest that bilateral activation in the PFC might differ between young and elderly cohorts (Rajah, Languay, & Valiquette, 2010).

Over time, performance is expected to correlate with a change in functional activity of MTL structures resulting from consolidation of the memory trace, namely the hippocampus and neocortical regions of the MTL. The hypothesis is predicted by current models of memory consolidation (SCT, MTT) that view the hippocampus as a structure critical to forming a new memory trace while neocortical circuits serve as the long term repository of memory (Dudai, 2004).

Methods

Participants

Twenty seven healthy participants, 16 young (mean age 25.3 years, SD = 3.2) and 11 elderly (mean age 68.1, SD = 7.6) were recruited for the visual episodic memory task. Young participants were recruited through the University of New South Wales while elderly participants were recruited through the FRONTIER research group database of people who had previously given consent to participate in research. During the course of the study one young participant was unable to attend the second MRI due to personal reasons and was excluded from analysis. One elderly participant was also excluded from analysis as she was unable to complete a significant portion of the online tests due to surgery.

All participants completed consent forms for both the behavioural memory testing as well as the MRI scans at the start of the study. Ethics for cognitive testing and MRI was approved by the higher research ethics committee at the University of New South Wales Higher Research Ethics Committee (HREC) and South Eastern Sydney & Illawara Area Health Service ethics committee (SESSIAHS). Prior to testing, participants were administered a battery of cognitive assessments, both verbal and visual, to assess overall cognitive function and intactness of memory. Assessments included: Addenbrooke's Cognitive Examination-Revised (ACE-R), Doors & People (doors subtest), Rey Auditory Verbal Learning Test (RAVLT), and Rey Complex Figure Test (RCFT). Mean participant scores on all cognitive assessments are shown in Table 1. Furthermore, all MRI scans were examined by radiologists for structural abnormalities, none were reported.

Table 1. Scores of healthy young and elderly participants on standardised cognitive assessments.

Tests	Young (n = 15) Mean	SD	Elderly (n = 10) Mean	SD
MMSE	29.8	0.3	29.4	0.8
ACE-R				
Memory	25.4	0.7	23.6*	2.4
Total	98.4	1.3	93.4*	5.8
Doors & People (Doors Subtest)				
Part A	12	0	10.1*	0.9
Part B	10.4	1.7	7.4*	2.9
RAVLT				
Immediate Recall (A6)	13.5	1.1	11	2.4
Delayed Recall (30min)	13.1	1.9	11.1	2.5
Recognition	14.4	0.5	12.7	1
Total	59.7	4.8	50.8	7.6
RCFT				
Copy	34.5	1.9	25.7*	6.1
Delayed Recall (30min)	22.9	5.1	13.3*	6.9

*Denotes significant difference in performance between young and elderly cohorts ($p < 0.05$).
Note: Mini-mental state examination (MMSE); Addenbrooke's cognitive examination revised (ACE-R); Rey auditory verbal learning test (RAVLT); Rey complex figure test (RCFT).

Procedure

As mentioned in Chapter 2, participants were assessed on a visual based item recognition and contextual source memory task. During training, participants explicitly learnt to criterion (≥ 90% correct, on two consecutive training runs) a set of 25 target objects presented on either the left or right hand side of the computer monitor. At test, the encoded stimuli were randomly intermixed with 25 novel stimuli and participants were asked to make an old/new recognition decision followed by a source decision (i.e. 'Was this object shown on the left or right side of the screen?'). Six memory tests were carried out after the following encoding delays: baseline (no delay), 1 hr, 24 hrs, 1 wk, 2 wks, and 4 wks. Importantly, different sets of novel stimuli were employed for each test to avoid confounding target memory retrieval with previously employed foils. The baseline memory test was performed during fMRI data acquisition. At the same time DTI and T1-weighted anatomical data was acquired for each subject. Tests after a delay of 1 hr, 24 hrs, 1 wk, and 2 wks, were conducted online via WebExp. The final test (4 week delay) was conducted during the second fMRI scan, which followed the same imaging protocol as the first.

Behavioural results were scored for identifying target (old) and novel (new) stimuli (recognition) and remembering the original location (left/right) target objects were presented (source). The mean of participants' recognition and source memory scores were compared statistically using SPSS across different time points.

Imaging results were analysed as described in Chapter 2. Briefly, FEAT and FEAT-query toolkits were used for the fMRI analysis and the TBSS toolbox was used for DTI (FA) analysis. The fMRI visual task of each participant was first scored and the onset timing as well as duration of response was used to match observed changes in haemodynamic activity. To ensure a pure measure of activity resulting from correct recognition (old/new) and source (left/right) responses, correct rejection (correct recognition of novel stimuli) responses were subtracted from each respective analysis. A gradient analysis, subtracting remote (4 week delay) from recent scores (baseline), resulting in a negative gradient for items forgotten) was also performed to examine whether increased or decreased activity in specific neural structures would predict successful long-term consolidation of memory. Correct recognition and source responses from the second MRI (4 weeks delay) were recorded and analysed independently from the remainder of responses in the first MRI.

In the first analysis, we collapsed both younger and older groups to observe any general consolidation effects. This was followed by an analysis comparing young and elderly participants to assess differences in long-term anterograde memory consolidation resulting from healthy ageing.

Results

Demographics & Background Neuropsychology

Fifteen young (mean age 25.6 years, SD = 3.1, 1 left handed) and 10 elderly (mean age 67.5 years, SD = 7.6, 2 left handed) healthy participants were included in the study. Table 1 shows mean young participant performance was higher than the elderly group on all standardised cognitive assessments (MMSE, ACE-R, Doors & People, RAVLT, RCFT). Independent samples t-test found significant group differences on the ACE-R; memory component: $t(23) = 2.78$, $p = 0.01$, total score: $t(23) = 3.21$, $p = 0.00$, Doors & People; part A: $t(23) = 3.41$, $p = 0.02$, part B: $t(23) = 2.47$, $p = 0.02$, and RCFT; copy: $t(23) = 3.59$, $p = 0.00$, delayed recall: $t(23) = 3.11$, $p = 0.00$.

Overall Group Analysis

Behavioural Results

As illustrated in Figure 3.1, old/new recognition performance remained very high (> 90%) over the 4 week period. At 4 weeks, correct recognition response was 93%, showing a 5% decrease from baseline. In contrast, source memory showed a gradual decline throughout the 4 week period. At 4 weeks correct source response was 69%, showing a 28% decrease from baseline. However, performance still remained significantly above chance.

ANOVA analysis found that there was a significant difference across time for recognition: $F(5, 120) = 8.37$, $p < 0.05$, and source memory: $F(5, 120) = 49.25$, $p < 0.05$. Paired samples t-test found a significant difference between recognition and source memory across all time-points ($p < 0.05$) except for baseline.

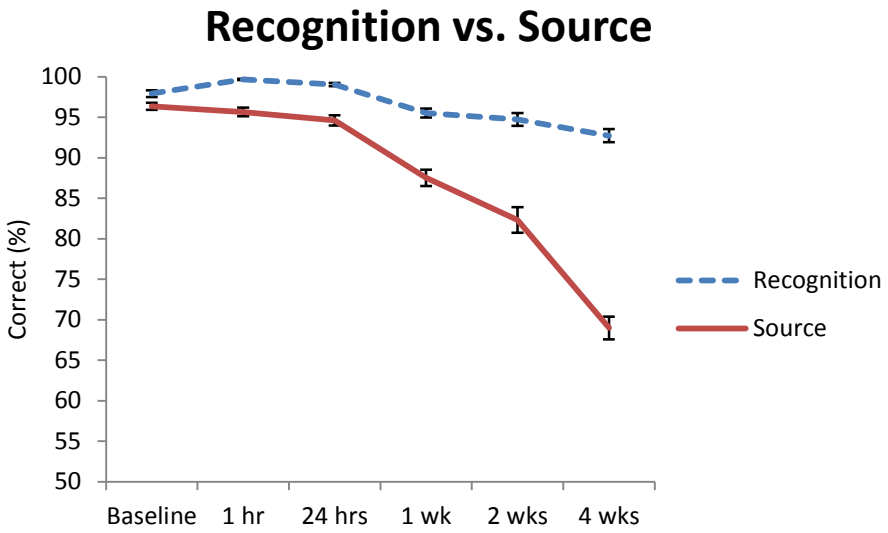


Figure 3.1. Correct recognition and source responses on the visual memory task over 4 weeks. Error bars indicate standard error of the mean.

Imaging Results - Functional Analysis

Functional analysis was first performed on individual participant scans then spatially normalized and registered to the MNI 152 standard image. The Harvard-Oxford Cortical/Subcortical Structural Atlas (http://www.cma.mgh.harvard.edu/fsl_atlas.html) was used to identify neural structures on the standardized image. Group analysis was performed on the combined scans of all participants. Recognition and source memory was examined separately. Focus is placed on functional activity in the MTL, in particular the hippocampus and extra-hippocampal structures. All clusters reported have significance at $p < 0.05$, corrected for multiple comparisons across family-wise error correction in space. Statistics of all significant clusters are included in Appendix 2.

Correct recognition and source responses elicited cingulate gyrus, paracingulate gyrus, precuneous cortex, bilateral frontal pole, and bilateral occipital cortex activation (Fig. 3.2 a, b). For source responses, activation was also observed in MTL structures (Fig. 3.2 b). Bilateral activation in the posterior tail of the hippocampus and adjacent structures was observed in correct source responses only.

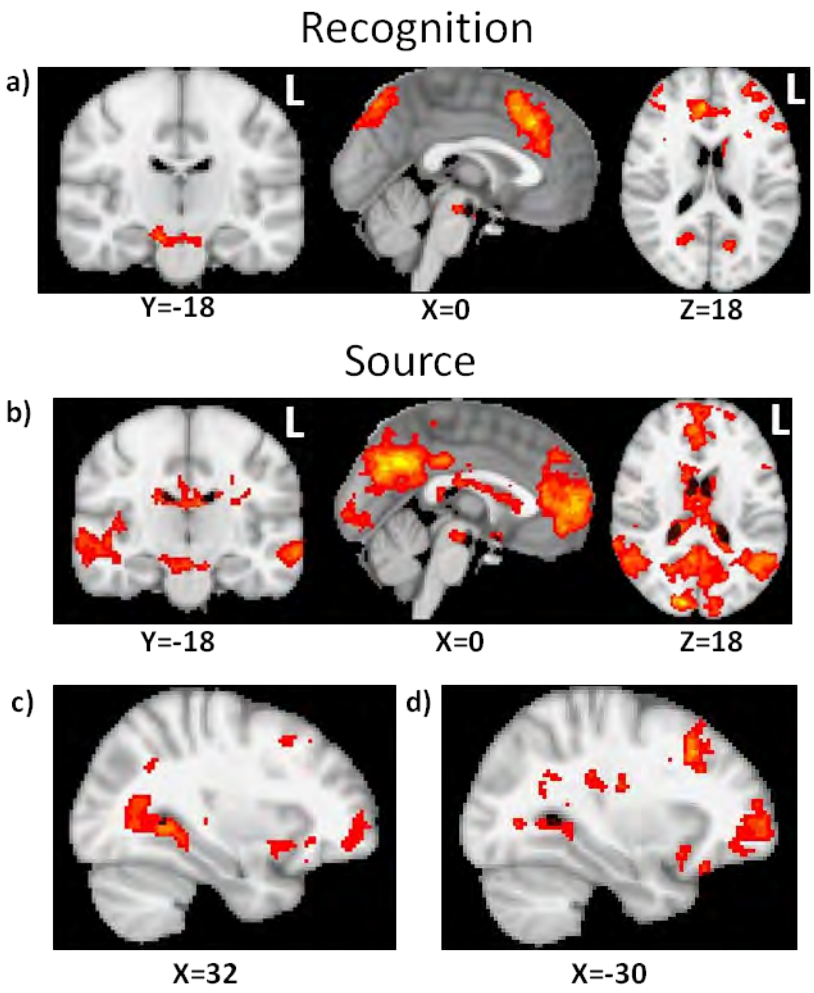


Figure 3.2. BOLD activity for correct recognition and source responses. (a) Significant clusters are found in frontal pole, cingulate gyrus, paracingulate gyrus, precuneus cortex and occipital cortex for recognition. (b) Significant clusters are found in frontal pole, cingulate gyrus, precuneus cortex and occipital pole for source. (c, d) Bilateral activation observed in the posterior tail of the right (c) and left (d) hippocampus. All significant clusters were thresholded Z > 2.3. Co-ordinates are given in MNI 152 standard space. BOLD, blood-oxygen-level-dependent.

The percentage of signal-change associated with our model of source and recognition responses in the hippocampus were calculated through FEAT-query by using the Harvard-Oxford Subcortical Structural Atlas to specify left and right hippocampus ROI. These ROI masks were then used to calculate the number of significant voxels in these regions individually and extrapolate percentage signal-change from the peak voxel of each participant's scan and the mean was obtained for the group (Table 2). Paired samples t-test found significant differences between recognition and source responses in the left

hippocampus: t (47) = 2.152, $p < 0.05$, and right hippocampus: t (47) = 1.633, $p < 0.05$, with source responses eliciting significantly higher activity in both regions (Fig. 3.3).

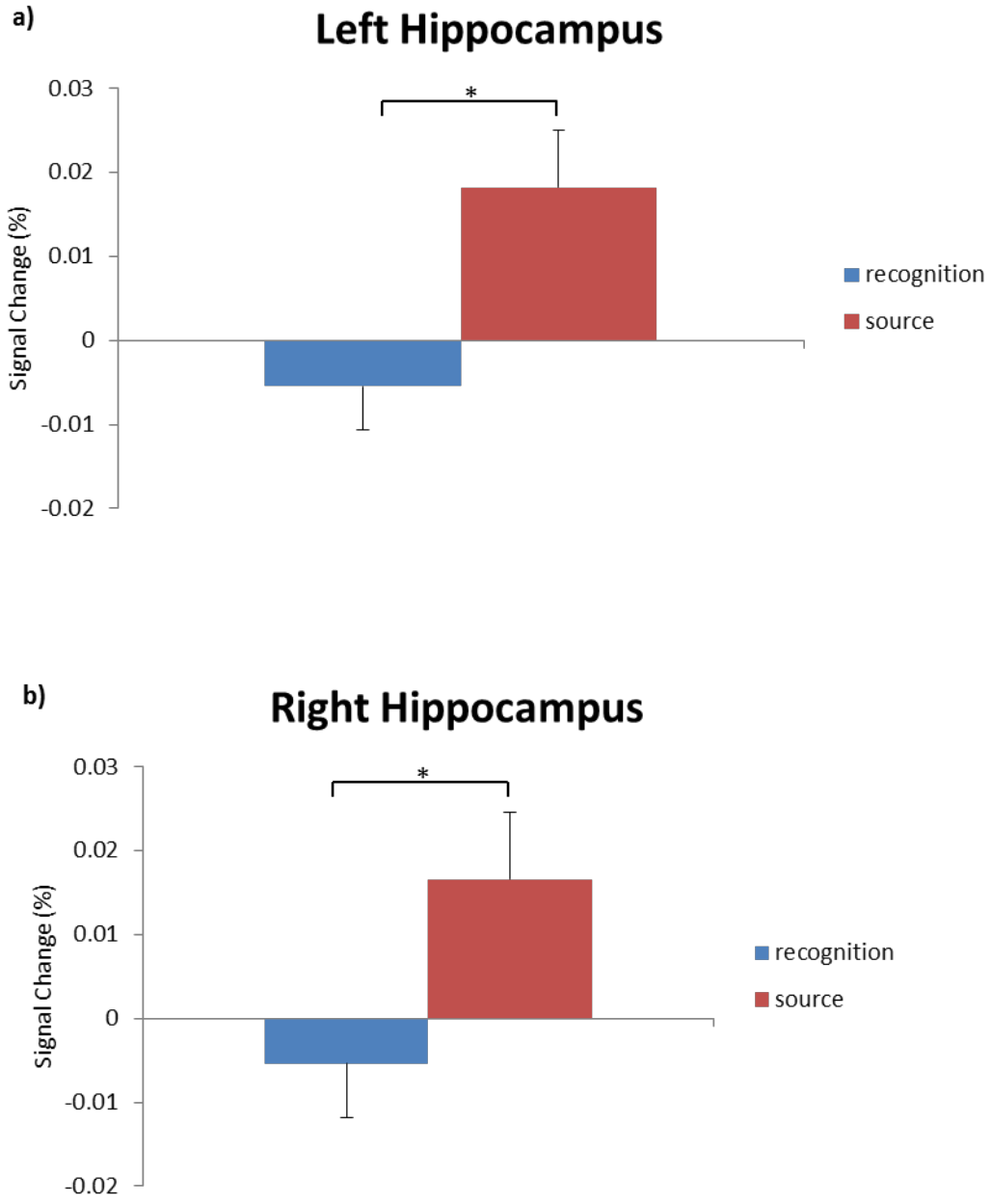


Figure 3.3. Percentage signal-change in BOLD activity for correct recognition and source responses in the left (a) and right (b) hippocampus. The asterisk (*) represents statistical significance, $p < 0.05$. Error bars indicate mean standard deviation. BOLD, blood-oxygen-level-dependent.

