Accelerated long-term forgetting (ALF)

and the role of sleep in memory consolidation

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A thesis submitted for the degree of

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Abstract

Accelerated long-term forgetting (ALF) is a recently described memory impairment associated with epilepsy. Patients with ALF appear to learn and initially retain new information normally, but forget it at an accelerated rate over subsequent days. ALF can have a profound impact on the lives of the people who suffer from it, but it is also of theoretical interest. In particular, the study of this disorder may provide insight into the mechanisms of memory consolidation. ALF is especially prevalent in transient epileptic amnesia (TEA), an epileptic syndrome in which the seizure focus is thought to be the medial temporal lobes (MTL). The MTL house the hippocampus and a number of other structures critical for declarative memory function. The aims of this doctoral thesis were to investigate which aspects of memory function are disrupted in patients with TEA-associated ALF, and to shed light on the neural basis of the memory impairment. Slow wave sleep (i.e. deep sleep) is known to exacerbate epileptic activity. It is also thought to play a key role in the consolidation of declarative memory. The most commonly posited explanation of ALF is the disruption of sleep-dependent memory consolidation. However, it remains possible that ALF is caused by a subtle problem with encoding that usually goes undetected until delayed memory tests. The results of this thesis demonstrate that sleep can actually benefit memory retention in TEA ALF patients just as much as it does in healthy people, and that it is not necessary for the retention interval to contain sleep in order for ALF to be seen. However, the relationship between slow wave sleep and memory was found to be abnormal in these patients. The amount of slow wave sleep, and the power in the slow oscillation frequency range, during the post-learning night correlated negatively with the benefit of that night of sleep for memory retention. Furthermore, resting-state brain activity patterns thought to reflect post-encoding memory reprocessing were found to correlate negatively with subsequent memory performance in these patients. Another chapter of this thesis provides evidence that TEA ALF patients encode memories abnormally; these patients showed reduced activity in the left hippocampus while viewing stimuli that they went on to forget. Furthermore, this encoding-related brain activity correlated with their long-term forgetting. The final experimental chapter reports a correlation in these patients between grey matter in the left hippocampus and long-term forgetting, which cannot entirely account for the encoding-related brain activity results. The hippocampus and its surrounding structures are thought to be critical to our ability to discriminate between similar stimuli and events. An intriguing hypothesis consistent with the pattern of results in this thesis is that ALF is caused by a functional impairment of the MTL that results in a diminished capacity to distinguish between similar experiences, ultimately causing memory problems; abnormally formed memories may interact with new material and memory consolidation processes in an aberrant manner, leading to retrieval deficits.

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I hope that Kia Nobre knows just how much I have valued her guidance. Had she not been my mentor, I would not be who or where I am today. Thank you to my parents for their unconditional love and support. Thank you, Alex, for keeping me sane and making me happy.

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1. Introduction

1.1. Accelerated long-term forgetting, in the context of memory research

Accelerated long-term forgetting (ALF) is a recently described memory impairment, principally associated with epilepsy, in which new consciously-accessible long-term memories appear to be learnt and initially retained normally, but then forgotten at an accelerated rate over subsequent days (Bell & Giovagnoli, 2007; Butler & Zeman, 2008b).

1.1.1. Memory sub-types

For many years, it has been known that memory is not unitary. Traditionally, memory has been divided into three major sub-types (Atkinson & Shiffrin, 1968): sensory memory, short-term/working memory, and long-term memory. Originally, the distinction between short-term and long-term memory was principally based on a double dissociation found in neuropsychological studies: patients with classic amnesia due to damage to the temporal lobes, including the hippocampi, displayed impaired long-term memory and apparently preserved short-term memory (Milner, 1966), while patients with damage to a different brain region (the perisylvian region of the left hemisphere) had impaired verbal short-term memory and spared long-term memory (e.g. Shallice & Warrington, 1970). While information is lost within a few seconds from the sensory registry, and is maintained only briefly in the short-term store, the long-term store was thought to be relatively permanent (Atkinson & Shiffrin, 1968) and was not further subdivided according to memory persistence. However, while patients with ALF typically demonstrate preserved performance on conventional tests of long-term memory, which assess performance approximately half an hour after learning, these patients have been reported to perform poorly in the longer term (e.g. Blake, Wroe, Breen, & McCarthy, 2000; Martin et al., 1991; Zeman, Boniface, & Hodges, 1998).

1.1.1.1. Long-term memory sub-types

Long-term memory has also been fractionated into different sub-types. Owing mainly to research on medial temporal lobe amnesics, long-term memory has been split into declarative/explicit memories and non-declarative/implicit memories (Graf & Schacter, 1985; Squire, 1987). Acquisition of declarative/explicit memories (for episodes and facts) is impaired by damage to the medial temporal lobes (MTL), and especially to the hippocampus. Declarative memories are multi-sensory, associative, and available to multiple effectors and to conscious report. They are further subdivided into episodic memories and semantic memories (Tulving, 1972). Episodic memory is memory for autobiographical events, in which information is bound in the spatial and temporal context in which it was encountered. In contrast, semantic memory is factual knowledge independent of the learning context. Non-declarative memories form a heterogeneous category. They are characterised by being independent of the MTL, but dependent instead on specialised perceptual and/or motor circuits, and being unavailable for conscious report (Schacter & Tulving, 1994). There is some reason to believe that ALF may be specific to declarative memories (Muhlert, Milton, Butler, Kapur, & Zeman, 2010). There is currently no evidence for impairments on non-declarative tasks (Deak, Stickgold, Pietras, Nelson, & Bubrick, 2011; Muhlert et al., 2010). This is perhaps unsurprising, as the seizure focus in epileptic ALF patients is commonly in the temporal lobes (Butler & Zeman, 2008b).

1.1.2. Memory stages

Memory processes have been subdivided into three stages: encoding; storage; and retrieval. Encoding is not an all-or-nothing activity, and the probability of successful retrieval is affected by the depth of processing at the encoding stage (Craik & Lockhart, 1972). For instance, processing the visual characteristics of a word stimulus results in poorer subsequent retrieval than processing its meaning. There are two main types of declarative memory retrieval: recall and recognition. Recall involves the reproduction of previously encoded material, while recognition involves the

identification of material as having been previously encountered. Recall can be 'free' (as in recalling a list of words in any order, or recalling a story) or cued (such as in paired associates learning, where two items (A and B) are encoded as a pair (A-B) and, at retrieval, one item (A) is used as a prompt for the recall of the other (B)). In a recognition paradigm, old items must be distinguished from new ones. This might involve a forced-choice judgement, in which old and new items are presented simultaneously and the participant must select the old one(s), or a yes/no procedure, in which each item is presented, and must be responded to, individually. Successful recognition can be achieved through recollection, in which the details of the encoding episode can be retrieved, or through familiarity, in which the decision is guided by a sense of knowing, in the absence of source memory (e.g. Atkinson & Juola, 1974; Jacoby & Dallas, 1981; Mandler, 1980). Given that encoding and early retrieval appear to be normal in patients with ALF, their memory impairment may be due to problems with the intermediate, storage phase. Initially, the storage stage of long-term memory was thought to be a relatively passive process, principally involving the maintenance of a permanent record of information. However, it is now understood that memory storage is much more dynamic than was once thought (e.g. Nader, 2003). In fact, it is thought that there are multiple post-encoding processes that alter memory traces and the likelihood that they will subsequently be successfully retrieved. This second stage of memory processing is now commonly referred to as 'consolidation' to highlight the active nature of this phase. It has frequently been suggested that ALF reflects a deficit in memory consolidation (e.g. Blake et al., 2000; Kapur et al., 1997; Tramoni et al., 2011; Wilkinson et al., 2012).

1.1.2.1. Memory consolidation

Memory consolidation can be subdivided into two families of processes, which operate on different timescales (e.g. Dudai, 2004).

Chapter 1.

Long-term memory formation is thought to be supported by the potentiation of synapses (neurochemical connections) between brain cells. This occurs when interconnected brain cells are synchronously active, and it results in the subsequent reactivation of the pre-synaptic cell producing a greater response than previously in the post-synaptic cell. The theoretical roots to this form of plasticity date back to William James (1890), Santiago Ramon y Cajal (1894) and Donald Hebb (1949). In the latter half of the 20th Century, long-term potentiation (LTP), which has become the leading model of learning-related synaptic plasticity (Whitlock, Heynen, Shuler, & Bear, 2006) was discovered in the hippocampus (Bliss & Lømo, 1973). One family of consolidation processes, which are commonly referred to as synaptic or fast consolidation, involve morphological modifications of the synapse achieved through protein synthesis, which result in the stabilisation of the change in synaptic weight. This kind of consolidation occurs within minutes to days after encoding (McGaugh, 2000); the disruptive effect of post-training protein synthesis inhibition on subsequent memory performance diminishes with time since encoding (Agranoff, Davis, & Brink, 1966; Dudai, 2004).

Slow, or systems-level, consolidation is typically a much longer process that occurs within a time frame of days to years. It is believed to involve the reorganisation of the memory trace (e.g. Dudai, 2004). This type of consolidation was initially inferred from the observation that MTL lesions result in a temporal gradient of retrograde amnesia (e.g. Ribot, 1882; Squire, Slater, & Chace, 1975; Zola-Morgan & Squire, 1990): memories that were formed shortly prior to brain injury are lost, but older memories are relatively spared. The standard model of systems consolidation (Squire, Cohen, & Nadel, 1984) was developed to account for this finding. According to this theory, memories are initially dependent on the hippocampal formation, but, over time, they are reorganised such that they can be supported by the neocortex and become independent of the hippocampus.

The possession of two separate long-term memory stores would allow us to resolve the stability-plasticity dilemma; we could preserve our precious store of pre-existing memories while quickly encoding what is going on around us in the present moment. According to this two-stage model of memory (e.g. Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Rasch & Born, 2007), the neocortex houses a long-term store of integrated memories, organised in such a way as to provide us with useful information about how to behave in the world. The neocortex learns slowly, which prevents this store of information being obliterated by the encoding of whatever is happening in the current moment. However, to ensure that we can rapidly encode new information, we have a second, fast-learning store. The hippocampus acts as the declarative memory system's fast-learning store, with synaptic plasticity in the hippocampus being able to support rapid, one-trial learning (e.g. McNaughton & Morris, 1987). Recently-formed memories are subsequently slowly incorporated into the long-term store, so as not to unbalance the network. It is thought that new sensory traces in disparate regions of the neocortex, which constitute the components of an episodic memory, are initially bound together through the connections in the hippocampus, which serve as an index. Over time, repeated reactivations of this hippocampal memory trace (which trigger the reactivation of the component parts of the memory in the neocortex) lead to the formation of intra-neocortical connections and to hippocampal independence of at least some aspects of the memory.

McClelland, McNaughton and O'Reilly (1995) developed a computational model in which repeated reactivation of hippocampal traces, over time, in conjunction with simultaneous reactivations of older, related information, leads to a gradual, interleaving learning process, allowing new information to adapt gradually to the pre-existing long-term memory network. In this way, the neocortex can slowly discover the structure in ensembles of experiences; reactivation of hippocampal memory traces restructures memories, allowing new memories to be integrated with older ones and invariants to be extracted.

A temporal gradient of retrograde amnesia for episodic memories has not been found in all patients with MTL lesions; some patients are unable to retrieve episodic memories from any stage of their past (e.g. Barr, Goldberg, Wasserstein, & Novelly, 1990; Cermak & O'Connor, 1983; Damasio, Eslinger, Damasio, Van Hoesen, & Cornell, 1985; McCarthy & Warrington, 1992; Tulving, Schacter, McLachlan, & Moscovitch, 1988). Multiple-trace theory (Nadel & Moscovitch, 1997) posits that semantic memories (factual knowledge, without context) are transferred from the hippocampus to the neocortex as stated in the standard model of systems consolidation, but that episodic memories (which are bound in time and space) remain always dependent on the hippocampus. In cases of incomplete hippocampal damage, a temporal gradient of retrograde amnesia for episodic memories may also be seen because those memories that have been retrieved a greater number of times (which are most likely to be the older memories) have a larger number of memory traces in the hippocampus and so are more likely to be spared.

A number of studies involving animal models have provided evidence for systems consolidation: hippocampal lesions affect recently formed memories more than older memories (Squire, Clark, & Knowlton, 2001). However, this has not been found consistently for all memory tasks. In some cases, older and newer memories have been equally severely affected (Broadbent, Squire, & Clark, 2006; Clark, Broadbent, & Squire, 2005a, 2005b; Clark, Broadbent, & Squire, 2007; Lehmann, Lacanilao, & Sutherland, 2007; Martin, de Hoz, & Morris, 2005; Sparks, Lehmann, Hernandez, & Sutherland, 2011; Sutherland, O'Brien, & Lehmann, 2008). Some types of memory, such as spatial memories, may be forever dependent on the hippocampal formation, or a functioning hippocampus may be necessary to process the retrieval cues in some tasks (Broadbent & Clark, 2013).

Neuroimaging studies also provide evidence that memories are reorganised over time. Retrieval of recent and remote memories is associated with different patterns of brain activity. A number of retrograde memory studies have found that remote memory retrieval is associated with less activity in the MTL than recent memory retrieval (e.g. Haist, Bowden Gore, & Mao, 2001; Lux, Bindrich, Markowitsch, & Fink, 2013; Niki & Luo, 2002; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003). Some studies of anterograde memory (in which retrieval of the same memories is studied at different time-points) have found similar results (e.g. Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999; Takashima et al., 2006). According to the transformation hypothesis, which is intimately related to multiple-trace theory, this reorganisation of declarative memory is associated with a change in the nature of the memory from episodic to semantic (Winocur & Moscovitch, 2011). It should be noted that some researchers have published evidence suggesting that recent autobiographical memories are only represented in the anterior portion of the hippocampus, while remote ones are represented throughout the structure, which could potentially account for the disproportionate effect of hippocampal lesions on recent vs. remote episodic memories (Bonnici et al., 2012; Bonnici, Chadwick, & Maguire, 2013; Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004).

Sleep is thought to play a major role in memory consolidation. The idea that the replay mediating systems consolidation may happen predominantly during sleep dates back to Marr (1971). Neuroimaging studies in humans, and electrophysiological experiments in animals, have recorded post-encoding memory reprocessing during sleep and periods of quiet rest. After learning, memory replay can be observed in the hippocampus (e.g. Karlsson & Frank, 2009; Kudrimoti, Barnes, & McNaughton, 1999; Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999; Pavlides & Winson, 1989; Peigneux et al., 2004; Skaggs & McNaughton, 1996; Tambini & Davachi, 2013; Wilson & McNaughton, 1994) and the neocortex (e.g. Euston, Tatsuno, & McNaughton, 2007), and this replay occurs in a coordinated fashion between these two structures (Ji & Wilson, 2007; Peyrache,

Khamassi, Benchenane, Wiener, & Battaglia, 2009; Qin, McNaughton, Skaggs, & Barnes, 1997) and between disparate regions within the latter (Hoffman & McNaughton, 2002). These memory reactivations have also been shown to be related to subsequent memory performance (e.g. Axmacher, Elger, & Fell, 2008; Dupret, O'Neill, Pleydell-Bouverie, & Csicsvari, 2010; Ego-Stengel & Wilson, 2010; Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009; Peigneux et al., 2004; Staresina, Alink, Kriegeskorte, & Henson, 2013; Tambini & Davachi, 2013).

It has been proposed that ALF reflects a deficit in slow consolidation (e.g. Blake et al., 2000; Butler et al., 2007; Kapur et al., 1997), though it has also been suggested that disruption of fast consolidation might underlie the impairment (Wixted, 2010). The two possibilities are not mutually exclusive.

1.1.2.1.1. The role of sleep in declarative memory consolidation

Sleep is not homogenous; it is divided into different stages (see Figure 1.1) on the basis of polysomnographic (PSG) activity (Iber, Ancoli-Israel, Chesson, & Quan, 2007; Rechtschaffen & Kales, 1968), which includes surface electroencephalographic (EEG), electrooculographic (EOG) and electromyographic (EMG) activity. Rapid Eye Movement (REM) sleep is characterized by a relatively low voltage, mixed frequency EEG. Non-REM sleep has four stages. The EEG in stage 1 is similar to that in REM sleep (these stages are principally distinguished on the basis of EOG and EMG activity). Spindle activity (~10-15Hz) and K complexes (negative sharp waves immediately followed by a positive component, which are longer than 0.5 seconds in duration and are generally largest at central electrodes) are prominent in the EEG in stage 2. Stages 3 and 4 are termed Slow Wave Sleep (SWS), and are characterized by slow-wave activity (<4Hz), including slow oscillations (<1Hz), in addition to spindles.

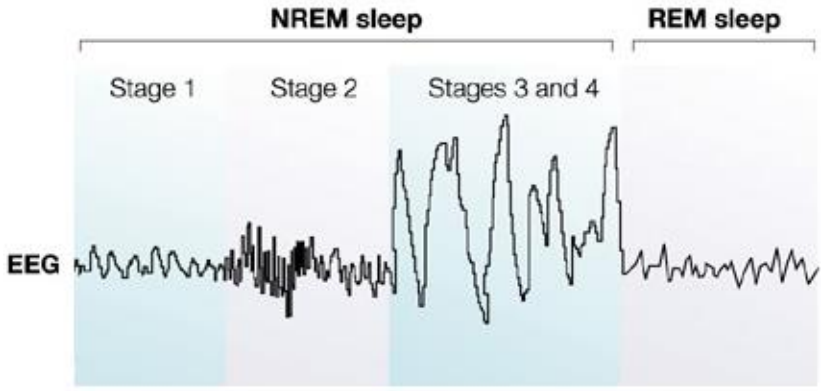


Figure 1.1. Surface EEG in different sleep stages. Adapted from Bryant, Trinder & Curtis (2004, p. 458).

Intracranial electrodes have been used to record activity in the hippocampus during different sleep stages. While theta activity is prominent in REM sleep in rats (Bland, 1986; Buzsaki, 2002; Jouvet, 1969), this has not typically been found in non-human primates (e.g. Tamura et al., 2013) or humans (Halgren, Babb, & Crandall, 1978; Uchida, Maehara, Hirai, Okubo, & Shimizu, 2001). One study has reported theta activity in the human hippocampus during REM sleep, occurring in bursts (Cantero et al., 2003), while others have found a lower frequency (delta) tonic activity (Bódizs et al., 2001; Clemens et al., 2009; Moroni et al., 2007), which may be the human analogue of animal hippocampal theta (Ferrara, Moroni, De Gennaro, & Nobili, 2012). During SWS, hippocampal activity is characterised by slower high-amplitude delta rhythms (Bódizs et al., 2001) and intermittent sharp-waves, associated with high-frequency ripples (140-200Hz) (e.g. Buzsaki, 1989).

Learning leads to changes in sleep architecture (e.g. De Koninck, Lorrain, Christ, Proulx, & Coulombe, 1989; Gais, Molle, Helms, & Born, 2002), and sleep (vs wakefulness) after learning improves memory retention (Walker & Stickgold, 2006). Post-learning sleep has also been shown to boost the

resistance of memory to subsequent interference (e.g. Korman et al., 2007). For instance, Ellenbogen et al. (Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006) trained participants on paired associates (A-B) and tested their performance 12 hours later, with or without interference training (A-C pairs) ten minutes beforehand. Despite equivalent performance on the interference training, participants who had slept during the 12-hour retention interval (vs those who had not) were much less susceptible to its disruptive effect on A-B pair performance.

SWS is the stage that has been most intimately linked with the consolidation of declarative memories (e.g. Diekelmann, Wilhelm, & Born, 2009). Many studies have found that the beneficial effect of sleep on declarative memory retention depends on the amount of SWS it contains (e.g. Alger, Lau, & Fishbein, 2012; Barrett & Ekstrand, 1972; Diekelmann, Biggel, Rasch, & Born, 2012; Fowler, Sullivan, & Ekstrand, 1973; Lau, Tucker, & Fishbein, 2010; Plihal & Born, 1997, 1999; Yaroush, Sullivan, & Ekstrand, 1971).

One way that sleep aids memory retention might be through permissive synaptic consolidation. Prior to the completion of synaptic consolidation, recently formed hippocampal memory traces are thought to be particularly susceptible to disruption from the encoding of new information/new LTP (e.g. Wixted, 2004, 2010). During waking hours, we are constantly encoding new information. During sleep, however, encoding of new sensory inputs is substantially reduced, meaning that new memory traces are protected from interference while the process of synaptic consolidation proceeds (e.g. Wixted, 2004, 2010). Therefore, if sleep follows shortly after learning, memories will become stabilised against subsequent interference before they can be disrupted, and memory retention will be improved (Gais, Lucas, & Born, 2006; Talamini, Nieuwenhuis, Takashima, & Jensen, 2008). SWS

may be a particularly protective climate (Wixted, 2010), as the formation of new (and therefore potentially interfering) LTP in the hippocampus appears to be suppressed during this sleep stage (Leonard, McNaughton, & Barnes, 1987).

However, there are also a number of lines of evidence for an important role of SWS in the systems consolidation of hippocampus-dependent memory. Firstly, SWS is associated with qualitative memory changes: SWS has been implicated in the formation of relational memory (e.g. Lau et al., 2010) and the abstraction of underlying rules and structure (e.g. Durrant, Taylor, Cairney, & Lewis, 2011), in line with predictions from models of systems consolidation (Lewis & Durrant, 2011; McClelland et al., 1995).

Secondly, SWS has been linked to the neural reorganisation of memories such that their dependence on the hippocampus diminishes. In a study by Takashima and colleages (2006), the amount of SWS in a post-learning nap was found to correlate negatively with the amount of hippocampal activity associated with correct confident recognition in a subsequent test. Over the next three months, hippocampal activity associated with correct confident recognition continued to decrease, while activity in a ventral medial prefrontal region of the neocortex increased.

Thirdly, there is evidence to suggest that several features of SWS play an active role in the consolidation of memory. One of these features is the slow oscillation, which reflects widespread neocortical alternating “up” and “down” states, associated with global depolarisation and hyperpolarisation respectively (Contreras & Steriade, 1995), and has a grouping effect, causing cells to fire in a synchronous manner. The amplitude of the up-state of the slow oscillation increases

following declarative learning (Molle, Eschenko, Gais, Sara, & Born, 2009), and slow oscillation amplitude and up-state lengths in post-learning sleep have been related to subsequent memory improvement on a declarative task (Heib et al., 2013). In 2006, Marshall and colleagues (2006) used transcranial oscillating electrical stimulation on the human scalp during emerging SWS to enhance endogenous slow-wave activity and observed an improvement in memory for paired associates learnt prior to sleep. The researchers interpreted this finding as evidence for a causal role of slow oscillations in sleep-associated consolidation of hippocampus-dependent memory.

Another brain activity pattern that occurs during SWS and has been specifically associated with memory consolidation is the sleep spindle, which originates from the thalamic nucleus reticularis and spreads to the whole cortex (Contreras & Steriade, 1995). Spindles, have been shown to increase in density following learning (e.g. Gais et al., 2002) and, in some cases, correlate with overnight retention (Schabus et al., 2004). Pharmacological enhancement of spindle density has been shown to lead to better verbal memory performance (Mednick et al., 2013).

A third feature of SWS that has been associated with consolidation is memory reactivation, the mechanism by which systems consolidation is thought to occur (McClelland et al., 1995). As discussed above, animal experiments have demonstrated that the activity patterns seen in the hippocampus during learning often re-emerge during SWS (e.g. Kudrimoti et al., 1999; Nadasdy et al., 1999; Pavlides & Winson, 1989; Wilson & McNaughton, 1994). These reactivations happen mainly during sharp-wave ripple events (Buzsaki, 1998; Kudrimoti et al., 1999). Similarly, imaging studies in humans have demonstrated that the hippocampus is more active during SWS following learning of a task that activates the hippocampus, and that the degree of hippocampal reactivation correlates with over-sleep memory change (Peigneux et al., 2004). Causal evidence for a role of

reactivations during SWS in memory consolidation comes from two main sources. In animal studies, microstimulation has been used to interfere with sharp-wave ripples, which has a negative impact on subsequent memory performance (Girardeau et al., 2009). It is also possible to induce memory reactivations artificially by presenting sensory cues during learning and then re-presenting the same cues during subsequent SWS (Bendor & Wilson, 2012; Rasch, Buchel, Gais, & Born, 2007). In humans, this technique has been used to demonstrate that memory reactivations during SWS enhance memory retention (Rasch et al., 2007; Rudoy, Voss, Westerberg, & Paller, 2009) and boost the resistance of the memory to subsequent interference (Diekelmann, Buchel, Born, & Rasch, 2011).

An influential model by Born and colleagues (Born, Rasch, & Gais, 2006; Marshall & Born, 2007) suggests that these features of SWS have interactive, rather than independent, roles in systems consolidation, and that it is the neocortical slow oscillations that drive the process.

According to Born's model, the up-phase of the slow wave drives, in parallel, replay in the hippocampus (associated with sharp-wave ripples) and spindles in the thalamus. Feedback from these areas, in the form of hippocampal-to-neocortical replay and thalamocortical spindles, converges on the neocortex at approximately the same time. Spindles have been linked to synaptic plasticity. Repeated spindle-associated spikes are able to trigger synaptic potentiation in neocortical cells (Rosanova & Ulrich, 2005), perhaps as a result of the massive Ca^{2+} influx that they can provoke (Steriade, 2006). There is also some evidence to suggest that synchronous spindle activity occurs preferentially at synapses recently potentiated through encoding of information (Werk, Harbour, & Chapman, 2005). According to the model, the co-occurrence of hippocampal-neocortical replay and spindle activity in the neocortex during excitable up-states leads to the changes that underlie systems consolidation of hippocampus-dependent memories.

Indeed, there is much evidence to suggest a close temporal relationship between sharp-wave ripples and spindles (e.g. Clemens et al., 2007; Molle, Marshall, Gais, & Born, 2002; Siapas & Wilson, 1998; Sirota, Csicsvari, Buhl, & Buzsaki, 2003) and for a grouping influence of the neocortical slow oscillation on both spindles (Molle et al., 2002; Sirota et al., 2003) and sharp-wave ripples (Clemens et al., 2007; Isomura et al., 2006; Molle, Yeshenko, Marshall, Sara, & Born, 2006), such that they are up-regulated during the up-state and suppressed during the down-state.

Strong support for the hippocampus-neocortical interaction during SWS outlined in Born's model comes from a neuronal reactivation study (Ji & Wilson, 2007). These researchers found that the multi-cell firing sequences recorded during a waking experience were replayed during subsequent SWS in both the hippocampus and the visual cortex, and also that replay in the two areas was coordinated, in that the same waking experience was simultaneously replayed in the two structures. Importantly for the theory discussed above, frames of neocortical activity preceded those of the hippocampus, while replay of sequences emerged in the hippocampus first, consistent with the hypothesis that neocortical slow waves drive hippocampal reactivation, which, in turn, drives neocortical reactivation.

1.1.3. Theories of forgetting in the healthy population and how they might relate to ALF

Forgetting is an ordinary part of a healthy person's life, and is considered to be an important part of normal memory functioning (e.g. Storm, 2011). But the mechanism by which we forget is relatively poorly understood. Theories of forgetting must explain the forgetting curve (see Figure 1.2), first described by Ebbinghaus (1885/1964), which is the line produced when memory retention is plotted against lapsed time. The shape of the forgetting curve in healthy populations is remarkably

consistent across many tasks and timescales (e.g. Rubin & Wenzel, 1996), and is thought to be well described by a power function (Wixted & Carpenter, 2007); the rate of forgetting is rapid initially and slows with time.

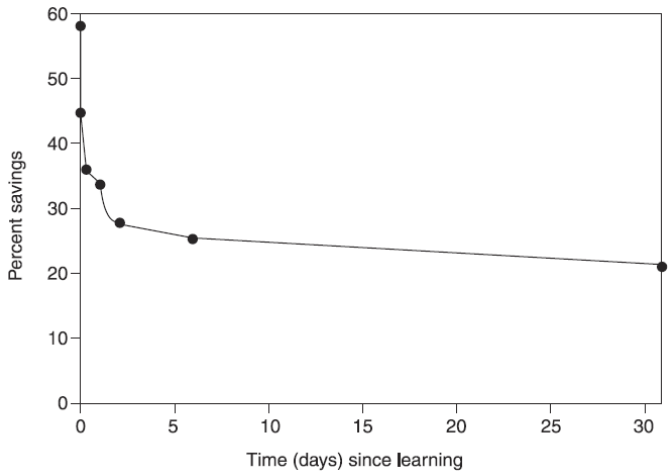


Figure 1.2. Forgetting curve adapted from Ebbinghaus (1885/1964, pp. 67-76), taken from Roediger, Weinstein & Agarwal (2010, p. 5).

One theory of forgetting is passive decay (e.g. Bailey & Chen, 1989): the notion that memory traces simply degrade over time. It has been argued that this theory provides neither a mechanism (McGeoch, 1932) nor an obvious explanation for the specific shape of the forgetting curve, and it has been largely discredited (e.g. McGeoch, 1932; Roediger et al., 2010). However, it should be noted that some researchers have recently argued that an active decay process is indeed one of the mechanisms of forgetting. According to Tononi and Cirelli's (2003, 2006) influential synaptic-homeostasis hypothesis, the major function of slow wave sleep is to downscale synaptic weights. These researchers claim that our synapses are potentiated during wakefulness as a consequence of learning and argue that this increase in synaptic weight is costly in terms of energy and space. They imply that, left unchecked, synaptic potentiation would saturate our capacity to learn. They suggest that synaptic potentiation during wakefulness produces slow wave activity during sleep, and that

this slow wave activity downscales synaptic weights, in a proportional manner, bringing the overall level back to baseline, conserving energy and space, making new learning possible, and improving memory performance by enhancing the signal-to-noise ratio. Hardt, Nader and Nadel (2013) also argue for a synaptic downscaling mechanism of forgetting that happens primarily during sleep, but they emphasise its selective, well-regulated nature. These researchers argue that important memories may be actively protected from the downscaling process in healthy people. Therefore, it is possible that ALF is a result of aberrant employment of a synaptic downscaling mechanism of forgetting.

However, most psychologists subscribe to the idea that forgetting is caused by some form of interference. This term has been used to refer to a great many things. There are many different types of interference: retroactive (the interfering effect of new information during the retention interval) and proactive (the interfering effect of pre-existing memories); input (interference between the items within the set to be encoded) and output (interference amongst items at the point of retrieval) (Tulving & Arbuckle, 1963); specific (i.e. information that is similar to the original memory) and general, non-specific, interference.

Two main mechanisms by which interference might cause forgetting have been proposed (e.g. Melton & Irwin, 1940). Some theories posit that forgetting is caused by interference with retrieval (i.e. an access failure). According to retrieval competition/cue-overload models, the chance of successful retrieval of the target memory is diminished if the retrieval cue is also associated with alternative memories (Anderson, 1983; McGeoch, 1942; Mensink & Raaijmakers, 1988; Robinson, 1920; Watkins & Watkins, 1975). The different memories that are simultaneously activated by the retrieval cue will compete for access, which can result in retrieval failure for the target memory.

Successful retrieval of a target memory (which may involve resolution of retrieval competition through inhibition of the interfering memories) can also lead to subsequent forgetting (Anderson, 2003; Anderson, Bjork, & Bjork, 1994; Levy & Anderson, 2002): retrieval induced forgetting is seen when a memory becomes the target of retrieval shortly after the retrieval of a related memory.

It is possible that ALF reflects a problem with retrieval, such as a difficulty with distinguishing the target memory from other similar ones (which could conceivably come about as a result of an encoding abnormality, see section 1.3). Some patient populations (e.g. those with lesions in the prefrontal cortex) exhibit memory problems as a result of abnormally poor resolution of retrieval competition (e.g. Shimamura, Jurica, Mangels, Gershberg, & Knight, 1995; Smith, Leonard, Crane, & Milner, 1995; Turner, Cipolotti, Yousry, & Shallice, 2007).