Table 2. Statistics of significant clusters in the hippocampus for correct source and recognition responses.

	Left Hippocampus		Right Hippocampus	
	No. of Voxels	Peak Voxel (x, y, z)	No. of Voxels	Peak Voxel (x, y, z)
Recognition	19	-10, -10, -20	31	10, -8, -20
Source	103	-26, -44, 0	142	34, -38, -6

*Peak voxel co-ordinates are reported in MNI 152 standard space.

Direct contrast analysis for recognition between the first and second MRI (4 weeks delay) showed there was greater activation in frontal pole, superior frontal gyrus, precuneous cortex, paracingulate gyrus, cingulate gyrus and occipital cortex for the initial MRI (Fig. 3.4 a). The second MRI showed significantly greater activation in the left hemisphere in inferior frontal gyrus, supramarginal gyrus, temporal occipital fusiform cortex and lateral occipital cortex structures (Fig. 3.4 b). Direct contrast between initial and delayed MRI scans of source performance did not show any significant differences.

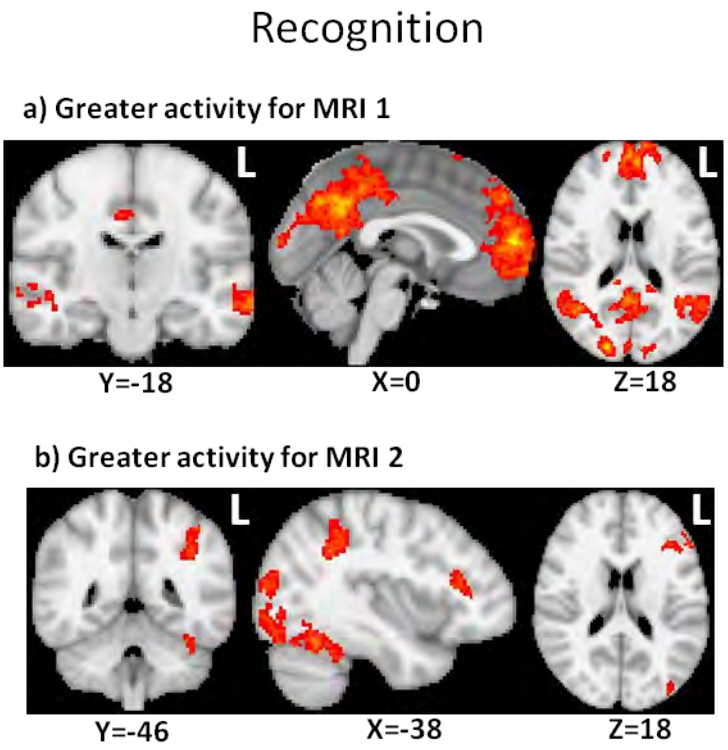


Figure 3.4. Direct functional contrast between MRI 1 and MRI 2. (a) Greater activity observed in frontal pole, superior frontal gyrus, precuneous cortex, paracingulate gyrus, cingulate gyrus and lateral occipital cortex for MRI 1. (b) Greater activity observed in left hemisphere in inferior frontal gyrus, supramarginal gyrus, temporal occipital fusiform cortex and lateral occipital cortex for MRI 2. All significant clusters were thresholded Z > 2.3. Co-ordinates are given in MNI 152 standard space.

Bidirectional gradient analysis was performed to assess involvement of neural structures in predicting successful long-term memory consolidation. Results showed increased activity in frontal pole, precentral gyrus, parietal cortex, occipital cortex and cerebellum predicted better consolidation of target objects (Fig. 3.5 a). However, decreased activity in the posterior tail of the left hippocampus predicted better consolidation of target objects (Fig. 3.5 b).

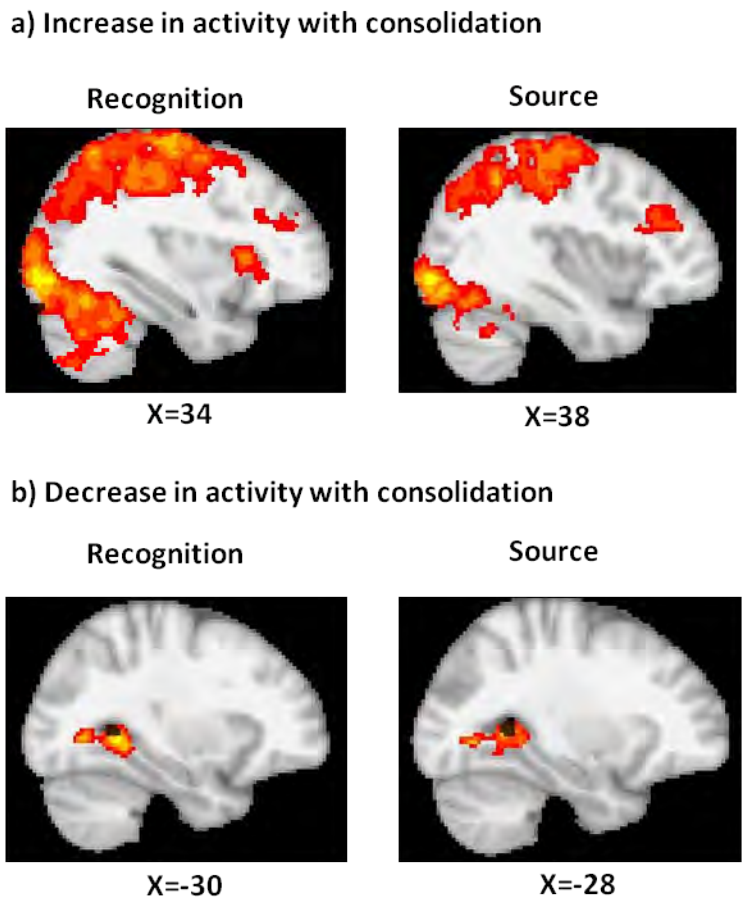


Figure 3.5. BOLD activity predicting intact long-term consolidation of anterograde episodic memory. (a) Increased activation of frontal pole, precentral gyrus, parietal cortex, occipital cortex and cerebellum predicted consolidation of recognition and source responses. (b) Decreased activity with consolidation was observed in posterior tail of left hippocampus in both recognition and source responses. All significant clusters were thresholded Z > 2.3. Co-ordinates are given in MNI 152 standard space. BOLD, blood-oxygen-level-dependent.

Imaging Results - DTI Analysis

FA maps of each individual were registered to the MNI standard space using the FMRIB58_FA template. The Harvard-Oxford Cortical/Subcortical Structural Atlas was used to identify neural structures on the standardized image. Analyses were run across all participant scans to assess correlation between white matter integrity and correct recognition and source responses. Clusters reported have significance at $p < 0.05$, corrected for multiple comparisons across family-wise error correction space.

Independent analysis of source and recognition responses did not result in any significant results, however, a gradient analysis (recent - remote scores) of recognition and source responses detected significant clusters in MTL structures, fonix and cingulum. An additional contrast was run where fornix and cingulum mask, constructed from John Hopkins University White Matter Tractography Atlas (cmrm.med.jhmi.edu), was applied to our analysis. We found a positive correlation between white matter microstructure in the fornix and cingulum, and long-term recognition and source performance (Fig. 3.6). Interestingly, recognition performance was only positively associated with greater white matter integrity in the right fornix (Fig. 3.6 a) while source performance was bilaterally associated with the fornix (Fig. 3.6 b).

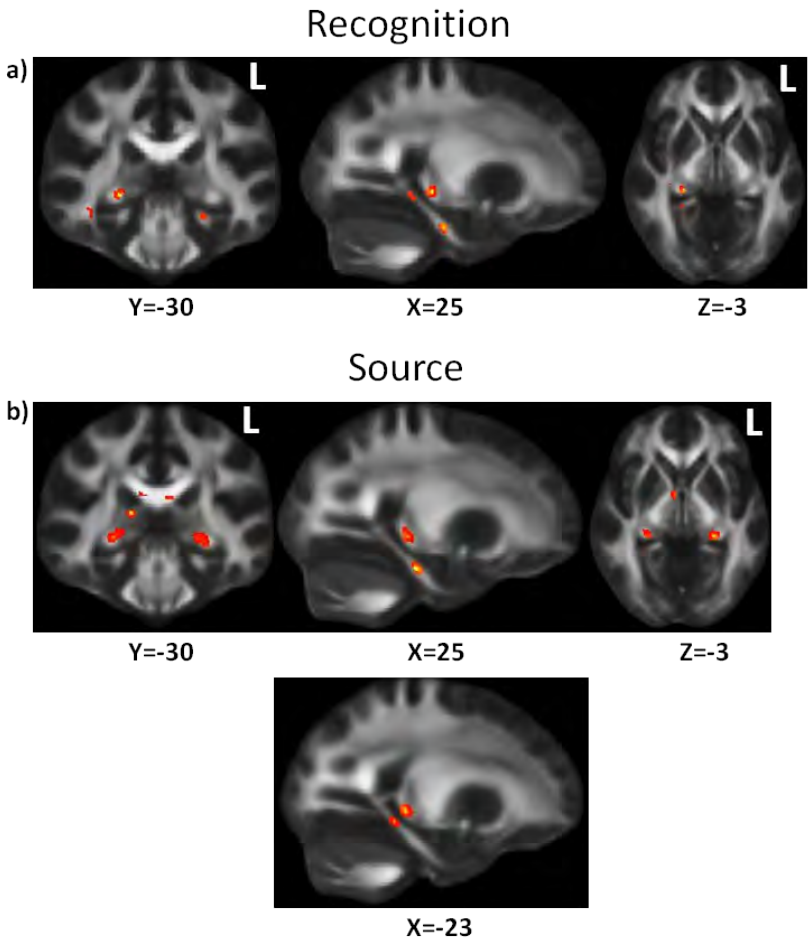


Figure 3.6. Greater FA integrity shows positive correlation with consolidation. (a) Increased white matter integrity in right fornix and bilateral cingulum predicted intact consolidation of recognition responses. (b) Increased white matter integrity in bilateral fornix and cingulum predicted consolidation of source responses. All significant clusters were thresholded Z > 2.3. Co-ordinates are given in MNI 152 standard space.

Ageing Analysis

Behavioural Results

As illustrated in Figure 3.7, old/new recognition performance remained high (> 90%) after 4 weeks for both young (95%) and elderly (89%) participants, with 4% and 8% decrease from baseline, respectively. There was a sustained drop in correct source responses for both groups of participants after period of 24 hrs, for the remainder of the tests. Overall young participants showed a 27% drop in source memory performance, while elderly participants showed a 30% decline by the end of the testing period. Recognition and source performance both remained significantly above chance for both groups of participants.

ANOVA analysis found that recognition scores differed significantly between young and elderly groups: $F(1, 23) = 7.31$, $p < 0.05$. Change in the two groups across time was also significant: $F(5, 115) = 9.78$, $p < 0.05$, however, there was no interaction effect between the two groups across time. For source scores, ANOVA revealed a significant change within groups over the 4 week period: $F(5, 115) = 47.46$, $p < 0.05$. Difference between groups was not significant and there was no interaction effect between the two groups across time.

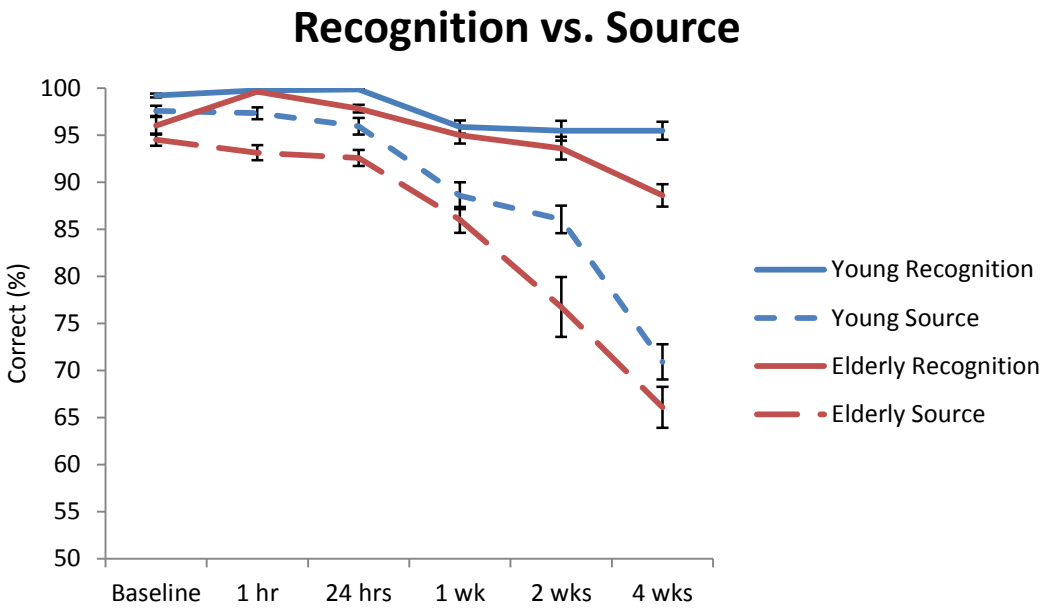


Figure 3.7. Percentage of correct recognition and source responses on the visual memory task over 4 weeks in young and elderly participants. Error bars indicate standard error of the mean.

To check whether participant responses between groups were skewed towards responding old or new, response bias for total recognition responses was calculated for young and elderly participants (Fig. 3.8). Bias to distinguish old and new items (C) was calculated for mean recognition responses across each test over the 4 week period. ANOVA analysis found response bias differed significantly within groups across time: $F(5, 115) = 2.94$, $p < 0.05$, but not between groups: $F(1, 23) = 0.18$, $p > 0.05$. Therefore, indicating that young and elderly participants showed the same pattern of increased conservative response bias across time.

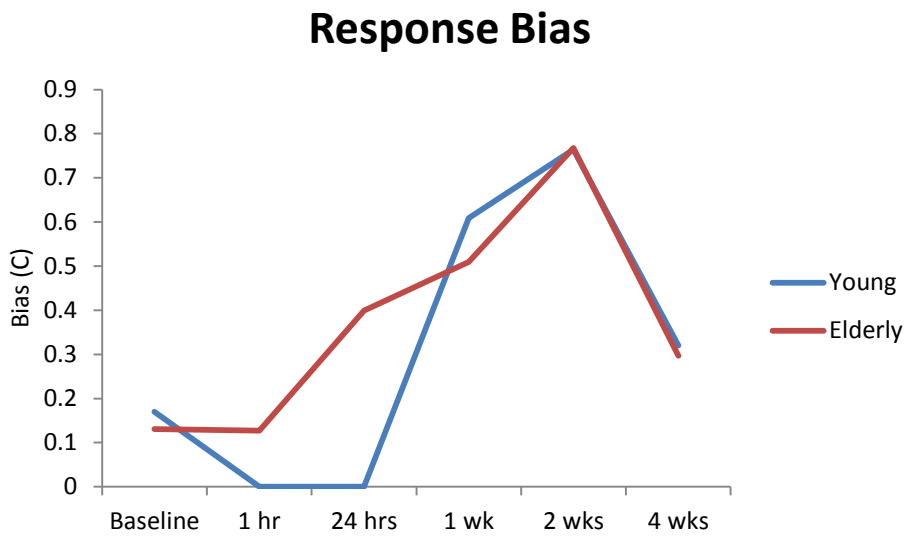


Figure 3.8. Mean response bias of young and elderly participants for making old/new recognition responses.