Other models suggest that normal forgetting is not simply an access failure; interfering inputs during the retention interval (i.e. retroactive interference) can actually degrade/alter the original memory trace (Müller & Pilzecker, 1900; Skaggs, 1925). It might be argued that the alternative notion that all encoded memories persist in their original form forever, and that loss of information is caused only by a disruption of access, does not fit particularly well with the fact that memories are stored as synaptic weights within a neural network that must constantly adapt to represent new information, nor with the idea that memories are worth keeping in storage only insofar as they are behaviourally relevant. On the other hand, there is a wealth of evidence that retrieval competition occurs, including overt intrusion (e.g. McKinney & McGeoch, 1935) and neural reactivation (e.g. Kuhl, Bainbridge, & Chun, 2012) of competing memories. Furthermore, if trace degradation/alteration were the only cause of forgetting, it would be difficult to account for situations in which memories cannot be retrieved on one occasion, but are successfully retrieved later. Access failure and memory

degradation are not mutually exclusive possibilities, however. Forgetting might be caused by interference with storage in some circumstances, and by retrieval failure in others. Retrieval failure might happen either as a result of interference-induced retrieval competition or due to ineffective retrieval cues (Tulving & Thomson, 1973), as might occur when there is a mismatch between encoding and retrieval contexts (Estes, 1955; Howard & Kahana, 2002; Mensink & Raaijmakers, 1989; Polyn, Norman, & Kahana, 2009). Access failure and memory degradation may indeed interact. For instance, memories that have been partially degraded by interference with storage might be expected to fare more poorly in subsequent retrieval competitions.

While patients with ALF typically show normal learning performance, it remains possible that their memory traces are abnormally formed in some way (see section 1.3) that makes them more vulnerable to disruption by interfering inputs.

General retroactive interference ultimately causes more forgetting in healthy people if it occurs relatively shortly after encoding, compared to when it occurs later (Müller & Pilzecker, 1900; Skaggs, 1925). However, while this is a reliable finding in experimental animals (e.g. Izquierdo, Schroder, Netto, & Medina, 1999), it can be difficult to replicate in humans. This is most likely because humans, as compared to experimental animals, have enriched environments even when they are not currently engaging in an experimenter-controlled learning task, and are constantly encoding new memories during waking hours (Wixted, 2010). One way to control the timing of general interference in humans is to introduce a period of minimal interference (in which there is little to no new encoding of any kind), such as a period of sleep. A period of sleep ultimately benefits retention most if it happens sooner, rather than later, after encoding (Gais et al., 2006; Talamini et al., 2008), i.e. it does not simply delay the onset of the steep section of the forgetting function, but actually

changes the shape of the forgetting curve. Together, this evidence suggests that retroactive interference may be able to account for the form of the forgetting curve(e.g. Wixted, 2010).

Brown and colleagues (Brown, Neath, & Chater, 2007) argue that the differential effects of interference with time relative to encoding can be explained by their 'temporal distinctiveness' model. In this model, all memories that are encoded persist in the brain, and forgetting occurs simply because memories (i.e. alternative response options) can be confused with one other, which affects the ease of access to any particular memory. The confusability of any two memories is the ratio of their 'time-since-encoding's. This means that older memories are more confusable (and therefore harder to remember) than more recent memories, and that older memories will be forgotten at a slower rate than newer memories. According to their model, memories that are formed close together in time are more confusable (less temporally distinctive) and therefore more difficult to successfully access.

However, it is not clear what this would mean neurally, and, as mentioned earlier, the persistence of all memories that have ever been encoded, irrespective of their behavioural relevance, might not be considered a very economical use of resources.

An alternative explanation (mentioned in section 1.1.2.1.1.), which is advocated by Wixted (2004, 2010), invokes the process of memory consolidation to account for the differing effects of retroactive interference at different time-points. According to this account, memories are initially fragile to disruption by new encoding but they consolidate over time, making them more resistant to subsequent interference. As mentioned earlier, it is known that early phase LTP (i.e. before the trace

has been consolidated) is vulnerable to disruption by new learning (e.g. Xu, Anwyl, & Rowan, 1998). If LTP induction is shortly followed by the administration of LTP-inhibitors (such as NMDA receptor antagonists), LTP is protected from the disruption that would usually occur (e.g. Villarreal, Do, Haddad, & Derrick, 2002). The memory retention facilitating effect of SWS (e.g. Yaroush et al., 1971) may be at least partially mediated by the same mechanism (e.g. Wixted, 2010): protection from interference as a result of suppression of new LTP in the hippocampus (Leonard et al., 1987). After sufficient time has passed, late-phase LTP (synaptic consolidation, which involves morphological changes to synapses) will have occurred, rendering the memory more robust to interference from new encoding (e.g. Xu et al., 1998), meaning that forgetting will be slower. Late-phase LTP involves protein synthesis; the administration of protein synthesis inhibitors shortly after encoding can block late-phase LTP (e.g. Frey, Krug, Reymann, & Matthies, 1988) and lead to accelerated forgetting of hippocampus-dependent memories (Davis & Squire, 1984).

Systems consolidation may further improve a memory's resistance to interference. Once consolidated into the slow-learning neocortical network, and less dependent on the fast-learning hippocampal system in which all new declarative information is rapidly encoded, the memory might be even less vulnerable to obliteration by new learning. Furthermore, reactivations during SWS (i.e. the posited mechanism of systems consolidation) have been shown to improve memory retention (e.g. Rasch et al., 2007) and render memories more resistant to interference (e.g. Diekelmann et al., 2011).

Therefore, according to this model, forgetting is caused by memory trace disruption by new encoding and, as the consolidation process proceeds, memories become more resistant to interference and forgetting slows.

Interestingly, when consolidated memories are retrieved/reactivated during wakefulness, they may become unstable again, until a process of 'reconsolidation' has occurred. During the destabilised state, the memories are vulnerable to the effects of electroconvulsive shock (e.g. Kroes et al., 2014; Misanin, Miller, & Lewis, 1968; Schneider & Sherman, 1968) and behavioural interference (e.g. Diekelmann et al., 2011; Hupbach, Gomez, Hardt, & Nadel, 2007; Walker, Brakefield, Hobson, & Stickgold, 2003). There is some evidence to suggest that reconsolidation, like consolidation, involves the synthesis of new proteins and can be blocked using protein synthesis inhibitors (e.g. Nader, Schafe, & Le Doux, 2000). The fragility caused by retrieval might provide an opportunity for old memories to be modified (e.g. Walker et al., 2003) and updated with new information, which would serve to maximise the behavioural relevance of our store of memories. For instance, Hupbach et al. (2007) trained participants on a list of objects, and then trained them on a second list of objects the following day, either with or without a reminder of the first list immediately beforehand. If participants were then immediately tested on the items from the first list, the reminder was found to have had no effect. However, if the test for the first list happened on the third day, participants who had received the reminder were found to also produce a number of objects from the second list. Retrieval of the second list on the third day was, however, unaffected by the reminder of the first list on the second day. This suggests that the effect of the retrieval cue just prior to interference learning was mediated by modification of the memory for the first list through a time- (and possibly sleep-) dependent process of reconsolidation, rather than retrieval competition.

Therefore, a third possible mechanism by which behavioural retroactive interference might cause forgetting in healthy people (in addition to direct disruption of the memory trace and interference with memory access) is disruption of the consolidation, or reconsolidation, process. Walker et al. (2003) provided evidence for this mechanism in a series of experiments on finger tapping, a motor

task for which delayed sleep-dependent performance improvements are typically seen. The researchers found that learning a second motor sequence shortly after a first one prevented subsequent overnight gains in accuracy for the first sequence (while normal overnight gains were seen for the second sequence). Importantly, the researchers found that the learning of the second sequence did not immediately impact accuracy on the first sequence, suggesting that the mechanism in this case was the specific disruption of subsequent consolidation, rather than immediate unlearning/trace degradation. When there was a 6- or 24-hour delay between the learning of the first and second sequences, this blocking of subsequent overnight gains was not seen. However, the introduction of rehearsal of the first sequence (which was initially learnt 24 hours previously) immediately prior to the learning of the second sequence resulted in severe accuracy impairments (and no overnight gains in speed) for the first sequence on the following day (while normal overnight gains were seen for the second sequence). Again, the researchers found that the learning of the second sequence did not immediately impact performance on the first (rehearsed) sequence, meaning that the effect of learning the second sequence was not related to immediate unlearning of the rehearsed sequence.

ALF may reflect a consolidation impairment. If consolidation processes were not functioning normally, then one might expect to see accelerated forgetting, as the normal benefits of consolidation (which might include overnight enhancements and/or development of the memory trace's resistance to disruption) would be reduced. In patients with ALF, memory consolidation might be compromised (e.g. Blake et al., 2000; Butler et al., 2007; Kapur et al., 1997), perhaps as a result of epileptiform activity (e.g. Buzsaki, 1989; Fitzgerald, Thayer, Mohamed, & Miller, 2013) or a lack of the requisite neural resources (Wixted, 2010).

1.1.4. ALF as a neuropsychological model of disrupted memory consolidation

Neuropsychological models play a central role in the scientific study of human memory, but models of a pure consolidation deficit have thus far been conspicuously absent. This may be because the brain structures involved in memory consolidation overlap with those involved in memory encoding (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011; Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011). Patients with brain lesions affecting the long-term retention of episodic memory therefore tend to have prominent learning deficits, which confound the investigation of consolidation in the hours and days after learning. Some researchers have inferred information about consolidation mechanisms by comparing retrograde memories of different ages in patients with MTL lesions (Ribot, 1882; Squire et al., 1975). However, anterograde studies give the experimenter more control over the memories under investigation, and make it possible to study memory of the same events (which can be made consistent across individuals) at different time-points. Ideally, a neuropsychological model of memory consolidation would exhibit normal learning performance but excessively rapid forgetting later. ALF, therefore, represents a rare opportunity. Research into precisely which aspects of memory are disrupted in this disorder and the neural correlates of the problem will help contribute to our understanding of human memory.

1.2. Accelerated long-term forgetting: what do we know?

ALF is particularly common in patients with transient epileptic amnesia (TEA). Much of the existing research on ALF, including the experimental work presented in this thesis, has been performed in groups of TEA patients.

TEA is a form of epilepsy in which seizures manifest as brief (approximately 30-60 minutes), recurrent episodes of transient memory loss (Butler et al., 2007; Kapur, 1990; Zeman et al., 1998).

TEA develops later in life (mean onset 62 years, Butler et al., 2007) and affects men more than women (Butler et al., 2007). The diagnostic criteria for TEA (taken from Zeman & Butler, 2010) are: (1) A history of recurrent witnessed episodes of transient amnesia (2) Cognitive functions other than memory judged to be intact during typical episodes by a reliable witness (3) Evidence for a diagnosis of epilepsy based on one or more of the following: (a) Epileptiform abnormalities on electroencephalography (b) The concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations) (c) A clear-cut response to anticonvulsant therapy.

During the memory attacks (which commonly happen upon waking from sleep, Butler et al., 2007), the patients typically suffer from both retrograde amnesia (problems with recalling events that have happened previously) and anterograde amnesia (difficulty retaining new information), but approximately half of patients remember their attacks to some extent, indicating that the anterograde amnesia is not complete (Zeman, Butler, Muhlert, & Milton, 2013; Zeman et al., 1998). In approximately one third of patients, amnesia is the only seizure manifestation (Zeman et al., 1998). In the remaining two thirds, there are other seizure manifestations, such as olfactory hallucinations, oral automatisms like lip-smacking, brief periods of unresponsiveness and other seizure types, such as complex partial seizures (Zeman & Butler, 2010). The frequency of attacks is variable, but the median is 12 attacks per year (Butler et al., 2007). While the patients typically perform within the normal range on interictal (between seizure) neuropsychological tests, complaints of interictal memory problems are common (Butler et al., 2007). The amnesic attacks are abolished by low doses of anticonvulsant medication in a large majority of cases, but the memory complaints often persist (Butler et al., 2007; Butler & Zeman, 2008b). Approximately 70% of TEA patients complain of patchy remote memory loss for autobiographical events. Approximately one third of patients have topographical problems, in that they have navigational difficulties in known places. And nearly half complain of accelerated forgetting (Butler et al., 2007).

The seizure focus in TEA is thought to be the MTL. A number of lines of evidence point in this direction. As discussed above, the principle manifestation of seizures in TEA patients is amnesia, which is usually associated with MTL disorders, such as lesions (Squire & Zola-Morgan, 1991) and transient global amnesia (Bartsch & Butler, 2013). TEA patients also report interictal problems with MTL-dependent (declarative and spatial) memories. When epileptiform abnormalities can be detected on an EEG, they indicate a temporal lobe seizure focus (Butler et al., 2007; Zeman et al., 1998), and the common seizure-related symptom of olfactory hallucinations most likely reflects epileptic activity spreading out from the MTL to the nearby piriform cortex (Zeman & Butler, 2010). Individual interictal neuroimaging scans in TEA patients are typically normal (Butler et al., 2007; Zeman et al., 1998). However, at the group level, TEA patients have been shown to have subtle bilateral hippocampal atrophy (Butler et al., 2013; Butler et al., 2009). TEA patients also have bilateral atrophy in another MTL region - the perirhinal cortex – as well as in the orbitofrontal cortex, at the group level (Butler et al., 2013). Furthermore, on the rare occasions that individual scans show structural abnormalities, they consistently impinge on the MTL (Butler & Zeman (2008b) found four cases in their literature review). A patient scanned during a flurry of attacks displayed high signal in the left hippocampus on a T2-weighted MR scan and hypermetabolism in the left hippocampus on a 2-Fluoro-2-[^{18}F]-deoxy-D-glucose PET (positron emission tomography) scan, which had resolved once his seizures had been successfully treated (Butler & Zeman, 2008a).

1.2.1. Specific to declarative memories?

ALF complaints concern declarative memories. Therefore, unsurprisingly, the majority of experimental studies of ALF to date have focused on declarative memory tasks. ALF has been found for both verbal and nonverbal declarative tasks (typically, word lists, stories, and/or abstract visual

designs have been used), and in both recall and recognition paradigms. Very few ALF studies have tested patients on non-declarative tasks.

However, Muhlert et al. (2010) tested TEA patients on a serial reaction-time task, and Deak et al. (2011) tested temporal lobe epilepsy (TLE) patients on a finger-tapping task. Both sets of researchers found that the patients performed normally (while they showed ALF for declarative tasks). However, in both studies, there was no loss of skill across the intervals tested. In such situations, i.e. when forgetting is at floor, it is not reasonable to conclude that the patient forgetting rate is normal for the type of task tested. Therefore, although it is well established that patients with ALF suffer from declarative memory deficits, the extent to which other types of memory are affected in the disorder is unclear.

1.2.2. Neural basis

It has been suggested that ALF might be caused by anti-epileptic medication. However, complaints of ALF in TEA typically pre-date the onset of treatment (Butler et al., 2007; Butler & Zeman, 2008b). Furthermore, people with TEA are usually on low doses of medication (e.g. Butler et al., 2007; Muhlert et al., 2010), and ALF patients often report some degree of memory improvement once they begin treatment (Butler et al., 2007; Gallassi, 2006; Gallassi, Morreale, Lorusso, Pazzaglia, & Lugaresi, 1988; Zeman et al., 1998).

Another possibility is that ALF is caused by psychosocial factors. However, while mood disorders can impair memory, there is no clear evidence that they can cause accelerated long-term forgetting. Lewis and Kopelman (1998) found that depressed patients did not forget more than controls, once

initial learning was equated. Furthermore, in many ALF studies, the patient and control groups have either been matched on measures of anxiety and depression, or these measures have been shown to be unrelated to ALF (e.g. Blake et al., 2000; Butler et al., 2007; Mameniskiene, Jatuzis, Kaubrys, & Budrys, 2006; Muhlert et al., 2010).

There is no known neural structural correlate of ALF. Structural abnormalities have been found in TLE patients who have ALF (e.g. Tramoni et al., 2011; Wilkinson et al., 2012). However, these have not been shown to correlate with ALF severity. As discussed above, TEA patients have reduced hippocampal, perirhinal and orbitofrontal volumes at the group level (Butler et al., 2013; Butler et al., 2009). Hippocampal volume correlates with performance on standard tests of anterograde memory (which typically test memory at only 30 minutes after encoding) in TEA patients (as has also been found in TLE, Kilpatrick et al., 1997; Lencz et al., 1992; Reminger et al., 2004), but it does not correlate with ALF (Butler et al., 2009). However, the data for these magnetic resonance imaging studies in TEA patients were collected using scanners with magnets of only 1.5 T, and it is possible that they were not sufficiently sensitive to detect an existing neural correlate of ALF.

Another possible neural basis for ALF is a functional brain abnormality. Some studies in TLE have linked ALF to seizure frequency (e.g. Jokeit, Daamen, Zang, Janszky, & Ebner, 2001; Mameniskiene et al., 2006). However, other studies have not found this relationship (e.g. Bergin, Thompson, Fish, & Shorvon, 1995; Blake et al., 2000) and ALF can be seen in patients who are medicated and seizure free (e.g. Butler et al., 2007; Muhlert et al., 2010). Subclinical epileptiform activity in the retention interval may be responsible for ALF (e.g. Fitzgerald et al., 2013). It would be possible for such activity to disrupt recently formed fragile memory traces, or their consolidation, and it would be interesting to record brain activity, particularly during sleep, in TEA patients.

1.2.2.1. Possible link between ALF and sleep-dependent consolidation

A disruption of sleep-dependent memory consolidation has been commonly posited as a likely neurological basis of ALF (e.g. Butler et al., 2009; Holmes & Lenck-Santini, 2006; Jansari, Davis, McGibbon, Firminger, & Kapur, 2010; Muhlert et al., 2011; Sud et al., 2014; Tramoni et al., 2011; Urbain, Di Vincenzo, Peigneux, & Van Bogaert, 2011; Zeman et al., 2013). Subclinical epilepsy-related activity during sleep could disrupt the consolidation process. Clemens and colleagues (2007) found ripples to be consistently associated with interictal spikes in a sample of epilepsy patients (70% of which had a mesiotemporal seizure focus) and Buzsáki (1989) has noted that disruption of sharp-wave ripples (which are associated with memory reactivations) by epileptic spikes could be damaging to memory. Studies in experimental animals support this idea: suppression of hippocampal sharp-wave ripples using electrical pulses during post-learning sleep leads to impairments on spatial memory tasks (Girardeau et al., 2009); and electrical induction of interictal spikes in the hippocampus during sleep impairs memory (Shatskikh, Raghavendra, Zhao, Cui, & Holmes, 2006).

A number of observations suggest a relationship between ALF and sleep. There is a widely documented reciprocal relationship between sleep and epilepsy. Sleep modulates epileptic activity; slow wave sleep, in particular, has often been shown to increase it (Bazil, 2000; Bazil & Walczak, 1997; Goncharova, Zaveri, Duckrow, Novotny, & Spencer, 2009; Kotagal, 2001; Mayanagi, 1977; Nazer & Dickson, 2009; Romcy-Pereira, Leite, & Garcia-Cairasco, 2009; Rossi, Colicchio, & Pola, 1984; Sammaritano, Gigli, & Gotman, 1991). In turn, epilepsy often disrupts sleep, both in terms of subjective sleep quality and objectively measured sleep architecture (Bazil, 2000; Derry & Duncan, 2013; Kotagal, 2001; Matos, Andersen, do Valle, & Tufik, 2010).

The amnesic attacks of TEA often occur upon waking, indicating that seizure activity may preferentially occur during sleep or at the transition from sleep to wakefulness (Butler et al., 2007). Further, TEA patients are more likely to show epileptiform abnormalities on sleep or sleep-deprived EEGs than wake EEGs (Butler et al., 2007; Zeman et al., 1998). And finally, ALF has been reported at delays as short as 24 hours (i.e. after the first post-learning night of sleep) in groups of patients who have been shown to learn and initially retain new information normally (Fitzgerald et al., 2013; Martin et al., 1991; Muhlert et al., 2010).

1.2.3. Methodological difficulties with investigating ALF

There are, however, various methodological difficulties of which researchers must be aware when investigating ALF (Elliott, Isaac, & Muhlert, 2014).

Firstly, it is important to match the patients and control groups in terms of age and IQ. While forgetting rates have often been found to be remarkably consistent across individuals, regardless of experimental and inter-individual factors (e.g. Underwood, 1964), there is some evidence to suggest that forgetting rates are affected by age and IQ (Davis et al., 2003; Huppert & Kopelman, 1989; Macdonald, Stigsdotter-Neely, Derwinger, & Backman, 2006). Interestingly, Mary, Schreiner and Peigneux (2013) recently reported that healthy older adults show ALF compared to younger adults, and related this to disrupted sleep-dependent memory consolidation as a result of increased sleep fragmentation caused by more frequent intra-sleep awakenings.

Another factor to consider is the importance of avoiding ceiling and floor effects, which could mask differences between groups at various time-points (Elliott et al., 2014). Ceiling effects might account for the apparent lack of accelerated forgetting over short intervals in some studies (Zeman & Butler, 2010).

Perhaps the most critical consideration when researching ALF is the matching of initial memory performance; different starting points severely complicate the comparison of forgetting rates. Different methods have been used to compare forgetting rates, including vertical parallelism (identifying whether the vertical distance between the forgetting curves remains constant over time, which might be investigated using the interaction term in an ANOVA, e.g. Slamecka, 1985; Slamecka & McElree, 1983) and horizontal parallelism (identifying whether the horizontal distance between the forgetting curves remains constant over time, e.g. Loftus, 1985a; Loftus, 1985b), which can lead to different conclusions if initial memory performance is not matched. In situations where the groups differ in terms of learning ability, this might be achieved by varying the exposure duration (Mayes, 1986; Shuell & Keppel, 1970) or the number of presentations (e.g. Isaac & Mayes, 1999a; Isaac & Mayes, 1999b), or using a trials-to-criterion procedure (Elliott et al., 2014).

1.3. Aims of the thesis

The aims of this doctoral thesis were to investigate which stages of memory are disrupted in ALF in TEA patients, and to shed light on the neural basis of the memory impairment. With regard to the memory stages involved, two alternative hypotheses were tested.

The first was that ALF in TEA reflects a disruption of memory consolidation.

The explanation of ALF most commonly suggested in the literature is a deficit in sleep-dependent memory consolidation (e.g. Butler et al., 2009; Holmes & Lenck-Santini, 2006; Jansari et al., 2010; Muhlert et al., 2011; Sud et al., 2014; Tramoni et al., 2011; Urbain et al., 2011; Zeman et al., 2013). To test this theory, I compared the benefit of sleep for memory retention in TEA patients with ALF and control participants. If ALF were related to sleep, then sleep would not benefit ALF patients as much as healthy people, and ALF might only be apparent over intervals containing sleep. Polysomnographic (PSG) data were gathered to test the prediction that ALF is related to abnormalities of brain activity during sleep. I anticipated that ALF severity would correlate with epileptic spikes, and that there might be slow wave sleep abnormalities in patients.

Instead, ALF might be caused by a consolidation impairment that is not sleep-specific. It is known that learning alters brain activity patterns during rest periods (e.g. Albert, Robertson, & Miall, 2009; Evers, Klaassen, Rombouts, Backes, & Jolles, 2012; Hasson, Nusbaum, & Small, 2009; Karlsson & Frank, 2009; Stevens, Buckner, & Schacter, 2010; van Kesteren, Fernandez, Norris, & Hermans, 2010) and brain activity during post-encoding periods of wakefulness has been linked to subsequent memory performance (e.g. Axmacher et al., 2008; Ben-Yakov & Dudai, 2011; Deuker et al., 2013; Ego-Stengel & Wilson, 2010; Groen, Sokolov, Jonas, Roebling, & Spitzer, 2011; Staresina et al., 2013; Tambini & Davachi, 2013; Tambini, Ketz, & Davachi, 2010; Wang, Liu, Li, & Zang, 2012). Consolidation processes during post-encoding rest might be abnormal in ALF patients. Resting state fMRI scans were collected before and after a memory encoding task to investigate this possibility. Learning-induced changes in the network of brain regions involved in episodic memory retrieval were of particular interest.

The alternative hypothesis was that the patients might actually suffer from a subtle encoding impairment that ultimately leads to accelerated forgetting. It is relatively common for patients with ALF to also suffer from some level of learning deficit or to reveal some degree of performance impairment within 30 minutes of encoding (e.g. Butler et al., 2007; Muhlert et al., 2011). While attempts have been made to show a dissociation between early and late memory problems (e.g. Muhlert et al., 2010), it is possible that initial learning difficulties at least partially account for ALF (e.g. Davidson, Dorris, O'Regan, & Zuberi, 2007). Some researchers have gone to great efforts to match patients and controls for learning and initial retention and have still demonstrated ALF over the longer-term (e.g. Hoefeijzers, Dewar, Della Sala, Zeman, & Butler, 2013), but it is conceivable that these behavioural measures were not sufficiently sensitive. The relationship between performance on a test and the state of the underlying memory is unknown, and may be a complex, nonlinear one (e.g. Wixted, 1990). Equal performance on an initial memory test does not necessarily imply equality of memory in terms of strength and nature.

According to many theories of the function of the MTL (including pattern separation (Marr, 1971; O'Reilly & McClelland, 1994; Treves & Rolls, 1994; Yassa & Stark, 2011); the perceptual-mnemonic feature-conjunction (PMFC) model (Bussey, Saksida, & Murray, 2005) and the emergent memory account (Graham, Barense, & Lee, 2010)), the hippocampus and its surrounding structures are critical to our ability to represent the multiple stimuli and events that we encounter in such a way that they can be readily distinguished from one another; by virtue of the type of representations that are formed in these structures, we are able to minimise interference between similar memories. Given that the MTL is the purported seizure focus in TEA, these patients may suffer from compromised MTL function. As has been shown in connectionist models (Bartko, Cowell, Winters, Bussey, & Saksida, 2010; Cowell, Bussey, & Saksida, 2006) and experimental animals (Bartko et al., 2010), impoverished memory encoding as a result of disrupted MTL functioning can lead to

catastrophic interference across a retention interval and result in poor memory retrieval performance. Indeed, there is evidence to suggest that patients with compromised MTL function are particularly susceptible to interference (e.g. Cowan, Beschin, & Della Sala, 2004; Dewar, Garcia, Cowan, & Della Sala, 2009; Warrington & Weiskrantz, 1978). If TEA patients with ALF suffer from an encoding deficit, they might display abnormal activity within the MTL during learning that relates to their subsequent memory performance.

To examine encoding-related brain activity, a subsequent memory fMRI paradigm was employed. In this type of paradigm, participants are scanned during the encoding phase and brain activity associated with subsequently remembered and subsequently forgotten stimuli is compared. This type of experiment has been used extensively in healthy people to show that successful encoding is associated with brain activity in regions of the medial temporal lobe, including the hippocampus, in addition to ventrolateral prefrontal cortex and dorsal parietal cortex (Blumenfeld & Ranganath, 2006; Davachi, 2006; Paller & Wagner, 2002; Uncapher & Wagner, 2009).

Encoding and consolidation deficits are not mutually exclusive candidate explanations of ALF. Indeed, it is likely that there is an intimate relationship between encoding and subsequent consolidation in the healthy population. A number of variables at the stage of encoding, such as memory strength (Drosopoulos, Schulze, Fischer, & Born, 2007), motivation (Fischer & Born, 2009; Rauchs et al., 2011; Wilhelm et al., 2011) and degree of hippocampal engagement (Diekelmann et al., 2009; Rauchs et al., 2011) might bias subsequent consolidation processes. Deficits in encoding and consolidation processes may interact with one another in patients with ALF.

Furthermore, while an anatomical neural correlate of ALF has not been discovered so far, it remains possible that ALF is related to brain structure. I therefore collected structural MR images using a higher strength magnet (3T) than those used in previous studies of TEA patients (1.5T, Butler et al., 2013; Butler et al., 2009) and looked for a structural correlate of ALF.

Through investigation of ALF in TEA, I hoped to gain an insight into the cause of this disorder and to contribute to our understanding of normal memory processing.

2. The benefit of sleep for declarative memory retention

2.1. Introduction

As discussed in the main introduction to this thesis, ALF may serve as a neuropsychological model of a consolidation deficit. In this chapter, I sought to investigate the cause of rapid forgetting in patients with ALF, focussing particularly upon the role of sleep in the memory impairment.

ALF is associated with epilepsy, and is particularly common in transient epileptic amnesia (TEA). The seizure focus in TEA is thought to be the medial temporal lobes (MTL) (Zeman & Butler, 2010), and there is some evidence to suggest that ALF may be specific to declarative memories, which are dependent on the MTL (Deak et al., 2011; Muhlert et al., 2010).

There appears to be a link between ALF and sleep. Slow wave sleep (SWS) enhances epileptic activity (Bazil, 2000; Bazil & Walczak, 1997; Goncharova et al., 2009; Kotagal, 2001; Mayanagi, 1977; Nazer & Dickson, 2009; Romcy-Pereira et al., 2009; Rossi et al., 1984; Sammaritano et al., 1991). It is common for unmedicated TEA patients to have the attacks of amnesia that are characteristic of this epileptic syndrome upon waking from sleep (approximately 70% of patients have attacks in this context, Zeman & Butler, 2010), indicating that seizure activity happens preferentially during sleep or at the transition from sleep to wakefulness in TEA (Butler et al., 2007). It is more likely for epileptiform abnormalities to be detected during sleep or sleep-deprived electroencephalographic recordings (EEGs) than during wake EEGs in TEA patients (Butler et al., 2007; Zeman et al., 1998). Additionally, ALF has been reported at delays as short as 24 hours (i.e. after the first post-learning night of sleep) in groups of patients who have been shown to learn and initially retain new information normally (Fitzgerald et al., 2013; Martin et al., 1991; Muhlert et al., 2010).

Furthermore there is a link between sleep and memory consolidation. Sleep, particularly SWS, is beneficial for the retention of declarative memory. Recently-acquired declarative memories are thought to be consolidated during SWS through the reactivation of their traces in the MTL (e.g. Diekelmann et al., 2011; Peigneux et al., 2004; Rasch et al., 2007; Rudoy et al., 2009; Wilson & McNaughton, 1994).

A disruption of sleep-dependent memory consolidation has been commonly posited as a likely neurological basis of accelerated long-term forgetting (e.g. Butler et al., 2009; Holmes & Lenck-Santini, 2006; Jansari et al., 2010; Muhlert et al., 2011; Sud et al., 2014; Tramoni et al., 2011; Urbain et al., 2011; Zeman et al., 2013). The experiment presented in this chapter sought to test this hypothesis. I compared retention over a night of sleep to that over a day of wakefulness in patients with TEA-associated ALF and healthy controls. I sought to determine whether the benefit of sleep for memory was reduced in these patients, and whether ALF could only be detected when the retention interval contained sleep.

2.2. Methods

Before completing the main experiment comparing individuals with TEA-associated ALF and their matched controls, I ran a pilot study to ensure that the task was sensitive to the benefits of sleep and not confounded by circadian factors.

2.2.1. Pilot experiment

I used a word-pair associates task, which is declarative and MTL-dependent (Jackson & Schacter, 2004) and therefore likely to be affected by ALF. As my aim was to determine whether the benefit of sleep for memory is reduced in ALF patients, it was important for me to have a task that was sensitive to the benefit of sleep for memory in healthy people. Word-pair associates are the most commonly used declarative memory task in the sleep-dependent consolidation literature (Diekelmann et al., 2009). Furthermore, if interference learning is introduced prior to testing, the benefit of sleep for memory consolidation can be demonstrated much more clearly, because sleep boosts memory's resistance to subsequent interference (Ellenbogen et al., 2009; Ellenbogen, Hulbert, et al., 2006). However, these studies have usually been carried out with young adults. The healthy participants for my main experiment would need to be matched in terms of age to the patients and so would all be over 50 years old. It has been proposed that there might be a decline in declarative memory consolidation during sleep with age (e.g. Backhaus et al., 2007). Therefore, I piloted the task to ensure that I had a robust sleep effect in healthy over 50s before embarking on the patient study.