Imaging Results - Functional Analysis

Functional analysis was first performed on individual participant scans then spatially normalized and registered to MNI 152 standard image. Group analysis was performed on first and second (4 week delay) MRI scans of all participants separately. Recognition and source memory was examined separately. All clusters reported have significance at $p < 0.05$, corrected for multiple comparisons via family-wise error correction across space. Statistics of all significant clusters are included in Appendix 2.

Correct recognition and source responses in MRI 1 elicited large clusters of activation in frontal pole, cingulate gyrus, paracingulate gyrus, precuneous cortex and occipital cortex for young participants (Fig. 3.9 a, b). In elderly participants activation in the cingulate gyrus and precuneus cortex was observed in recognition and source responses (Fig. 3.10 a, b). Additionally for elderly source responses, we observed significant activated clusters in the frontal pole (Fig. 3.9 b). The posterior tail of the right hippocampus was also active for both young (Fig. 3.9 c) and elderly (Fig. 3.10 c) participants for source responses. MRI 2 of young participants showed significantly less activation, with paracingulate gyrus active for both recognition and source, and the precuneus cortex was also active for source responses (Fig. 3.9 d, e). Analysis of elderly participants' MRI 2 data did not detect any significant clusters. Direct contrast between young and elderly groups on MRI 1 and MRI 2 did not detect any significant clusters.

Bidirectional gradient analysis was performed to assess involvement of neural structures in predicting successful long-term memory consolidation for young and elderly groups. Both groups showed increased activity in frontal pole, orbitofrontal cortex, precentral gyrus and occipital cortex predicted better consolidation of recognition and source information (Fig. 3.11 a, c). Increased activity in frontal pole predicted better consolidation only for recognition in both groups. Similar to our overall analysis, we found decreased activity in the tail of the left posterior hippocampus predicted better consolidation (Fig. 3.11 b, d). However, in young participants this was only detected for source performance while in elderly participants only recognition performance showed this.

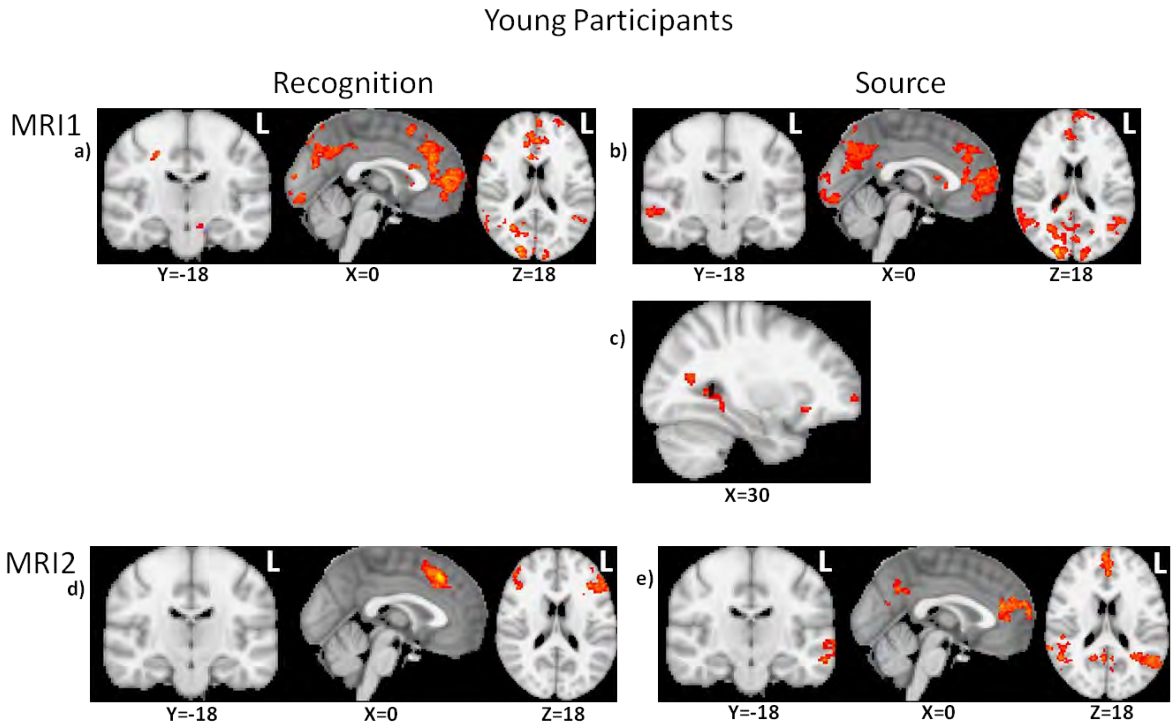


Figure 3.9. BOLD activity for correct recognition and source responses in young participants during MRI 1 (a, b, c) and MRI 2 (d, e). (a, b) Significant frontal pole, cingulate gyrus, paracingulate gyrus, precuneous cortex and occipital cortex activated for both recognition and source responses. (c) Significant clusters observed in posterior right hippocampus area for source responses in MRI 1. (d) Paracingulate gyrus activation for recognition responses in MRI 2. (e) Paracingulate gyrus and precuneus cortex activation for source responses for MRI 2. All significant clusters were thresholded $Z > 2.3$. Co-ordinates are given in MNI 152 standard space. BOLD, blood-oxygen-level-dependent.

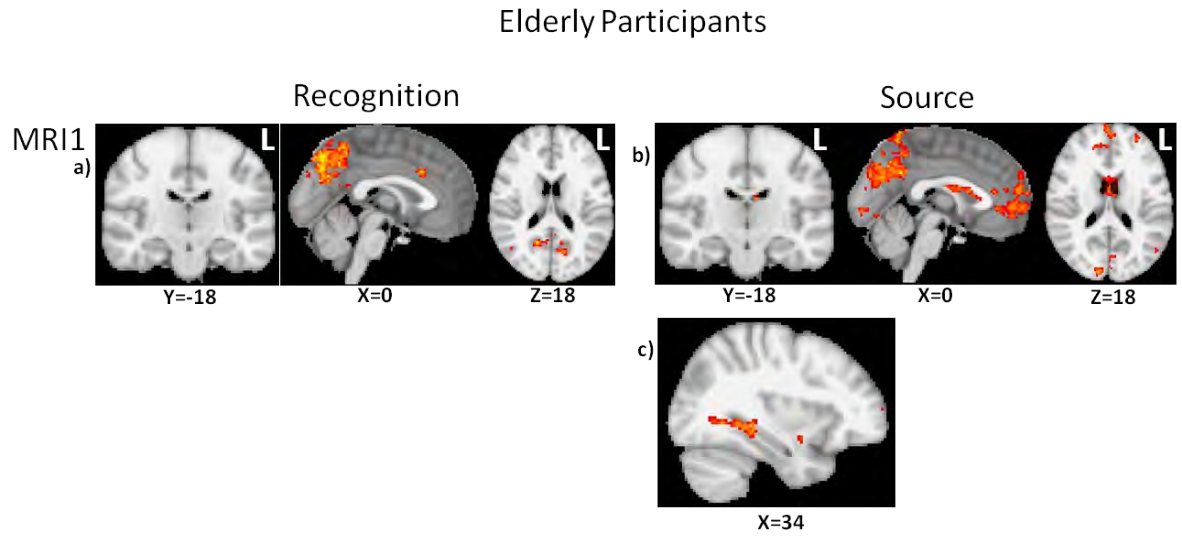


Figure 3.10. BOLD activity for correct recognition and source responses in elderly participants during MRI 1 (a, b, c). (a) Significant cingulate gyrus and precuneus cortex activation for recognition responses. (b) Significant frontal pole, cingulate gyrus and precuneus cortex activation for source responses. (c) Significant clusters found in posterior tail of right hippocampus for source responses in MRI 1. All significant clusters were thresholded Z > 2.3. Co-ordinates are given in MNI 152 standard space. BOLD, blood-oxygen-level-dependent.

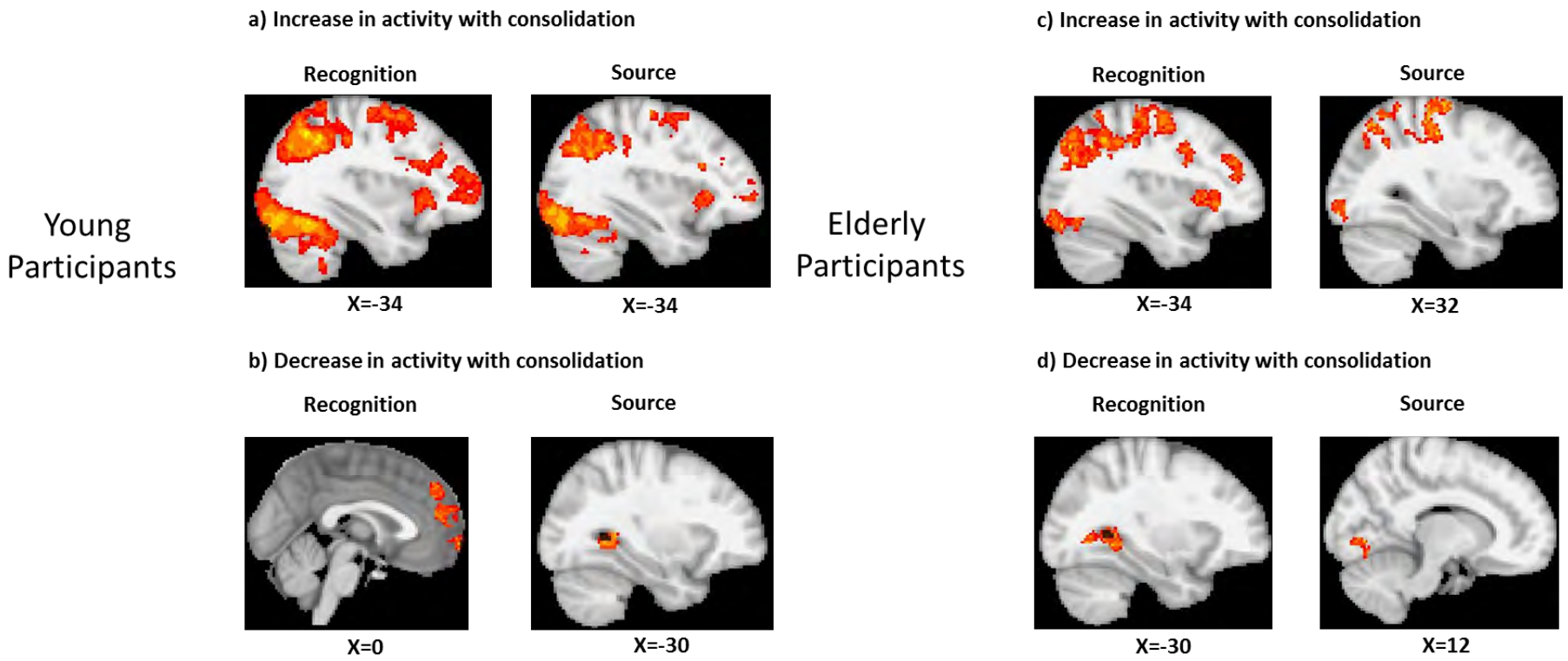


Figure 3.11. BOLD activity that predicts intact long-term consolidation of episodic memory in young (a, b) and elderly (c, d) groups. (a) In young participants, increased activation of frontal pole, front-orbital cortex, precentral/middle fontal gyrus, occipital cortex, temporal occipital fusiform and the cerebellum predicted consolidation of recognition and source responses. (b) In young participants, decreased activity with consolidation was observed in frontal pole for recognition and posterior tail of left hippocampus for source responses. (c) In elderly participants, increased activation of frontal pole, front-orbital cortex, precentral gyrus and occipital cortex predicted consolidation of recognition responses, and occipital cortex predicted consolidation of source responses. (d) In elderly participants, decreased activation in the posterior tail of the left hippocampus predicted better recognition while the occipital cortex was identified for source information. BOLD, blood-oxygen-level-dependent.

Discussions

In this first experiment participants successfully consolidated target recognition and source information over a 4 week period. Both young and elderly participants were consistently able to accurately retrieve recognition memory of target objects throughout the testing period. On the other hand, correct recall of additional contextual information (source) showed steady decline for both groups after a period of 24 hrs. The pattern of anterograde episodic memory retrieval over time was similar across the two groups. However, as expected, the young cohort significantly outperformed elderly participants. Our fMRI and DTI analyses revealed that the cingulum as well as MTL structures, including the posterior hippocampus and fornix, were critical in predicting successful consolidation of newly acquired episodic memory.

Behavioural Performance - Overall Analysis

From the overall analysis we observed dissociation between recognition and source performance over time. While a high level of item recognition was maintained throughout the 4 week delay, contextual source recall responses showed a sustained drop after a period of 24 hrs. This was expected as recognition memory is viewed as a relatively easy cognitive task while source memory is more cognitively challenging. In the literature, it has been reported in studies with immediate recall or short delays of a few hours that item recognition has greater memory strength than contextual judgements after training with both verbal and visual stimuli (Wais, Squire, & Wixted, 2010; Yu, Johnson, & Rugg, 2012).

Neuroimaging - Overall Analysis

Functional neuroimaging consistently identified significant clusters of activity in the parietal and frontal lobe regions during episodic retrieval, consistent with previous anterograde memory fMRI studies without any test delay (Rajah, Languay, & Valiquette, 2010; Soderlund et al., 2012). Of greater interest is the activation observed in the hippocampus for long term source recall. In the overall fMRI analysis of correct source response, we found significant bilateral activation in the posterior tail of the hippocampus at baseline testing. When we investigated further by contrasting recent-remote responses, this same region was highlighted in our gradient analysis of recognition and source components.

Gradient analysis aimed to correlate specific neural structures with long-term behavioural performance on the visual memory task. Activation in the first MRI was specifically analysed for objects that had been successfully consolidated (i.e. encoded, stored

and retrieved) over the 4 week period. We found, in the overall analysis, that reduced activity in the posterior tail of the left hippocampus for both recognition and source components predicted better long-term consolidation. This appears to be consistent with previous autobiographical memory studies in the literature that have found the posterior region of the hippocampus to be activated during retrieval of older memories, while the anterior region is active for retrieval of more recent memories (Gilboa et al., 2004; Piolino, Desgranges, & Eustache, 2009; Rekkas & Constable, 2005).

This region at the tail of the posterior hippocampus was further implicated in our gradient analysis of white matter integrity in diffusion tensor imaging. DTI analysis identified greater white matter integrity in the fornix to positively correlate with long-term consolidation of recognition and source information. It is important to note that the posterior hippocampus contributes the majority of efferent fibres to the fornix, making it the gateway connecting the hippocampus to subcortical memory Papez circuit structures. Therefore from an anatomical standpoint it makes sense that greater white matter integrity in this region would promote memory consolidative processes occurring in the hippocampus.

A similar de-activation of the posterior hippocampus has previously been shown in healthy young participants after a period of 24 hrs. Takashima and colleagues (2009) carried out a face-location association memory task on a group of 27 healthy individuals. They were trained on one set of facial stimuli on day one (remote memory) then a second set on the next day (recent memory) immediately followed by an MRI scan. Comparisons of functional activity between correct recent and remote responses showed consolidation resulted in bilateral decreased activity in the posterior tail of the hippocampus. Furthermore, in a previous long-term study by Takashima and colleagues (2006), they found continued decrease in hippocampal activity over 3 months for correct retrieval of visual recognition information in healthy young participants.

An interesting result from the DTI analysis is contrasting hemispheres of the fornix implicated in recognition and source components. Both the left and right fornix regions were identified for the source component while only the right fornix region was identified for recognition. Significant clusters in the left fornix correlates with our gradient analysis for functional activity, but as for why there is a discrepancy between recognition and source is interesting. It should be noted that recognition and source components in our study design are, however, not independent. Source components are in essence a selective subset of correct

recognition responses. Consequently, we would expect imaging analyses of source responses to have greater sensitivity and show the same as well as additional clusters that may not reach threshold from recognition responses, although not vice versa. Age may also be a mediating variable, given the difference in memory performance between young and elderly groups.

Behavioural Performance - Ageing Analysis

Following on from the overall analysis, when we analysed young and elderly cohort's behavioural performance individually, we found that both groups showed the same pattern of gradual memory decline over time. While younger participants did significantly outperform their elderly counterparts in recognition, the pattern of change in correct recognition and source memory retrieval over time was not significantly different. Global cognitive decline is a proven effect of ageing, however, other than a small overall decrease in episodic memory retrieval, behaviourally, the consolidation process in elderly participants does not differ from young participants.

Traditionally, this age-related decline in laboratory designed tests of episodic memory has been viewed as a result of decline in encoding ability, specifically the ability to form new connections between the newly acquired item and the spatial context they appear (Burke & Mackay, 1997; Grady & Craik, 2000). However, when we examined the number of training runs required to encode our set of training stimuli, there was no significant difference between young and elderly participants. Seeing as how presentation of stimuli during acquisition was the same for all participants (3 seconds), it appears that at least for our task the ability to successfully encode visual stimuli and also accurately form a left/right contextual association was not affected by cognitive declines resulting from ageing. In contrast, successful retrieval of target stimuli, even at baseline, showed young participants outperformed elderly participants. Therefore while retrieval of long-term anterograde episodic memory is behaviourally well preserved, there are age-related differences. Whether this is also reflected in the functional activity of neural substrates underlying this process needs to be explored.

Neuroimaging - Ageing Analysis

Following on from the functional analysis of all participants, fMRI data for young and elderly participants was analysed independently and contrasted. Separate fMRI gradient analysis of young and elderly cohorts showed similar dissociation to our overall analysis, as decreased

activity in the posterior tail of the left hippocampus predicted better consolidation of source information for young participants, but in the elderly group this was found only for item recognition. One possible explanation is elderly participants require greater cognitive processing for the retrieval of item recognition, essentially retrieving additional contextual information to aid item recognition. Previous ageing studies have shown compensatory mechanisms in elderly participants whereby dorsal-lateral PFC showed greater activity compared to young participants for recognition memory (Rajah, Languay, & Valiquette, 2010).

Within the literature functional imaging studies comparing healthy young and elderly cohorts have typically been focused on changes in the PFC particularly at encoding. The majority of ageing studies that have examined the hippocampus found the greatest age-related changes to be located in the dentate gyrus showing both functional changes, particularly for pattern separation (Toner, Pirogovsky, Kirwan, & Gilbert, 2009; Yassa et al., 2010) and also hypometabolism (Small, Tsai, DeLaPaz, Mayeux, & Stern, 2002; Small et al., 2011). To our knowledge, there has not been any prior functional imaging ageing studies that have looked at long-term anterograde episodic memory. There has, however, been a previous fMRI study by Maguire and Frith (2003) that examined the effects of healthy ageing on autobiographical episodic memory retrieval. Their results indicated an overall commonality in medial frontal and parietal regions being activated across both groups, similar to our results. Although for activity in the hippocampus for autobiographical recall, they observed bilateral activity in the elderly group but only left hippocampal activity for the younger group. This age-related laterality difference in the hippocampus was not observed in our study. However, the posterior tail of the hippocampus was identified in our gradient analysis to be critical for predicting long-term anterograde memory consolidation.

In the autobiographical memory literature, there have also been reports of asymmetry in MTL activation. Patients suffering from left lateralised MTL damage are more often associated with severe episodic memory impairment than right lateralised damage (Spiers, Maguire, & Burgess, 2001; Svoboda, McKinnon, & Levine, 2006), suggesting that the left hippocampus is more engaged by retrieval of contextual details (Maguire, 2001a; Maguire, 2001b). Our gradient analysis of young participants' fMRI data identified changes in activity over time within the left hippocampus was associated with consolidation of newly acquired episodic memory. By contrast, we found activation in the right hippocampus for immediate retrieval, which is puzzling as most previous studies of episodic memory have identified

either the left or bilateral hippocampal involvement. Even in studies that have reported laterality differences in hippocampi function (Maguire & Frith, 2003), where the right hippocampus showed a temporal gradient decreasing in activation for remote autobiographical memories, they still found bilateral hippocampal activation. It is currently not clear why there is such a dichotomy of left vs. right hippocampus in our data, which clearly needs to be investigated in the future.

Theoretical Implications

Our observation that only source components elicited hippocampal activity, is supported in the literature, albeit debated, by the view that recognition and source memory represent two different memory processes with contrasting neuroanatomical bases. It has been suggested that while both memories elicit PFC activity (Rugg, Fletcher, Chua, & Raymond, 1999; Rugg, Henson, & Robb, 2003; Rajah, Languay, Valiquette, 2010), contextually dependent memory retrieval is hippocampal dependent while item recognition in the absence of encoding context relies on extra-hippocampal regions of the MTL. However, Squire and colleagues (2007) have argued that the observed difference in hippocampal activation reflects a difference in memory strength rather than different underlying neuroanatomical bases for these two memory processes. In support of this, Wais and colleagues (2010) contrasted recognition and source responses based on confidence scores rather than correct/incorrect responses and found memory strength to be the dependent factor for hippocampal activation.

In regard to cognitive models of long-term memory consolidation (SCT, MTT), our findings support the MTT as our results indicated the hippocampus is always implicated in successful retrieval of long-term anterograde episodic memory. In both overall and ageing analyses, we found decreased activity in the posterior tail of the left hippocampus to predict successful long-term memory retrieval. While it may seem counterintuitive that decreased activity in this structure is associated with better performance, this pattern of results has been found in previous studies (Bosshardt, 2005b; Takashima et al., 2006; Takashima et al., 2009). Alternatively, other studies have also shown no change or decreased functional activity with consolidation (Addis, Moscovitch, Crawley, & McAndrews, 2004b; Gilboa et al., 2004; Bosshardt et al., 2005a; Spiers & Maguire, 2007). Nevertheless, the common finding in these previous studies and ours is that successful retrieval of consolidated episodic memory does not become hippocampally independent and supports the MTT view of long-term memory organisation.

While our analyses also implicated parietal and frontal lobe regions, structures shown to be functionally connected with the hippocampus for episodic memory retrieval (Addis, Moscovitch, & McAndrews, 2007; Diana, Yonelinas, & Ranganath, 2007; Takashima et al., 2009), we did not detect any significant clusters of activation within neocortical regions of the medial MTL. Furthermore, we failed to detect any significant MTL activity through our direct analyses of remote episodic memory activation (MRI 2 scans). This could reflect a power issue or our anterograde visual memory task not being as hippocampally demanding as autobiographical memory recall, which is often reported to engage hippocampal activity (Svoboda et al., 2006; Cabeza & Jacques, 2007). However, autobiographical imaging studies testing for remoteness of memory is problematic in the sense that certain memories may have been re-encoded, the memories have different levels of vividness and detail, both of which alter the strength of the retrieved memory. This in turn has been shown to alter the strength of resulting hippocampal activity (Wais, Squire, & Wixted, 2010).

Clinical Implications

Our behavioural results have mapped out the rate of normal memory trace decline for newly consolidated episodic memory over a 4 week period. Both young and elderly cohorts showed the same pattern of results, highlighting that while ageing results in an overall diminished level of long-term memory retrieval the function remains intact. Our neuroimaging results have highlighted a specific region of interest located at the posterior tail of the hippocampus that appears critical to successful consolidation of episodic memory. Both changes in haemodynamic response as well as greater white matter integrity in this region were found to correlate with improved remote episodic memory retrieval. These findings would be particularly relevant in accounting for the severe anterograde amnesia suffered by AD patients.

A characteristic of early stage AD is focal atrophy within the hippocampus (Mueller, Kesser, Reiser, Teipel, & Meindl, 2011), with histological findings suggesting the CA1 and subiculum are heavily affected while CA3 and dentate gyrus are relatively preserved (Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006; Thal, Rub, Orantes, & Braak, 2002; West, Coleman, Flood, & Troncoso, 1994). CA1 and the subiculum are the primary mediators of hippocampal output to a range of cortical and subcortical structures (Small et al., 2011). Therefore, damage to these subregions of the hippocampus severely impairs its function and involvement in processes, such as consolidation of episodic memory.

In addition to the hippocampus, it has long been postulated that the earliest stages of AD is accompanied by atrophy in the fornix. More recently, Copenhaver and colleagues (2006) conducted volumetric analyses comparing patients with mild AD and mild cognitive impairment (MCI, premorbid AD), and found while there was no difference in overall brain volume, atrophy in the fornix and mamillary bodies (located at the anterior arches of the fornix) predicted progression of MCI to AD. Similarly, Ringman and colleagues (2007) found reduced white matter integrity in the fornix of patients with genetically inherited dementias. Therefore, in AD at least, it seems that while the hippocampus is critical for the acquisition of new episodic memory it is disruption in the main output from this structure that leads to an inability to consolidate new memories for long-term storage and retrieval.

Conclusions

From this experiment, we have converging evidence from functional and diffusion analyses highlighting the importance of the posterior hippocampal region in the consolidation of long-term anterograde episodic memory. For DTI, the accuracy of the fornix clusters were checked by creating a mask labelling the fornix structure and overlaying our identified clusters over it. We found these clusters to overlap, indicating that they indeed belong to the fornix.

Imaging analyses comparing young and elderly groups were less informative as it was difficult to reach the significance threshold. This was particularly evident in the 4 week delay MRI scans. We did, however, observe asymmetry differences between the two groups in MTL activation, which has previously been reported in amnesic patients for episodic memory retrieval.

The lack of a stronger hippocampal activation may be the result of our task being too laboratory based and not having a strong enough temporal-spatial aspect that autobiographical memories have. However, while autobiographical memory is the prime example of Tulving's (1972) original description of episodic memory as 'mental time travel', functional imaging of autobiographical memory is confounded by many factors and has led to discrepant findings in the literature. Furthermore, there is an absence of prospective long-term study of any long-term memory consolidation process in amnesic patients. Given our findings implicating the fornix in the consolidation process and evidence associating changes in this structure during early stages of AD, this experiment should be explored further within an amnesic patient population.

Chapter 4. Memory Consolidation in Dementia

Experiment 2. Memory Consolidation for Visual Stimuli in Alzheimer's Disease and Semantic Dementia

The second experiment follows on from the previous experiment to assess long-term anterograde episodic memory in a sample of AD and SD patients. Having tested a healthy population in the previous experiment, the same experimental paradigm was applied to test dementia patients. We examined participants' ability to accurately retrieve recognition and source information of learnt stimuli over a period of four weeks. Importantly, AD and SD patients show different patterns of atrophy in temporal lobe regions in the early stages of their respective disease, with AD showing more hippocampal atrophy (Chan et al., 2001; Graham, Simons, Pratt, Patterson, & Hodges, 2000) while SD patients show more inferior and anterior temporal lobe (Hodges & Patterson, 2007; Nestor et al., 2002). According to the standard consolidation theory, the pattern of long-term behavioural performance on the visual task should therefore differ between the two patient groups due to contrasting atrophy in the MTL region, containing structures critical in consolidation of memory. Specifically, hippocampal atrophy should affect long-term consolidation of newly learnt contextual (source) information in AD, while SD would only show a longer-term degradation of consolidated contextual memory due to more lateral temporal lobe atrophy. Therefore, we predicted that SD patients will show a significantly lower rate of contextual memory degradation than AD after short delays, but will be significantly impaired compared to controls after longer delays. By contrast, recognition memory would remain intact for both groups.

Methods

Participants

Eleven Alzheimer's disease (mean age 66.2 years, SD = 5.8) and 6 semantic dementia (mean age 65 years, SD = 3.2) patients were recruited for the visual episodic memory task. Participants were all registered in the FRONTIER research group database of patients who had given consent to be contacted about research participation opportunities. We contacted all existing AD and SD patients under the age of 75 with an MMSE score above 20 and confirmed disease diagnosis with no cognitive associated atypical symptoms. Consent for behavioural memory testing and MRI scans were collected at the start of the study.

Prior to testing, participants were administered the same battery of cognitive assessments given to participants in Experiment 2 to assess overall cognitive function and intactness of memory. Assessments included: Addenbrooke's Cognitive Examination-Revised (ACE-R), Doors & People (doors subtest), and Rey Complex Figure Test (RCFT). The RAVLT, however, proved too be too cognitively demanding and was not administered. One AD and one SD participant was excluded from the study due to significantly impaired ACE-R score. The mean score of remaining participants (10 AD, 5 SD) on the cognitive assessments are shown in Table 3 and were trained on the visual memory task.

For control behavioural data, long-term source and recognition memory performance from the elderly cohort (mean age 68.1, SD = 7.6) in Experiment 1 was used for comparison with patient groups.

Table 3. Scores of Alzheimer's disease and semantic dementia patients on standardised cognitive assessments.

Tests	Alzheimer's Disease (n = 10) Mean	SD	Semantic Dementia (n = 5) Mean	SD
MMSE	23.8	2.3	25.6*	2.3
ACE-R				
Memory	14.3	3.7	13.2	3.3
Total	72.3	7.3	60.2	7.1
Doors & People (Doors Subtest)				
Part A	6.7	1.9	7.8	2.5
Part B	N/A	N/A	N/A	N/A
RCFT				
Copy	23.2	11.8	32.8	0.8
Delayed Recall (30min)	3.4	3.8	14	4.8

*Denotes significant difference in performance between AD and SD patient groups ($p < 0.05$).

Note: Mini-mental state examination (MMSE); Addenbrooke's cognitive examination revised (ACE-R); Rey complex figure test (RCFT).

Procedure

For the visual memory task, the procedure is the same as that of Experiment 1 and is explained in detail in Chapter 2. Briefly, participants were assessed on a visual based recognition and source memory task. Participants explicitly learnt to criterion (≥ 90% correct, on two consecutive training runs) a set of 25 target objects presented on either the left or right hand side of the monitor. At test, the encoded stimuli were randomly intermixed with 25 novel stimuli and participants were asked to make an old/new recognition decision followed by a left/right source decision. Six memory tests were carried out with the following delays: baseline (no delay), 1 hr, 24 hrs, 1 week, 2 weeks, and 4 weeks. Different sets of novel stimuli were employed for each test to avoid confounding target memory retrieval with previously employed foils. The baseline memory test was performed during fMRI data acquisition. At the same time DTI and T1-weighted anatomical data was acquired for each subject. Tests after a delay of 1 hr, 24 hrs, 1 wk, and 2 wks, were conducted online via WebExp. The final test (4 week delay) was conducted during the second MRI scan. MRI scans followed the same imaging protocol as Experiment 1.

Behavioural results were scored for identifying target (old) and novel (new) stimuli (recognition memory) and remembering the original location (left/right) target objects were presented at training (source memory). The mean of participants' recognition and source memory scores were compared statistically using SPSS across different time points.

Results

As illustrated in Figure 4.1 and Table 4, AD performance for old/new recognition showed a gradual decline of 11% over the 4 week delay. The SD group also showed high performance for recognition across tests, with a decline of 15%, but performed worse than AD after a 4 week delay. For the source component, AD showed a drop in performance of 16% with a 1 hr delay. Decline beyond the 1 hr delay was more gradual with an overall drop in performance of 26%. SD participants showed an initial increase in performance after a 1 hr delay, compared to baseline, followed by a steady drop over the 4 week testing period, overall decline of 20%.