2.2.1.1. Participants

I tested eight healthy participants in the pilot study. Four of the participants were male. The mean age (±SEM) was 59 ±1.65years.

2.2.1.2. Stimuli

The word-stimuli were nouns drawn from the MRC psycholinguistic database (Coltheart, 1981) with 4-7 letters, familiarity scores of 350-700, concreteness scores of 350-700, imagibility scores of 350-700, and British National Corpus frequency scores of 800-4300. Words were not used if they were emotionally potent or highly semantically similar to another word in the set. The words were split into six lists (set 1 A_1, B_1, C_1 and set 2 A_2, B_2, C_2) that were not significantly different on any of the aforementioned variables. Word-pairs, which were consistent across subjects, were made by combining the lists within the two sets. Words with obvious semantic relationships were not paired with each other.

2.2.1.3. Task

The paradigm had a sleep condition, in which participants were trained in the evening and tested in the morning (after a night of sleep) and a wake condition, in which participants were trained in the morning and tested in the evening (after a day of wakefulness, during which the participants were not permitted to nap). Stimuli were presented using Presentation (Neurobehavioral Systems, Albany, NY). The initial learning stage of the task involved training the participants to 60% criterion on 30 pairs of unrelated nouns (A-B). Memory performance was assessed using cued recall tests without immediate feedback, in which the participants were presented with the A words only and asked to produce the B words. Until they reached criterion on one of these tests, the participants were repeatedly re-exposed to the full set of pairs, with coloured borders around each pair (green for correct and red for incorrect) providing feedback on their most recent response.

Thirty minutes after the participants reached criterion, their memory was tested again. Twelve hours after the beginning of A-B pair training, following a retention interval of a night of sleep or a day of wakefulness, the participants were trained (with only one exposure) and immediately tested on 30 A-C interference pairs. These new pairs had the same cue words as the original pairs, but different paired associates. After a ten-minute interval the participants were presented with the A words only and asked to produce both the B and C words. While I was primarily interested in performance on the A-B pairs, I asked for the C paired associates as well in order to minimize retrieval competition (Ellenbogen et al., 2009; Ellenbogen, Hulbert, et al., 2006). More details on the procedure can be found in Appendix A. The A-B and A-C stimulus sets contained four additional word-pairs each (two at the start and two at the end), which were used to buffer primacy and recency effects and were excluded from analyses.

In contrast to Ellenbogen's experiments (Ellenbogen et al., 2009; Ellenbogen, Hulbert, et al., 2006), on which the paradigm was based, I used a within-subjects design (to reduce the number of patients that would be required in the main experiment); everyone took part in both the sleep and wake conditions, with twenty-four hours in between. Two different sets of A-B and A-C word-pairs were used, so that the stimuli were novel in each condition. The order of the conditions and the distribution of stimuli across conditions were counterbalanced across participants.

The test sessions were performed in a laboratory. For the pilot, the participants were allowed to go home to sleep and testing start times varied between seven and nine o'clock but were consistent for each participant.

2.2.2. Main Experiment

2.2.2.1. Participants

Thirteen patients who met the diagnostic criteria for TEA, reported symptoms suggestive of ALF, and did not exhibit impairments on standard neuropsychological tests designed to measure general cognitive ability (i.e. had an IQ of at least 80, according to the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) and the National Adult Reading Scale (Nelson & Willison, 1991; Nelson, 1982)) were recruited. The diagnostic criteria for TEA are described in the main introduction to this thesis. Fifteen control participants were recruited by advertisement. To reduce the likelihood that the advertisements would attract people with concerns about their memory or sleep, these advertisements simply appealed for volunteers for psychology experiments and did not specify the cognitive functions under investigation. One control did not reach criterion on the task and did not complete the experiment. A control was excluded from analyses because he was an outlier on the 12-hrs test (his performance was more than two standard deviations below the mean of the other participants). A further three participants were excluded. The youngest control participant was removed to make the patient and control groups more closely matched in terms of age. One patient repeatedly delayed the experimental proceedings, meaning that he took an unusually long time over the training procedure (his average response time in the training tests was more than four standard deviations greater than the mean of the included participants), and the other was removed to allow better counterbalancing of the versions of the experiment. Exclusion of these three participants did not alter the significance of any of the long-term memory retention results I report (though it should be noted that, if these participants had been included, the patients would have been found to perform significantly worse than the controls overall on the word-pair associates memory tests (i.e. a main effect of group in the first ANOVA reported in section 2.3.2.1), rather than just numerically worse, with $p = 0.062$, see section 2.3.2.1.). However, if they had not been excluded, the two groups would not have been matched in terms of age, experiment version and performance over the first 30 minutes of the experiment, which could have confounded interpretation of the results.

Details about the eleven remaining patients are provided in Table 2.1, including information from clinical EEG and MRI assessments. Prior to recruitment, the patients were assessed by a consultant neurologist with experience in the diagnosis and management of epilepsy and, specifically, of transient epileptic amnesia. Assessments included detailed history and physical examination. Clinical EEG recording was obtained for each patient at the referring centre (Oxford or Exeter) and reported by a Consultant Clinical Neurophysiologist, with particular reference to the presence or absence of epileptiform features (spikes or sharp wave transients). Clinical MR imaging (T1, T2, FLAIR, DWI and gradient echo sequences) was also obtained at the referring centre and examined for pathological features (within and beyond the medial temporal lobes) by a Consultant Neuroradiologist. All patients were on anticonvulsant monotherapy (detailed in Table 2.1) and, in all cases but one, had been free of seizures for at least six months prior to testing (the approximate number of months between the experiment and each patient's most recent seizure/amnesic attack is provided in Table 2.1). No patients reported seizures during the experiment. These eleven patients were matched in terms of age, IQ and performance on a range of standard neuropsychological tests (see Table 2.2) to the group of twelve remaining control participants. The control participants did not suffer from any psychiatric, central nervous system or sleep disorders and did not complain of ALF. The participants did not do shift work, did not consume alcohol during the experiment, and had not crossed time zones in the preceding weeks.

Gender	**Age**	**Age at onset**	**AEDs** (type & mg per day)	**Time since seizure** (months)	**Evidence for a diagnosis of epilepsy**			**MRI**
					EEG	Other Features	Treatment Response	
M	70	66	Le 2000	31	Non-specific bilateral temporal lobe slowing	Oroalimentary automatisms, gustatory hallucinations	Complete	Normal
M	62	54	La 200	93	L temporal epileptiform	Oroalimentary automatisms	Complete	Normal
M	68	65	C 400	27	Non-specific L temporal slowing	No	Complete	Normal
M	72	71	La 200	9	Non-specific R temporal slowing	Déjà vu	Complete	Bilateral high T2 signal in hippocampus
M	68	62	C 400	60	Bilateral (L more marked) mid-anterior temporal sharp and slow-wave epileptiform	Oroalimentary automatisms; brief unresponsiveness	Complete	Normal
M	76	65	La 100	97	Non-specific bilateral temporal slowing	Olfactory hallucinations; oroalimentary automatisms	Complete	Normal
M	66	56	La 150	110	Normal	Olfactory hallucinations; brief unresponsiveness	Complete	Normal
M	64	61	SV 800	30	Bilateral temporal epileptiform	Olfactory hallucinations; oroalimentary automatisms	Complete	Normal
M	63	59	Le 500	0	Normal	No	Partial	Normal
M	76	73	SV 400	6	Normal	Oroalimentary automatisms; brief unresponsiveness	Complete	Small area of right frontal encephalomalacia
F	60	55	C 300	44	Non-specific bilateral temporal slowing	Brief unresponsiveness	Complete	Normal

Table 2.1. TEA patient information.

NB the time between the sleep experiment and the patient's last seizure/amnesic attack is only approximate. The seizures experienced by TEA patients are not as clear cut as those in other types of epilepsy. Furthermore, the patients suffer from interictal memory problems. Therefore, reliable accounts were not always available, and this measure should be interpreted with caution. AEDs = Anti-Epileptic Drugs that the patients were taking when they took part in the sleep experiment, Le = Levetiracetam, C = Carbamazepine, La = Lamotrigine, SV = Sodium Valproate.

	TEA Patients	Controls
N	11	12
Gender	1 female	5 females
Duration of epilepsy (months)	69.55(±10.45)	n/a
Time between neuropsychological tests and experiment (months)	-7.36(±3.32)	3.17(±1.09)
Age	67.73(±1.63)	63.50(±1.44)
Years of full-time education	13.45(±2.84)	13.04(±3.44)
IQ tests		
National Adult Reading Test (NART)[a] errors (50 words in test)	12.09(±2.07)	11.17(±2.06)
Predicted WAIS[b] verbal IQ from NART errors	117.91(±1.89)	118.67(±1.87)
WASI[c] vocabulary raw score (max 80)	68.27(±6.08)	70.83(±1.85)
WASI similarities raw score (max 48)	37.73(±1.04)	39.67(±1.06)
WASI verbal IQ	116.27(±2.22)	120.83(±3.05)
WASI block design raw score (max 71)	45.09(±9.86)	45.92(±3.55)
WASI matrix reasoning raw score (max 42)	26.00(±1.03)	25.17(±1.15)
WASI performance IQ	120.18(±2.73)	117.00(±3.30)
WASI full scale-4subtests IQ	120.36(±1.97)	121.42(±3.01)
Anterograde memory		
WMS-III[d] Logical memory story: Immediate recall (max 25)	14.73(±0.82)	17.50(±1.31)
WMS-III Logical memory story: Delayed recall (30mins) (max 25)	12.18(±1.30)	14.75(±1.41)
WMS-III Logical memory story: Delayed recognition (30mins) (max 15)	13.18(±0.38)	13.00(±0.41)
Rey-Osterrieth Complex figure[e]: Copy (max 36)	33.50(±0.93)	32.38(±0.51)
Rey-Osterrieth Complex figure: Delayed recall (30mins) (max 36)	16.86(±1.62)	18.25(±1.08)
Recognition Memory Test (RMT)[f]: Words (max 50)	46.36(±0.81)	47.50(±0.87)
Recognition Memory Test (RMT): Faces (max 50)	41.72(±1.40)	44.83(±0.81)
Semantic memory		
Graded Naming Test (GNT)[g] (max 30)	24.27(±1.18)	25.08(±0.63)
Executive function		
DKEFS[h] verbal fluency letters (No. of words in 1min)	46.73(±2.76)	48.75(±4.74)
DKEFS verbal fluency categories (No. of words in 1min)	39.45(±3.00)	46.33(±2.76)
DKEFS verbal fluency switching (No. of words in 1min)	13.45(±0.73)	15.75(±0.92)
DKEFS trails 1 (visual scanning) (seconds to complete)	28.71(±6.13)	28.50(±2.59)
DKEFS trails 2 (number sequencing) (seconds to complete)	40.85(±5.04)	37.92(±4.14)
DKEFS trails 3 (letter sequencing) (seconds to complete)	39.36(±4.27)	38.50(±4.02)
DKEFS trails 4 (switching) (seconds to complete)	87.57(±9.99)	84.38(±12.99)
DKEFS trails 5 (motor speed) (seconds to complete)	25.93(±3.23)	24.42(±1.95)
WMS-III Digit span forwards (max 16)	12.36(±0.79)	11.00(±0.65)
WMS-III Digit span backwards (max 14)	9.27(±1.05)	7.67(±0.76)
Anxiety and Depression scores		
Hospital Anxiety and Depression Scale (HADS)[i] anxiety (max 21)	6.36(±1.19)	5.33(±0.71)
Hospital Anxiety and Depression Scale (HADS) depression (max 21)	4.36(±0.87)	2.58(±0.80)

Table 2.2. Participant information. Means with SEMs in brackets. Patients and controls did not significantly differ in terms of age, years of full-time education or test scores (ps>0.05).

[a]NART (Nelson & Willison, 1991; Nelson, 1982); [b]WAIS = Wechsler Abbreviated Intelligence Scale (Wechsler, 1955); [c]WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); [d]WMS-III = Wechsler Memory Scale-III (Wechsler, 1997); [e]Rey-Osterrieth complex figure (Rey, 1941); [f]RMT (Warrington, 1984); [g]GNT (McKenna & Warrington, 1980); [h]DKEFS = Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001); [i]HADS (Zigmond & Snaith, 1983).

The 'time between neuropsychological tests and experiment' was calculated as the difference in months between the first day of the sleep experiment and the date of the neuropsychological test session. For individuals in whom the neuropsychological tests were split across more than one session, the average time difference was calculated. A negative value indicates that the neuropsychological tests preceded the sleep experiment. It should be noted that, owing to practical factors (notably, that many of the patients' neuropsychological tests were conducted by clinicians or their assistants prior to their recruitment to the study), the neuropsychological tests were, on average, administered earlier (relative to the sleep experiment) in the patients than the controls.

The study received ethical approval from the Scotland A Research Ethics Committee and written informed consent was obtained from all participants.

2.2.2.2. Tasks

2.2.2.2.1. Word-pairs

The procedure for the word-pair task was the same as that used in the pilot study. See Figure 2.1 for an illustration of the procedure. The A-B pair training began at approximately eight o'clock (in the morning in the wake condition, and in the evening in the sleep condition) and A-C pair training began twelve hours later. All training and test sessions took place in a sleep laboratory. The participants slept in the sleep laboratory during the sleep condition. Every participant had an adaptation night of sleep in the laboratory prior to their sleep condition.

For the main analysis, I performed a mixed-effects ANOVA with A-B pair performance as the dependent variable, sleep condition (two levels: sleep and wake) and retrieval time point (three levels: final training test, 30-mins test and 12-hrs test) as the within-subjects factors and group as the between-subjects factor.

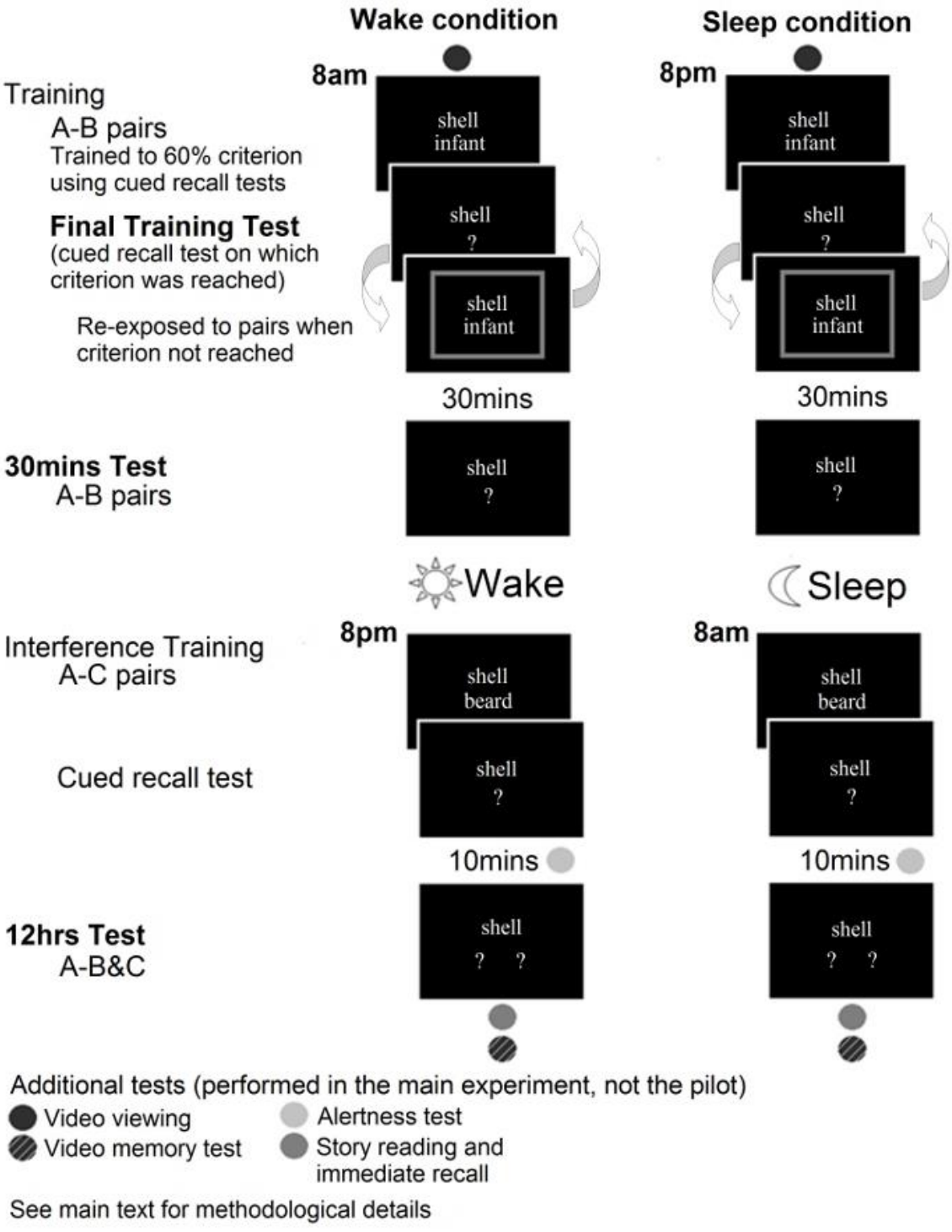


Figure 2.1**.** An illustration of the word-pair associates paradigm. Each participant took part in both the sleep and wake conditions, with 24 hours between them. Two word-pair sets were used in the experiment (examples from only one of the word-pair sets are shown in the figure). The order of the conditions and the distribution of stimuli across conditions were counterbalanced across participants. Additional tests (represented by circles and detailed later in the methods) appear on the schematic to illustrate the order of events. These additional tests were performed in the full experiment only, and not in the pilot experiment.

2.2.2.2.2. Subsidiary tasks

2.2.2.2.2.1. Video

A video-based memory test was performed during the same experimental sessions. This task was intended to provide a more naturalistic memory test, involving moving images of people, sounds and dialogue. The procedure involved showing the participants a short film (just prior to A-B pair training). They were instructed to pay close attention to the film and were informed that their memory would be tested later. Approximately twelve hours later (shortly after the 12-hrs word-pair test), after a night of sleep or a day of wakefulness, the participants were reminded that they had been shown a short film twelve hours earlier, and were asked to recall the chain of events that happened in the film, not missing anything out if possible.

The two films that were used for this experiment were dramatised short stories and they were counterbalanced across the sleep and wake conditions. They were of similar length (approximately three minutes each) and were both made by the same local film company. Prior to the experiment, I identified the plot points in each film. The participants were scored according to the percentage of the plot points they successfully recalled twelve hours after viewing the film. Given that TEA patients with ALF have been shown to forget real-life events at an accelerated rate (Muhlert et al., 2010), I predicted that the patients in this experiment would perform more poorly than the controls on this task. However, since it involved neither a baseline memory assessment (i.e. there was no test prior to the night of sleep/day of wakefulness) nor interference learning, I was not confident that a benefit of sleep for memory performance would be detected in this task. The data were arcsine transformed for the purpose of statistical tests, but the means and SEMs are reported in untransformed form. The data were analysed using a mixed-effects ANOVA with recall performance as the dependent variable, sleep condition (sleep and wake) as the within-subjects factor and group as the between-subjects factor.

The data from one of the patients had to be excluded because he was not wearing his hearing aid while viewing one of the films, and this may have contributed to his poor recall results. Two of the control subjects did not participate in the video test.

2.2.2.2.2.2. Alertness

The alertness task was designed to test the participants' reaction times in the morning and evening and thereby provide a circadian control for the word-pair experiment. The task was performed during the ten-minute interval between A-C pair training and the 12-hrs word-pair tests. The experiment was implemented in Presentation (Neurobehavioral Systems, Albany, NY). Two white circles (3.1cm in diameter) were presented side by side in the centre of the screen (0.9cm apart) against a black background for the duration of the experiment. Each circle was associated with a particular button on the keyboard ('x' for the left circle and ',' for the right circle, which were operated with the left and right index fingers, respectively). Whenever a white asterisk (1.6cm in diameter) appeared in one of the two circles, the participant had to respond as quickly as possible with the corresponding button, at which point the asterisk would disappear. The inter-stimulus-interval varied unpredictably between 0.5 seconds, 1 second, 2 seconds and 4 seconds. Each participant performed the task twice: once in the evening just before the wake condition's 12-hrs word-pair test, and once in the morning, just before the sleep condition's 12-hrs word-pair test. The first ten trials were considered practice trials and were excluded from the analysis. The reaction times from the following 38 trials were analysed.

The data were analysed using a mixed-effects ANOVA with reaction time as the dependent variable, time of day (morning and evening) as the within-subjects factor and group as the between-subjects factor.

2.2.2.2.2.3. Immediate story recall

The immediate story recall task was designed to test the participants' memory processes in the morning and evening and thereby provide a circadian control for the word-pair experiment. Following each 12-hrs word-pair test, the participants were read a story. The stories were numbers three and four from the BMIPB tests (Birt Memory and Information Processing Battery, Coughlan, Oddy, & Crawford, 2007), and they were counterbalanced across conditions. The participants were instructed to pay close attention to the story because they would be asked to say it back to me shortly after hearing it. Once I had finished the story, the participants were asked to count back from 100 in 3s to prevent rehearsal of the story in working memory. After approximately 40 seconds of this distraction, the participants were asked to recall the story they had just heard. Performance was scored according to the BMIPB criteria.

The data were analysed using a mixed-effects ANOVA with story recall score as the dependent variable, time of day (morning and evening) as the within-subjects factor and group as the between-subjects factor.

The data from two of the patients had to be excluded. One patient thought he had heard one of the stories before, and another had a severe emotional reaction to one of the stories because it reminded him of the circumstances surrounding his friend's death.

2.3. Results

2.3.1. Pilot experiment

The pilot data clearly demonstrate a benefit of sleep vs. wake for retrieval of paired associates. Figure 2.2 plots the final training test, 30-mins and 12-hrs A-B pair scores for the sleep and wake conditions. An ANOVA revealed not only a significant main effect of retrieval time point ($F_{(2,14)}$=41.28, p<0.001, with poorer performance on the 12-hrs test (estimated marginal mean (EMM) ± standard error of the mean (SEM): 16.50 ±1.31) than the 30-mins test (EMM ±SEM: 22.69 ±1.17) (p=0.001) and the final training test (23.19 ±0.74) (p<0.001)), but also a significant interaction between retrieval time point and sleep condition ($F_{(1.21,8.44)}$=13.04, p=0.005). There was no significant difference between the sleep and wake conditions on the final training test (24.00 ±1.04 and 22.38 ±0.98, respectively, p= 0.28) or the 30-mins test (23.30 ±1.28 and 22.13 ±1.53, respectively, p=0.50), but the A-B pair score at twelve hours was significantly greater in the sleep condition (20.38 ±1.61) than the wake condition (12.63 ±1.74) (p= 0.008).

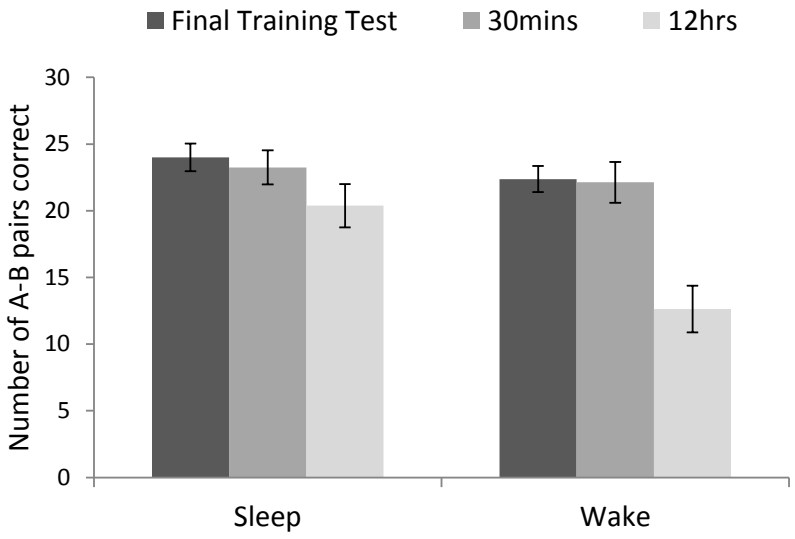


Figure 2.2. A-B pair performance on the final test of the training session, the 30-mins test and the 12-hrs test in the sleep and wake conditions of the healthy older adults pilot. Error bars represent standard errors of the mean. The data clearly demonstrate a benefit of sleep vs. wake for retrieval of paired associates.

A significantly greater percentage of pairs was lost between the 30-mins and 12-hrs tests in the wake condition (42.68 ±7.38%) than the sleep condition (12.82 ±3.67%, $t_{(7)}$=-4.00, p=0.005).

The conditions differed in terms of time of day of learning and testing as well as whether or not there was sleep in the interval. Notably, testing took place in the morning in the sleep condition but in the evening in the wake condition. However, performance at the learning phase (in the morning for the wake condition and in the evening for the sleep condition) was not significantly different between the conditions, making it unlikely that circadian factors could account for the superior performance in the sleep condition. There was no significant difference between sleep and wake conditions in score on the first training test (15.50 ±3.03 and 14.63 ±2.90, respectively, p=0.57) or number of trials to criterion (1.88 ±0.30 and 1.88 ±0.30, p=1.00). Furthermore, there was no significant difference between sleep and wake conditions in immediate interference pair score

(14.75 ±2.55 and 15.38 ±2.24, respectively, p=0.76) or interference pair score on the second test (13.75 ±2.90 and 15.00 ±2.26, respectively, p=0.51).

2.3.2. Main experiment

2.3.2.1. Word-pairs

Table 2.3 contains the performance scores on the word-pair task. Figure 2.3 displays the A-B performance scores on the final test of the training phase, and on the 30-mins and 12-hrs tests in the sleep and wake conditions for the patient and control groups.

	Controls		Patients	
	Sleep	Wake	Sleep	Wake
1st training test score (/30) (A-B)	10.17(±2.39)	10.75(±1.75)	8.45(±1.83)	7.91(±1.21)
No. trials to criterion (A-B)	2.00(±0.21)	2.50(0.26)	2.82(±0.48)	2.27(±0.14)
Final training test score (/30) (A-B)	**21.92(±0.68)**	**23.17(±1.01)**	**22.27(±0.75)**	**21.72(±0.91)**
30-mins test score (/30) (A-B)	**20.50(±0.89)**	**22.17(±0.95)**	**20.55(±0.91)**	**19.36(±1.06)**
Immediate interference pair score (/30) (A-C)	8.50(±2.04)	9.67(±1.94)	10.00(±1.68)	8.36(±1.01)
12-hrs test score (/30) (A-B)	**18.17(±0.98)**	**16.83(±1.36)**	**15.64(±1.15)**	**11.45(±0.98)**
Interference pair score (/30) (A-C)	8.17(±1.85)	9.42(±1.94)	7.91(±1.68)	8.09(±1.25)

Table 2.3**.** Performance on the word-pair associates task. Means with SEMs in brackets. The three A-B word-pair tests that were used to look at memory retention (and which are plotted in Figure 2.3) are in boldface.

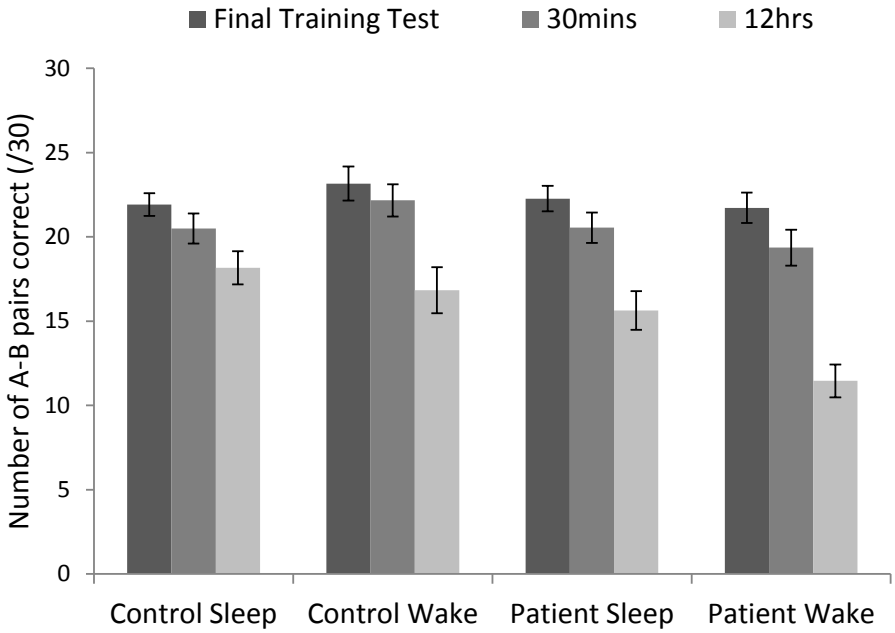


Figure 2.3. A-B pair performance across the three memory test sessions in the sleep and wake conditions of the word-pair associates task, in TEA patients with ALF and control participants. Error bars represent standard errors of the mean. The patients demonstrated ALF over twelve hours, but the benefit of sleep for memory retention was not reduced in the patients compared to the controls.

As expected, there was a significant main effect of retrieval time point ($F_{(1.34,28.15)} = 99.24$, $p<0.001$). Memory performance declined significantly between each test ($p<0.001$ in all cases, EMMs ±SEMs: 22.27 ±0.47, 20.64 ±0.53, 15.52 ±0.70, for the final training test, 30-mins test and 12-hrs test, respectively).

There was a significant interaction between retrieval time point and group ($F_{(1.34,28.15)} = 6.33$, $p=0.012$). The patients performed significantly worse than the controls on the 12-hrs test (EMMs ±SEMs: 13.55 ±1.01 and 17.50 ±0.97, respectively, $p= 0.01$), but not on the final training test (EMMs ±SEMs: 22.00 ±0.68 and 22.54 ±0.65, $p=0.57$) or the 30-mins test (EMMs ±SEMs: 20.00 ±0.76 and 21.33 ±0.73, $p=0.21$). The overall main effect of group was not quite significant ($p = 0.062$). This is in

keeping with the typical profile of ALF: normal learning and initial retention but rapid forgetting over the longer-term.

There was a clear benefit of sleep for memory in this experiment; there was a significant interaction between sleep condition and retrieval time point ($F_{(2,42)}$ = 20.15, p<0.001). The participants performed significantly better in the sleep condition than the wake condition on the 12-hrs test (EMMs ±SEMs: 16.90 ±0.75 and 14.14 ±0.85, p=0.002), but not on the final training test (EMMs ±SEMs: 22.10 ±0.51 and 22.45 ±0.68, p=0.74) or the 30-mins test (EMMs ±SEMs: 20.52 ±0.64 and 20.77 ±0.71, p=0.85).

However, there was no significant interaction between sleep condition, retrieval time point and group (p=0.55), meaning that the patients did not show a reduced benefit of sleep for memory compared to controls. Both groups showed a benefit of sleep for memory: there was a significant interaction between sleep condition and retrieval time point for both the patients ($F_{(1,10)}$ = 7.73, p= 0.019) and the controls ($F_{(1,11)}$ = 21.21, p= 0.001) when repeated-measures ANOVAs were performed separately for the two groups (with sleep condition (sleep and wake) and retrieval time point (30-mins and 12-hrs) as factors). In fact, the patients only performed significantly more poorly than the controls on the 12-hrs test in the wake condition ($t_{(21)}$ = 3.16, p=0.005) and not in the sleep condition ($t_{(21)}$ = 1.69, p=0.11), which is the reverse of what would be expected if ALF were caused by a disruption of sleep-dependent memory consolidation.

A mixed-effects ANOVA, with the percentage of A-B pairs lost between the 30-mins and 12-hrs tests as the dependent variable, showed that more was forgotten in the wake condition (EMM ±SEM:

32.81 ±2.84%) than the sleep condition (EMM ±SEM: 17.10 ±3.52%) ($F_{(1,21)}$ = 28.58, p<0.001), and more was forgotten by the patients (EMM ±SEM: 32.03 ±4.10%) than the controls (EMM ±SEM: 17.88 ±3.93%) ($F_{(1,21)}$ = 6.21, p =0.021). There was no interaction between sleep condition and group (p=0.57), confirming that there was no reduction in the benefit of sleep for memory in the patients. In fact, patients only forgot significantly more than the controls in the wake condition (40.75 ±4.11% vs. 24.88 ±3.93%, $t_{(21)}$ = -2.79, p = 0.011) and not in the sleep condition (23.32 ±5.08% vs. 10.88 ±4.86%, $t_{(21)}$ = -1.77, p = 0.091).

There were more women in the control group than the patient group. However, this cannot account for my results. It is not the case that the difference between the patients and the controls on the 12-hrs test was due to the women in the control group performing particularly well (female control performance on the 12-hrs test in the wake condition: 16.60 ±1.72, males: 17.00 ±2.10; female control performance on the 12-hrs test across both conditions: 17.40 ±1.51, males: 17.57 ±1.52). It is also not the case that poor sleep-dependent memory consolidation in the female controls relative to the males obscured a true deficiency in sleep-dependent memory consolidation in the patients. The benefit of sleep for memory consolidation (measured in terms of the difference in percentage forgetting (between the 30-mins and 12-hrs tests) between the wake and sleep conditions) in the male control participants alone (15.17 ±5.27%), while slightly greater than the control group mean (14.00 ±3.40%), was still numerically smaller than that in the patient group (16.93 ±4.99%) i.e. the patients showed a numerically greater benefit of sleep for memory than the controls, and this was still true when only the results from the male controls were considered.

2.3.2.2. Control tests

2.3.2.2.1. Learning performance

The patients and controls did not differ in terms of learning performance. There was no significant difference between the patients and controls in terms of score on the first A-B pair training test in the sleep (p=0.58) or wake (p=0.20) conditions, or when the scores were collapsed across conditions (p=0.35). The same was true for the trials to criterion (p=0.17, p=0.55 and p=0.48).

2.3.2.2.2. Circadian

2.3.2.2.2.1. Learning performance

In this experiment, the two conditions did not differ only in terms of whether the retention interval contained sleep, but also in the time of day of training and testing. This provides a potential circadian confound, which could account for the apparent benefit of sleep for memory in this experiment i.e. if the participants generally performed better in the morning, this could explain their better performance on the 12-hrs test in the 'sleep' condition relative to the 'wake' condition. However, if this were true, then the participants would have performed better in the A-B training session in the wake condition than in the sleep condition, and this was not the case. As in the pilot study, participants did not perform significantly better in terms of trials to criterion (p=0.62) or score on the first training test (p=0.97) in the wake condition than the sleep condition.

Additional evidence that an effect of time of day on general performance levels cannot account for the results comes from the alertness test and the immediate story recall test, which were administered during the 12-hrs test sessions.

2.3.2.2.2.2. Alertness

The participants were not faster to respond in the morning than the evening (p= 0.64), suggesting that they were not more alert during the test session in the sleep condition than the wake condition. The patients' reaction times were not significantly different from those of the controls (p= 0.19), and there was no interaction effect between time of day and group (p= 0.47), suggesting that time of day was not differentially affecting performance in the two groups. See Figure 2.4 for the reaction time data.

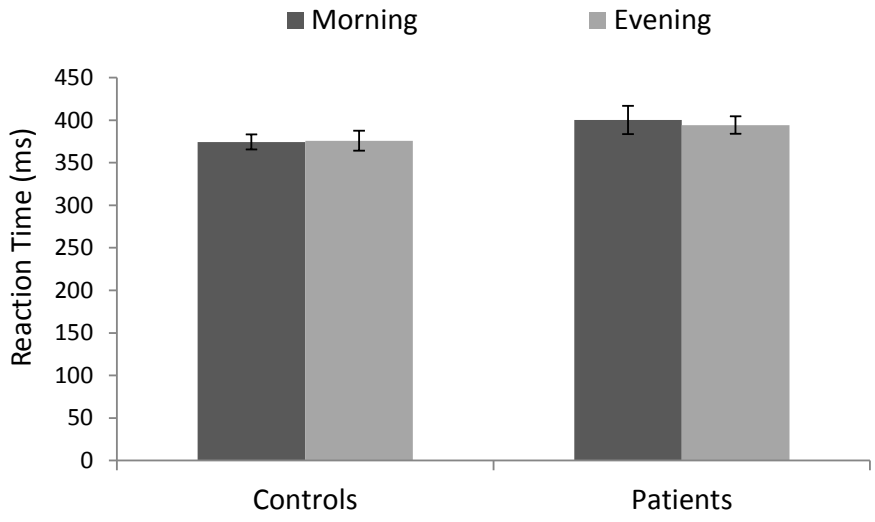


Figure 2.4. Reaction time data from the alertness test. Error bars represent standard errors of the mean. Time of day had no effect on reaction time.

2.3.2.2.2.3. Immediate story recall

Similarly, there was no effect of time of day on performance in the immediate story recall task (p= 0.99), no significant difference between the groups (p= 0.14) and no interaction effect (p= 0.77). See Figure 2.5 for the immediate story recall data. This suggests that the benefit of sleep for memory in the experiment cannot be accounted for by the participants' memory retrieval systems simply

functioning better in the morning than the evening. The lack of an interaction effect shows that a greater general cognitive decline in the patient group across the course of a day is not the explanation for the patients' poor 12-hrs word-pair test performance in the wake condition and normal performance in the sleep condition.

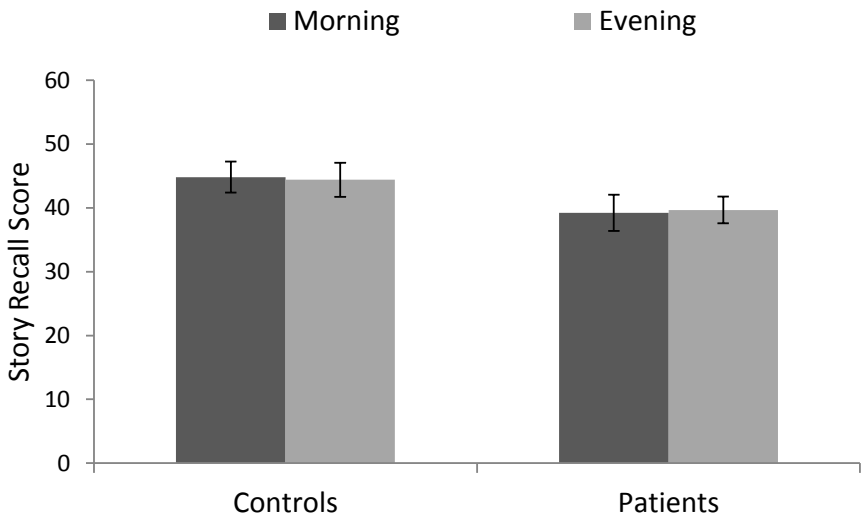


Figure 2.5. Retrieval performance on the immediate story recall task. Error bars represent standard errors of the mean. Time of day had no effect on performance.

2.3.2.2.3. Interference

Another possible confound for the benefit of sleep for memory would be differential A-C pair performance in the sleep and wake conditions, which would mean different levels of interference. However, A-C pair performance was not significantly different in the two conditions for the controls ($p=0.37$) or patients ($p=0.25$) or when collapsed across the two groups ($p=0.85$).

If the patients had performed better than the controls on the A-C pairs, this would have provided a confound for the group differences in A-B pair performance on the 12-hrs test and forgetting rates

between the 30-mins and 12-hrs tests. However, A-C pair performance was not significantly different in the two groups for the wake condition (p=0.56) or the sleep condition (p=0.58) or when collapsed across the two conditions (p=0.97). See Figure 2.6 for performance data on the immediate A-C pair test.

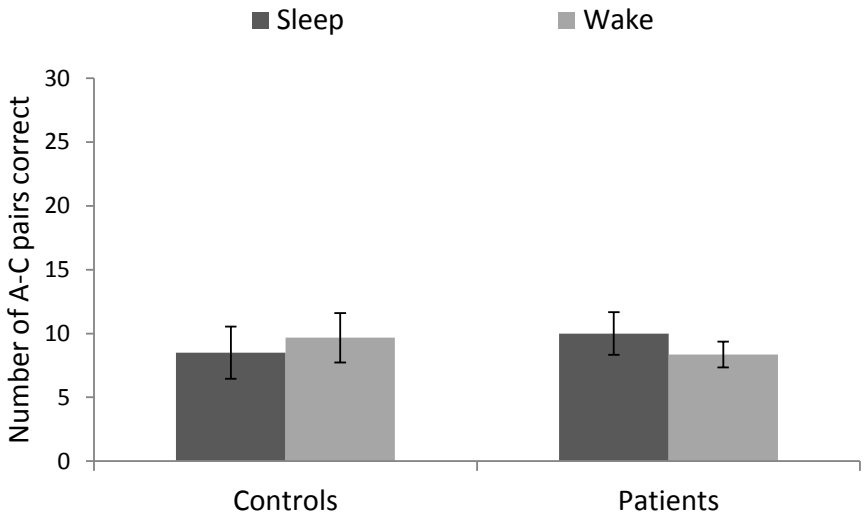


Figure 2.6. Performance on the immediate A-C pair test. Error bars represent standard errors of the mean. Performance was not different in the two conditions and was not different in the two groups.

2.3.2.3. Video task

The patients were significantly worse than controls at recalling the content of a film twelve hours after viewing it ($F_{(1,18)} = 9.11$, p= 0.007). However, the task was apparently not preferentially consolidated by sleep - there was no effect of sleep condition in the ANOVA (p=0.85) nor was there a significant difference between conditions for the healthy controls alone (p=0.80) – and there was no interaction between sleep condition and group (p=0.91), suggesting that sleep did not affect the two groups differently. See Figure 2.7 for the video memory test data.

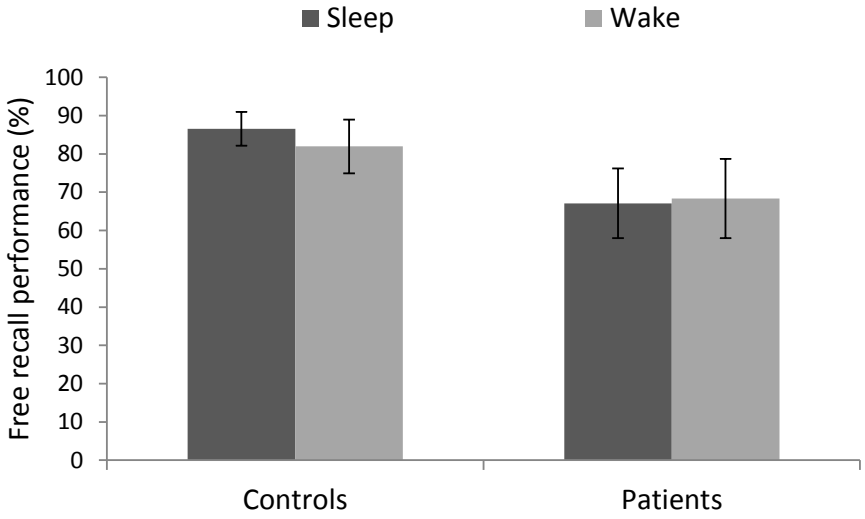


Figure 2.7. Free recall performance on the video memory test, which was administered approximately twelve hours after the video was viewed. Error bars represent standard errors of the mean. The patients performed more poorly than the controls.

2.4. Discussion

This experiment was designed to test the frequently proposed hypothesis that ALF is caused by a disruption of sleep-dependent memory consolidation (e.g. Butler et al., 2009; Holmes & Lenck-Santini, 2006; Jansari et al., 2010; Muhlert et al., 2011; Tramoni et al., 2011; Urbain et al., 2011; Zeman et al., 2013). I compared memory retention over a night of sleep and a day of wakefulness in TEA patients with ALF and control participants.

I first used a pilot study in a separate group of healthy participants to establish that the word-pair associates paradigm was sensitive to the benefit of sleep for memory retention in healthy older adults. This meant that it was a suitable instrument with which to test for a reduced benefit of sleep for memory in the patient group.

In sharp contrast to my expectations, I found that sleep boosted memory retention in the TEA ALF patients and that this sleep-benefit was equivalent in the patients and in the controls. In fact, if sleep disruption were the cause of ALF, then one might expect patients to show a memory impairment only when the retention interval contains sleep. This was not the case. Indeed, the opposite was found: the patients showed a significant memory impairment relative to controls in the wake condition only, and not in the sleep condition. This suggests that sleep is not causing or exacerbating the memory problem in these patients. If anything, it may protect them from it in some cases.

These results are in line with a pilot study in temporal lobe epilepsy (Deak et al., 2011) in which patients forgot significantly more than controls over a day of wakefulness but not over a night of sleep. This pilot study did not fully control for potential group differences in learning and circadian

fluctuations in performance, and the task was not sensitive to the benefit of sleep for memory consolidation in healthy control subjects. Therefore, my findings, in a different and larger group of patients, add weight to their conclusion that ALF is not caused by a deficit in sleep-dependent memory consolidation. My results are also compatible with those of Fitzgerald et al. (2013), who found no relationship between night-time sleep architecture (recorded with EEG) and ALF in epilepsy patients.

I also report the novel finding that ALF in TEA can be seen across an interval as short as twelve hours. Before this study, twenty-four hours was the shortest interval over which ALF in TEA had been reported (Muhlert et al., 2010), which contributed to the conjecture that memory loss was mediated by sleep (Muhlert et al., 2011). I found poorer performance in the patients than the controls twelve hours after encoding for both word-pair associates with interference learning and for more naturalistic video-based stimuli. In contrast to the word-pair associates task, the video test was not sensitive to the benefit of sleep for memory retention. One reason for this may be that the task did not involve interference learning.

It is worth noting that both the pilot study and the main experiment demonstrate that sleep is still beneficial for memory in older people. The vast majority of sleep-dependent memory consolidation experiments have used only young healthy participants, and it has been suggested that sleep-dependent memory consolidation may decline with age (e.g. Backhaus et al., 2007; Peters, Ray, Smith, & Smith, 2008; Spencer, Gouw, & Ivry, 2007; Wilson, Baran, Pace-Schott, Ivry, & Spencer, 2012). However, my finding that sleep still benefits memory in some tasks in older adults is in line with the results of some other recent studies (Aly & Moscovitch, 2010; Tucker, McKinley, & Stickgold, 2011; Wilson et al., 2012).

The TEA patients in this study forgot at an accelerated rate after apparently normal learning and initial retention, but did not show a reduced benefit of sleep for memory. If not disrupted sleep-dependent memory consolidation, then what is the cause of ALF? One possible explanation is that the patients actually suffer from a subtle encoding deficit that goes undetected during learning and early retention, but ultimately leads to accelerated forgetting. This may seem unlikely, as researchers have gone to great efforts to match patients and controls for learning and initial retention and still demonstrate ALF over the longer-term (e.g. Hoefeijzers et al., 2013). However, it remains possible that these behavioural measures were not sufficiently sensitive, and it would be interesting to study encoding-related brain activity in ALF patients.

Alternatively, ALF may be caused by a disruption of consolidation processes that are not sleep-specific. The processes that are disrupted in ALF patients might primarily occur during the waking state in healthy people. It may be that ALF patients struggle to cope with the competing demands of consolidating recently-acquired information and processing new information, making them particularly susceptible to the interference from ongoing cognitive processes that occurs during waking hours. Temporal lobe amnesics have been shown to be particularly vulnerable to interference immediately after encoding (Dewar et al., 2009). Unfortunately, the design of the current experiment cannot be used to investigate susceptibility to interference because, due to power concerns, all of the A-B pairs were interfered with. Another possibility is that patients with ALF are unable to consolidate normally during rest while awake, as healthy people do (e.g. Mednick, Makovski, Cai, & Jiang, 2009; Tambini et al., 2010).

A consolidation deficit in ALF patients could be caused by structural or functional brain abnormalities. Some structural brain imaging studies have been done in patients with ALF, and while abnormalities have been found, notably in the MTL (e.g. Butler et al., 2009), a structural correlate of ALF has not been identified (e.g. Butler et al., 2013). However, it is conceivable that the methods used were not sufficiently sensitive. Furthermore, studies to date have focused on regions of grey matter, and it is possible that ALF patients suffer from abnormalities in structural connectivity between brain areas. Epilepsy is characterised by the aberrant propagation and synchronisation of electrical activity through neural connections. Abnormal structural connectivity could be a contributing factor to, or a consequence of, the epilepsy that is associated with ALF. Neural network dynamics are thought to play a critical role in systems consolidation (e.g. Battaglia et al., 2011; Tambini et al., 2010), and so abnormal structural connectivity could lead to a consolidation deficit. Even if structural abnormalities cannot be detected, it may be the case that the functional connectivity on which consolidation depends is abnormal in ALF patients. Precisely-timed communication between the hippocampus and regions of the neocortex is thought to underlie declarative memory consolidation (e.g. Battaglia et al., 2011; Ji & Wilson, 2007), and this may be disrupted in ALF patients. One possible source of disruption would be epileptiform activity. The patients were seizure-free in the current study, but interictal discharges could have occurred during the experiment, and some studies have found a relationship between ALF and electrical discharges in the retention interval in patients with epilepsy (e.g. Fitzgerald et al., 2013).

Other possible explanations for ALF include the effects of anti-epileptic medications and psychosocial factors. However, I consider these to be unlikely explanations. Complaints of ALF in TEA typically pre-date the onset of treatment (Butler et al., 2007; Butler & Zeman, 2008b), the patients are on low doses of medication, and they often report some degree of memory improvement once they begin treatment (Butler et al., 2007; Gallassi, 2006; Gallassi et al., 1988; Zeman et al., 1998).

Mood disorders do not clearly impair long-term memory retention. Lewis and Kopelman (1998) found that depressed patients did not forget more than controls, once initial learning was equated. Furthermore, the patients in the current study did not differ significantly from controls on the anxiety or depression measures of the HAD scale.

Given that ALF can be seen on the day of encoding, it is natural to ask what the time course of ALF looks like and how quickly it emerges. McGibbon and Jansari (2013) found that ALF became apparent in a patient with temporal lobe epilepsy within 55 minutes. A very recent experiment in a group of TEA ALF patients has revealed that memory deficits can appear within three to eight hours of wakefulness after encoding (Hoefeijzers, Dewar, Della Sala, Butler, & Zeman, 2014). This study, which also found no further forgetting over the first post-encoding night of sleep, confirms that ALF in TEA is not caused by a disruption of sleep-dependent memory consolidation.

In summary, accelerated long-term forgetting (ALF) is not caused by a deficit in sleep-dependent memory consolidation, and ALF can be detected within a matter of hours in patients with transient epileptic amnesia. Further work will be needed to elucidate the neural basis of this memory impairment. It may be that memory consolidation processes that occur during wakefulness are disrupted in patients with ALF, but it remains possible that ALF is a result of subtly abnormal processing at the stage of encoding.

3. The role of slow wave sleep in declarative memory retention

3.1. Introduction

3.1.1. The role of sleep in declarative memory retention

Sleep is thought to have an important role in declarative memory. A number of studies have demonstrated that sleep, versus wakefulness, is beneficial for declarative memory retention (e.g. Gais et al., 2006; Peigneux et al., 2004), and the results of the previous chapter contribute to this literature. The finding that less declarative information is forgotten over a period of sleep compared to a period of wakefulness is by no means new (e.g. Jenkins & Dallenbach, 1924), and has been replicated in young healthy volunteers many times over the past century.

Given that retroactive interference is thought to be a major cause of normal forgetting (as discussed in section 1.1.3 of this thesis), a key role of sleep in memory retention is likely to be temporary shielding from interfering inputs. There are three main mechanisms by which retroactive interference might cause forgetting. One of these is interference with access at the point of retrieval and another is disruption of the existing memory trace. The minimal interference afforded by sleep would reduce both these types of forgetting.

According to the temporal distinctiveness model (Brown et al., 2007), memories interfere with one another less at the point of retrieval if they were formed further apart in time. According to consolidation theorists (e.g. Wixted, 2004, 2010), the vulnerability of the memory trace to disruption by interference is thought to decrease with time as the memory consolidates. Therefore, according to both of these models, a period of shielding would be expected to have a greater benefit for memory retention if it happened sooner, rather than later, after encoding and indeed a number of

studies have shown this to be the case for a period of sleep (e.g. Gais et al., 2006; Talamini et al., 2008).

The third mechanism by which retroactive interference might enhance forgetting is by disruption of memory consolidation processes. Some scientists suggest that consolidation processes are at least partially incompatible with the encoding of new memories, and argue that sleep provides a period of reduced interference, during which consolidation processes can proceed unimpeded (e.g. Mednick et al., 2011; Wixted, 2004).

Indeed, there is evidence that memory consolidation processes occur preferentially during sleep. Ellenbogen and colleagues (Ellenbogen et al., 2009; Ellenbogen, Hulbert, et al., 2006) have demonstrated that memories are much more robust to the effects of specific interference following a night of sleep (twelve hours) than a day of wakefulness (twelve hours). Critically, the researchers showed that a third group of participants who had a night of sleep followed by a day of wakefulness (24 hours in total) between initial learning and specific interference performed similarly well to the sleep group (twelve hours) and significantly better than the wake group (twelve hours). This suggests that processes that stabilise memories occur preferentially during sleep.

Further evidence that memory consolidation occurs preferentially during sleep comes from studies that have shown an absolute improvement in memory performance over a period of sleep (e.g. Gais & Born, 2004), and others that have demonstrated that memories change in nature during sleep, such that the neural representations are reorganised (Takashima et al., 2006) and people gain insight into the rules and structure in ensembles of experiences (e.g. Durrant et al., 2011;

Ellenbogen, Hu, Payne, Titone, & Walker, 2007; Fischer, Drosopoulos, Tsen, & Born, 2006; Lau et al., 2010; Wagner, Gais, Haider, Verleger, & Born, 2004).

Therefore, it seems that sleep has a positive impact on declarative memory. While a major role of sleep in memory may be to reduce interference from external inputs (e.g. Jenkins & Dallenbach, 1924; Mednick et al., 2011; Wixted, 2004), many researchers argue that sleep further plays an active role (e.g. Ellenbogen, Payne, & Stickgold, 2006).

Sleep is not homogenous, but can be subdivided into stages on the basis of polysomnographic features: Rapid eye movement (REM) sleep and the four stages of Non-REM (NREM) sleep. Specific aspects of sleep have been shown to be especially important for declarative memory retention.

3.1.1.1. The role of SWS in declarative memory retention

Slow Wave Sleep (SWS) refers to stages 3 and 4 of NREM sleep, in which slow wave activity (SWA, <4Hz) dominates the EEG. It is thought to be especially important for retention of declarative memory (e.g. Diekelmann et al., 2009). Half-night experiments have been useful for investigating the relative contributions of different sleep stages to memory. They exploit the fact that the earlier half of a night of sleep is dominated by SWS, while the later half is dominated by REM sleep. This paradigm has been used to demonstrate that SWS-rich sleep improves declarative memory retention more than SWS-poor sleep (Barrett & Ekstrand, 1972; Fowler et al., 1973; Plihal & Born, 1997, 1999; Yaroush et al., 1971). Other researchers have presented correlations between the amount of SWS during post-learning sleep and subsequent memory performance/retention (e.g. Alger et al., 2012; Diekelmann et al., 2012; Lau et al., 2010).

Slow waves, specifically, and especially very slow oscillations (which have a mean spectral peak frequency of 0.7-0.8Hz, Achermann & Borbely, 1997) are intimately linked with the benefit of sleep for declarative memory retention. A number of studies have found positive correlations between power in the slow wave frequency range and declarative memory retention (e.g. Holz et al., 2012; Prehn-Kristensen et al., 2011). Heib et al. (2013) found that slow oscillation amplitudes and up-state lengths (i.e. the duration of the depolarization state) relate to memory improvement. Moreover, electrical (Marshall et al., 2006) and auditory (Ngo, Martinetz, Born, & Molle, 2013) stimulation has been used to enhance the endogenous slow oscillation, resulting in improved memory performance for information learnt prior to sleep.

There are two different, but not mutually exclusive, theories regarding the nature of the role of SWS in declarative memory retention.

The first is that recently learnt memories are potentiated, stabilised and integrated with pre-existing memories through a process of reactivation. Reactivation is thought to be the mechanism of systems consolidation. According to McClelland et al.'s (1995) computational model, the reactivation of recently-learnt memories in the hippocampus, interleaved with reactivations of related pre-existing memories, leads to integration of new memories with the long-term neocortical network (which enables the extraction of invariants) and hippocampal independence. In humans, brain areas involved in encoding are reactivated during post-learning SWS (e.g. Peigneux et al., 2004). In animals, memory replay has been observed at the cellular level in the hippocampus (associated with sharp-wave ripple events, Buzsaki, 1998; Kudrimoti et al., 1999) (Kudrimoti et al., 1999; Nadasdy et al., 1999; Pavlides & Winson, 1989; Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994) and,

simultaneously, and in a coordinated fashion, in the neocortex (Ji & Wilson, 2007; Peyrache et al., 2009; Qin et al., 1997). These reactivations have been linked with subsequent memory performance. Peigneux et al. (2004) found that the degree of hippocampal activity during post-learning SWS was correlated with memory change over sleep. Suppression of sharp-wave ripple events using microstimulation in experimental animals leads to subsequent memory impairments (Girardeau et al., 2009), while artificial induction of memory reactivations during SWS (Bendor & Wilson, 2012; Rasch et al., 2007) leads to increased memory retention and stabilisation in humans (e.g. Diekelmann et al., 2011; Rasch et al., 2007; Rudoy et al., 2009). Recently, Yang et al. (2014) provided compelling evidence that sleep can facilitate memory through reactivation-mediated synaptic potentiation. These researchers showed that learning-induced spine formation was promoted by post-learning sleep and prevented if memory replay during NREM sleep was blocked.

Born and colleagues developed an influential model of this reactivation process (Born et al., 2006; Marshall & Born, 2007). According to this model, reactivation is triggered by slow oscillations. There is indeed a close temporal relationship between slow oscillations and sharp-wave ripple events, such that the latter appear to occur during the up-state, and not during the down-state, of the former (Clemens et al., 2007; Isomura et al., 2006; Molle et al., 2006). Furthermore, in a multi-cell recording study in the rat, Ji and Wilson (2007) found that frames of neural activity in the neocortex preceded those in the hippocampus, while replay of memory traces emerged in the hippocampus first, consistent with the hypothesis that the neocortical slow oscillation triggers replay in the hippocampus which, in turn, drives replay in the neocortex.

The second theory is that the major role of SWS is to downscale synaptic weights. According to Tononi and Cirelli's (2003, 2006) synaptic homeostasis hypothesis, slow waves are a result of, and a

solution to, the net synaptic potentiation that occurs during wakefulness. These researchers posit that synaptic potentiation is costly in terms of energy and space, and saturates our capacity for new learning. They propose that SWS improves memory performance indirectly by increasing the signal-to-noise ratio. There is ample evidence that SWA is homeostatically regulated, with pressure building up during wakefulness and dissipating as SWA occurs (e.g. Borbely & Achermann, 1999; Dijk, Beersma, & Daan, 1987; Webb & Agnew, 1971). Furthermore, the level of SWA detectable over different regions of the cortex depends on the level of learning activity and synaptic potentiation that occurred in that region during the preceding period of wakefulness (e.g. Huber et al., 2006; Huber, Ghilardi, Massimini, & Tononi, 2004; Huber et al., 2008). This local increase in SWA correlates with memory performance improvement over sleep (Huber et al., 2004). In support of the notion that SWA downscales synaptic weights, in vivo regular 1Hz stimulation for a period of a number of minutes induces long-term depression of synaptic strength in experimental animals (e.g. Mulkey & Malenka, 1992). Furthermore, Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna and Tononi (2008) found that the decline in the slope of cortical evoked responses that occurs across a period of sleep correlates with the amount of SWA during sleep.

Tononi and Cirelli's model suggests that each synapse is downscaled proportionally to its strength. They argue that, provided there is a threshold under which synapses become silent, ineffective or disappear, weak memories may be lost. Talamini, Nieuwenhuis, Takashima and Jensen (2008) found that forgetting over a period of sleep is greatly increased if a day of wakefulness intervenes between the learning event and the period of sleep. The researchers interpreted this as evidence that weaker memories (in this case, those that have been degraded by daytime interference) are lost during sleep while stronger memories are preserved. However, this might seem incompatible with studies that have shown that weaker memories receive the greatest benefit from sleep. For instance, Droposoulos, Schulze, Fischer and Born (2007) showed that sleep's benefit (over wakefulness) for

memory retention was greater for word-pairs learnt to 60% criterion than for those learnt to 90% criterion. While it might be argued that such studies suffer from ceiling effects, there may in fact be mechanisms that could allow memories that are weak at the point of learning to show the greatest benefit from synaptic downscaling during subsequent sleep. Hardt et al. (2013) discuss mechanisms by which behaviourally relevant memories, which are known to particularly benefit from sleep (e.g. Fischer & Born, 2009), might be protected from the downscaling that occurs during sleep. These scientists claim that important memories are strengthened post-acquisition, making them more likely to survive downscaling during sleep. They also note that the metaplasticity of synapses involved in important memory traces can be regulated, i.e. it is possible to influence the changes that a synapse will undergo in the future. This latter mechanism could potentially be used to shield specific memories from the downscaling process. In this case, weaker memories would presumably benefit more from sleep than stronger memories would, as their signal-to-noise ratio would receive a relatively larger boost from the pruning of other connections.

3.1.2. The role of sleep, especially SWS, in ALF

It is well established that SWS enhances epileptic activity (Bazil, 2000; Bazil & Walczak, 1997; Goncharova et al., 2009; Kotagal, 2001; Mayanagi, 1977; Nazer & Dickson, 2009; Romcy-Pereira et al., 2009; Rossi et al., 1984; Sammaritano et al., 1991). In TEA patients, half of whom complain of ALF (Butler et al., 2007), the attacks of transient amnesia characteristic of TEA often occur upon waking from sleep, suggesting that seizure activity might occur primarily during sleep (Butler et al., 2007). Furthermore, EEGs are much more likely to reveal epileptic abnormalities if they are performed while the TEA patient is asleep or sleep deprived (Butler et al., 2007; Zeman et al., 1998).

ALF was hypothesised to be caused by a disruption of sleep-dependent memory consolidation (e.g. Butler et al., 2009; Holmes & Lenck-Santini, 2006; Jansari et al., 2010; Muhlert et al., 2011; Sud et al., 2014; Tramoni et al., 2011; Urbain et al., 2011; Zeman et al., 2013). However, the behavioural data from my word-pair associates task, presented in the previous chapter, suggest that sleep-dependent memory consolidation is normal in this patient group, as the benefit of sleep (vs wakefulness) for memory retention was no smaller in magnitude in patients than controls.