Overall ANOVA analysis of AD, SD and elderly controls found that recognition performance across time differed significantly within groups: $F(5, 135) = 9.74$, $p < 0.05$, between groups: $F(2, 27) = 6.5$, $p < 0.05$, and also a significant interaction effect between

groups across time: F (10, 135) = 2.71, $p < 0.05$. Similarly, source performance across time differed significantly within groups: F (5, 135) = 40.35, $p < 0.05$, between groups: F (1, 27) = 30.46, $p < 0.05$, and also a significant interaction effect between groups across time: F (10, 135) = 6.5, $p < 0.05$.

ANOVA analysis of patient groups found that recognition scores differed significantly across time within the two participant groups: F (5, 65) = 5.2, $p < 0.05$. There was no significant difference between groups or interaction effect between the two groups across time. For source scores, ANOVA showed a significant difference between groups: F (1, 13) = 18.32, $p < 0.05$ and within groups across time: F (5, 65) = 19.34, $p < 0.05$. There was also a significant interaction effect between groups across time: F (5, 65) = 7.75, $p < 0.05$.

ANOVA comparisons of recognition performance with the control group indicated there was a significant difference between groups in both AD (Fig. 4.2) and SD (Fig. 4.3) participants: F (1, 23) = 8.11, $p < 0.05$; F (1, 18) = 28.4, $p < 0.05$, respectively. For recognition, there was also a significant interaction effect between groups across time for SD: F (5, 90) = 11.5, $p < 0.05$. Analysis of source responses found, compared to controls, there was a significant difference between groups for AD: F (1, 23) = 51.68, $p < 0.05$, and also a significant interaction effect: F (5, 115) = 9.13, $p < 0.05$. These differences were not significant when comparing source performance between control and SD.

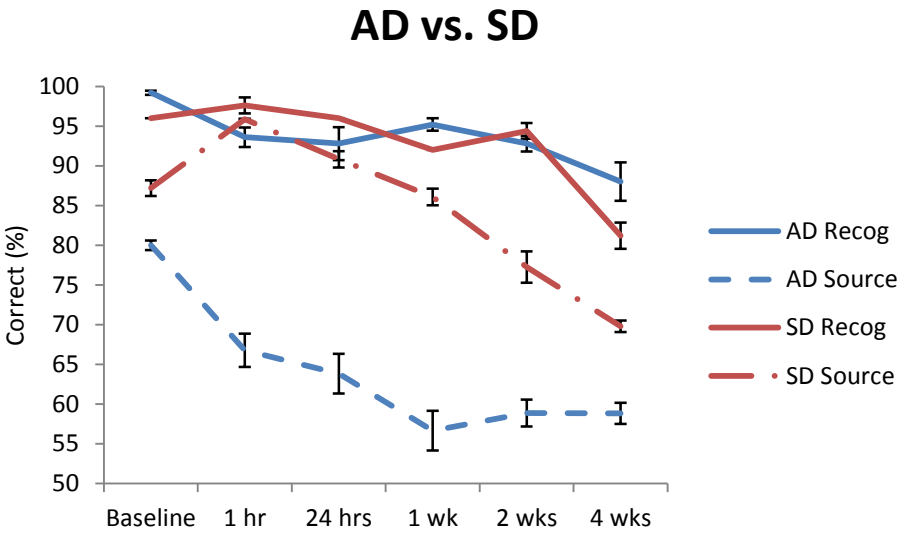


Figure 4.1. Correct recognition and source responses in AD and SD participants over 4 weeks. Error bars indicate standard error of the mean.

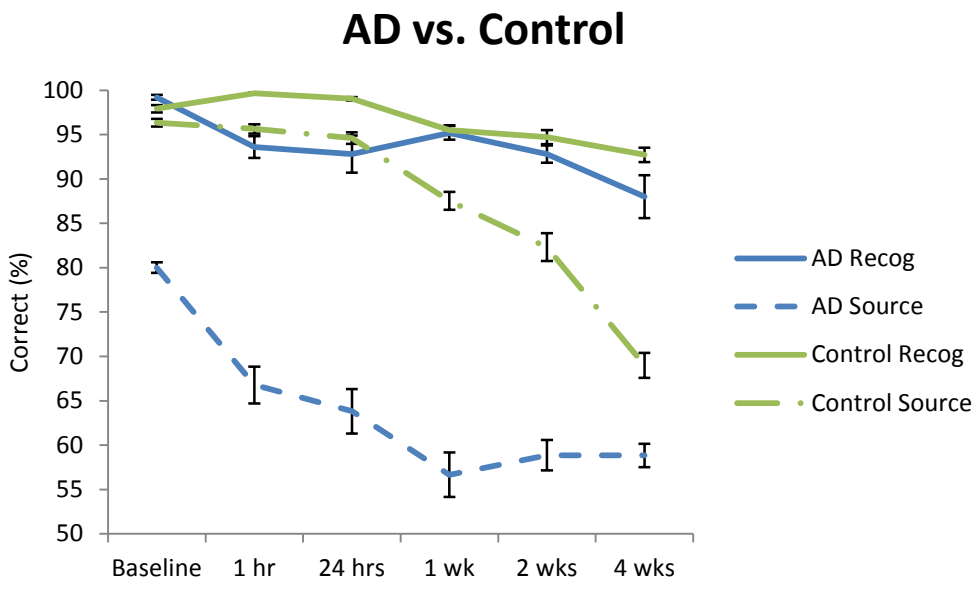


Figure 4.2. Correct recognition and source responses in AD and control participants over 4 weeks. Error bars indicate standard error of the mean.

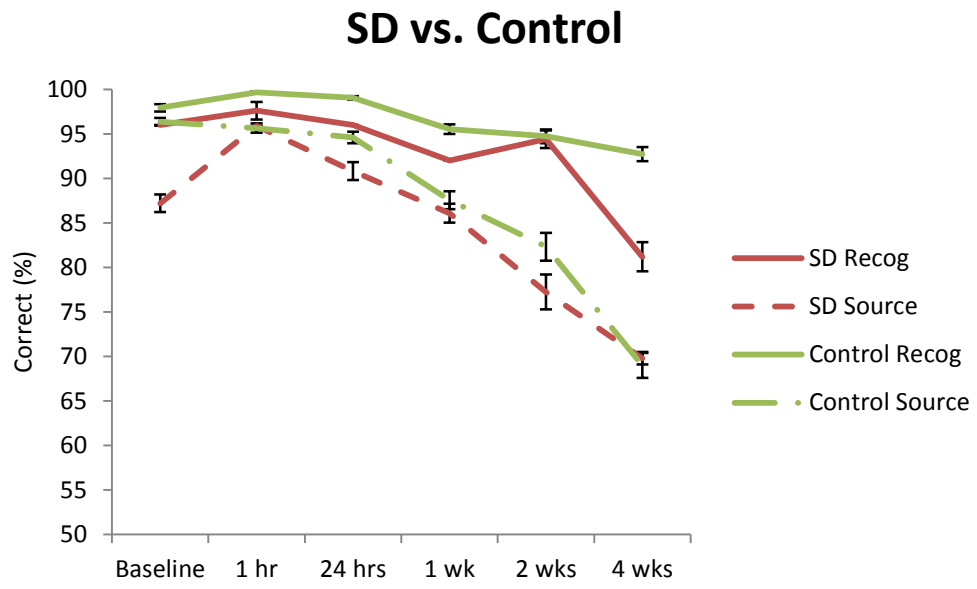


Figure 4.3. Correct recognition and source responses in SD and control participants over 4 weeks. Error bars indicate standard error of the mean.

Table 4. Mean percentage of correct recognition and source scores on the long-term visual memory task for Alzheimer's disease, semantic dementia and control groups.

	AD	SD	Control
Recognition			
Baseline	99.2	96	99.1
1 hr	93.6	97.6	99.7
24 hrs	92.8	96	99.9
1 wk	95.2	92	96.8
2 wks	92.8	94.4	96.8
4 wks	88	81.2	96.7
Source			
Baseline	80	87.2	97.6
1 hr	66.8	95.9	97.3
24 hrs	63.8	90.8	95.9
1 wk	56.7	86.1	88.6
2 wks	58.9	77.2	86
4 wks	58.8	69.8	70.9

Response bias for total recognition responses was made for AD, SD and control groups (Fig. 4.4). Bias (C) was calculated for mean recognition responses across each test over the 4 week period. Overall ANOVA analysis of bias across time differed significantly within groups: $F(5, 110) = 2.4$, $p < 0.05$, between groups: $F(2, 22) = 6.37$, $p < 0.05$, and also a significant interaction effect across time: $F(10, 110) = 2.74$, $p < 0.05$. ANOVA analysis of AD and SD groups found bias differed significantly within groups across time: $F(5, 65) = 6.44$, $p < 0.05$. There was no significant difference between groups, but there was a significant interaction effect between groups across time: $F(5, 65) = 4.95$, $p < 0.05$. ANOVA analysis comparing the control group with AD and SD groups found there was a significant difference in bias across time between groups: $F(1, 18) = 10.56$, $p < 0.05$; $F(1, 13) = 7.27$, $p < 0.05$, respectively. There was also a significant interaction effect between control and SD across time: $F(5, 65) = 4$, $p < 0.05$. Essentially, AD patients tended to make more liberal responses (i.e. more prone to say a new stimuli was old) across assessments. SD patients showed conservative responding at baseline and 4 weeks, but were more liberal for assessments in between these two time points.

Figure 4.4. Mean response bias of AD and SD participants for making old/new recognition responses.

Discussions

In Experiment 3 we compared episodic memory between AD and SD patients to dissociate differences in long-term anterograde memory consolidation in these two patient populations. Our results showed both groups had surprisingly intact retention of recognition information. As predicted in our hypothesis, SD showed intact recognition memory similar to controls. However, for source, performance dropped considerably after the 4 week delay. More surprisingly was the fact that SD patients mirrored the source memory performance of the older control group even after the long consolidation delays. By contrast, AD patients showed severe source memory performance even at baseline, where their performance never reached over 80% correct response rate. Not surprisingly, source memory degraded much faster in AD after the delays and plateaued just above chance at around 60% correct for later retrieval delays (1wk, 2 wks and 4 wks). The discrepancy in performance on the source component of the visual memory task alludes to the contrasting atrophy observed in Alzheimer's disease and semantic dementia patients. In particular, the contributions of MTL structures, the hippocampus and neocortical areas, to the consolidation process.

It is often reported that atrophy in AD, in the early stages of the disease, is confined to the medial temporal areas, in particular the hippocampus (Braak & Braak, 1998) while in early SD neocortical areas of the temporal lobe, in particular the anterior temporal pole, show significant atrophy with the hippocampus remaining relatively intact (Hodges & Graham, 2001; Hodges & Patterson, 2007). This has important implications on cognitive models of consolidation. Standard consolidation theory (SCT) essentially views the hippocampus as a structure necessary for the initial acquisition of a memory trace while neocortical regions of the medial temporal lobe act as the repository of long-term memory (Dudai, 2004). Multiple trace theory (MTT) shares this view in part but also suggests that during consolidation the semantic and contextual components of the memory trace is segregated, such that retrieval of contextual components requires the hippocampus in addition to neocortical regions (Winocur & Moscovitch, 2011) .

Comparing recognition and source components of AD performance, our results in part support MTT. We can see that AD subjects were able to encode the 'what' and 'when' aspects of newly acquired anterograde episodic memory very well, but were unable to retrieve this contextual information after longer encoding delay periods. In fact after a delay of only one hour we see the most significant drop in source performance for the entire 4

weeks in AD. Performance remains low for the remaining duration of testing but stays above chance. Recognition performance on the other hand is on par with that of healthy participants in Experiment 2, indicating that they are able to recognise learnt objects over longer time intervals. Despite widespread reports of impaired recognition memory in AD patients (Abe et al., 2011; Wolk, Signoff, & Dekosky, 2008; for a review see Salmon, 2000), our findings are consistent with previous neuropsychological findings that showed visual recognition memory in AD can be intact, and on the same level as controls, when assessed via a simple forced choice response, without delay (Anderson et al., 2008; Westerberg, et al., 2006). By contrast, the impaired performance for contextual or recall memory tests in the AD group is consistent the cognitive impairments associated with the condition (Salmon, 2000).

Similar to AD, SD patients showed excellent retention of recognition information over time, but there were clear difference in the source recall between the patient groups. SD patients' contextual memory recall remained at a very high level throughout the testing period and only significantly changed from controls after a 4 week delay. Such a dissociation of long-term contextual memory between SD and AD has been reported numerous times in studies of autobiographical memory, i.e. looking at retrograde memory. Many early studies in SD reported a temporal step-function where autobiographical recall of memories from the past 2 years was intact while memories beyond this period show impaired retrieval, while the reverse was shown in AD (Graham & Hodges, 1997; Nestor et al., 2002). This pattern of results along with the contrasting MTL atrophy in these two neurodegenerative diseases has been used as evidence for SCT, where intact hippocampal function in SD accommodates successful retrieval of recent memories while retrieval of more long-term memories stored in neocortical regions of the MTL is impaired, and vice versa for AD. This finding of a temporal gradient for long-term autobiographical recall, however, is not universal with some studies reporting intact memory retrieval for all periods of life in SD (Westmacott et al., 2001; McKinnon et al., 2006; Maguire, Kumara, Hassabis, & Kopelman, 2010). Taken together, AD and SD source performance and the contrasting MTL pathology associated with these two diseases, our results support the critical role an intact hippocampus plays in the acquisition and consolidation of contextual aspects of episodic memory whereas recognition memory may remain mainly intact.

The high performance on recognition for AD was surprising, but it should be noted that we targeted patients in the early stages of the disease during recruitment. All patients who underwent this task received their clinical AD diagnosis less than 2 years prior to testing.

Therefore, they still retain a higher level of cognitive function. Furthermore, all AD and SD patients showed considerable response bias (C) towards responding ‘old’ for newly shown stimuli during the course of the study, which would have affected the accuracy of performance. Another observation we made during the participant feedback session at the end of testing was a clear discrepancy in cognitive strategies used to aid in remembering target contextual information, between control and AD patients. When asked if they employed any techniques to help them remember left/right item locations control participants typically responded with logical strategies that were often specific to one or more stimuli i.e. the hammer was on the right; I use a hammer with my right hand. In contrast, when patients created a connection they tended to generalise across similar stimuli based on one observation i.e. the ashtray was on the right; all bad objects are on the right. In the literature it has been suggested that one of the reasons AD patients perform more poorly on remote memory tasks is impaired ability to utilise effective recall strategies (Kopelman, 1991).

Chapter 5. Implicit and Explicit Memory Consolidation

Experiment 3. Memory Consolidation for Verbal Stimuli in Semantic Dementia: A Case Study

In the third experiment we investigated long-term anterograde episodic memory in a single SD patient. Previous experiments have all utilised a visual based recognition and source paradigm, in this case study we wanted to explore how patients would respond on a verbal based assessment. Previous studies of word re-learning in SD (Graham et al., 1999; Jokel, Rochon, & Leonard, 2006; Snowden & Neary, 2002) have all had variable success with training and maintenance of learnt words up to a period of 6 months (Jokel, Rochon, & Leonard, 2006). While these studies have demonstrated that learning processes are intact in SD, it appears the consolidation process is disrupted. Furthermore, the assessments used in these studies have all probed for explicit recall only. To our knowledge, no studies have explored implicit long-term consolidation of new information and whether this could benefit rehabilitation strategies in SD. In this study we wanted to examine the durability of newly learnt verbal information more closely as well as long-term implicit retention of newly acquired information. We hypothesised that the initial and short-delay episodic explicit retrieval would be good, followed by a deterioration over longer delays. We further assumed that despite an impaired explicit memory performance, some memory information should be intact on an implicit level even after a long delay, as this information does not require an intactness of MTL structures.

Case Report

Patient RW (born in 1951) presented in June 2008 with anomia and word finding difficulties. Previously, he was an avid crossworder, but noticed in the past 5 years a progressive difficulty in thinking of word meanings. His wife also reported changes in personality, including socially inappropriate behaviour and difficulty with personal boundaries, of which RW has no insight. RW's verbal recall of autobiographical details was good, although frequently interrupted by word finding pauses and anomia. The patient was good at repeating long words, such as chrysanthemum, but had no knowledge of their meaning. When given an array of toy animals, he had great difficulty identifying any of them when asked to point in response to their name. On formal neuropsychological assessments, he showed reduced overall cognitive functioning with a score of 26 (out of 30) on the MMSE and 62 (out of 100) on the ACE-R (Table 5). Importantly, his episodic memory was quite impaired with total memory sub-score of 7 out of 26 on the ACE-R. Additional assessments of verbal and non-verbal anterograde memory (RAVLT, RCFT, Doors & People) showed significant impairment in verbal episodic memory, while non-verbal memory was good, compared to controls (Table 5). Semantic memory, as expected was poor with a total of 3 (out of 15) on the Boston Naming task. A more detailed investigation of semantic memory was carried out using the Sydney Language Battery (SYD-BAT), a computer administered test of language that teases apart naming, repetition, comprehension and semantic association performance. The test revealed significantly impaired naming performance (7 out of 30), albeit relatively intact comprehension, repetition and semantic association (Table 5).

In 2009, follow-up assessments showed RW's anomia and comprehension problems had further deteriorated, but his nonverbal memory performance remained on a similar level to controls (Table 5).

Table 5. Neuropsychological scores for patient RW in 2008 and 2009, and normative data. Normative data taken from 4 age-matched controls recruited from the FRONTIER patient database. SD = standard deviation of the mean. N/D represents no data due to task not being administered.

Test Scores	2008	2009	Normal Mean (SD)
MMSE (total)	26	25	29.3 (1)
ACE-R			
Memory	7	6	25.5 (0.6)
Total	62	57	96.5 (1.7)
RAVLT		N/D	
Immediate Recall (A6)	2		12 (1.2)
Delayed Recall (30 min)	2		11.8 (2.5)
Recognition	13		14.5 (1)
Total	29		57.3 (9.1)
RCFT			
Copy	32	35	34.8 (1.5)
Delayed Recall (30min)	15	23.5	23.4 (3.6)
Doors & People		N/D	
Part A	13		11.5 (1.7)
Part B	9		11.3 (1.7)
SYD-BAT			N/D
Naming	7	5	
Comprehension	29	18	
Repetition	30	27	
Semantic Association	23	25	
Boston Naming			N/D
Total	3	2	

*Note: Mini-mental state examination (MMSE); Addenbrooke's cognitive examination revised (ACE-R); Rey auditory verbal learning test (RAVLT); Rey complex figure test (RCFT); Sydney Language Battery (SYD-BAT).

**SYD-BAT is a recently developed neuropsychological assessment used routinely within the FRONTIER research group in conjunction with standardised tests to categorise frontotemporal dementia patients into sub-types of the disease.

Verbal Task Procedure

The task used to assess long-term anterograde episodic memory is described in Chapter 2. Briefly, an adapted version of the word-stem completion test, as described by Schott and colleagues (2002), was employed. RW and an age-matched control were shown a list of 15 high-frequency words (Appendix 1) on a computer screen and asked to explicitly recall the list without delay. The words used were selected to have approximately equal word frequency across three sets (A, B, C) and to have between 5 and 7 letters. Word-stems were created for each word by only retaining the first three letters of each word (e.g. BRI for BRIDGE). Piloting in young control participants showed that some word-stems were easier to complete than others, but importantly this did not affect the implicit memory results in the patient, i.e. words implicitly successfully completed by the patient were not only those easier completed by the controls. Both participants were shown the list of words until they were able to accurately recall the entire list on two consecutive occasions. At test, 30 three letter word stems were presented and participants were asked to verbally complete them with a word from the study list, but if they could not, use the first word that came to mind. Afterwards, they were required to state whether the word they used was part of the study list or not with an old/new response. Critically, of the 30 word stems presented at test, only 15 could be completed with words from the study list.

Testing occurred immediately following training (set A) and after a 2 (set B), 4 (set C), and 8 (set A) week delay. Implicit memory was scored as the percentage of correct responses when the study list word was completed but not identified as ‘old’. Explicit memory was scored as the percentage of correct responses when the study list word was completed and identified as ‘old’. Therefore, explicit and implicit memory scores were mutually exclusive as the scoring protocol categorises a correct implicit response as successfully recalling the primed study list word, but not explicitly stating its membership in the study list.

Previous studies have found this task to be effective in assessing implicit and explicit memory in both healthy participants and amnesic patients (Schott et al., 2006).

Structural Imaging

3D structural (T1-weighted) MRI was acquired as stated in Chapter 2. The scan was reviewed by a clinical radiologist, and from visual inspection, clearly showed left temporal lobe atrophy involving particularly the temporal pole and inferior temporal region. We conducted a more formal manual tracing of the hippocampi, using the tracing protocol as defined by Konrad and colleagues (2009). Briefly, hippocampal grey and white matter were included in our trace and the internal landmarks used to define the borders of the hippocampus were: alveus for anterior border; lateral ventricle for posterior border; alveus for superior border; white matter of parahippocampal gyrus for inferior border; lateral ventricle for lateral border; cistern ambiens for superior medial border; a arbitrary linear boundary ascending from the medial angle where the hippocampus curves down into the parahippocampal gyrus was used for inferior medial border. VBM analysis was carried out as stated in Chapter 2, using our manual tracings, and tested for significance at $p < 0.05$ corrected for multiple comparisons via family-wise error correction across space.

Results

As evident in Figure 5.1, RW and the control showed similar high performance for completing and explicitly recognising the word stems at baseline, i.e. immediately after learning the list of words to criterion. After a 2 week delay the SD patient still completed over 70% of word stems correctly and recognised them. However, after the 4 and 8 week delays none of the word stems were explicitly recognised, although 60% and 40% of them, respectively, were completed implicitly.

By contrast, the control participant was able to recognise 90% of the words correctly even after an 8 week delay and showed only minimal need for implicit memory retrieval with only the 4 week delay eliciting ~10% correctly completed word stems.

VBM volumetric analysis, using our structural tracing results, showed that RW's hippocampal volumes did not differ significantly from mean hippocampal volumes of 4 age-matched controls (Fig. 5.2).

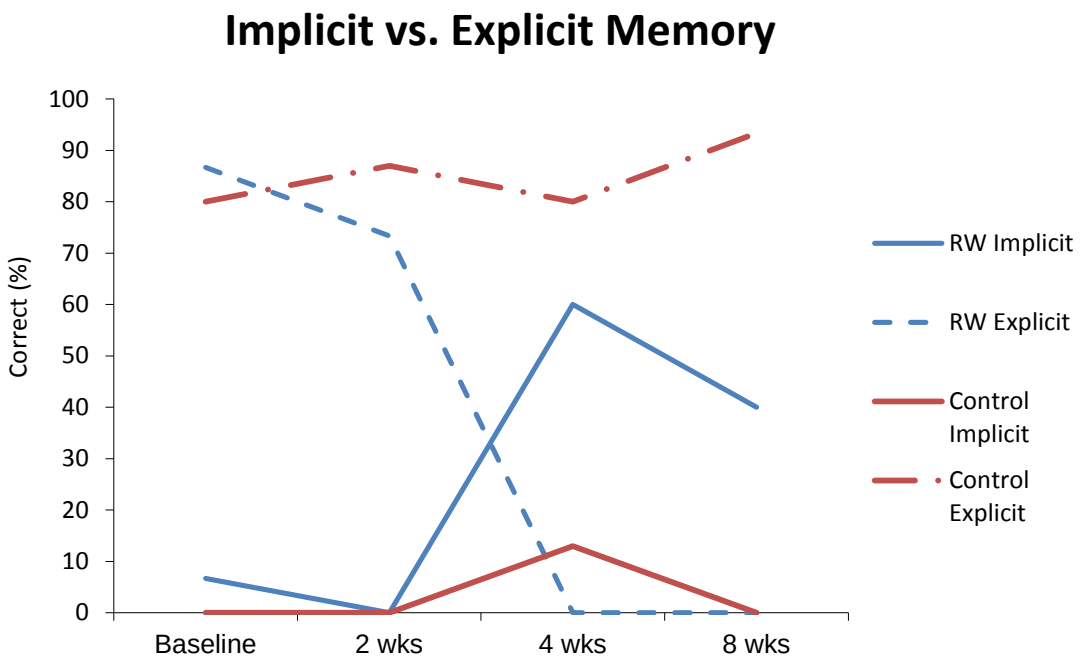
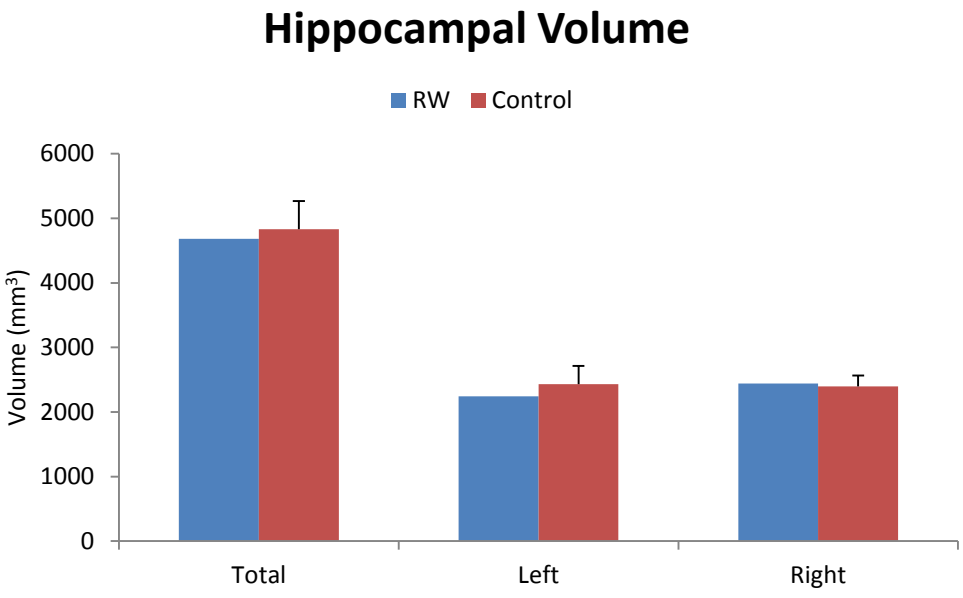


Figure 5.1. Implicit and explicit memory task performance of RW and age-matched control at baseline, and 2, 4, 8 weeks post-training. Performance is shown as the percentage of total correct response.



*Note: Hippocampal volumes corrected for intracranial volume differences between subjects.

Figure 5.2. Hippocampal volume of RW and controls. Control values are the average volume of 4 age-matched participants recruited from our patient database. Error bars indicate standard error of the mean.

Discussions

Our findings show that long-term consolidation of episodic memory in SD is particularly vulnerable after a 2 week delay of encoding verbal information. More specifically, patient RW showed intact recognition of word list items for immediate and 2 week delay assessments. However, he could not explicitly recognise any of the words after 4 and 8 weeks post-training. By contrast, he was still able to complete a high percentage of word stems even after 4 and 8 weeks, despite not being able to recognise them as having been learnt before. These findings have important theoretical and clinical implications.

On a clinical level, these findings have implications for word re-learning rehabilitation programs in semantic dementia. It has been argued in the literature which is the best time frame for patients to relearn words and at what time interval these need to be re-encoded. Certainly, in the studies carried out by Graham and colleagues (1999), and Snowden and Neary (2002), daily rehearsal of stimuli lists significantly improved patient performance. However, this approach does not always result in a beneficial effect. Most notably the well published SD patient, AM, practiced similar lists, but showed no improvement. Furthermore, the long-term effects of this behaviour can also 'spiral out of control' or lead to obsessive behaviour and depressive symptoms. Graham and colleagues (1999) noted that as DM's semantic impairment progressed the lists he diligently rehearsed grew alarmingly longer. Continued rehearsal also had a negative effect on his state of mind, as it was a constant reminder of his disease progression. Our results suggest that SD patients need to re-encode the newly learnt material after a two week period to increase the chance of retaining this information. It is not clear, however, if a re-activation of those memories would increase the time these memories are kept, which would be interesting to explore in future studies. Furthermore, our findings suggest that implicit memory techniques in semantic dementia might help or even facilitate the retrieval of newly learnt information, which could benefit the patient's everyday functioning.

On a theoretical level, our results replicate the findings of Adlam and colleagues (2009) that day-to-day memory in SD is intact, with our patient showing fairly intact explicit episodic memory even after a two week delay. The pattern of results, therefore, fits the constraints of the standard model of consolidation, where acquisition and retrieval of newly formed memories are dependent upon the hippocampus while long-term memories are independent of the hippocampus and require instead the intactness of the temporal neocortex

(Squire & Alvarez, 1995). The model predicts that RW would be able to encode the study list and perform on par with control for retrieval of recent episodic memory, but show increasing impairment for retrieval of remote memory, which is the pattern observed in this study. Nevertheless, it is interesting to note that storage of the actual information was only partly affected by the atrophy in the temporal neocortex, since RW was able to implicitly complete a percentage of word stems.

Previous functional neuroimaging studies have found this adapted word stem paradigm provides measures of priming that is uncontaminated by either unintentional or intentional explicit memory (Schott et al., 2005; Schott et al., 2006). Assessment of implicit episodic memory performance, therefore, is clearly distinguished from explicit memory interference. Consequently, we were able to obtain relatively pure measures of implicit anterograde episodic memory, despite moderate semantic impairment and severely impaired long-term episodic memory.

In conclusion, the findings reported here indicate that although recent anterograde episodic memory is preserved in SD, the durability of the memory is relatively short. This finding presents important implications for rehabilitation programs in SD. Nevertheless, it would be important to replicate our findings in a group study in the future. Furthermore, the current study was not a rehabilitation study per se in that it did not employ an errorless learning paradigm or unknown stimuli to the patient. Thus, it would be important to replicate our findings in a rehabilitation context.

Chapter 6. Conclusions

Summary of Results

The main objective of this thesis was to investigate consolidation of long-term anterograde episodic memory in healthy individuals and patient cohorts, and the underlying neuroanatomical bases involved in this process. This aim was carried out in three parts. We began our investigation by correlating behavioural performance with functional (BOLD) and structural (DTI) imaging in healthy participants using a visual stimuli task designed to assess item recognition and contextual source memory retrieval. This was followed by assessing two groups of dementia patients (AD, SD) on the same visual task to compare how the consolidation process is affected by contrasting MTL atrophy in the hippocampus (AD) and neocortical regions (SD). We concluded our study by comparing the effect of explicit and implicit testing procedures on retrieval of long-term anterograde episodic memory retrieval in a single case patient. The main findings of each experiment are summarised below.

Memory Consolidation in Healthy Ageing

In the first experiment correct recognition and source memory retrieval was assessed over a 4 week period in healthy young and elderly cohorts. Our imaging analysis yielded converging evidence from fMRI and DTI data highlighting the region located at the posterior tail of the left hippocampus to be critically involved in predicting successful long-term consolidation of recognition and source memory. While there is consensus that the hippocampus is a structure critical for memory, speculation remains over the specific role regions within the hippocampus play in memory and also whether a functional difference exists in left/right hippocampi. Our finding from the gradient analysis (recent-remote responses) found that decreased activity in the hippocampus predicts successful consolidation, which is supported by previous fMRI studies that have shown a similar pattern of de-activation when contrasting recently acquired to more remote episodic memory (Bosshardt et al., 2005b; Takashima et al., 2006; Takashima et al., 2009). Evidence from previous studies of autobiographical memory retrieval and activity along the anterior-posterior axis of the hippocampus have observed increased functional activity in the posterior region for remote memories while the anterior region showed greater activity for more recent memories (Gilboa et al., 2004; Piolino, Desgranges, & Eustache, 2009; Rekkas & Constable, 2005). Furthermore, it is often reported

that autobiographical memory elicits left lateralised functional activation during retrieval (Svoboda, McKinnon, & Levine, 2006). Therefore our finding of the region located at the posterior tail of the left hippocampus map correlates well with existing functional imaging findings for episodic memory within the literature. The addition of DTI results highlighting greater white matter integrity in the fornix and cingulum, located in the same region as our fMRI analysis, predicted better consolidation further implicates this region. Anatomically, the fornix is the main efferent output from the hippocampus connecting it to subcortical memory relay structures located further down along the Papez circuit. In light of the severe anterograde amnesia characterised by AD and recent evidence suggesting one of the earliest indicators of progression to AD from MCI is changes in the fornix (Copenhaver et al., 2006), our results suggest disruption in output from the hippocampus is the main cause of impaired consolidation.