3.1.3. The relationship between SWS and memory in this study

There has been very little investigation of the role of SWS in the benefit of sleep for declarative memory retention in older adults, despite the well-established decline in SWS (e.g. Van Cauter, Leproult, & Plat, 2000) and memory performance (e.g. Prull, Gabrieli, & Bunge, 2000) in this population. However, a few studies have found evidence that the benefit of sleep for declarative memory retention may be reduced in older people (e.g. Backhaus et al., 2007; Cherdieu, Reynaud, Uhlrich, Versace, & Mazza, 2014; Mander et al., 2013) (However, c.f. Aly & Moscovitch, 2010; Wilson et al., 2012).

If SWS facilitates memory throughout healthy life, then SWS would be expected to correlate with memory performance in older adults as well as younger adults and, to the extent that SWS is reduced in old age, the benefit of sleep for memory retention would be concomitantly reduced. Confirmatory evidence that SWS is positively related to memory retention in later life comes from Westerberg et al. (2012), who reported a correlation between overnight declarative memory change and delta (0.5-4.5Hz) power in a group of people in their 60s and 70s. Backhaus and colleagues (2007) found that older people showed reduced SWS and memory retention over a period of early sleep compared to younger people, in spite of matched memory performance prior to sleep. A

regression analysis with memory retention across early sleep as the dependent variable and SWS, REMS and age as independent variables found a significant effect for SWS but not for REMS or age. The relationship between age and memory retention was non-significant when controlling for SWS. Furthermore, Mander et al. (2013) found that SWA was positively correlated with overnight memory retention in both young and older adults separately. They found that both SWA and overnight memory retention were reduced in older relative to younger adults, and that the association between age and overnight memory retention was mediated by SWA.

However, the case is not entirely settled, and there is some evidence to suggest that the relationship between SWS and declarative memory performance seen in young adults might not be preserved in older adults. For instance, Gerrard, Burke, McNaughton and Barnes (2008) found that sequence reactivation, which is positively correlated with subsequent spatial memory, is impaired in older rats. Furthermore, Scullin (2013), who reported a positive relationship between SWS and word retention in younger adults, did not find this relationship in older adults.

Given that the literature highlights the key role of SWS and slow wave activity, especially very slow oscillations, in the benefit of sleep for declarative memory retention in young healthy people, I sought to investigate the relationship between memory performance in my word-pair associates task and SWS in this experiment. I also sought to check that the relationship between SWS and memory was the same in my patient and control groups. Given that the benefit of sleep for memory retention was equivalent in both groups, I did not have an a priori reason to expect a group difference in the relationship.

Chapter 3.

3.2. Methods

The study received ethical approval from the Scotland A Research Ethics Committee and written informed consent was obtained from all participants.

3.2.1. Participants

Details about the relevant TEA patients who reported symptoms suggestive of ALF and the twelve control participants involved in the experiment are provided in the previous chapter. However, for the current chapter (in which the benefit of sleep for memory retention was correlated against the amount of SWS and slow oscillation power, in an attempt to determine the role of SWS in the benefit of sleep for memory retention), one patient was excluded from the analyses because he was found to have an unusually large benefit of sleep for memory retention over twelve hours – more than two standard deviations above the mean of the other participants. This was most likely a result of an unusually large discrepancy in the number of trials to criterion between the two conditions, rather than a genuine benefit of sleep for memory retention. While all other participants had a difference of only one or zero in their numbers of trials to criterion in the sleep and wake conditions, this patient was exposed to the set of word-pairs four more times during training in his sleep condition (which was his first condition) than he was to the set of word-pairs used in his wake condition. This discrepancy most likely accounts for his unusually superior memory retention in the sleep condition. With this patient excluded, the groups still did not significantly differ in terms of age, years of full time education, or performance on neuropsychological tests. As shown in the results section, the exclusion also did not affect the significance of the behavioural results of the experiment.

3.2.2. Procedure

To give the participants an opportunity to acclimatise to the sleep laboratory and the polysomnography (PSG) equipment, the participants spent an adaptation night in the sleep laboratory the night before the experiment began. The same equipment was used to record data during the night of the sleep condition of the experiment.

The details of the word-pair associates task are provided in the previous chapter (see Figure 2.1, in Chapter 2). Briefly, participants were trained to 60% criterion on 30 unrelated A-B word-pairs at eight am/pm and tested 30 minutes later. Twelve hours later (eight pm/am, after a night of sleep or a day of wakefulness) participants were exposed to, and then immediately tested on, interference (A-C) pairs. Ten minutes later, participants were shown the cue (A) words and asked to produce both the paired associates (B & C). Performance on the B paired associates was of primary interest; interference was introduced only to unmask the benefit of sleep for memory (Ellenbogen et al., 2009; Ellenbogen, Hulbert, et al., 2006). Each person participated in both the sleep and wake conditions, with 24 hours in between. The order was counterbalanced across participants. Two sets of word-pairs were used so that the stimuli were novel for each condition. The order in which the stimuli were used, and the distribution of stimuli across conditions, were counterbalanced across participants.

There was an additional memory test one week later, which was performed over the telephone. The internet was used to deliver the stimuli to the participants' own computer on the day of testing. In the event that the participant did not have access to a computer, he/she was provided with a digital photoframe, preloaded with the test stimuli, or a stimulus booklet. The word-pairs from the first condition were tested first, followed by those from the second condition. The procedure for each

trial was very similar to that in the 12-hrs (A-B&C) tests, except that there was no presentation time limit - each cue (A) word was presented until the participant had made an attempt to produce both paired associates - and no stimuli (such as fixation crosses, as described in Appendix A) intervened between the cue words.

3.2.3. Data collection and analysis

A Somnoscreen polysomnography system (SOMNOmedics, Randersacker, Germany) and Domino software (SOMNOmedics, Randersacker, Germany) were used to collect PSG data. The following recording electrodes from the 10-20 system were used: O1; O2; T5; P3; P4; T6; T3; C3; C4; T4; F7; F3; F4; F8; FP1; FP2). Cz was used as the online reference. In addition, the electrooculogram, chin electromyogram and electrocardiogram were also recorded. The sleep EEG signals were sampled at 256Hz and filtered using a 0.2-128Hz bandpass. Recording electrodes were re-referenced to the contralateral mastoid. Sleep stages were scored for each 30 seconds of data by an experienced rater according to the Rechtschaffen & Kales (1968) criteria. For the purpose of analysis, NREM3 and NREM4 epochs were re-labelled as SWS. The scorer was blind as to whether each participant belonged to the patient or the control group.

Sleep latency was calculated as the time from lights off until sleep onset. Sleep efficiency was calculated as the total sleep time as a percentage of the time in bed. Unless otherwise stated, the benefit of sleep for memory retention in each individual was calculated as the number of A-B pairs forgotten between the 30-mins and the delayed (12-hrs or 1-week) tests in the wake condition minus that in the sleep condition; therefore, the more positive the value, the greater the benefit of sleep for memory retention.

Following manual artefact rejection on a three second basis, spectral analyses were performed using Welch's average periodogram method, implemented in Python. Fast Fourier Transformation was applied on four seconds-long detrended windows, with Hanning tapering and a 50% overlap, producing a frequency resolution of 0.25Hz. Averaged spectral values were calculated for each 30 seconds-long sleep stage-aligned epoch for which there was at least twelve seconds of artefact-free data. Subsequently, estimates were averaged across all epochs of the night that were assigned a sleep stage, and across all recording EEG channels, to provide an absolute power estimate for each studied frequency bin for each individual. Power values for the frequency bins within the range 0.25-1.25Hz were averaged together to calculate an estimate of the power in the slow oscillation frequency range. Power values were log10 transformed to normalize distributions (Yordanova, Kolev, Wagner, Born, & Verleger, 2012) before statistical analysis. The first control participant was excluded from the spectral analysis because he had a much reduced EEG montage, sharing only C3 and C4 with the rest of the participants.

The patient neural data from the sleep-condition night were examined for epileptic activity by a clinical neurophysiologist with expertise in epilepsy and sleep medicine.

3.3. Results

A full description of the behavioural results for the word-pair associates task is provided in Chapter 2. With the additional patient excluded, the significance of the results remained unchanged. Briefly, while there were no significant group differences in A-B learning (score on the first training trial or trials to criterion) or A-C performance, the patients demonstrated ALF (there was an interaction between retrieval time point and group, $F_{(1.31,26.27)} = 6.88$, p=0.009): they performed significantly more poorly than the controls on the 12-hrs test (estimated marginal means (EMMs) ±SEMs: 13.40 ±1.08 and 17.50 ±0.99, respectively, p=0.011), but not on the 30-mins test (EMMs ±SEMs: 20.15 ±0.81 and 21.33 ±0.74, p=0.29) or the final training test (EMMs ±SEMs: 22.00 ±0.73 and 22.54 ±0.67, p=0.67). There was a benefit of sleep for memory retention (there was interaction between sleep condition and retrieval time-point, $F_{(2,40)} =19.33$, p<0.001): participants performed significantly better in the sleep condition than the wake condition on the 12-hrs test (EMMs ±SEMs: 16.83 ±0.78 and 14.07 ±0.89, respectively, p=0.003), but not on the 30-mins test (EMMs ±SEMs: 20.8 ±0.61 and 20.68 ±0.74, p=0.89) or the final training test (EMMs ±SEMs: 22.16 ±0.53 and 22.38 ±0.72, p=0.77). The benefit of sleep for memory retention was no smaller in magnitude for the patients than the controls (no significant interaction between sleep condition, retrieval time point and group, p=0.36). Furthermore, the patients performed significantly more poorly than the controls on the 12-hrs test in the wake condition (11.3 ±1.32 and 16.83 ±1.20, $t_{(20)} = 3.10$, p=0.006, but not in the sleep condition, 15.50 ±1.16 and 18.17 ±1.06, $t_{(20)} = 1.70$, p=0.10), indicating that it is possible for ALF to be seen over intervals that do not contain sleep.

The patients also performed significantly more poorly than the controls on the 1-week test (4.65 ±1.19 and 8.13 ±1.09, respectively, $t_{(20)} = 2.15$, p = 0.044). However, the participants did not perform significantly better in the sleep condition than the wake condition on the 1-week test (EMMs ±SEMs:

6.73 ±1.10 and 6.04 ±0.90), and there was no significant interaction between sleep condition and group.

During the night of the sleep condition, the patients and controls did not significantly differ in terms of total sleep time (411.80 ±16.46 mins in patients and 376.21 ±15.43 mins in controls, p=0.13), sleep latency (12.35 ±3.69 and 13.54 ±5.36 mins, p=0.86), sleep efficiency (82.15 ±3.04 % and 81.13 ±2.52 %, p=0.80), number of awakenings (36.50 ± 3.09 and 35.33 ±4.00, p=0.83), or minutes spent awake between sleep onset and final awakening (74.70 ±14.25 and 64.00 ±11.54, p=0.56). They also did not differ in terms of minutes spent in each sleep stage or percentage of total sleep time spent in each sleep stage (see Table 3.1). A total of five minutes of data across all participants could not be idenitified as a particular sleep stage or the waking state: 1.5 mins in the controls and 3.5 mins in the patients.

	Patients	Controls	P value
NREM1 %	19.69(±6.30)	16.35(±1.92)	0.24
NREM2 %	51.09(±2.34)	48.91(±2.38)	0.54
SWS %	9.31(±2.47)	13.73(±2.49)	0.23
REM %	19.96(±0.88)	21.01(±1.18)	0.50
NREM1 mins	81.40(±8.95)	62.38(±8.41)	0.14
NREM2 mins	211.10(±13.74)	185.46(±13.28)	0.20
SWS mins	37.30(±9.08)	48.71(±7.92)	0.35
REM mins	82.00(±4.66)	79.67(±6.40)	0.78

Table 3.1. Time spent in each sleep stage. The means (and standard errors of the mean) are presented for the number of minutes and the percentage of total sleep time spent in each sleep stage by the patients and the controls. There were no significant group differences in time spent in each sleep stage.

In a two-tailed Pearson correlation test, the patients showed a significant negative correlation between %SWS and the benefit of sleep for memory retention over twelve hours (-0.756, $p = 0.011$, see Figure 3.1). The controls did not show this negative correlation; their Pearson correlation coefficient was positive and non-significant (0.266, $p=0.403$). A Fisher's transformation analysis revealed that the correlation was significantly different in the two groups ($Z = 2.50$, $p<0.05$). A similar pattern of results was seen if minutes of SWS was used instead of % SWS, and/or the benefit of sleep for memory retention was calculated as a difference between the conditions in terms of percentage forgetting, rather than the absolute number of pairs lost. In all cases, these analyses revealed a significant negative correlation in the patients, but not in the controls, with a significant difference in the correlation between the two groups.

The controls showed a significant positive correlation between %SWS and the benefit of post-learning sleep for memory retention over one week ($r = 0.589$, $p = 0.044$, see Figure 3.1). The patients did not show this positive correlation. The patients' Pearson correlation coefficient was negative and non-significant ($r = -0.239$, $p=0.51$). However, the Fisher's transformation analysis did not reach significance ($Z = 1.83$).

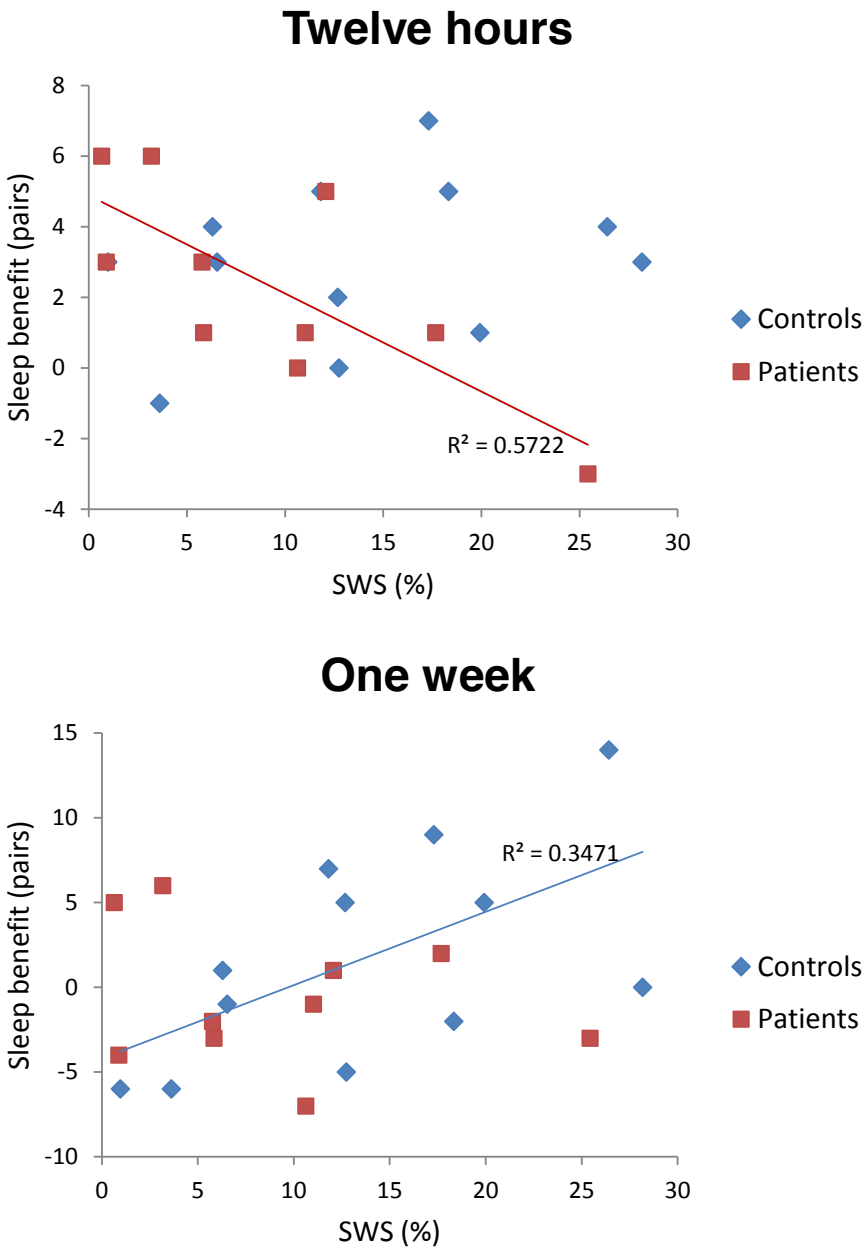


Figure 3.1. The benefit of post-learning sleep for memory retention over twelve hours (top chart) and one week (bottom chart) plotted against the percentage of total sleep time spent in SWS during the sleep condition night. The lines of best fit and R^2 values are displayed for the significant correlations. The patients showed a significant negative correlation between SWS (%) and the benefit of post-learning sleep for memory retention over twelve hours. This correlation was not seen in the controls and the correlation significantly differed between the two groups. The controls showed a significant positive correlation between SWS (%) and the benefit of post-learning sleep for memory retention over one week. There was no significant correlation between SWS (%) and the benefit of sleep for post-learning memory retention over one week in the patients.

The groups did not significantly differ in terms of power in the slow oscillation frequency range, averaged across all sleep epochs of the night (means and SEMs of the log10 transformed values in patients and controls: 2.06 ±0.051 and 2.14 ±0.037, $t_{(19)} = 1.23$, p=0.24). In a two-tailed Pearson correlation test, the patients showed a significant negative correlation (r= -0.624, p=0.049, see Figure 3.2) between power in the slow oscillation frequency band and the benefit of post-learning sleep for memory retention over twelve hours, measured as the difference between the two conditions in percentage forgotten. The controls did not show this correlation (r= 0.033, p=0.923).

However, the controls did show a significant positive correlation (r= 0.619, p=0.042, see Figure 3.2) between power in the slow oscillation frequency band and the benefit of post-learning sleep for memory retention over one week, measured as the difference between the two conditions in the number of pairs lost. The patients did not show this correlation (r = -0.034, p= 0.926).

The same pattern of results was observed if power in the slow oscillation frequency range was averaged across NREM sleep epochs only, rather than across all sleep epochs of the night.

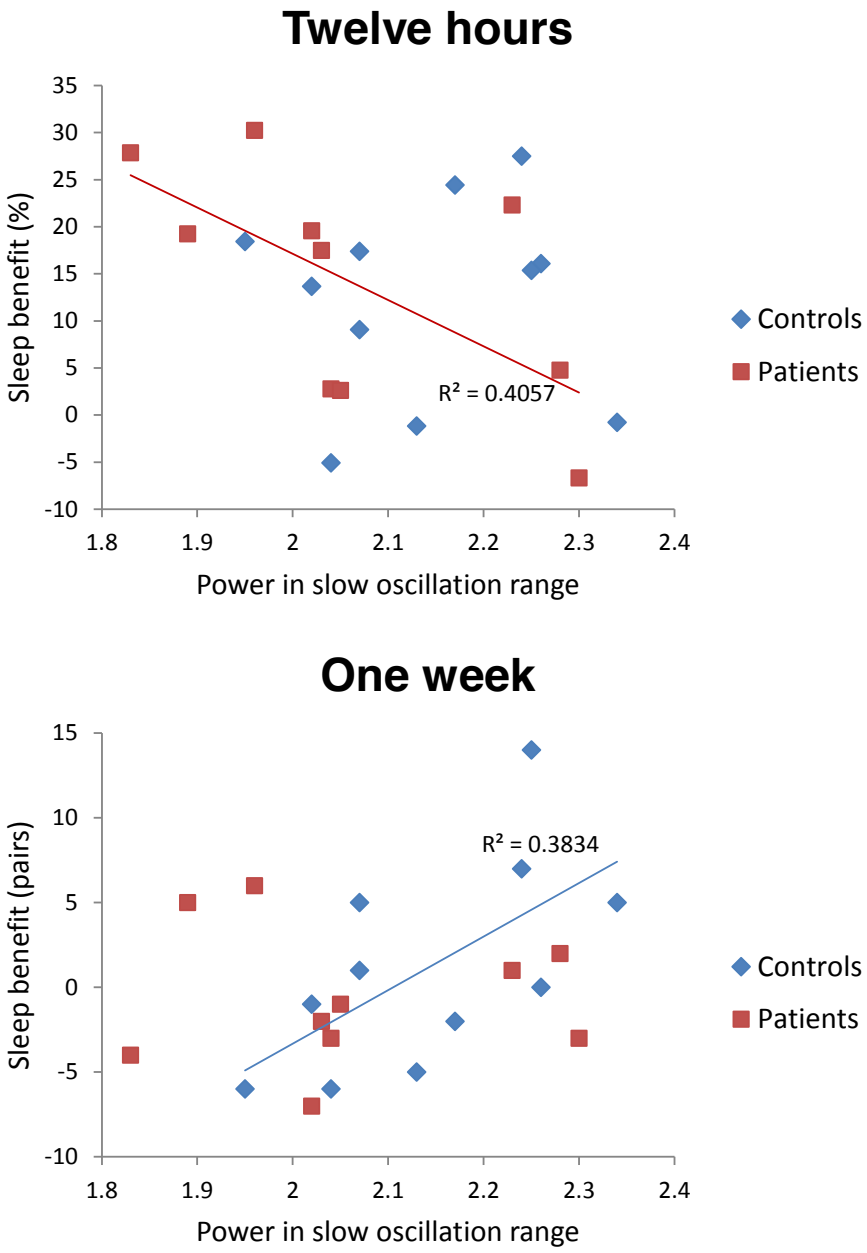


Figure 3.2. The benefit of post-learning sleep for memory retention over twelve hours (top chart) and one week (bottom chart) plotted against the power in the slow oscillation frequency range (log10 transformed) during the sleep condition night. The lines of best fit and R^2 values are displayed for the significant correlations. The patients showed a significant negative correlation between slow oscillation power and the benefit of post-learning sleep for memory retention over twelve hours. This correlation was not seen in the controls. The controls showed a significant positive correlation between slow oscillation power and the benefit of post-learning sleep for memory retention over one week. There was no significant correlation between slow oscillation power and the benefit of sleep for post-learning memory retention over one week in the patients.

The clinical neurophysiologist found no evidence of epileptic activity in any of the patients' sleep-condition EEGs.

3.4. Discussion

This study revealed a striking difference in the relationship between SWS and the benefit of sleep for memory retention in patients with TEA-associated ALF and healthy older adults. SWS, and specifically slow oscillations, are thought to exert a positive influence on declarative memory retention in young healthy people. In the current study, the amount of slow wave sleep and power in the slow oscillation frequency range were positively correlated with the benefit of post-learning sleep for memory retention over one week in healthy older adults. However, these relationships were not found in the patients. Furthermore, the amount of slow wave sleep and power in the slow oscillation frequency range were negatively correlated with the benefit of sleep for memory retention over twelve hours in patients. These relationships were not observed in the controls. Indeed, the correlation between the amount of SWS and the benefit of sleep for memory retention over twelve hours was significantly different in the two groups. This suggests that the role played by sleep in memory retention is not entirely the same in the two groups, and that SWS is deleterious, rather than advantageous, for memory retention in TEA patients with ALF.

SWS may be deleterious to memory in these patients because it promotes epileptic activity. Epileptic activity might unbalance the network of connections in the medial temporal lobes (thereby disrupting memory); scramble activity patterns during reactivations; and/or interfere with post-reactivation reconsolidation. However, there was no evidence of epileptic activity in the patients' EEGs.

Alternatively, SWS may interact abnormally with memories in this patient group. In healthy people, SWS may improve memory retention through increasing the signal-to-noise ratio by downscaling synaptic weights. It may be the case that memories usually need to be actively protected in order to ensure that they survive this downscaling process. This may be achieved through post-encoding memory consolidation processes that increase memory strength, or through regulations of metaplasticity. The patients' memories might be especially vulnerable to being downscaled. If the patients' memories are particularly weak at the onset of SWS (either as a result of poor encoding processes or a failure of post-encoding memory strengthening processes) or the metaplasticity of their synapses has not been appropriately regulated, then SWS may have a negative, rather than positive, effect on memory retention. It would be interesting to see if it is possible to produce a negative effect of SWS for memory retention in healthy experimental animals by blocking protein synthesis during the period of wakefulness between memory acquisition and sleep, or by blocking the action of signaling molecules (Abraham, 2008) that alter metaplasticity.

Another way in which the slow oscillation might interact abnormally with memory in these patients is to trigger disorganised, rather than faithful, memory reactivations.

A third possibility is that the reactivations are normal but that they exert a negative, rather than positive effect on memory. During SWS in healthy people, new memories are thought to be reactivated in an interleaved manner with related older memories. This process is thought to allow integration of memories and the extraction of invariants (McClelland et al., 1995). However, if memories are abnormal in TEA patients with ALF as a result of a poorly functioning hippocampal complex, these patients might have difficulty separating memories with overlapping components (Bartko et al., 2010; Bussey et al., 2005; Cowell et al., 2006; Graham et al., 2010; Hardt et al., 2013;

Lee, Yeung, & Barense, 2012; Yassa & Stark, 2011), and the reactivation of related memories might promote catastrophic interference. It would be interesting to conduct a cued replay experiment in TEA ALF patients and healthy controls in which reactivations of related older memories are induced during post-learning SWS; the patients' memory performance might be particularly severely affected.

However, the current study provides only correlational evidence of a negative relationship between SWS and the benefit of sleep for memory retention in TEA ALF patients. To obtain causal, rather than correlational, evidence, slow oscillations could be manipulated in these patients. Slow waves can be enhanced or suppressed using acoustic stimuli. It is possible to interrupt slow wave activity by presenting acoustic stimuli whenever slow waves are detected in the EEG (e.g. Landsness et al., 2009). Alternatively, if the sounds are presented in a rhythmic fashion at the appropriate frequency, in phase with the ongoing slow oscillations, they can actually be used enhance slow oscillation activity through entrainment (e.g. Ngo et al., 2013). If SWS is indeed deleterious in the patients, then, while slow wave enhancement improves memory in healthy people (Marshall et al., 2006; Ngo et al., 2013), it might impair memory in the patients, and, while slow wave suppression impairs memory in healthy people (Landsness et al., 2009), it might improve memory in the patients. If effective, slow wave suppression could be considered as a treatment to help reduce ALF severity. However, there might be negative consequences. For instance, Tononi and Cirelli (2006) argue that, in healthy people, the synaptic downscaling process associated with slow wave activity not only improves retention of existing memories by increasing the signal-to-noise ratio, but also improves our ability to subsequently learn new information by de-saturating synaptic weights. If this is the case, slow wave suppression might result in diminished learning capacity, difficulty concentrating, emotional disturbance and fatigue (Tononi & Cirelli, 2006). These potential side effects should be fully explored in an experiment with a group of patients before use as a regular treatment. However,

in the case of important life events, slow wave suppression during the following nights might be a useful technique to help preserve a patient's memory for the occasion.

To date, very little research has been done on the role of SWS in declarative memory retention in healthy older adults. Some studies suggest that, while SWS is reduced in older people, the relationship between SWS and memory retention is preserved (e.g. Backhaus et al., 2007; Mander et al., 2013). However, other studies have failed to find a relationship between SWS and memory retention in older adults (e.g. Scullin, 2013). The current study did not find a relationship between SWS, or slow oscillations, and the benefit of sleep for memory retention over twelve hours in healthy older adults. However, (while the participants in this study did not show a significant benefit of post-learning sleep for memory retention over one week at the group level) the amount of SWS, and power in the slow oscillation frequency range, were positively correlated with the individual's benefit of post-learning sleep for memory retention over one week. This might suggest that post-learning SWS is still beneficial for memory retention in healthy older people, but that the benefit might not be seen until later. Perhaps SWS shortly after learning initiates a memory consolidation process that progresses over time and/or further sleep, and this process is slower in older people.

It does not appear that any part of the benefit of sleep for memory retention in TEA patients with ALF is mediated by SWS. Nevertheless, sleep must have some form of positive role in declarative memory retention in these patients as they showed a behavioural benefit. It is possible that a different stage of sleep has taken over the memory-enhancing role of SWS in this patient population. The relationship between other sleep stages and the benefit of sleep for memory should be investigated in a future study with a larger sample size, where multiple comparisons corrections would be less problematic. However, as discussed in the introduction, sleep may make a major

contribution to declarative memory retention by minimizing interference. This role would be especially important if the patients' memory traces or consolidation processes were particularly vulnerable to interference. While it is not yet known if TEA patients with ALF are especially vulnerable to interference, there is ample evidence that medial temporal lobe (MTL) abnormalities result in increased susceptibility to interference (e.g. Bartko et al., 2010; Cowan et al., 2004; Cowell et al., 2006; Dewar et al., 2009; Warrington & Weiskrantz, 1978). According to many theories of MTL function (such as pattern separation (e.g. Marr, 1971; O'Reilly & McClelland, 1994; Treves & Rolls, 1994; Yassa & Stark, 2011) and theories based on the representational-hierarchical framework (e.g. Cowell, Bussey, & Saksida, 2010), such as the emergent memory account (Graham et al., 2010)), the hippocampus is critical to the brain's ability to represent memories in such a way that they are distinguishable from each other, at least until systems consolidation is complete (e.g. Hardt et al., 2013). If the function of this structure is compromised, memories with overlapping neocortical components would be more likely to interfere with one another. Future work should involve assessing whether TEA patients with ALF are more susceptible to interference than healthy people.

In conclusion, while TEA patients with ALF have a normal behavioural benefit of sleep for memory retention, the more SWS they have on the post-learning night, the smaller the benefit of sleep for their memory. This apparently deleterious effect of SWS may be due to promotion of epileptic activity, although none was detected, or an aberrant interaction between memory traces and slow oscillations.

4. Non-declarative memory

4.1. Introduction

The literature currently suggests that the anterograde memory problems in ALF patients with transient epileptic amnesia (TEA) might be restricted to classically declarative/explicit tasks. This is perhaps unsurprising given that the seizure focus in TEA is thought to be the medial temporal lobes (MTL) (Zeman & Butler, 2010), and it has traditionally been thought that declarative/explicit memories rely on the MTL, while non-declarative/implicit memories do not (Graf & Schacter, 1985; Squire, 1987). However, recent research suggests that the MTL's involvement in memory may not be restricted to declarative/explicit tasks; it appears that some forms of implicit memory also depend on the MTL. The current experiment was designed to investigate whether TEA ALF patients show deficits on non-declarative tasks that are thought to be dependent on the MTL.

The serial reaction time task (SRTT) is a typical implicit task (e.g. Nissen & Bullemer, 1987; Reed & Johnson, 1994). In an SRTT, there are a set number of locations on a computer screen at which a stimulus can occur and each is associated with a particular response button. When the stimulus occurs at one of these locations, the participant must press the corresponding button as quickly as possible. Unbeknownst to the participants, the stimulus locations occur in a repeating sequence. Over time, reaction times decrease. Much of this reaction time decrease is due to non-specific factors. To assess sequence-specific skill, the reaction time difference between sequence trials and probe trials (often a series of random locations) is calculated.

Sequences contain information of varying complexity. Pairwise associations between temporally adjacent stimuli are considered to be 'lower order' sequence information, while anything more complex is considered to be 'higher order' sequence information (Curran, 1997). A commonly used

type of sequence that contains higher order information is the second order conditional (SOC) sequence. In an SOC, the current stimulus-location is completely predicted by the two preceding stimulus-locations, but each stimulus-location is immediately followed by each of the other possible stimulus-locations equally often. The MTL is not required for the learning of lower order sequence information. However, research using human lesion patients (Curran, 1997), brain imaging (Schendan, Searl, Melrose, & Stern, 2003) and animal models (Ergorul & Eichenbaum, 2006) suggests that the hippocampus is involved in higher order skill acquisition, even when learning is implicit.

The study of higher order sequence information acquisition requires more than the use of sequences that contain higher order information; the probe used is also very important. Reed and Johnson (1994) have demonstrated that when a random probe is used, the learning of complex sequence information and simple frequency information are confounded. A number of types of simple frequency information will typically differ between a repeating sequence that contains higher order information, such as an SOC sequence, and a random probe (location frequency; pairwise transition frequency; reversal (e.g. 1-2-1) frequency; rate of full coverage of all locations; rate of complete pairwise transition usage) and so participants do not need to acquire the higher order sequence information to appear skilled when a random probe is used (Reed & Johnson, 1994). These researchers recommend that simple frequency information be held constant between learned sequence and probe trials.