Memory Consolidation in Dementia

In the second experiment correct recognition and source memory retrieval was assessed over a 4 week period in AD and SD patients. The same visual memory task in the first experiment was used to assess consolidation so we could compare what pattern of anterograde episodic memory retrieval would emerge as a result of atrophy in MTL structures involved in memory. We found a strong dissociation in long-term retrieval of contextual information between the patient groups, namely SD showed a pattern of retrieval similar to healthy controls while AD were much more impaired. Previous autobiographical studies in these two patient populations have shown a similar dissociation in memory retrieval where AD showed greater retrieval for remote memories relative to recent memories while the reverse is observed in SD (Graham & Hodges, 1997; Nestor et al., 2002). In regard to cognitive models of long-term memory (SCT, MTT), these behavioural results appear to support MTT.

The principle concept separating SCT and MTT is the issue of whether retrieval of consolidated memories becomes independent of the hippocampus, with SCT arguing for and MTT against. In addition, there is another issue of whether the memory trace itself undergoes change during consolidation. According to SCT, with consolidation, the original memory trace is copied and transferred to neocortical regions becoming hippocampally independent. Alternatively, MTT posits the memory trace itself undergoes a transformation such that retrieval of contextual details depend on the hippocampus, but retrieval of semantic details associated with the memory activates extra-hippocampal structures (Winocur & Moscovitch, 2011). We can see from our results that this appears to be the case for the AD group. While their item recognition performance remained intact and at a high level throughout the testing

period they showed significant impairment in retrieving recently acquired contextual information 1hr after training. It should be made clear that to pass training all participants were required to score ≥ 90% on two consecutive training trials, where they needed to correctly identify the target stimuli as well as their associated source location (left/right). Therefore, AD patients were able to successfully encode the set of target stimuli though they never reached control and SD performance levels. As mentioned earlier, a volumetric study by Copenhaver and colleagues (2006) determined that structural change in the fornix preceded transition from MCI (premorbid AD) to AD. Furthermore, studies in rats have shown in fear extinction paradigms that when neurotoxic lesions are induced in the fornix contextual retrieval is impaired (Ji & Maren, 2008). Taken together, this suggests in the early stages of the disease, when hippocampus is still largely intact, contextual retrieval deficits in AD results from disruption to hippocampal output. However, neuroimaging correlating structural integrity/functional activity with our behavioural results is required to provide more concrete evidence.

Implicit and Explicit Memory Consolidation

In Experiment 3 we investigated the difference between implicit and explicit assessment on the durability of long-term memory retrieval in a typical SD patient using a word-stem completion task. On verbal based learning tasks, previous studies have shown while their learning abilities are intact, without some form of rehearsal newly acquired learning is rapidly lost (Graham et al., 1999; Jokel, Rochon, & Leonard, 2006; Snowden & Neary, 2002). Yet, in the previous experiment our results indicated, for visual stimuli, the pattern of long-term memory retrieval in SD is quite similar to healthy individuals. Following these findings, we discovered in Experiment 3 that despite losing all explicit memory of having learnt the target set of words, they could still successfully complete the target word at test. Certainly this seems to suggest that consolidation of training items has occurred however, conscious retrieval of remote memory is disrupted.

The second main finding from this experiment is the two week period where conscious retrieval of newly encoded verbal stimuli is forgotten. Contrary to visual stimuli, a two week delay appears to be the critical time point where some form of re-training is necessary to maintain newly learnt information. Although in Experiment 2, the SD group did show a drop in performance for recognition from two to four week post-training. Whether this drop marked the beginning of a steady decline in recognition memory should be explored in further.

Long-Term Memory and Ageing

A key aim of this study was to investigate changes associated with long-term anterograde episodic memory performance as a result of healthy ageing. Typically, ageing studies have taken a longitudinal approach by repeating neuropsychological testing over long periods (e.g. years, decades). Results have consistently shown that episodic memory shows one of the greatest changes as a function of age (Nyberg et al., 2003; Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012; Ronnlund, Nyberg, Backman, & Nilsson, 2005; Schaie, 2005). The onset age and rate of deterioration in memory performance, however, varies significantly across studies, with some reporting decline beginning at 20 years of age (Li et al., 2004; Nillson et al., 1997; Park et al., 1996) and others observing stable performance until 60 years of age, once test re-test practice effects were accounted for (Ronnlund et al., 2005; Schaie, 2005). In our visual memory task, practice effects were negated with the introduction of new foils at each assessment. Behaviourally, we found that our cohort of young and elderly participants showed a similar pattern of long-term memory performance, albeit at a lower level, despite a mean age difference of 40 years. Considering our elderly participants were all over 60 years of age, our findings suggest that episodic memory functions does remain stable well into late adulthood at least for delays up to 4 weeks.

In regard to neuroimaging, we did not observe a significant difference in young and elderly cohorts when we directly contrasted functional activity from fMRI scans. Although, there were clear visible differences, when fMRI analyses of the two groups were analysed independently, in particular for lateral parietal and frontal lobe regions. These differences, however, did not survive statistical thresholding when directly contrasted. Neuroimaging in ageing studies has traditionally focused on structural changes and their association with cognitive function. More recently, however, there has been an increase in functional imaging, in particular concerning age-related changes in regions of functional activity (Cabeza, 2002; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Maguire & Frith, 2003; Park & Reuter-Lorenz, 2009). Maguire and Frith (2003) reported a discrepancy in hippocampal activity for autobiographical recall, with elderly participants eliciting bilateral hippocampal activation while only left hippocampal involvement was observed for the young participants. This was not observed in our study and could reflect a difference in age-related functional activity between retrieval of long-term anterograde and retrograde episodic memory. Alternatively, it has been shown that declining episodic memory performance results in reduced BOLD signal in the hippocampus (Persson et al., 2011). Certainly, there was a substantial difference in overall BOLD activity between young and elderly cohorts, in

particular for MRI 2, making statistical analysis difficult to reach threshold. This view also correlates with our behavioural data. While the pattern of memory performance over time did not significantly differ between young and elderly groups, elderly participants showed a significantly lower level of correct recognition and source memory performance over four weeks. Therefore, with our current functional imaging data, we cannot rule out that there is no age-related difference in functional activity.

Theoretical Implications for Models of Long-Term Memory

As we mentioned in the introduction, reports of both temporally graded and uniform retrograde episodic memory impairment, following hippocampal damage, has led to debate over two prominent models of long-term memory (SCT, MTT). When we compare the features of these two models there are two key differentiating features:

1. Time-limited role of the hippocampus
2. Dissociation of episodic and semantic memory components

Cumulatively, the results of our experiments appear to support MTT when considering these aspects of the two models.

Time-Limited Role of the Hippocampus

Traditional SCT proposes that the role of the hippocampus is time-dependent while MTT (Nadel & Moscovitch, 1997) suggests it is always involved in the retrieval of episodic memory. Within the literature, a growing number of fMRI studies have shown hippocampal involvement, regardless of memory age, during retrieval of retrograde episodic memory (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004a; Piolino et al., 2004; Rekkas & Constable, 2005; Ryan et al., 2001; Soderlund et al., 2012; Steinvorth, Corkin, & Halgren, 2006; Viard et al., 2007) and also anterograde episodic memory (Bosshardt et al., 2005b; Takashima et al., 2006; Takashima et al., 2009). The results of Experiment 1 are consistent with these findings, indicating that the left hippocampus is activated for retrieval of recent anterograde episodic memory, and we assume from gradient analysis that this is also the case for remote memory. To our knowledge, this experiment is the first to examine consolidation of anterograde episodic memory over an extended period of time.

While the delay used for previous anterograde studies (Takashima et al., 2009) are short (24 hrs), the authors argue that given molecular changes, such as the synthesis of new proteins, is observed immediately after encoding (Kandel, 2001; Dudai, 2004) and behavioural changes resulting from consolidation can be observed after a night of sleep (Stickgold & Walker, 2007), measuring consolidation after a delay of 24 hrs is valid. While this may be true, behavioural studies in humans have shown that the strength of a newly

acquired memory trace follows an exponential function (Rubin & Schulkind, 1997). Therefore, greater phenomenological difference in neural activity, resulting from the consolidation process, should be observed over a time period extending weeks rather than hours (Soderlund et al., 2012). Nevertheless, the pattern of hippocampal activity reported by Takashima and colleagues (2009) was the same as our findings. However, examination of this process prospectively over a longer time period, as we did in our study, is more ecologically valid in determining that the hippocampus does not play a time-limited role in anterograde consolidation.

Dissociation of Episodic and Semantic Memory Components

The second key aspect differentiating SCT from MTT is whether the consolidated memory is an exact representation of the originally encoded event (SCT) or, alternatively, whether the memory undergoes a 'transformation' during consolidation (MTT). While Moscovitch and colleagues (2010) have not been explicitly stated how this transformation occurs, they argue that both types of memory exist and can be accessed concurrently. Furthermore, retrieval of one or the other is impaired disproportionately depending on damage to the hippocampus or neocortex. Accordingly, we would expect to see patients with hippocampal damage to show greater impairment in recalling contextual memory, compared to semantic memory, and vice versa for patients with neocortical damage. This is indeed the pattern of memory impairment which emerged when we tested our AD and SD patients

This behavioural dissociation in episodic (context-specific) and schematic (non-context-specific) types of memory has been consistently observed in both rodents (Winocur, Moscovitch, & Sekeres, 2007; Wiltgen & Silva, 2007) and healthy adults (Westmacott & Moscovitch, 2003; for a review see Conway, 2009). In humans, tests have been devised to separate the episodic and semantic components from autobiographical memories. One example is that of Levine and colleagues (2002) who devised a scoring system that classified recollected details as either 'internal' (specific to the event) or 'external' (generic to the event). In general, these autobiographical studies in patients with MTL damage, particularly to the hippocampus, have shown loss of episodic components of memory with intact semantic components (Winocur, Moscovitch, & Bontempi, 2010). In contrast, damage to anterior lateral temporal lobes, particularly in the left hemisphere, was associated with loss of semantic aspects.

As mentioned in the introduction, prospective studies that have examined long-term anterograde episodic memory is rare and to our knowledge none have examined the dissociation between episodic and schematic types of memory, especially in dementia

patients. While previous studies, such as Takashima et al. (2009), may have used tasks (face-location) that had a recognition and source component, none have analysed these components separately. In our study, Experiments 1 and 2 examined the behavioural dissociation between episodic and schematic types of memory through scoring of the visual task into recognition and source memory components. Essentially, correct source responses (L/R) can be considered to be episodic type memory as participants are required to retrieve contextual information specific to the event. By comparison, item recognition can be considered to be less episodic but more schematic as successful recall does not necessarily require retrieval of contextual information.

Our results indicated that, in the long-term, consolidation of anterograde episodic memory fits the constraints of MTT. In healthy participants there was a clear dissociation in recognition and source performance across time, with intact retention of item recognition memory over the four week period while contextual source memory showed gradual deterioration beginning after a delay of 24 hrs. This pattern is consistent with the theorisation of Conway (2009), who noted that for healthy adults perceptual details specific to episodic memories are lost within days of the event transpiring, while schematic memories of the episode remain.

In dementia patients this dissociation was even more significant as AD participants showed intact recognition memory on the same level as controls while contextual source recall showed a significant drop starting at one hour delay. In contrast, SD participants showed similar pattern of recognition and source memory performance to controls. Assuming typical pathological atrophy progression, this observed pattern of behavioural performance for AD participants is exactly as predicted by the transformation hypothesis of MTT. SD performance, however, did not follow the prediction, although we did observe a drop in recognition performance between two and 4 weeks. If this decline had continued with further assessments beyond the 4 week period while source performance remained on par with controls, then SD performance would also follow the predictions of the transformation hypothesis. However, it should be noted that schematic memory is semantic-like in the sense that it consists of a schema formed through semantic information. In addition, the stimuli used for the visual task were high frequency everyday objects that we believed would still be intact in early-stage SD patients to facilitate training, as our main goal was to assess long-term memory. Therefore, the likelihood of this outcome occurring is slim given our task design.

In regard to how independent our segregation of recognition and source components were, fMRI data confirmed that recognition and source components did represent two functionally different processes, with hippocampal activity only present for successful contextual source responses. This functional dissociation was most evident in our overall gradient analysis as increased activity in lateral frontal, parietal and occipital lobe regions predicted long-term recognition retrieval, while posterior hippocampal activity predicted long-term source retrieval.

Overall, MTT is able to account for much of the variation reported in the autobiographical memory literature. In particular, the reports of no temporal gradient for autobiographical memory impairment in patients with MTL damage, which is one of the key observations supporting SCT (Winocur & Moscovitch, 2011). While further work on clearing the ambiguity of the mechanism behind the transformation hypothesis and also the location of the cortical repository of consolidated memories is required to validate MTT, at this point in time the behavioural and neuroimaging results from Experiments 1 and 2 favour MTT over SCT.

Neural Correlates of Long-Term Memory Consolidation

One of the key aims of this study was to examine the neural correlates of long-term anterograde consolidation. From the overall analysis, retrieval of source memory activated the majority of core regions highlighted in the autobiographical network (Svoboda, McKinnon & Levine, 2006), derived from a meta-analysis of autobiographical fMRI studies. The core regions where we found activation included the medial prefrontal cortex, cingulate, medial temporal lobe and middle lateral temporal lobe. Two remaining core regions where we did not find activation included the ventrolateral prefrontal cortex and cerebellum. A lack of activation in the ventrolateral prefrontal cortex is believed to be due to the nature of our experimental task, since activity in this region is mainly associated with strategic retrieval (Henson, Shallice & Dolan, 1999; Petrides, 2002). Activity in the cerebellum has been observed in a variety of cognitive tasks, particularly for executive functions, however, the precise role it plays in these processes is still unclear (Vokaer et al., 2002).

As we mentioned earlier, previous retrograde consolidation studies have found differences in activation along the anterior-posterior plane of the hippocampus (Gilboa et al., 2004; Rekkas & Constable, 2005; Soderlund et al., 2012). Most recently, Soderlund and colleagues (2012) investigated recent and remote autobiographical memory retrieval in healthy young participants and found that the mean BOLD response remained consistent for the posterior hippocampus while anterior activity level was higher for recent memory and

lower for remote memory, relative to posterior activation. This pattern of anterior-posterior hippocampal activity was, however, not observed in our study. In regard to anterograde studies of consolidation, while differences have been reported in anterior-posterior subregions of the hippocampus, namely decreased activation of the posterior hippocampus in anterograde consolidation (Takashima et al., 2009), the pattern of change in activity across time reported in retrograde studies has not been observed. Similarly, our findings are consistent with those of Takashima and colleagues (2009), although our analysis only implicated the left posterior hippocampus rather than bilateral activity. This discrepancy in level of hippocampal activity as a function of time could reflect a functional difference dissociating retrograde and anterograde consolidation. Alternatively, this may also be a result of fundamental differences between the types of memories acquired and retrieved in anterograde and retrograde memory tasks, or simply due to the difference in age of the retrieved memories. In our experiment we have built upon previous anterograde consolidation studies by significantly extending the typically used delay of 24 hrs to more closely mimic that of retrograde studies.