To date, only one study has tested TEA patients who complain of ALF on an SRTT (Muhlert et al., 2010). The researchers found skill acquisition and retention to be normal, while ALF was observed for real-life events and a word-list task. They concluded that memory impairments in this population are likely restricted to classically declarative tasks. However, while Muhlert et al (2010) did use an

SOC sequence, they used a random probe to assess sequence skill. Therefore, it is not possible to conclude that higher order sequence information learning is normal in these patients on the basis of these results. Interestingly, these researchers used a procedure that involved interleaved presentation of the sequence and random series; this would have allowed them to compare reaction times for pairwise associations between sequence and random trials, and thereby investigate group differences in higher order skill (Curran, 1997), but they did not present such analyses in their paper.

Furthermore, it is difficult to claim to have provided evidence that the rate of forgetting is not accelerated in a patient group when there was no forgetting in the control group with which to compare it. In the study by Muhlert et al. (2010) there was no loss of skill over the time-period studied in either the patients or the healthy control group. While this certainly means that the patients retained the skill normally over the tested time-period, it is possible that once the healthy participants began to forget the skill, the patients would have done so at a faster rate. Similarly, Deak et al. (2011) found no evidence for skill retention problems on another motor sequence task (the finger-tapping task, an explicitly learned 5-item sequence) in a group of temporal lobe epilepsy patients who demonstrated ALF on a word-recall task. Once again, it is difficult confidently to conclude that these patients do not suffer from an accelerated performance decline in this type of task on the basis of these results, because there was no evidence of a performance decline over the 24-hour retention interval in the control group with which to compare it.

Therefore, it remains possible that TEA patients who complain of ALF, who are thought to have a medial temporal lobe epileptic focus (Zeman & Butler, 2010) and are known to have hippocampal atrophy at the group level (Butler et al., 2013; Butler et al., 2009), may have difficulty acquiring and/or retaining higher order sequence information in a visuomotor task. In the current study, I

investigated this possibility using probe sequences that were carefully matched to the learned sequences in terms of simple frequency information; in this experiment, reaction time differences between learned sequence and probe trials should be a true reflection of higher order sequence-specific skill.

4.2. Methods

The study received ethical approval from the Scotland A Research Ethics Committee and written informed consent was obtained from all participants.

4.2.1. Participants

Thirteen patients who met the diagnostic criteria for transient epileptic amnesia and reported symptoms suggestive of ALF, and twelve control participants, took part in this study. The diagnostic criteria for TEA have been published by Zeman and Butler (2010) and are described in the main introduction to this thesis. Two patients were excluded from analyses because they had Dupuytren's disease, which can affect hand function, and the results of another patient were excluded because testing was interrupted by alarm sounds. Details of the remaining patients are provided in Table 4.1. All patients were on anticonvulsant monotherapy and, in all cases but one, had been free of seizures for at least six months prior to testing. No patients reported seizures during the experiment. Ten of the controls, and eight of the ten remaining patients, were also included in the sleep experiment analyses discussed in the first two experimental chapters of this thesis. The SRTT experiment was performed during the same experimental sessions as the word-pair associates task, as outlined in Appendix A.

The patients and controls used for the analyses in the current experiment did not differ significantly in terms of age, IQ, and years of full-time education (see Table 4.2). Their performance on a range of neuropsychological tests is presented in Table 4.2.

Gender	Age	Age at onset	AEDs (type & mg per day)	Time since seizure (months)	Evidence for a diagnosis of epilepsy			MRI
					EEG	Other Features	Treatment Response	
M	66	63	Le 1000	11	Normal	Brief unresponsiveness	Complete	Normal
M	72	64	C 600	9	Bilateral (L more marked) anterior temporal sharp and slow-wave epileptiform	Brief unresponsiveness	Complete	Normal
M	70	66	Le 2000	31	Non-specific bilateral temporal lobe slowing	Oroalimentary automatisms, gustatory hallucinations	Complete	Normal
M	68	65	C 400	27	Non-specific L temporal slowing	No	Complete	Normal
M	72	71	La 200	9	Non-specific R temporal slowing	Déjà vu	Complete	Bilateral high T2 signal in hippocampus
M	68	62	C 400	60	Bilateral (L more marked) mid-anterior temporal sharp and slow-wave epileptiform	Oroalimentary automatisms; brief unresponsiveness	Complete	Normal
M	76	65	La 100	97	Non-specific bilateral temporal slowing	Olfactory hallucinations; oroalimentary automatisms	Complete	Normal
M	64	61	SV 800	30	Bilateral temporal epileptiform	Olfactory hallucinations; oroalimentary automatisms	Complete	Normal
M	63	59	Le 500	0	Normal	No	Partial	Normal
F	60	55	C 300	44	Non-specific bilateral temporal slowing	Brief unresponsiveness	Complete	Normal

Table 4.1. TEA patient information.

NB the time between the experiment and the patient's last seizure/amnesic attack is only approximate. The seizures experienced by TEA patients are not as clear cut as those in other types of epilepsy. Furthermore, the patients suffer from interictal memory problems. Therefore, reliable accounts were not always available, and this measure should be interpreted with caution. AEDs = Anti-Epileptic Drugs that the patients were taking when they took part in the experiment, Le = Levetiracetam, C = Carbamazepine, La = Lamotrigine, SV = Sodium Valproate.

	TEA Patients	Controls
N	11	12
Gender	1 female	5 females
Age	67.80(±1.54)	63.67(±1.63)
Years of full-time education	13.00(±0.95)	13.46(±1.08)
IQ tests		
National Adult Reading Test (NART)[a] errors (50 words in test)	14.90(±3.46)	11.83(±2.01)
Predicted WAIS[b] verbal IQ from NART errors	115.20(±3.18)	118.08(±1.84)
WASI[c] vocabulary raw score (max 80)	67.30(±1.99)	69.92(±1.79)
WASI similarities raw score (max 48)	38.80(±1.18)	39.00(±1.14)
WASI verbal IQ	117.30(±2.62)	119.08(±3.02)
WASI block design raw score (max 71)	44.70(±3.32)	47.08(±3.79)
WASI matrix reasoning raw score (max 42)	25.50(±1.08)	24.25(±1.86)
WASI performance IQ	119.30(±3.16)	117.33(±4.07)
WASI full scale-4subtests IQ	120.30(±2.05)	120.58(±3.32)
Anterograde memory		
WMS-III[d] Logical memory story: Immediate recall (max 25)	16.30(±1.63)	17.00(±1.31)
WMS-III Logical memory story: Delayed recall (30mins) (max 25)	11.80(±1.42)	14.58(±1.44)
Recognition Memory Test (RMT)[e]: Words (max 50)	44.40(±1.38)	46.33(±1.10)
Recognition Memory Test (RMT): Faces (max 50)	41.30(±1.37)	44.75(±0.81)*
Semantic memory		
Graded Naming Test (GNT)[f] (max 30)	22.60(±1.30)	24.83(±0.61)
Anxiety and Depression scores		
Hospital Anxiety and Depression Scale (HADS)[g] anxiety (max 21)	6.40(±1.23)	5.33(±0.57)
Hospital Anxiety and Depression Scale (HADS) depression (max 21)	4.60(±0.93)	2.58(±0.58)

Table 4.2. Participant information. Means with SEMs in brackets. The groups did not differ significantly in terms of age or full time education. *Patients performed significantly more poorly on this test (Recognition Memory Test for faces, $t_{(20)} = 2.25$, $p=0.036$). For all other tests, there was no significant difference between the groups ($p>0.05$).

[a]NART (Nelson & Willison, 1991; Nelson, 1982); [b]WAIS = Wechsler Abbreviated Intelligence Scale (Wechsler, 1955); [c]WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); [d]WMS-III = Wechsler Memory Scale-III (Wechsler, 1997); [e]RMT (Warrington, 1984); [f]GNT (McKenna & Warrington, 1980); [g]HADS (Zigmond & Snaith, 1983).

4.2.2. Task

4.2.2.1. Stimuli

Each participant performed the experiment twice; everyone participated in both a sleep and a wake condition (in which the retention interval of twelve hours between the training and test sessions contained a night of sleep and a day of wakefulness, respectively). There were two sets of learned and probe sequences so that the stimuli would be novel for each condition. The order of the

conditions, and the distribution of the two stimulus sets across the conditions, was counterbalanced across participants.

The learned sequences were 12-item second-order conditional (SOC) sequences. Each of the two learned sequences had a corresponding probe sequence with which it was matched in terms of simple frequency information (location frequency; transition frequency, reversal frequency; rate of full coverage; rate of full transition usage, see Table 4.3), but from which it differed completely in terms of SOC information.

	Sequence	**Type of simple frequency information**				
		Each Location	Each transition	Reversal	Rate of full coverage	Rate of full transition usage
Learned A	1-2-1-3-4-2-3-1-4-3-2-4	0.25	0.083	0.083	4.58	13.0
Probe A	1-2-3-4-1-3-2-1-4-2-4-3	0.25	0.083	0.083	4.58	13.0
Learned B	2-3-4-2-1-4-1-3-1-2-4-3	0.25	0.083	0.25	5.42	13.0
Probe B	3-4-3-1-4-2-4-1-2-3-2-1	0.25	0.083	0.25	5.50	13.0

Table 4.3. Sequence information. The probe sequences were matched to their respective learned sequences in terms of simple frequency information, but differed from them completely in terms of SOC information. Learned A and Probe A were taken from Reed & Johnson (Reed & Johnson, 1994). Learned B was taken from Reber & Squire (1994).

4.2.2.2. Procedure

During the experiment, four solid white boxes were displayed horizontally across the centre of the computer screen (3.3 x 3.3 cm, separated by 0.8cm) against a black background that filled the entire screen. There was no fixation cross and the participant was given no specific instructions regarding eye movements. The participant was instructed to rest the four fingers of their dominant hand on four buttons on a keyboard (‘J’ ‘I’ ‘O’ ‘;’ for right-handed participants, and ‘A’ ‘W’ ‘E’ ‘F’ for left-

handed participants). Each button (and finger) was associated with a particular white box (with the leftmost button corresponding to the leftmost box, and so forth). When the stimulus (a black box of 2 x 2cm) appeared inside one of the boxes, the participant was required to press the corresponding button as quickly as possible. The stimulus remained present until the appropriate button was pressed. As soon as the participant had pressed the correct button, there was a 200ms inter-stimulus-interval before the stimulus appeared in a different location. See Figure 4.1 for an illustration of the task.

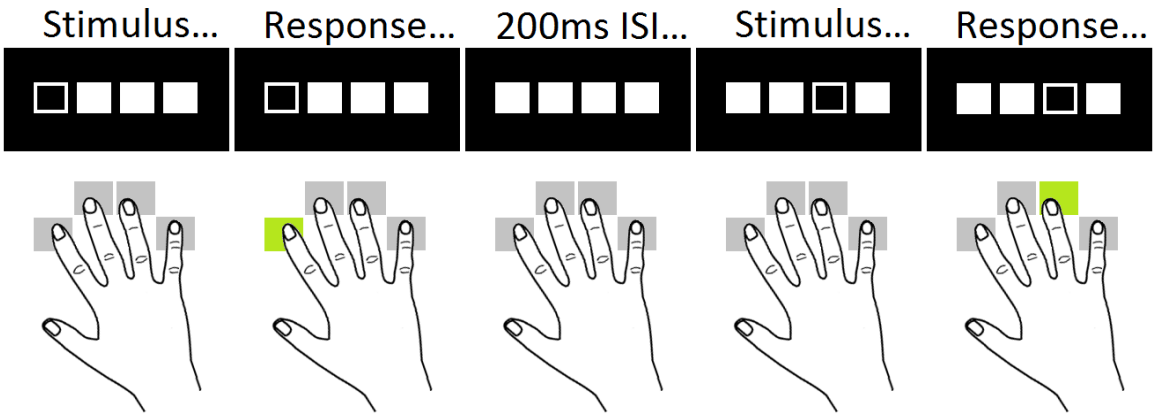


Figure 4.1. An illustration of the serial reaction time task. The stimulus could appear at one of four possible locations, each of which was associated with a response button on the keyboard. When a stimulus appeared, the participant pressed the corresponding button as quickly as possible. Purely for illustrative purposes, the colour green is used to represent button-presses in the figure. As soon as the correct button was pressed, the stimulus disappeared for 200ms and then reappeared at a different location. Unbeknownst to the participants, the stimulus locations followed a repeating 12-item second order conditional sequence.

The trials were divided into blocks. Between blocks, participants were informed how many blocks remained in the session, were reminded to respond as quickly as possible to the stimuli, and invited to press a button when they were ready to resume the task. The experiment was divided into training and test sessions, which were approximately twelve hours apart. The training session involved five blocks of 24 repetitions of a 12-item SOC sequence and a sixth block that contained

sixteen repetitions of this learned sequence, followed immediately and seamlessly by four repetitions of a 12-item probe sequence and another four repetitions of the learned sequence. Approximately twelve hours after the training was completed, a single block was performed (the test session), which was made up of six repetitions of the learned sequence, four repetitions of the probe sequence and another four repetitions of the learned sequence.

There was a single random trial at the beginning of each block of the training and test sessions (which was excluded from analyses) to ensure that the blocks did not always begin with the same stimulus-location. See Figure 4.2 for a schematic of the procedure.

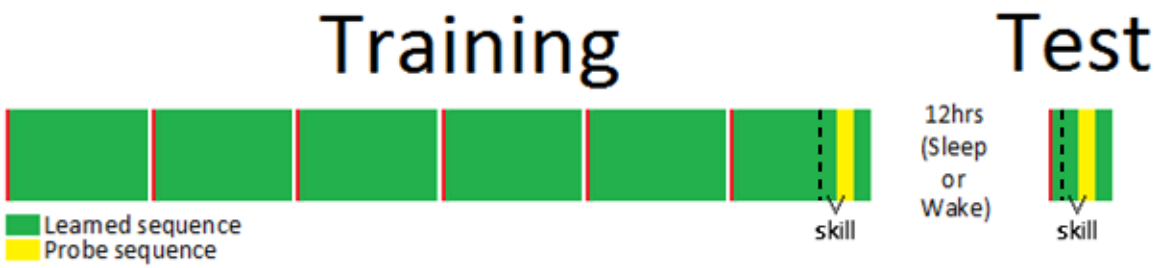


Figure 4.2. A schematic of the training and test procedure. Training involved six blocks of trials. There were self-timed breaks in between blocks. The first five blocks each contained 24 repetitions of the learned 12-item second order conditional sequence. The final block contained sixteen repetitions of the learned sequence, four repetitions of the probe sequence and another four repetitions of the learned sequence. After twelve hours (a night of sleep or a day of wakefulness), the test session was administered. This was a single block containing six repetitions of the learned sequence, four repetitions of the probe sequence and another four repetitions of the learned sequence. Each block began with a single random trial (illustrated in red) so that the blocks did not always begin with the same stimulus-location. Skill was calculated as the difference in reaction time between the probe trials and the preceding four repetitions of the learned sequence.

4.2.2.3. Analyses

Reaction time was the measure of interest. For analysis, the trials were separated into 12-trial units. The median reaction time for each unit was calculated. The mean of each four consecutive medians was used to calculate the reaction time for each four repetitions of a 12-item sequence.

To analyse the change in reaction time over the course of the training sessions (prior to the probe trials), an ANOVA with reaction time as the dependent variable, sleep condition (two levels: sleep and wake) and trials (34 levels, one for each set of four repetitions of the learned sequence) as the within-subjects factors, and group as the between-subjects factor, was performed.

At the end of the training sessions, and in the test sessions twelve hours later, skill was calculated as the reaction-time difference between the probe trials and the preceding four repetitions of the trained sequence.

To investigate skill, an ANOVA was performed, with skill as the dependent variable, sleep condition (two levels: sleep and wake) and session (two levels: training and test) as the within-subjects factors, and group as the between-subjects factor.

4.3. Results

There was no significant effect of sleep condition, nor interaction between sleep condition and any other factor, in any of the analyses, and so the data presented here are collapsed across the two conditions.

Figure 4.3 displays the reaction-time data from the training sessions. The ANOVA with reaction time as the dependent variable, group as the between-subjects factor, and trials (34 levels, one for each set of four repetitions of the learned sequence) as a within-subjects factor revealed a significant main effect of trials ($F_{(6.31,126.16)} = 25.02$, $p<0.001$). A significant linear contrast of trials ($F_{(1, 126.16)} = 69.94$, $p<0.001$) revealed that reaction time decreased linearly across trials. There was no significant difference in reaction times between patients and controls ($p = 0.50$), and no interaction between trials and group ($p = 0.54$). Indeed, a t-test revealed that the group difference in reaction time did not reach significance even for the final four repetitions of the learned sequence, immediately before the probe was introduced (estimated marginal means (EMMs) ±SEMs for controls and patients: 442.49 ±130.99 and 457.67 ±109.43, $t_{(20)} = -1.08$, $p=0.29$).

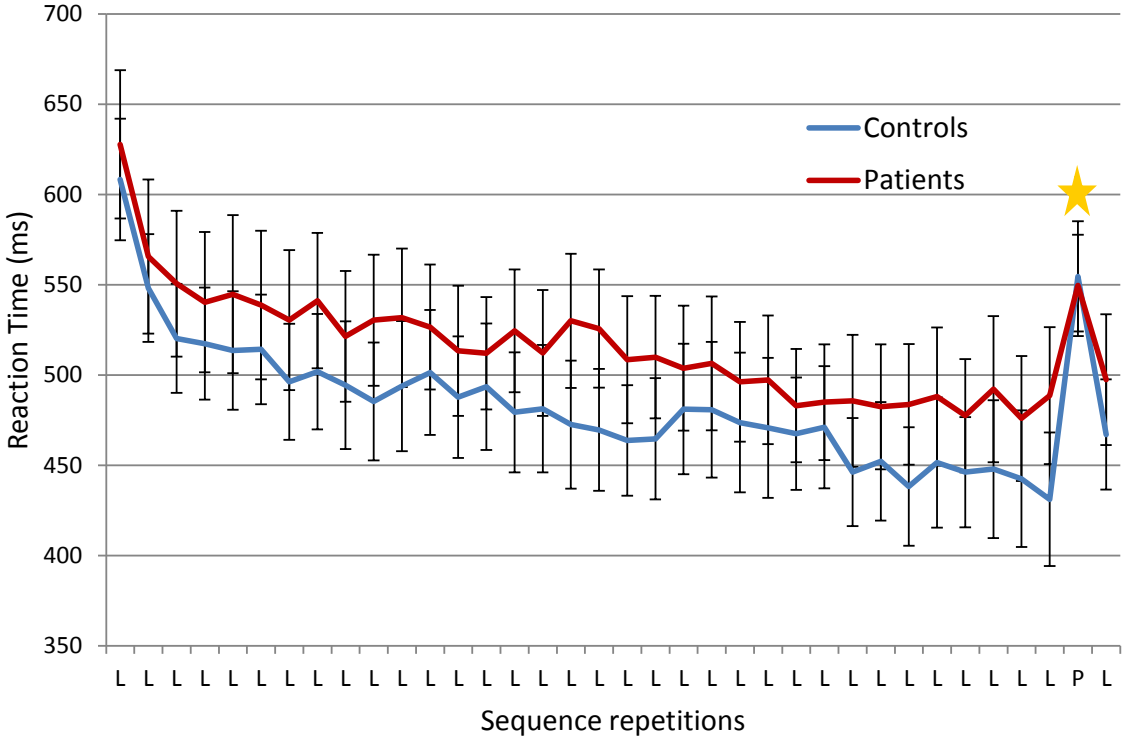


Figure 4.3. Reaction times during training for patients and controls. Error bars represent the standard error of the mean. Each 'L' on the x-axis represents four repetitions of the learned sequence. The four probe sequence repetitions are marked with a 'P' and a star. Reaction times decreased across the training session. When the probe was introduced, reaction times increased, revealing sequence-specific skill.

At the end of the training session, and in the test session twelve hours later, the reaction-time difference between the probe trials and the preceding four repetitions of the learned sequence was taken as the measure of sequence-specific skill (see Figure 4.4).

The ANOVA with sequence-specific skill as the dependent variable, group as the between-subjects factor and session (training and test) as a within-subjects factor revealed that skill was greater in the training sessions than the test sessions (EMMs ±SEMs: 92.24 ±14.39ms and 27.65 ±6.83ms, $F_{(1,20)}$ = 22.60, $p<0.001$), suggesting that sequence-specific skill declined over the 12-hrs interval. Furthermore, there was an interaction between session and group ($F_{(1,20)}$ = 6.25, $p = 0.021$). Post hoc

t-tests showed that the patients displayed significantly less skill than the controls in the training sessions (61.02 ±18.02ms and 123.46 ±21.51ms, $p = 0.042$), but not the test sessions (30.41 ±8.92ms and 24.90 ±9.99ms, $p=0.69$). Only the controls ($p<0.001$), and not the patients ($p=0.14$), showed a significant decline in skill between the training and test sessions. One sample t-tests revealed that sequence-specific skill was significantly greater than zero in both the training and the test sessions for both the controls ($p<0.001$ and $p=0.030$) and the patients ($p=0.008$ and $p=0.008$), which means that both groups acquired and retained some level of higher order sequence-specific skill (see Figure 4.4).

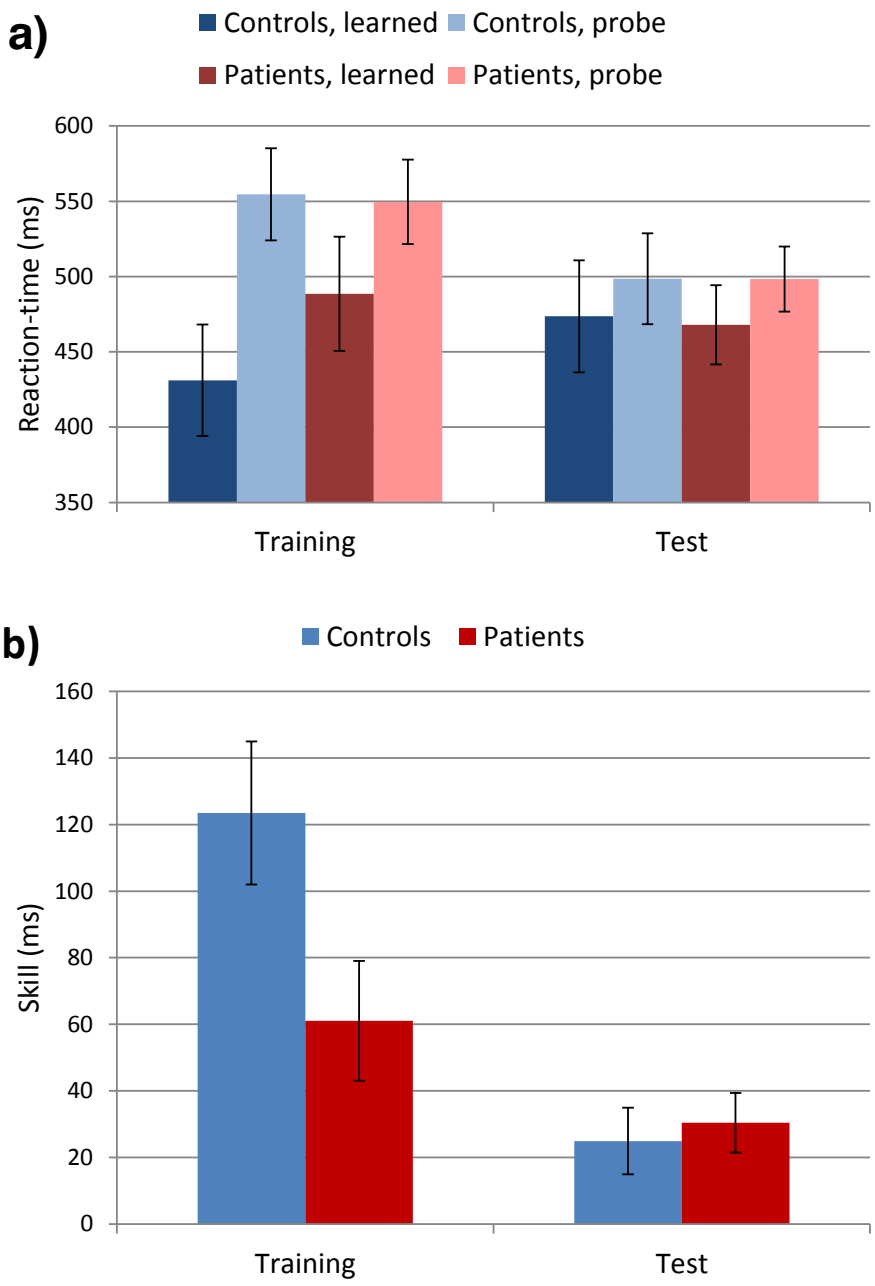


Figure 4.4. (a) Reaction times for the probe sequence trials and the preceding four learned sequence repetitions in the training and test sessions for the patients and controls. (b) Sequence-specific skill in the training and test sessions in the patients and controls. Significant sequence-specific skill was detected in both the training and the test sessions in both groups. The patients showed significantly less skill than the controls at the end of the training session but not in the test session. The controls, but not the patients, showed a significant decline in skill over twelve hours.

4.4. Discussion

This experiment demonstrates that both healthy older adults and TEA patients who report symptoms suggestive of ALF are able to acquire some level of higher order sequence-specific skill, and to retain at least some of this skill over twelve hours.

To date, the majority of SRTT studies using sequences that contain higher order information have used random probes. This means that the acquisition of higher order and simple frequency information were confounded. There have been very few SRTT studies in older adults in which the probe trials were carefully matched to the learned sequences in terms of simple frequency information. Therefore, this study provides valuable evidence that older adults can acquire higher order sequence information, at least to some degree. The healthy controls in this experiment showed a significant decline in higher order sequence-specific skill over twelve hours. Some existing studies suggest that higher order sequence information *acquisition* might be impaired in older compared to younger adults (e.g. Howard et al., 2004; Howard & Howard, 1997; Schendan, Tinaz, Maher, & Stern, 2013), but there has been relatively little carefully-controlled research into the effect of age on the *retention* of higher order skill information, so this would be an interesting area for further research. Sleep did not affect retention of higher order sequence-specific skill in this experiment. This is in line with a number of other studies that have found no behavioural evidence of sleep-dependent consolidation of implicit sequence knowledge (e.g. Nemeth et al., 2010; Robertson, Pascual-Leone, & Press, 2004; Song, Howard, & Howard, 2007).

Unfortunately, the results of this study are ambiguous with regard to differences between patients and controls, the investigation of which was the main aim of the experiment. The difference in reaction times for learned sequence and probe trials (i.e. the measure of sequence-specific skill) was

significantly greater for the healthy controls than for the patients at the end of the training sessions. This suggests that the patients had a problem with the acquisition of higher order sequence-specific skill, which would imply that TEA ALF patients' anterograde memory impairments are not restricted to the long-term retention of classically declarative tasks. Interestingly, there was no evidence of ALF for this type of information; while there was a significant decline in higher order sequence-specific skill over twelve hours in the healthy controls, this was not the case in the patients (though it should be noted that it is difficult to assess ALF when initial memory performance is not matched, as discussed in the main introduction to this thesis). However, if it were truly the case that the patients acquired less sequence-specific skill during training than the controls, then one would expect the patients to perform significantly more slowly than the controls on the learned sequence trials immediately preceding the probe (or otherwise for the patients to perform faster than the controls on the probe trials, which would indicate that the patients had greater non-specific skill than the controls, which was masking the patients' lower level of sequence-specific skill during the learned sequence trials). However, this was not the case. Perhaps it was possible to detect a group difference in skill in the absence of a significant group difference in reaction time in either learned sequence or probe trials because the skill analysis represents an investigation of a group difference in a within-subjects effect. However, to increase confidence in the finding that higher order sequence skill acquisition is impaired in TEA ALF patients, the study should be replicated in a larger sample in the future.

During such a replication, a limitation of the current study could be addressed: while the SRTT is a classic implicit task, and while the participants were not told that the task contained a sequence, they may have become aware of the presence of the sequence over the course of training, in which case conscious processes could have contributed to skill learning. Indeed, a few participants spontaneously mentioned that they had noticed a sequence and, after debriefing, more than half of

the participants claimed to have noticed a repeating pattern. A future study could investigate acquisition of explicit knowledge of higher order sequence information more rigorously in additional experimental conditions. A group of participants (group A) could perform a single training session of the task that terminates before the introduction of probe trials, and then have their explicit knowledge of higher order sequence information assessed, using cued-generation tests followed by recognition memory tests. According to Reed and Johnson (1994), the presence of simple event frequency information in second order conditional sequences means that chance performance is inappropriate for use as a benchmark in explicit memory tests for higher order sequence information. Therefore, for the purpose of comparison, a second group of participants (group B) should take the same explicit memory tests, after performing the same number of training trials as group A, but on a string of stimulus-locations that contain no consistent SOC information, while being matched with group A's learned sequence in terms of simple frequency information. If group A have gained explicit knowledge of higher order sequence information, they should exhibit better explicit memory test performance than group B.

Some strategies that could be employed in future studies to minimize explicit learning of the sequence include a reduction in the number of training trials, and the simultaneous performance of another task, such as a tone-counting task (Cohen, Ivry, & Keele, 1990; Nissen & Bullemer, 1987).

In conclusion, this experiment demonstrates that healthy older adults and TEA patients who report symptoms suggestive of ALF are able to acquire and retain some degree of higher order sequence information in an SRTT. The results suggest that these patients might have been relatively impaired in the acquisition or expression of higher order sequence information in this visuomotor skill task. This would represent a substantial departure from the kinds of anterograde memory deficits that

have been reported in this patient population to date, which have been largely restricted to the long-term retention of explicitly reported verbal/visual information. However, the results are somewhat ambiguous and would benefit from replication in a larger sample. Furthermore, a link between these patients' skill acquisition impairments and their ALF remains to be established.

5. Encoding-related brain activity

5.1. Introduction

ALF in TEA is thought to be caused by a memory consolidation deficit (e.g. Kapur et al., 1997) and to be unrelated to encoding. However, often patients with ALF also show learning deficits, or memory deficits over short time-scales (e.g. Butler et al., 2007; Zeman & Butler, 2010). While attempts have been made to dissociate these early problems from forgetting over the longer-term in studies of ALF, either by training participants to criterion, excluding patients with learning problems, restricting analyses to the trials on which learning was equivalent in the two groups (e.g. Hoefeijzers et al., 2013), or presenting non-significant correlations between early and late forgetting rates in patients (e.g. Muhlert et al., 2010), it remains possible that a memory encoding problem contributes to ALF.

Ensuring that learning and early memory behaviour are closely matched between patients and controls does not preclude the possibility that memories in ALF patients are abnormally formed, with consequences usually only becoming apparent later. For instance, a major role of the hippocampus and its surrounding structures (which are critical for long-term memory (e.g. Squire, 1992; Squire & Zola-Morgan, 1991) and are the posited seizure focus in TEA patients (e.g. Zeman & Butler, 2010)) is thought to be the formation of representations that allow us to discriminate between similar experiences (e.g. Bussey et al., 2005; Graham et al., 2010; Lee, Barense, & Graham, 2005; Marr, 1971; O'Reilly & McClelland, 1994; Treves & Rolls, 1994). If the hippocampus were not functioning properly, memories with overlapping components could severely interfere with each other, and it might not be possible to distinguish them. If patients with ALF have a malfunctioning hippocampus, then learning and initial memory performance could potentially appear normal, but the subsequent processing of material with shared features could lead to memory deficits.

Chapter 5.

In the current study, I investigated encoding of novel material using fMRI in order to investigate the possibility that TEA patients who report symptoms suggestive of ALF have abnormal brain activity at the point of encoding that predicts their subsequent memory problems.

In healthy participants, memory encoding has commonly been studied using the subsequent-memory paradigm (e.g. Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Paller, Kutas, & Mayes, 1987; Wagner et al., 1998), in which the brain activity associated with viewing subsequently remembered stimuli is contrasted with that associated with subsequently forgotten stimuli. In these studies, successful encoding has typically been found to be associated with activity in medial temporal lobe memory structures, including the hippocampus, and with prefrontal regions (especially the inferior frontal gyrus), the dorsal posterior parietal cortex, and the fusiform cortex (e.g. Spaniol et al., 2009; Uncapher & Wagner, 2009). A limitation of such event-related designs is that they tend to be underpowered compared to blocked designs. Event-related designs are based on hemodynamic responses to individual stimuli. However, in blocked designs, batches of stimuli are presented with short inter-stimulus intervals, with the result that the responses to the individual stimuli summate, producing large, sustained relative signal changes between stimulation and baseline. Therefore some researchers have sought to look at brain activity relevant to memory encoding by contrasting blocks of novel stimuli, which participants encode, with blocks of familiar stimuli that the participants have seen many times before, and therefore receive only limited encoding (e.g. Filippini et al., 2009; Voets et al., 2009; Voets et al., 2014). For instance, Voets et al. (2014) used this paradigm to show that patients with unilateral temporal lobe epilepsy show reduced activity in the MTL during memory encoding. The current experiment used a mixed design incorporating aspects of these two commonly used paradigms to enhance statistical power yet still reveal neural activity specific to successful versus unsuccessful encoding. Blocks of novel scenes were compared with blocks of repeating scenes, and memory for the novel stimuli was subsequently

tested to reveal stimuli that were successfully encoded. In this type of design, both types of analysis are possible, which means that the block analysis can provide a fall-back option for looking at encoding-related brain activity if the subsequent memory analysis should fail to yield significant results.

According to prevailing views of ALF, patients are expected to have normal memory over the first minutes and hours after encoding but to show significantly poorer memory performance than healthy people after days and weeks. As this experiment was designed to look at encoding-related brain activity relevant to forgetting over the long-term, it involved two subsequent memory tests – one shortly after encoding and one four days later. The majority of subsequent memory experiments in healthy people have used only one subsequent memory test, but some recent studies have used multiple tests and have typically found subsequent memory durability to be related to activity in the medial temporal lobes or posterior cingulate cortex (e.g. Carr, Viskontas, Engel, & Knowlton, 2010; Ritchey, Dolcos, & Cabeza, 2008; Uncapher & Rugg, 2005).

I hypothesised that, contrary to prevalent theories of ALF, TEA patients who report symptoms suggestive of ALF might show brain activity abnormalities at the stage of encoding in the hippocampus or surrounding MTL that predict their forgetting over the long-term.

Chapter 5.

5.2. Methods

The study received ethical approval from the Scotland A Research Ethics Committee and written informed consent was obtained from all participants.

5.2.1. Participants

Ten patients, who met the diagnostic criteria for transient epileptic amnesia and reported symptoms suggestive of ALF, and twelve control participants, took part in this study. The diagnostic criteria for TEA have been published by Zeman and Butler (2010) and are described in the main introduction to this thesis. Details of the ten patients are provided in Table 5.1. Eight of the patients and ten of the control participants were also included in the sleep experiment analyses presented in the first two experimental chapters of this thesis.

The groups did not differ significantly in terms of age, IQ or years of full-time education (see Table 5.2). Their performance on a range of neuropsychological tests is displayed in Table 5.2. All patients were on anticonvulsant monotherapy and, in all cases but one, had been free of seizures for at least six months prior to testing. No patients reported seizures during the experiment. The control participants did not suffer from any psychiatric or central nervous system disorders.

Gender	Age	Age at onset	AEDs (type & mg per day)	Time since seizure (months)	Evidence for a diagnosis of epilepsy			MRI
					EEG	Other Features	Treatment Response	
M	66	63	Le 1000	11	Normal	Brief unresponsiveness	Complete	Normal
M	72	64	C 600	11	Bilateral (L more marked) anterior temporal sharp and slow-wave epileptiform	Brief unresponsiveness	Complete	Normal
M	70	66	Le 2000	31	Non-specific bilateral temporal lobe slowing	Oroalimentary automatisms, gustatory hallucinations	Complete	Normal
M	62	54	La 200	93	L temporal epileptiform	Oroalimentary automatisms	Complete	Normal
M	72	71	La 200	9	Non-specific R temporal slowing	Déjà vu	Complete	Bilateral high T2 signal in hippocampus
M	68	62	C 400	60	Bilateral (L more marked) mid-anterior temporal sharp and slow-wave epileptiform	Oroalimentary automatisms; brief unresponsiveness	Complete	Normal
M	66	56	La 150	110	Normal	Olfactory hallucinations; brief unresponsiveness	Complete	Normal
M	63	59	Le 500	0	Normal	No	Partial	Normal
M	76	73	SV 400	6	Normal	Oroalimentary automatisms; brief unresponsiveness	Complete	Small area of right frontal encephalomalacia
F	60	55	C 300	44	Non-specific bilateral temporal slowing	Brief unresponsiveness	Complete	Normal

Table 5.1. TEA patient information.

NB the time between the fMRI experiment and the patient's last seizure/amnesic attack is only approximate. The seizures experienced by TEA patients are not as clear cut as those in other types of epilepsy. Furthermore, the patients suffer from interictal memory problems. Therefore, reliable accounts were not always available, and this measure should be interpreted with caution. AEDs = Anti-Epileptic Drugs that the patients were taking when they took part in the fMRI experiment, Le = Levetiracetam, C = Carbamazepine, La = Lamotrigine, SV = Sodium Valproate.

	TEA Patients	Controls
N	11	12
Gender	1 female	5 females
Age	67.13(±1.92)	63.67(±1.63)
Years of full-time education	13.50(±0.93)	13.46(±1.08)
IQ tests		
National Adult Reading Test (NART)[a] errors (50 words in test)	11.88(±2.86)	11.83(±2.01)
Predicted WAIS[b] verbal IQ from NART errors	118.13(±2.60)	118.08(±1.84)
WASI[c] vocabulary raw score (max 80)	69.75(±1.88)	69.92(±1.79)
WASI similarities raw score (max 48)	38.25(±1.33)	39.00(±1.14)
WASI verbal IQ	118.50(±2.58)	119.08(±3.02)
WASI block design raw score (max 71)	42.63(±2.87)	47.08(±3.79)
WASI matrix reasoning raw score (max 42)	26.50(±1.34)	24.25(±1.86)
WASI performance IQ	119.63(±2.85)	117.33(±4.07)
WASI full scale-4subtests IQ	121.25(±2.42)	120.58(±3.32)
Anterograde memory		
WMS-III[d] Logical memory story: Immediate recall (max 25)	14.88(±1.14)	17.00(±1.31)
WMS-III Logical memory story: Delayed recall (30mins) (max 25)	11.88(±1.67)	14.58(±1.44)
Recognition Memory Test (RMT)[e]: Words (max 50)	46.38(±0.71)	46.33(±1.10)
Recognition Memory Test (RMT): Faces (max 50)	40.13(±1.56)	44.75(±0.81)*
Semantic memory		
Graded Naming Test (GNT)[f] (max 30)	25.63(±1.16)	24.83(±0.61)
Anxiety and Depression scores		
Hospital Anxiety and Depression Scale (HADS)[g] anxiety (max 21)	5.75(±1.15)	5.33(±0.57)
Hospital Anxiety and Depression Scale (HADS) depression (max 21)	4.13(±1.01)	2.58(±0.58)

Table 5.2. Participant information. Means with SEMs in brackets. The groups did not differ significantly in terms of age or years of full time education. *Patients performed significantly more poorly on this test (Recognition Memory Test for faces, $t_{(20)} = 3.19$, $p=0.005$). For all other tests, there was no significant difference between the groups ($p>0.05$).

[a]NART (Nelson & Willison, 1991; Nelson, 1982); [b]WAIS = Wechsler Abbreviated Intelligence Scale (Wechsler, 1955); [c]WASI = Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); [d]WMS-III = Wechsler Memory Scale-III (Wechsler, 1997); [e]RMT (Warrington, 1984); [f]GNT (McKenna & Warrington, 1980); [g]HADS (Zigmond & Snaith, 1983).

5.2.2. Task Procedure

5.2.2.1. Main task

The task involved participants viewing blocks of novel and blocks of familiar images, deciding whether each image contained an animal and making a forced-choice response accordingly. The experiment was designed and presented using Presentation software (Neurobehavioral systems, Albany, CA).

The stimuli were full colour digital images (of consistent dimensions: 768 x 512 pixels) derived from photographs of real-life scenes. The majority were taken from the stimulus set used by Voets and colleagues (2009) and Filippini and colleagues (2009). Half of the images were dominated by a picture of an animal(s). No animals were visible in the other half of the images.

Before entering the scanner, the participant was given an opportunity to practise the task. During this practice, the stimulus presentation durations and inter-stimulus-intervals were identical to those used in the subsequent main experiment in the scanner (detailed below) and, as in the scanner session, there was no feedback on their button presses. However, in contrast to the main experiment in the scanner, the practice session comprised only sixteen picture presentations, and these were not separated into different blocks. Twelve of these picture presentations were repeated presentations of the same two images, which would make up the 'familiar' blocks of the experiment in the scanner.

In the scanner, the participant was presented with alternating blocks (of 13.5 seconds, each containing ten picture presentations) of novel and familiar pictures. Novel and familiar stimulus blocks were separated by five seconds of rest during which the participant maintained central fixation. The experiment was divided into two runs of sixteen blocks (eight novel, eight familiar), one immediately after the other, to minimise movement artefacts.

In novel blocks, all pictures were unique. There were 160 novel pictures in all during the scan. In familiar blocks, only two pictures appeared, in a pseudo-randomised order. Each picture was

presented for one second. The intervening inter-stimulus interval (ISI) contained only a fixation cross, and had a varying duration (1, 1.5 or 2 seconds). The participant's task was to indicate (with a forced-choice button press on an MR-compatible box) whether the picture contained an animal. Participants were also instructed to memorise the novel stimuli. Figure 5.1 displays an example of the stimuli.

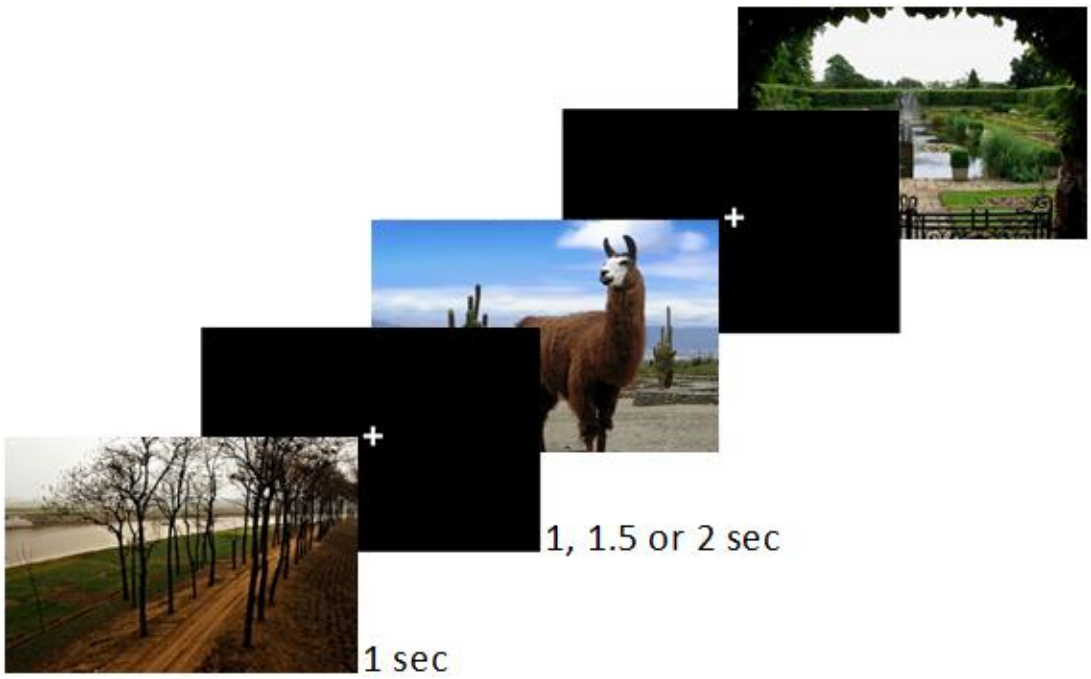


Figure 5.1. Three example stimuli from a novel block of the study task performed during the fMRI scan. Each image was presented for one second. There was an interval of varying duration (1, 1.5 or 2 seconds) between stimuli, during which a fixation cross was presented. The participant's task was to indicate, using an MR-compatible button box, whether each image contained an animal. The participant was also instructed to memorise the novel stimuli.

The first recognition test (*Early*) was performed soon after the participant left the scanner, approximately 40 minutes after the encoding task. This test was performed in a separate room from the scanner, on a laptop computer, with the participant's eyes approximately 55 cm from the screen. No feedback was given. This was a test for half of the pictures that were presented in the scanner (80/160). The participant was shown 160 pictures, half of which were foils. For each image, the

participant was asked to indicate whether the picture was old or new to him/her and to provide a confidence rating. Memory and confidence values were combined using a scale of six numbers, which were displayed on the screen (1 = old, confident; 2 = old, probably; 3 = old, guess; 4 = new, guess; 5 = new, probably; 6 = new, confident). The picture remained on the screen until one of these buttons was pressed. A fixation cross was presented for one second between stimuli.

Four days later, the participant completed another recognition test at home, where they viewed the stimuli on a computer screen and gave responses from the six point scale for each image verbally over the telephone. The internet was used to deliver the images to the participants' own computer on the day of testing. In the event that the participant did not have access to a computer (three cases), he/she was provided with a digital photoframe, preloaded with the test images. During this delayed test, the participant was tested on the other half of the pictures that were presented during the scan (*Late(A)*), with the same number of novel foils (160 images in total). Once this test was completed, the participant was asked to repeat the recognition test that they took on the day of the scan (*Late(B)*), with the same targets and foils. During this repeat test, the participant used the six point scale to indicate whether they had seen the picture in the scanner. While it was known that the results of this test would be contaminated by the prior testing (*Early*), it was hoped that it would allow brain imaging of the encoding of stimuli that could be correctly recognised both initially and four days later, compared to those that could be correctly recognised only initially. The foils were repeated because it would otherwise be possible for the participant to perform the recognition task purely on the basis of having seen the targets in the Early test, without any reliance on encoding done during the scan. However, as will be discussed later, this does complicate the interpretation of the imaging results, as memory durability and source memory are confounded.

The identity of the stimuli presented in the Early and Late(A) tests was counterbalanced across participants; the targets used in the Early test for half of the participants were used in the Late(A) test for the other half of the participants, and vice versa (see Figure 5.2). The order of stimulus presentation within the Early, Late(A) and Late(B) tests was randomised.

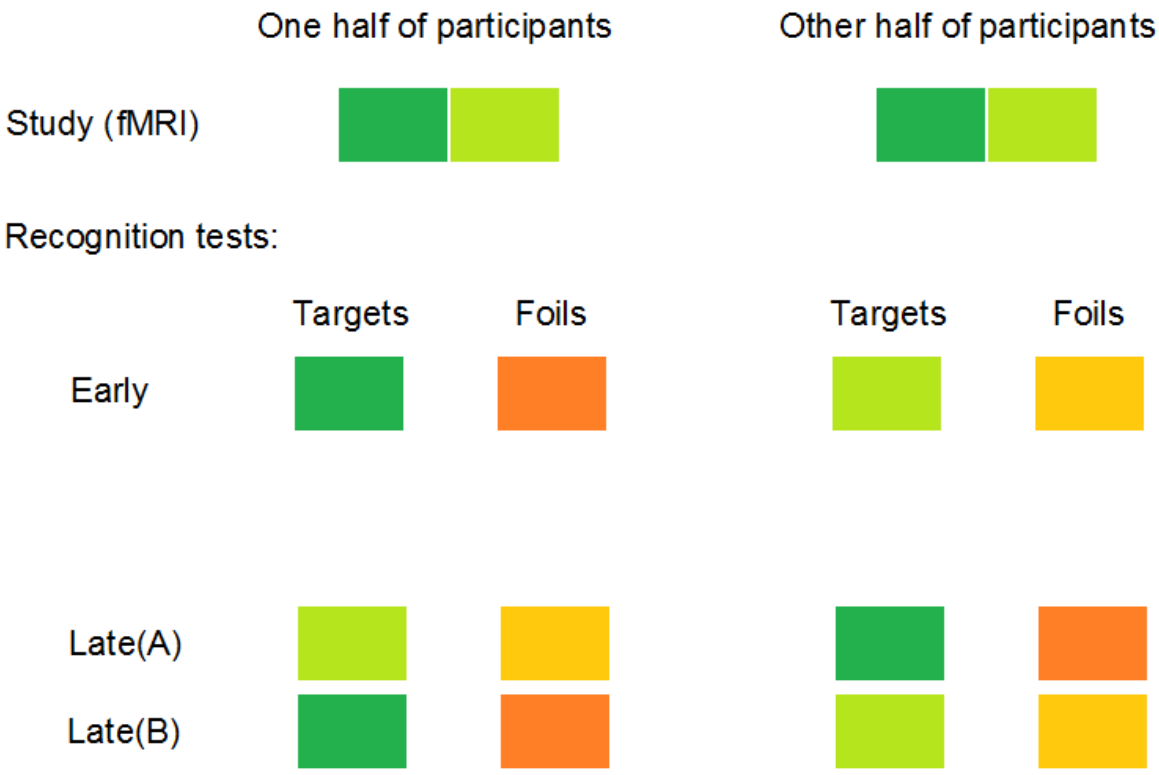


Figure 5.2. An illustration of how the identity of the targets in the Early and Late(A) recognition tests was counterbalanced across participants. Each colour represents a particular set of 80 stimuli. The studied stimuli that served as targets in the Early test for half of the participants were used as targets in the Late(A) test for the other half of the participants and vice versa. Within the study phase and within each of the subsequent recognition tests, the stimuli from the two different sets of 80 (represented by different colours) were presented in an intermixed fashion.

The order in which the stimuli were presented in the scanner was also counterbalanced across participants; half of the participants viewed the blocks of novel and familiar pictures in one order, and the other half viewed the blocks in the reverse order. This means that half of the participants

viewed familiar stimuli during the first and penultimate blocks, while the other half viewed novel stimuli during the first and penultimate blocks. Furthermore, the novel stimuli that were viewed during the first of the two runs of the experiment by half of the participants were viewed during the second run by the other half of participants.

5.2.2.2. Subsidiary tasks

The MRI scan was performed in the 24 hours between the two conditions of the word-pair associates task that was described in the first experimental chapter of this thesis (with the exception of one patient and one control, who could not be scanned at this time, and so had the MRI scan two or three months after the sleep experiment).

On a different occasion, typically separated from the MRI scanning session by at least two weeks, the participants were also tested on an adapted version of the Rey Auditory Verbal Learning Test (RAVLT, Schmidt, 1996). In this task, participants were read a list of fifteen nouns aloud (at a rate of approximately one word every three seconds). After the reading was complete, the participant attempted to recall as many of the words as possible, in any order. If fewer than twelve out of the fifteen were recalled, the full list was read aloud to the participant again before they had a second attempt. This process was repeated until the participant reached a criterion of twelve out of fifteen words. The participant was then distracted for approximately 40 seconds (during which time they were asked to count back from 100 in 3s) before being asked to recall as many of the words from the list as they could (without another exposure). This recall process was repeated after 30 minutes, and then again after one week (over the telephone). Unfortunately, the first two patients who were tested had to be excluded from the analysis because they were given a different criterion and were tested at different time-points, and a third patient was excluded because he admitted to rehearsing

the word-list during the intervening week. The number of months between the MRI scanning session and the RAVLT learning session was not significantly different in the patients and the controls (-0.71 ±2.40 and 3.17 ±2.04, p = 0.25).

5.2.3. Data Acquisition

Imaging data were acquired using a 3 Tesla scanner (SIEMENS MAGNETOM Verio syngo MR B17) and a 32-channel head coil. Functional data were acquired using a gradient echo EPI (echo-planar imaging) sequence (TE: 30 ms, TR: 2410ms, flip angle: 90^{o}, field of view (FOV): 192mm, phase encoding: anterior-posterior, GRAPPA Factor = 2, slices per volume: 44, slice thickness: 3mm, voxel size: 3x3x3mm). Two dummy scans from the beginning of each run were discarded, to allow for T1 saturation. Each of the two runs lasted 8 minutes and 21 seconds.

High resolution structural images were acquired using a T1-weighted MEMPRAGE sequence (van der Kouwe, Benner, Salat, & Fischl, 2008) (slice orientation: sagittal, TR: 2530ms, 4 TEs: 1.69ms, 3.55ms, 5.41ms and 7.27ms (the average image was used), flip angle: 7^{o}, field of view: 256mm, slice thickness: 1mm, voxel size: 1x1x1mm, acquisition time: 6minutes and 3 seconds).

Resting-state scans were performed before and after the encoding task. These scans and the analyses of these data are described in the next chapter of this thesis.

5.2.4. Data Analysis

5.2.4.1. Behavioural analyses

Chapter 5.

Behavioural analyses for the main task of the experiment concentrated on the Early and Late(A) tests, as the Late(B) test results would have been contaminated by the Early test, which used identical stimuli.

Sensitivity (d') was calculated for each recognition test of the main task as: Z(hit rate) – Z(false alarm rate). An ANOVA was performed with d' as the dependent variable, time (two levels: Early and Late(A)) as the within-subjects factor and group as the between-subjects factor. Response bias (criterion, c) was calculated for each recognition test of the main task as: -(Z(hit rate) + Z(false alarm rate))/2. An ANOVA was performed with criterion as the dependent variable, time (two levels: Early and Late(A)) as the within-subjects factor and group as the between-subjects factor. The confidence rating data were analysed using an ANOVA with the number of responses as the dependent variable, time (two levels: Early and Late(A)), stimulus type (two levels: targets and foils) and response(six levels: 1, 2, 3, 4, 5 and 6) as the within-subjects factors and group as the between-subjects factor. Confidence rating data can also be used to derive parameter estimates that are relevant to the memory processes that underlie recognition decisions. See Appendix B for an analysis in which the confidence rating data are used to calculate estimates of recollection and familiarity (an alternative measure of d').

The data from the adapted version of the RAVLT were analysed using an ANOVA with words recalled as the dependent variable, time (four levels: final training trial; 40 seconds; 30 minutes; and one week) as the within-subjects factor and group as the between-subjects factor. Long-term forgetting on this task was defined as the percent forgotten between the 30-mins test and the 1-week test and was compared in the two groups using an independent samples t-test.

5.2.4.2. Imaging data

The imaging data were analysed using FSL (FMRIB's Software Library, Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) version 6.00. The structural images were reoriented using fslreorient2std, and then brain extracted using fsl_anat. The functional data were processed and analysed using FEAT (FMRIB's Expert Analysis Tool, part of FSL). Preprocessing included: brain extraction using BET (Brain Extraction Tool, Smith, 2002); motion correction with MCFLIRT (motion correction using FMRIB's Linear Image Registration tool, Jenkinson, Bannister, Brady, & Smith, 2002); B0 unwarping (which was carried out using BBR (Boundary-Based Registration, Greve & Fischl, 2009), and for which the fieldmap image had to be processed using fsl_prepare_fieldmap and the magnitude fieldmap image had to be skull stripped using BET); spatial smoothing (FWHM: 8mm); and high pass temporal filtering (high pass filter cutoff: 132s for the block analysis and 90s for the event-related analyses).

The data were analysed using a General Linear Model, and temporal autocorrelation correction was achieved using FILM (FMRIB's Improve Linear Model, Woolrich, Ripley, Brady, & Smith, 2001) prewhitening. The first-level design matrix of the block analysis (novel vs. familiar) involved two experimental explanatory variables (EVs, novel and familiar). These were generated using onset and duration information for each of the blocks from the Presentation logfiles to produce a square wave model of neural activity, which was then convolved with a double-gamma HRF (hemodynamic response function). For each experimental EV, a temporal derivative was added (to allow for differences in slice acquisition times, and slight variability in the timing of the explanatory variable stimulation and the HRF delay), and temporal filtering was used. Additional confound EVs (generated from the preprocessed data) were included in the analysis: fsl_motion_outliers was used to identify volumes corrupted by substantial motion; and the mean timecourses from an ROI in the cerebrospinal fluid (CSF) of the anterior lateral ventricle and an ROI in the white matter of the dorsal posterior frontal lobe were used to account for physiological noise (Leech, Braga, & Sharp, 2012).

These ROIs were 3-mm radius spheres centred on the MNI coordinates 2 10 8 and -26 -22 28, respectively, before registration to native space using nearest neighbour interpolation.

For the event-related subsequent-memory analysis, each novel stimulus was coded according to whether it was correctly identified as old (remembered) or incorrectly labelled as new (forgotten) in the subsequent Early and Late(A) tests. The stimuli presented during familiar blocks were coded separately. There were five experimental EVs at the first level: Early remembered; Early forgotten; Late(A) remembered; Late(A) forgotten; Familiar.

For the additional analysis pertaining to memory persistence, each stimulus that appeared in the Early test (which was also tested in the Late(B) repeat test) was coded according to its mnemonic fate in both the Early and Late(B) tests. The stimuli tested in the Late(A) test and the stimuli presented during familiar blocks were coded separately. There were seven experimental EVs at the first level: Remembered Remembered; Remembered Forgotten; Forgotten Forgotten; Forgotten Remembered; Late(A) remembered; Late(A) forgotten; Familiar. One patient was excluded from this analysis for having no Remembered Forgotten trials in one of their fMRI runs.

Contrasts of the parameter estimates for the experimental EVs (COPEs) were used in second-level analyses. The two runs from each participant were combined using a second-level fixed-effects analysis. At the third level, mixed-effects voxel-wise group analyses were conducted. Unless stated otherwise, third level z-statistic images were thresholded using clusters identified by $z>2.3$ and a corrected cluster significance threshold of $p=0.05$ (Worsley, 2001).

Within FEAT, FLIRT_BBR was used to register each participant's functional data to his/her high-resolution structural image and FNIRT (Andersson, Jenkinson, & Smith, 2010) (with 12 degrees of freedom for the linear component, and a warp resolution of 10mm) was used to register each participant's structural image to standard space (MNI-152 template).

The hippocampus was of particular interest in this study, as this brain area is implicated in both memory encoding and transient epileptic amnesia. For ROI analyses, left and right hippocampus masks were taken from the Harvard-Oxford subcortical atlas, thresholded and binarised such that all voxels with an intensity value below 20 were excluded from the mask and all other voxels took a value of 1, and transformed into the native space of each participant. The mean percent signal change for the contrasts of interest within these masks were then calculated for each participant using Featquery. Statistical analyses were then performed on these data and reported as significant when $p<0.05$ (as was also the case for behavioural analyses).

As shown in the results section of this chapter, the patients had a significantly lower d' than the controls on the Early test but not on the Late(A) test, indicating that the main task of this experiment was not sensitive to ALF in these patients. A significant group difference was found for the left hippocampal response for stimuli that would go on to be forgotten. To investigate the relevance of this neural finding for ALF, I looked at the relationship between the left hippocampal response for stimuli that went on to be forgotten in the Early test (i.e. the test on which the patients showed a behavioural deficit, and the stimuli for which the patients showed the smallest left hippocampal response at encoding) and long-term forgetting in other tasks, which are sensitive to ALF, i.e. the word-pair associates task and the adapted RAVLT. Long-term forgetting in these tasks was calculated as the percent forgotten between the 30-mins test and the delayed test (12-hrs in the word-pair

associates task and 1-week in the adapted version of the RAVLT). Two-tailed Pearsons correlation tests were performed. Fisher's Z transformation was used to look for group differences in the correlations. The same analyses were performed for the left hippocampal response for stimuli that went on to be remembered on the Early test but subsequently forgotten on the Late(B) test. The significant results are reported.

5.3. Results

5.3.1. Behaviour

5.3.1.1. Main task

5.3.1.1.1. Performance

Figure 5.3 displays the d' for the patients and controls in the Early and Late(A) memory tests. An ANOVA with d' as the dependent variable, time (two levels: Early and Late(A)) as the within-subjects factor and group as the between-subjects factor, revealed: a main effect of group ($F_{(1,20)}$ = 6.46, p=0.019), with the patients performing more poorly (estimated marginal mean (EMM) and standard error of the mean (SEM): 0.71 ±0.11) than the controls (EMM ±SEM: 1.07 ±0.097); a main effect of time ($F_{(1,20)}$ = 85.70, p<0.001), with performance declining between the Early test (EMM ±SEM: 1.18 ±0.088) and the Late(A) test (EMM ±SEM: 0.60 ±0.068); and an interaction between time and group ($F_{(1,20)}$ = 15.03, p=0.001), with the patients performing significantly more poorly than the controls on the Early test (0.88 ±0.13 and 1.49 ±0.12, p=0.002) but not on the Late(A) test (0.54 ±0.10 and 0.66 ±0.092, p=0.385), and both the controls (p<0.001) and the patients (p<0.002) showing a significant performance decline with time.

While the patients had a lower d' than the controls in the Early memory test, their hit rate was not lower than that of the controls (0.69 ±0.041 and 0.70 ±0.031, respectively), but their false alarm rate

was higher than that of the controls (0.36 ±0.040 and 0.18 ±0.025, respectively, $t_{(20)}$ = -3.94, p = 0.001).

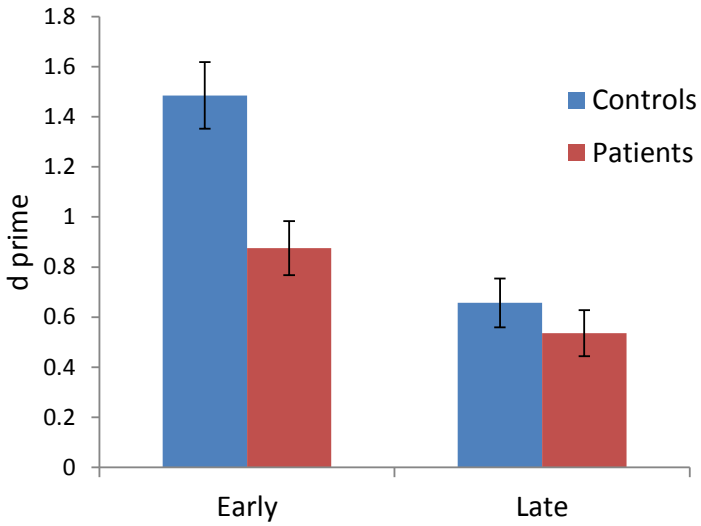


Figure 5.3. D' in the Early and Late(A) recognition memory tests. The patients had a significantly lower d' than the controls on the Early test, but not on the Late(A) test.

The patients also performed significantly more poorly than the controls on the Late(B) test (d' in the patients: 0.25 ±0.073, d' in the controls: 0.50 ±0.067, $t_{(20)}$= 2.51, p= 0.021).