The convergence of our fMRI and DTI data highlighted that functional activation in the posterior hippocampus and increased white matter integrity in the fornix and cingulum is associated with intact long-term memory consolidation processes. From a structural view, the fornix and cingulum contain the main efferent and afferent fibre bundles of the hippocampus, respectively. Together, these structures, along with the anterior thalamus, form the Papez circuit which is crucial for intact mnemonic function (Barbizet, 1963; Papez, 1995).

Typically, damage to the hippocampus has been the focus of studies relating to amnesia, however, unilateral or bilateral damage isolated to the fornix also results in memory impairment (Hattingen et al., 2007; Korematsu, Hori, Morioka, & Kuratsu, 2010; Laplane, Degos, Baulac, & Gray, 1981; Moudgil, Azzouz, Al-Azzaz, Haut, & Gutmann, 2000; Park, Hahn, Kim, Na, & Huh, 2000; Shiota & Kawamura, 1995). There is also evidence that atrophy in the fornix is one of the earliest indicators of patient progression from MCI (premorbid AD) to AD (Copenhaver et al., 2006) and reduced white matter integrity in the fornix of patients with genetically inherited dementias (Ringman et al., 2006). This suggests that memory impairment in early stage dementias is more dependent on intact fornix function rather than the hippocampus. From a clinical point of view, perhaps more focus should be attributed to the fornix as an early indicator of dementia onset.

Chapter 7. Future Research Directions

Research uncovering the neural bases of cognitive processes will only grow at a more rapid rate as further advances are made in neuroimaging equipment and statistical analysis tools. The experiments in this thesis have offered new evidence for the critical role the left posterior hippocampus and fornix play in long-term consolidation of anterograde episodic memory, as well as highlighting the impact contrasting neurodegenerative pathology in MTL structures have on this process. It is important to keep in mind that consolidation is not solely dependent on one structure and depends on intact functional connectivity between hippocampal and extra-hippocampal structures. Further exploration of changes in activity over time between structures and also within sub-regions of structures is important to further our understanding of this complex process. Our understanding of the hippocampal and neocortical interaction would also greatly benefit from further prospective investigation of long-term episodic memory, in particular, through patient populations with contrasting MTL atrophy, such as AD and SD.

It should be noted that the study of long-term anterograde memory consolidation in amnesic patients is rare. However, development of rehabilitation programs is dependent upon continued research in this area. In our third experiment we identified in an SD patient the critical period of two weeks where conscious retrieval of newly learnt information became impaired. Despite this the patient was still able to accurately retrieve learnt information, although having no conscious knowledge of doing so. This finding certainly warrants more exploration particularly whether administering re-training at two weeks can improve the durability of newly acquired information and ultimately what long-term pattern this may result in.

Setting aside the aims and findings of this thesis, one of the achievements accomplished was the development and successful application of a stable, easily accessible and reliable online testing platform allowing us to easily reach remotely located participants for long-term assessments. Online testing will no doubt prove to be an increasingly powerful

research tool in the future, particularly in countries such as Australia where the population is so scattered and also for longitudinal research in general.

Theoretical models of the neural organisation of long-term memory are a heavily debated topic within the domain of memory research. Findings from these experiments favour the MTT, in particular the transformation hypothesis of their model, where the original episodic memory is segregated into semantic information used to create a schematic map of the event (retrieval is hippocampal independent) and contextually vivid information (retrieval is hippocampal dependent). However, it is still unclear how this transformation, in particular the neural correlates responsible for this process and at what time point during the consolidation process this occurs. The mechanism of this process should be explored in greater detail for greater acceptance of MTT.

Finally, functional analysis and even functional connectivity techniques are in essence observed correlations in neural activity. Certainly within the literature studies have used functional connectivity to explore the relationship between the hippocampus and neocortical regions of the MTL, but findings are limited to determining temporal correlation rather than causation. A new emerging technique that proves to be more promising is effective whole brain connectivity. Rather than examining temporal correlations between predefined regions of interest, effective connectivity is defined as the influence one neural system exerts over another. Consequently, this technique has great potential implications for ageing studies as well as the exploration of cognitive models including, but not limited to, SCT and MTT.

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Appendix 1. Word study list and word stem test list of verbal episodic memory task.

Word List	**Word Stem Sets**		
	(A)	(B)	(C)
BRIDGE	BRI	FIN	TAL
	BEA	GAR	WIN
CAPITAL	CAP	STE	BRI
	SCO	MEA	SNA
BIRTH	STE	ORI	ENJ
	BIR	ENJ	ORI
CIRCUS	CIR	BEA	FIN
	DIN	CIR	OPE
BELIEF	BEL	LIM	MEA
	FIN	DIN	VIS
MOBILE	MOB	OPE	BRU
	PIL	SNA	BEA
REVIEW	OPI	SIL	MOB
	REV	WIN	LIM
TALENT	TAL	FLI	GAR
	SMO	TAL	SCO
ENJOY	ENJ	SMO	FLI
	FLI	PIL	SMO
FLIGHT	WIN	BIR	DIN
	SMI	BEL	BEL
OPERA	OPE	SMI	PIL
	MEA	VIS	BIR
SILENCE	LIM	REV	CAP
	SIL	OPI	STE
ORIGIN	FAS	FAS	FAS
	ORI	CAP	REV
VISION	SNA	BRU	OPI
	VIS	BRI	SIL
GARDEN	GAR	SCO	SMI
	BRU	MOB	CIR

* Three sets of word stems used for testing (A/B/C).

Appendix 2. fMRI image statistics of all significant clusters from experiment 1.

*Peak voxel co-ordinates are reported in MNI-152 standard space.
***L*: left; *R*: right; B: bilateral

Overall Group Analysis

Figure 3.2. BOLD activity for correct recognition and source responses.					
	No. of Voxels	**Z-Max**	**Peak Voxel (x, y, z)**	**Hemi sphere**	**Anatomical Structure**
Recognition	4681	5.46	-32, -58, 38	L	lateral occipital cortex
	2817	5.33	-40, 50, 8	R	frontal pole
	1984	4.92	0, 26, 38	B	paracingulate gyrus
	1607	5.33	14, 16, -4	R	caudate
	947	4.46	38, 12, 50	R	middle frontal gyrus
	935	4.03	42, 52, 4	R	frontal pole
	667	4.21	30, 22, -8	R	frontal orbital cortex/insular cortex
	595	4.31	-34, 18, -10	L	insular cortex/frontal orbital cortex
Source	31297	5.85	0, -60, 34	B	precuneus cortex
	823	4.82	-34, 22, 44	L	middle frontal gyrus

Figure 3.4. Direct functional contrast between MRI 1 and MRI 2.					
	No. of Voxels	**Z-Max**	**Peak Voxel (x, y, z)**	**Hemi sphere**	**Anatomical Structure**
MRI1	5428	4.75	4, 56, 10	R	frontal pole/paracingulate gyrus
	3894	4.65	20, -90, 20	R	occipital pole
	3033	4	-50, -68, 28	L	lateral occipital cortex
	1875	3.85	44, -62, 20	R	lateral occipital cortex
	707	3.74	64, -2, -22	R	anterior middle temporal gyrus
MRI2	974	3.48	-38, -56, -20	L	temporal occipital fusiform cortex
	587	3.35	-38, -48, 34	L	posterior supramarginal gyrus
	445	3.33	-46, 36, 10	L	inferior frontal gyrus/frontal pole

Figure 3.5. BOLD activity predicting intact long-term consolidation of anterograde episodic memory.

	No. of Voxels	Z-Max	Peak Voxel (x, y, z)	Hemi sphere	Anatomical Structure
↑ **Activity**	31519	6.16	-4, 14, 44	L	paracingulate gyrus
Recognition	10800	6.14	36, -86, -6	R	inferior lateral occipital cortex
	839	4.46	32, 22, 4	R	insular cortex
	683	4.6	42, 28, 26	R	middle frontal gyrus
	402	4.94	-2, -34, 26	L	posterior cingulate gyrus
↑ **Activity**	12281	4.74	44, -28, 44	R	postcentral gyrus
Source	2989	4.76	-26, -90, -8	L	occipital pole/occipital fusiform gyrus
	2543	5.18	36, -86, -8	R	lateral occipital cortex
	2536	4.36	-46, 28, 26	L	middle frontal gyrus
	428	3.83	40, 30, 26	R	middle frontal gyrus
	343	3.91	-2, -34, 26	L	cingulate gyrus
↓ **Activity**	1533	4.06	56, -42, 10	R	posterior supramarginal gyrus
Recognition	1436	3.87	8, 56, 16	R	superior frontal gyrus, frontal pole
	1367	5.01	-32, -50, -2	L	temporal occipital fusiform cortex/lingual gyrus
	880	3.63	52, 0, -12	R	anterior superior temporal gyrus
	512	3.32	4, 46, 36	R	superior frontal gyrus
	508	4	-60, -6, -16	L	anterior middle temporal gyrus
	417	3.57	0, -90, 4	B	occipital pole
↓ **Activity**	1275	4.01	-32, -50, 0	L	temporal occipital fusiform cortex
Source	456	3.48	-2, 56, 8	L	paracingulate gyrus/frontal pole
	420	3.12	52, -2, -10	R	anterior superior temporal gyrus
	372	3.55	52, -56, 10	R	middle temporal gyrus
	367	3.27	12, -88, 16	R	occipital pole
	325	3.28	66, -50, 28	R	angular gyrus

*Note: ↑, increase in activity; ↓, decline in activity.

Figure 3.9. BOLD activity for correct recognition and source responses in young participants during MRI 1 and MRI 2.

	No. of Voxels	Z-Max	Peak Voxel (x, y, z)	Hemi sphere	Anatomical Structure
MRI 1	6169	3.91	10, 10, -8	R	acumbens
Recognition	1531	3.52	50, -66, 30	R	superior lateral occipital cortex
	1315	3.31	16, -62, 14	R	supracalcarine cortex/precuneus cortex
	1071	4	-8, -98, 4	L	occipital pole
	666	3.21	46, 14, 44	R	middle frontal gyrus
	616	3.31	-44, -54, 46	L	angular gyrus
	414	3.38	-34, 16, -10	L	insular cortex
	342	3.34	-60, -52, 32	L	posterior supramarginal gyrus/angular gyrus
	304	3.25	-40, 8, 42	L	middle frontal gyrus
	293	3.16	8, 22, 56	R	superior frontal gyrus
MRI 1	5386	4.49	-10, -96, 4	L	occipital pole
Source	3248	3.95	-6, 54, -2	L	paracingulate gyrus
	1793	3.74	-52, -52, 28	L	angular gyrus/posterior supramarginal gyrus
	501	3.72	-32, 24, 38	L	middle frontal gyrus
	489	3.83	10, 10, -8	R	acumbens
	307	3.24	46, 12, 40	R	middle frontal gyrus
MRI 2	1706	3.67	-56, 16, 30	L	inferior frontal gyrus
Recognition	825	4.14	-30, -54, 36	L	superior parietal lobule/angular gyrus
	727	3.95	2, 26, 42	R	paraginculate gyrus
	561	3.48	40, 28, 24	R	middle frontal gyrus
	351	3.16	40, -60, 54	R	superior lateral occipital cortex
MRI 2	1771	3.38	-40, -60, 22	L	angular gyrus,
Source	1754	3.73	44, -62, 30	R	superior lateral occipital cortex
	892	3.28	4, -56, 34	R	precuneous cortex
	642	3.36	0, 40, 18	B	anterior cingulate gyrus/paracingulate gyrus

Figure 3.10. BOLD activity for correct recognition and source responses in elderly participants during MRI 1.

	No. of Voxels	Z-Max	Peak Voxel (x, y, z)	Hemi sphere	Anatomical Structure
MRI1	2573	3.63	-2, -76, 44	L	precuneous cortex
Recognition	698	3.64	-44, -72, 36	L	superior lateral occipital cortex
	647	3.47	50, -70, 28	R	superior lateral occipital cortex
	530	3.43	-12, 24, 26	L	anterior cingulate gyrus/paracingulate gyrus
	374	3.4	32, 4, -36	R	temporal pole/anterior temporal fusiform cortex
MRI1	2260	3.58	4, 66, 22	R	frontal pole
Source	2081	3.99	2, -52, 32	R	posterior cingulate gyrus/precuneous cortex
	693	3.53	66, -52, 8	R	middle temporal gyrus
	642	3.39	-10, -90, 2	L	occipital pole/intracalcarine cortex
	618	3.48	18, 14, -12	R	putamen
	605	3.46	-38, -78, 38	L	superior lateral occipital cortex
	509	3.79	54, -58, 28	R	angular gyrus/superior lateral occipital cortex
	265	3.4	38, -40, -6	R	lingual gyrus
	248	3.46	-40, 16, -34	L	temporal pole

Figure 3.11. BOLD activity that predicts intact long-term consolidation of episodic memory in young and elderly groups.

	No. of Voxels	Z-Max	Peak Voxel (x, y, z)	Hemi sphere	Anatomical Structure
Young	15615	4.71	-34, -52, 42	L	superior parietal lobule/posterior supramarginal gyrus
↑ Activity	11776	4.95	-26, -86, -12	L	occipital fusiform gyrus
Recognition	4157	4.73	-46, 26, 24	L	middle frontal gyrus/inferior frontal gyrus
	1311	4.06	-30, 28, -4	L	frontal orbital cortex
	901	3.95	30, 22, 2	R	insular cortex
	432	4.03	-2, -34, 26	L	posterior cingulate gyrus
	414	4.45	40, 34, 22	R	frontal pole/middle frontal gyrus
Young	5737	3.79	-36, -60, 44	L	superior lateral occipital cortex
↑ Activity	2886	4.2	-26, -86, -10	L	occipital fusiform gyrus
Source	2631	4.23	36, -86, -8	R	inferior lateral occipital cortex
	975	3.78	-4, 14, 44	L	paracingulate gyrus
	840	3.37	-28, 22, -4	L	insular cortex
	688	3.59	-46, 26, 26	L	middle frontal gyrus
	571	3.51	-24, -2, 54	L	superior frontal gyrus
	334	3.58	-2, -32, 26	L	posterior cingulate gyrus
Young	2029	3.39	10, 72, 10	R	frontal pole
↓ Activity	1660	3.7	54, -42, 8	R	middle temporal gyrus/supramarginal gyrus
Recognition	605	3.34	56, 6, -20	R	temporal pole
Young	623	3.33	6, 56, 16	R	superior frontal gyrus/frontal pole/ paracingulate gyrus
↓ Activity	374	3.2	-34, -48, 0	L	temporal occipital fusiform cortex
Source	355	3.35	52, -58, 8	R	middle temporal gyrus/inferior lateral occipital cortex

Figure 3.11. BOLD activity that predicts intact long-term consolidation of episodic memory in young and elderly groups. (continued)

	No. of Voxels	Z-Max	Peak Voxel (x, y, z)	Hemi sphere	Anatomical Structure
Elderly	14732	4.31	-34, -60, 38	L	superior lateral occipital cortex
↑ Activity	1965	3.71	-30, 26, -4	L	frontal orbital cortex/insular cortex
Recognition	1686	3.81	32, -88, 8	R	occipital pole/lateral occipital cortex
	922	3.81	-32, -90, -18	L	inferior lateral occipital cortex/occipital fusiform gyrus
	496	3.6	34, 42, 32	R	frontal pole
Elderly	3732	3.9	24, -76, 52	R	superior lateral occipital cortex
↑ Activity	413	3.31	-30, -12, 52	L	precentral gyrus
Source	292	3.59	44, -80, -12	R	inferior lateral occipital cortex
Elderly	724	3.84	-24, -48, 4	L	precuneous cortex/posterior cingulate gyrus/lingual gyrus
↓ Activity	332	3.61	2, 2, 8	R	cerebral white matter
Recognition					
Elderly	341	3.68	16, -72, -12	R	lingual gyrus/occipital fusiform gyrus
↓ Activity					
Source					