Figure 5.4 displays the criterion (c, a measure of response bias) for the patients and controls in the Early and Late(A) memory tests. An ANOVA with criterion as the dependent variable, time (two levels: Early and Late(A)) as the within-subjects factor and group as the between-subjects factor, revealed only a significant main effect of group ($F_{(1,20)}$ = 10.36, p=0.004), with the controls exhibiting a greater bias to respond 'new' (EMM ±SEM: 0.27 ±0.076) than the patients (EMM ±SEM: -0.088 ±0.083). The controls' criterion was significantly different from zero in both the Early test (0.21 ±0.057, $t_{(11)}$ = 3.59 , p= 0.004) and the Late(A) test (0.34 ±0.070, $t_{(11)}$ = 2.91, p= 0.014), while the

patients' criterion was not significantly different from zero in either test (-0.068 ±0.097 and -0.11 ±0.085).

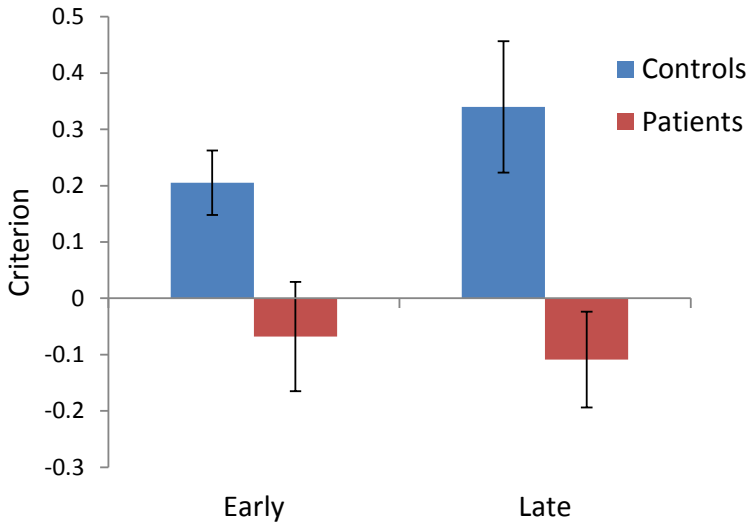


Figure 5.4. Response bias (criterion) in the Early and Late(A) tests. Positive values indicate a bias towards responding new/no and negative values indicate a bias towards responding old/yes. The response bias was significantly different in the two groups.

There was no significant group difference in criterion in the Late(B) test. For this test, the controls' mean criterion was not significantly different from zero (-0.11 ±0.070), while the patients' mean criterion was significantly more negative than zero (-0.23 ±0.071, $t_{(10)} = -3.26$, p= 0.01), indicating a bias towards responding 'old'.

5.3.1.1.2. Confidence ratings

Figure 5.5 displays the confidence rating information for the Early and Late(A) tests.

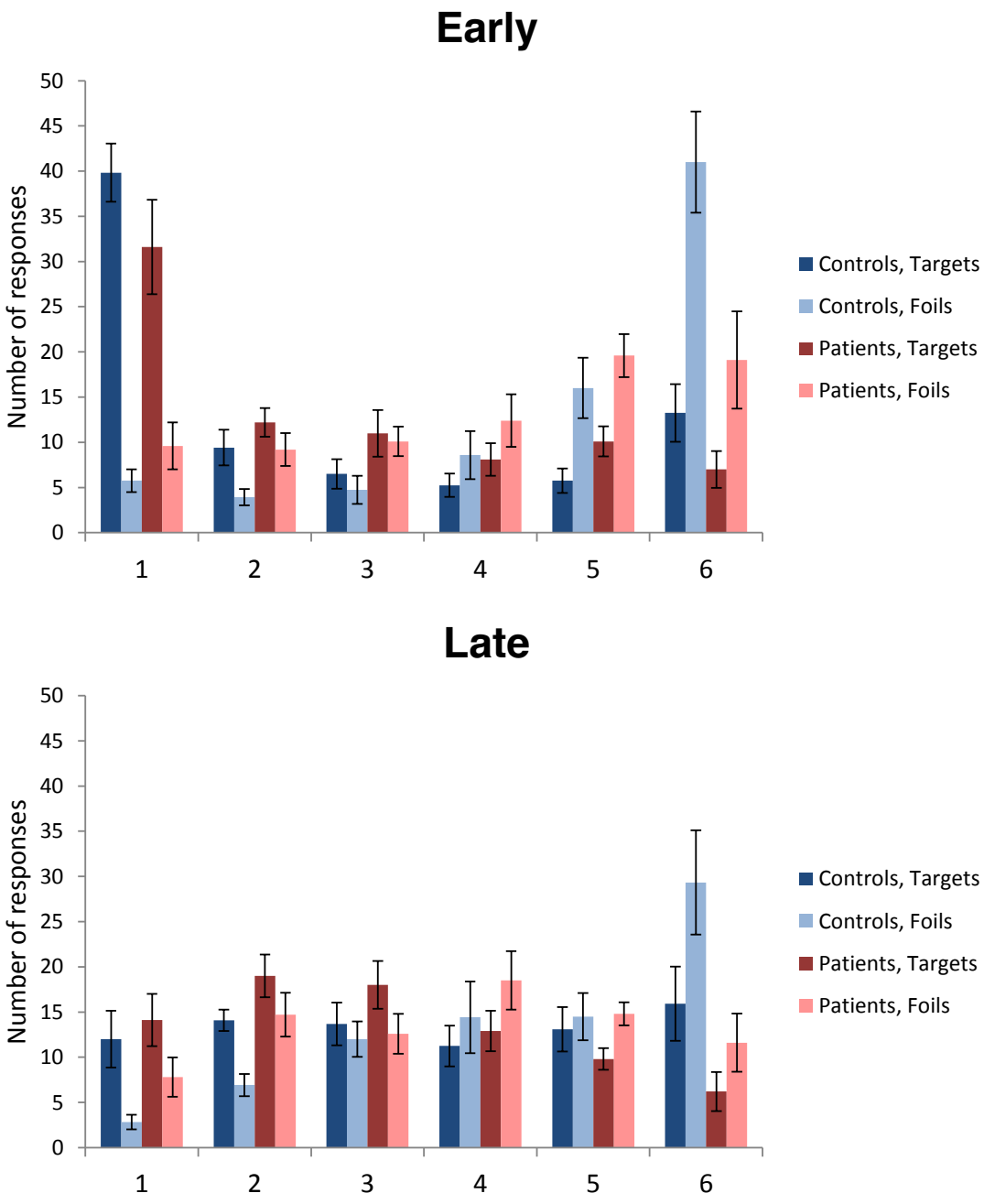


Figure 5.5. Confidence rating information. The mean (and SEM) number of responses of the different types for the targets and foils in the Early test and the Late(A) test in the controls and the patients are displayed. There were 80 targets and 80 foils in each test.

The ANOVA with number of responses as the dependent variable, time (two levels: Early and Late(A)), stimulus type (two levels: targets and foils) and response (six levels: 1, 2, 3, 4, 5 and 6) as the within-subjects factors and group as the between-subjects factor revealed: an interaction between stimulus and response ($F_{(2.16,43.24)} = 52.704$, $p<0.001$); an interaction between time and response ($F_{(3.48,69.56)} = 17.47$, $p<0.001$); an interaction between time, stimulus and response ($F_{(3.45,69.05)} = 30.22$, $p<0.001$); an interaction between response and group ($F_{(1.88,37.63)} = 3.98$, $p=0.029$); and an interaction between stimulus, response and group ($F_{(2.16,43.24)} = 4.43$, $p=0.016$). The interaction between time, response and group was non-significant ($p=0.31$). The interaction between time, stimulus, response and group also did not reach significance once the Greenhouse-Geisser correction was applied.

Post-hoc t-tests were then performed for the significant ANOVA effects involving group. The patients produced fewer 6s ($p=0.015$), but more 2s ($p=0.004$), than the controls did. The controls gave more 6s than they gave 2s ($p=0.015$), but this was not the case for patients. The EMMs and SEMs for the number of 1s, 2s, 3s, 4s, 5s, and 6s produced by the controls were 15.10 ±1.95, 8.58 ±1.09, 9.23 ±1.63, 9.88 ±2.28, 12.33 ±1.69 and 24.88 ±3.51, respectively. The equivalents in the patients were 15.78 ±2.13, 13.78 ±1.18, 12.93 ±1.79, 12.98 ±2.50, 13.58 ±1.85 and 10.98 ±3.85.

The patients gave more 1s ($p=0.036$) and 2s ($p=0.001$) to foils than the controls did. The controls gave more 6s to foils than the patients did ($p=0.008$). In the controls, there were more 1s than 2s ($p=0.014$), 3s ($p=0.026$), 4s ($p=0.008$) or 5s ($p=0.009$) for targets, and there were more 6s than 1s ($p<0.001$), 2s ($p<0.001$), 3s ($p=0.003$) or 5s ($p=0.042$), for foils, and more 5s than 1s ($p=0.030$) or 2s ($p=0.012$) for foils. In the patients, the only significant difference was more 1s than 6s for targets ($p=0.018$). The EMMs and SEMs for the number of 1s, 2s, 3s, 4s, 5s, and 6s for targets in the controls

were 25.92 ±3.05, 11.75 ±1.33, 10.08 ±1.79, 8.25 ±1.64, 9.42 ±1.54 and 14.58 ±2.81, respectively. The equivalents for foil stimuli were 4.29 ±1.32, 5.42 ±1.12, 8.38 ±1.58, 11.50 ±3.00, 15.25 ±2.10 and 35.17 ±4.55. The EMMs and SEMs for the number of 1s, 2s, 3s, 4s, 5s, and 6s for targets in the patients were 22.85 ±3.34, 15.60 ±1.46, 14.50 ±1.96, 10.50 ±1.79, 9.95 ±1.68 and 6.60 ±3.08, respectively. The equivalents for foil stimuli were 8.70 ±1.45, 11.95 ±1.23, 11.35 ±1.73, 15.45 ±3.29, 17.20 ±2.30 and 15.35 ±4.98.

5.3.1.2. RAVLT word-list task

Both the training and testing of the subsidiary word-list task occurred outside of the scanner. The patients and controls did not require a significantly different number of trials to reach criterion in the word-list task (5.14 ±1.26 and 4.75 ±1.45, respectively, p=0.23). The performance on the final training trial, and on the tests after 40 seconds, 30 minutes and one week are displayed in Figure 5.6. An ANOVA with words recalled as the dependent variable, time (four levels: final training trial; 40 seconds; 30 minutes; and one week) as the within-subjects factor and group as the between-subjects factor revealed a significant main effect of group, with the patients performing significantly more poorly on the task than the controls (EMMs ±SEMs: 8.68 ±0.54 and 10.54 ±0.41, $F_{(1, 17)} = 7.63$, p=0.013), a significant main effect of time ($F_{(1.89, 32.07)} = 75.08$, p<0.001), and a significant interaction between time and group ($F_{(1.89, 32.07)} = 4.82$, p=0.016). Post-hoc t-tests showed that the groups did not perform significantly differently on the final training trial (12.43 ±0.30 and 12.96 ±0.23, p=0.54) or the 40-seconds test (10.29 ±0.64 and 11.42 ±0.49, p=0.18), but that the patients performed more poorly than the controls on the tests after 30 minutes (9.43 ±0.67 and 11.25 ±0.51, p=0.046) and one week (2.57 ±1.17 and 6.83 ±0.90, p=0.010).

The percent forgotten between the 30-minutes test and the 1-week test was significantly greater in the patients than the controls (72.79 ± 7.97% and 40.32 ± 7.66%, $t_{(17)} = -2.76$, p=0.013, see Figure 5.6).

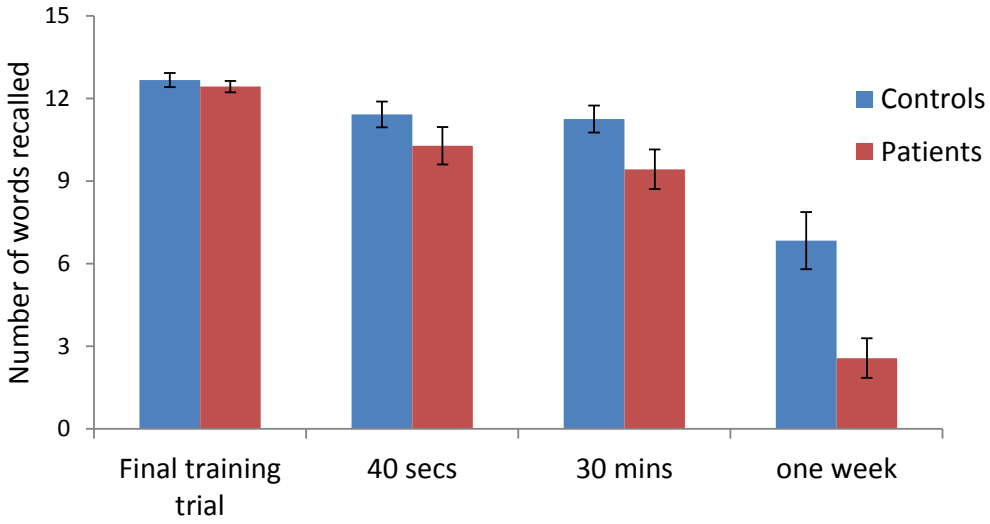


Figure 5.6. Performance on the word-list recall task (RAVLT). The error bars represent SEMs. The patients performed significantly more poorly than the controls on the 1-week test and the 30-minutes test, but not on the final training trial or the 40-seconds test. The percent forgotten between the 30-minutes test and the 1-week test was significantly greater in the patients than the controls.

5.3.2. Imaging

5.3.2.1. Novel vs. Familiar

Across all participants, several brain regions were found to be more strongly activated during the novel blocks than the familiar ones. These included temporal regions (the temporo-occipital part of the inferior temporal gyrus, the temporal occipital fusiform cortex and the medial temporal lobes), frontal regions (the anterior cingulate cortex, the inferior frontal gyrus, the middle frontal gyrus, the superior frontal gyrus, the frontal orbital cortex and the ventromedial frontal pole/frontal medial cortex), parietal regions (the superior parietal lobule and the retrosplenial cortex/precuneus) and occipital regions (the occipital pole, the occipital fusiform gyrus, the lingual gyrus, the intracalcarine

and supracalcarine cortices, the cuneal cortex, and the inferior and superior lateral occipital cortex), in addition to parts of the thalamus and basal ganglia. Figure 5.7 displays these results, thresholded using clusters defined by $z>3.1$ and a cluster significance threshold of $p=0.05$ (Worsley, 2001). The maxima can be viewed in Table 5.3.

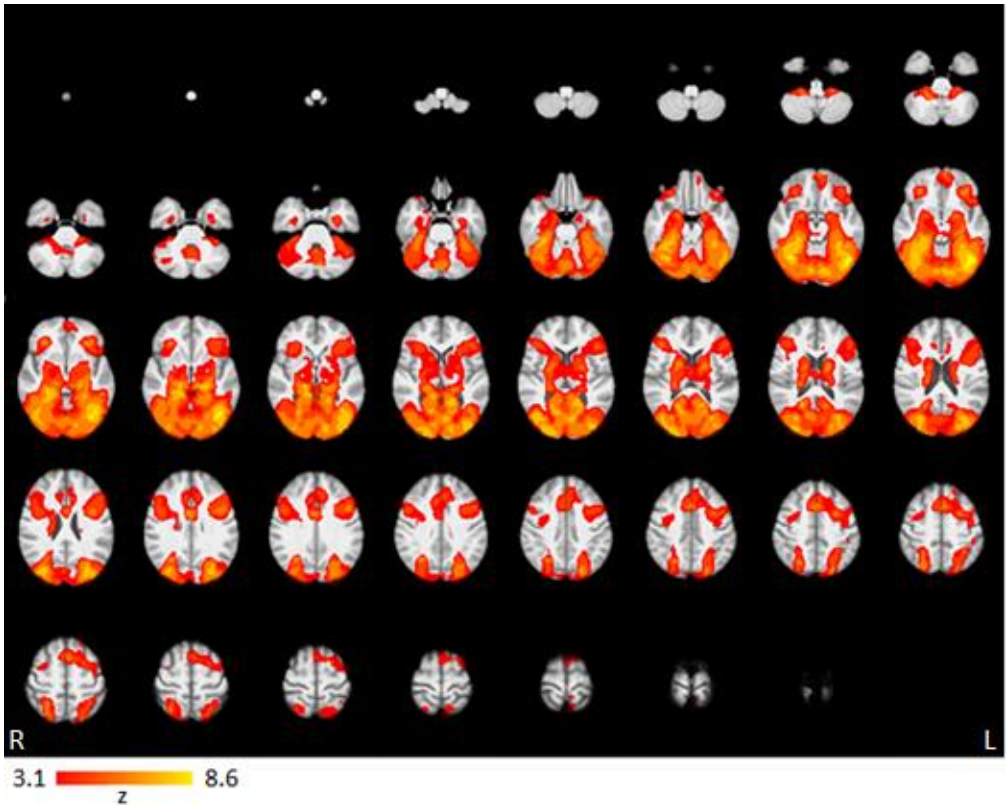


Figure 5.7. Mean activity across all participants for the contrast novel > familiar, thresholded using clusters identified by z>3.1 and a corrected cluster significance threshold of p=0.05 (Worsley, 2001). The areas include the fusiform cortex and the medial temporal lobes, the inferior frontal gyrus and the ventromedial frontal pole, the retrosplenial cortex and visual cortical areas.

Brain Region	**x**	**y**	**z**	**Z**
Temporo-occipital inferior temporal gyrus/inferior lateral occipital cortex	-46	-64	-16	8.62
Temporal occipital fusiform cortex	32	-50	-14	7.86
Ventromedial frontal pole	-2	60	-14	6.14
	0	70	-6	3.31
Frontal medial cortex	-8	52	-16	5.20
	-6	42	-18	4.32
Occipital fusiform gyrus/temporal occipital fusiform cortex	38	-60	-14	7.86
Occipital fusiform gyrus/inferior lateral occipital cortex	-36	-74	-12	8.08
Inferior lateral occipital cortex	-42	-68	-6	8.10
	-38	-72	-2	8.06

Table 5.3. Maxima in MNI coordinates (mm) for the mean activity across all participants for the contrast novel > familiar.

There were no brain areas that were significantly more active in the controls than the patients for this contrast. Areas found to be more active in the patients than the controls can be seen in Figure 5.8. These include the posterior division of the superior temporal gyrus and planum temporale in the right hemisphere, the insular/central operculum bilaterally, and the post and pre central gyri of the right and left hemispheres. The maxima can be viewed in Table 5.4.

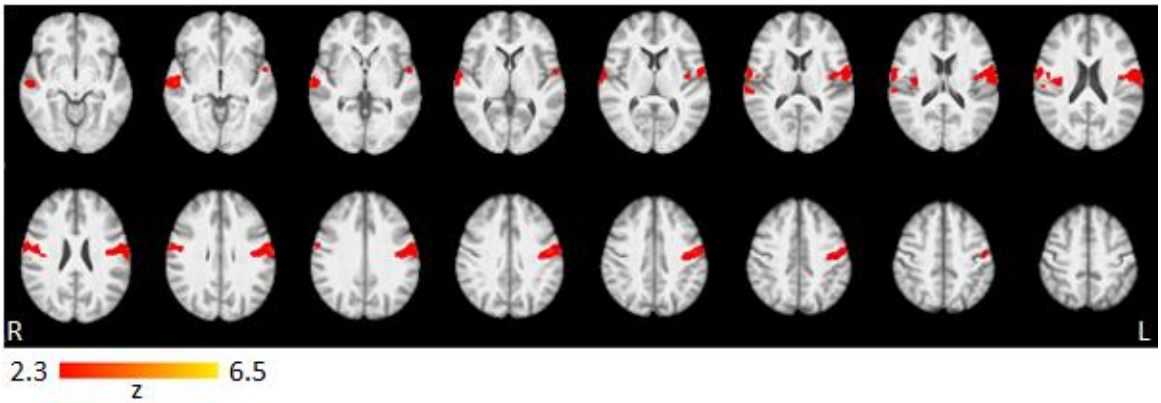


Figure 5.8. The brain areas in which the novel > familiar contrast was significantly greater in the patients than the controls. These include the posterior division of the superior temporal gyrus and planum temporale in the right hemisphere, the insular/central operculum bilaterally, and the pre and post central gyri in the right and left hemispheres.

Brain Region	**x**	**y**	**z**	**Z**
Right posterior superior temporal gyrus	56	-18	-4	3.31
	68	-18	0	3.29
Central opercular cortex	40	-16	20	2.96
Right postcentral gyrus	50	-8	24	2.94
	66	-8	16	2.93
Right precentral gyrus	66	-2	12	3.17
Left postcentral gyrus	-62	-6	30	3.28
	-64	-16	24	3.17
	-64	-8	20	3.09
Left precentral gyrus	-50	-10	36	3.29
	-56	-4	30	3.11
	-60	-4	36	3.09

Table 5.4. Maxima in MNI coordinates (mm) for patients > controls for the contrast novel > familiar.

To identify the nature of this group difference, the difference image was binarised and transformed into the native space of each participant, where it was used as a mask from which to extract the mean percent signal change associated with the novel and familiar lower level contrasts. The results are plotted in Figure 5.9.

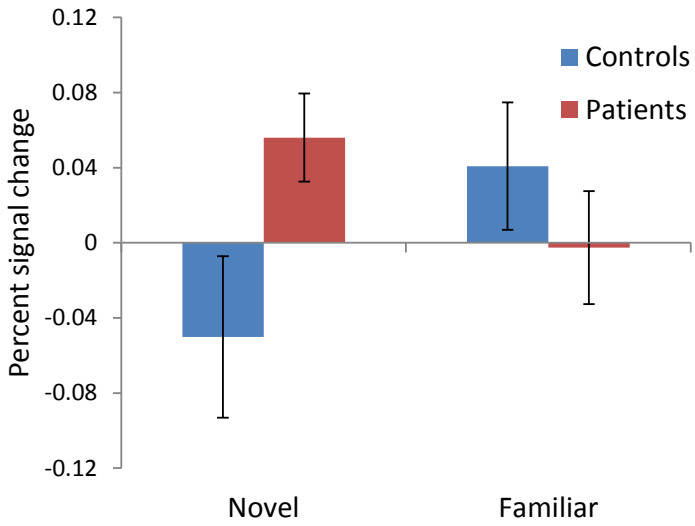


Figure 5.9. Mean percent signal change for the novel and familiar contrasts within the areas that showed a group difference (patients > controls) for the contrast between novel and familiar blocks (novel > familiar). The bars each represent a mean across a group of participants. The error bars represent SEMs. These regions were deactivated in novel compared to familiar blocks in the controls ($p<0.001$) but activated in novel compared to familiar blocks in the patients ($p=0.013$).

As shown in Figure 5.9, the control participants appear to have deactivated these brain regions in response to novel stimuli relative to familiar ones ($t_{(11)} = -4.01$, $p<0.001$), while the patients did not; instead, they activated them for novel stimuli relative to familiar ones ($t_{(9)} = 3.60$, $p=0.013$).

5.3.2.2. Subsequent memory analyses

5.3.2.2.1. Remembered vs Forgotten

5.3.2.2.1.1. Whole-brain analysis

The novel stimuli were coded according to whether they were subsequently remembered (hits) or forgotten (misses) the first time they were tested (Early or Late(A)). The brain regions that were more active for subsequently remembered stimuli than for subsequently forgotten stimuli, across all participants, are displayed in Figure 5.10. The activation was in bilateral ventral occipitotemporal regions, and included the lateral occipital cortex (which was the locus of the peak activation in both the left hemisphere cluster (MNI coordinates (mm): -36 -84 4, z=4.39) and the right hemisphere cluster (46 -64 -6, z=3.9)), the occipital fusiform gyrus, the temporal occipital fusiform cortex and the temporo-occipital part of the inferior temporal gyrus bilaterally, in addition to a little of the posterior temporal fusiform cortex in the right hemisphere.

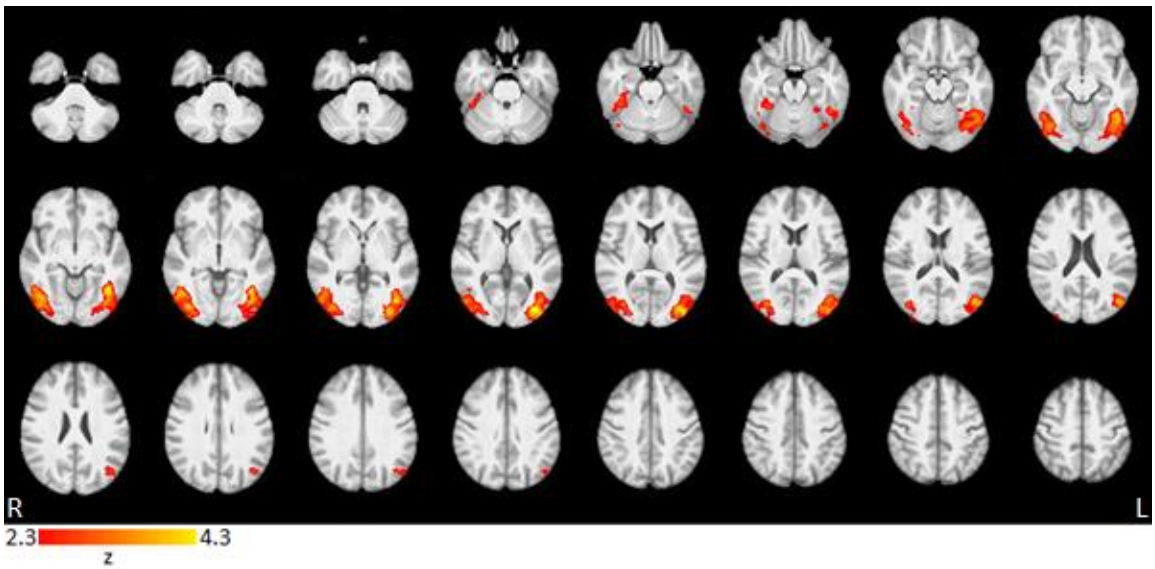


Figure 5.10. Brain areas that were significantly more active for subsequently remembered stimuli than for subsequently forgotten stimuli. These are bilateral ventral occipitotemporal regions. They include the inferior lateral occipital cortex, the occipital fusiform gyrus, the temporal occipital fusiform cortex and the temporo-occipital part of the inferior temporal gyrus bilaterally, in addition to a little of the posterior temporal fusiform cortex in the right hemisphere.

There were no significant group differences at the whole brain level. There were no brain areas that showed a greater subsequent memory effect for stimuli tested at the Late(A) time-point compared to the Early time-point, nor vice versa.

5.3.2.2.1.2. Hippocampus ROIs

Figure 5.11 displays the percent signal change in the left (left hand charts) and right (right hand charts) hippocampi associated with stimuli that were subsequently remembered and subsequently forgotten on the Early (top charts) and Late(A) (bottom charts) tests.

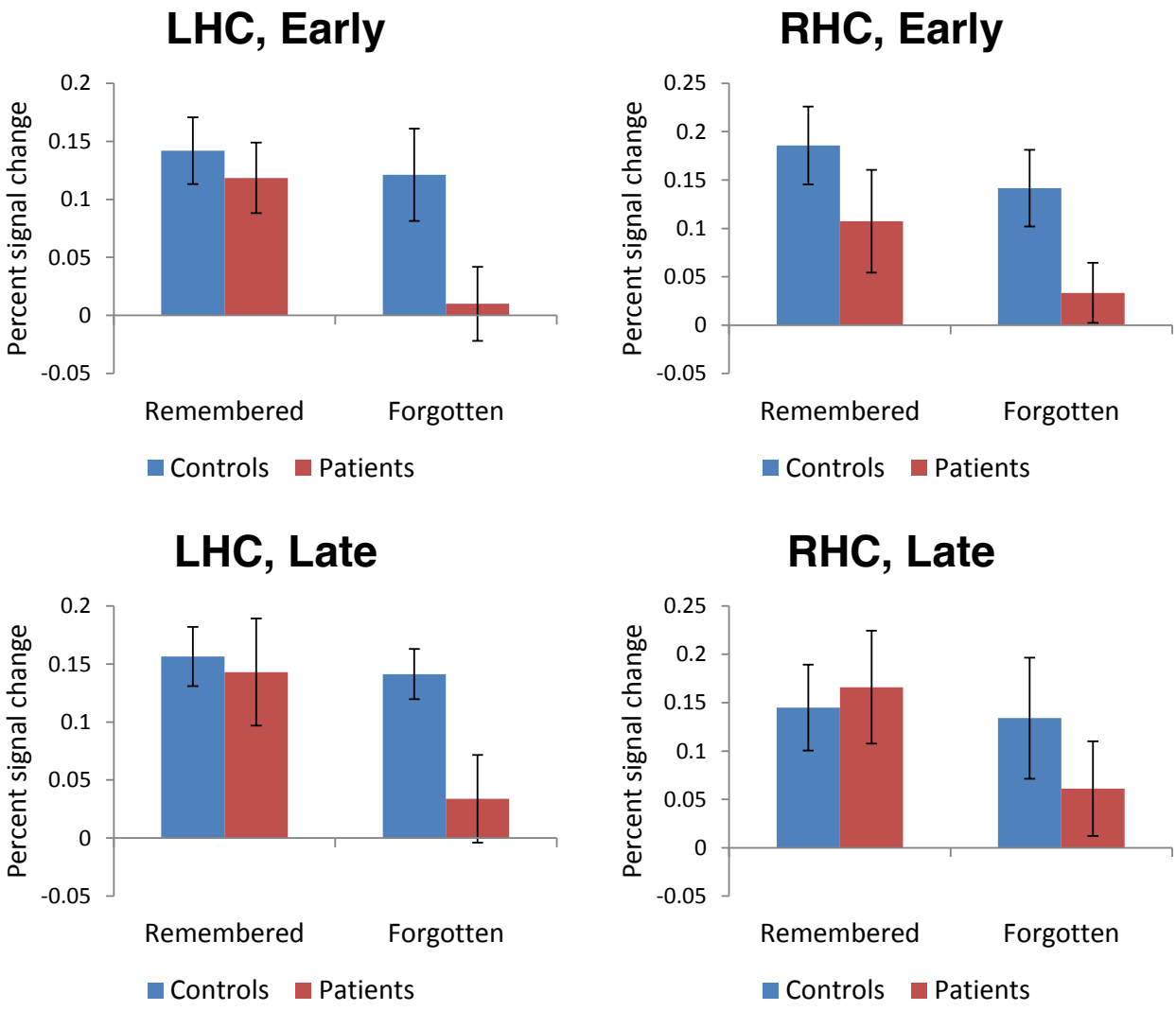


Figure 5.11. Mean percent signal change in the left and right hippocampi (left and right sides of the figure, respectively) associated with the stimuli that were subsequently remembered and subsequently forgotten on the Early (top half of the figure) and Late(A) (bottom half of the figure) tests. Each bar represents a mean across a group. The error bars represent SEMs. Subsequently remembered stimuli were associated with more activity in the hippocampus than subsequently forgotten stimuli. In the left hippocampus, this effect was significantly greater in the patients than the controls. There was significantly less left hippocampal activity associated with subsequently forgotten stimuli in the patients than the controls, but this was not the case for subsequently remembered stimuli.

For the left hippocampus, an ANOVA with percent signal change as the dependent variable, testing time (two levels: Early and Late(A)) and subsequent memory (two levels: remembered and forgotten) as the within-subjects factors and group as the between-subjects factor was performed. It revealed a significant main effect of subsequent memory ($F_{(1,20)}$ = 20.78, p<0.001), with greater activity associated with subsequently remembered (EMM ±SEM: 0.14 ±0.021%) than subsequently forgotten (EMM ±SEM: 0.077 ±0.019%) stimuli, and a significant interaction between subsequent memory and group ($F_{(1,20)}$ = 10.64, p = 0.004). Post hoc t-tests showed that the percent signal change was significantly lower in the patients than the controls for the subsequently forgotten stimuli only (EMMs ±SEMs: 0.022 ±0.028% and 0.13 ±0.025%, p=0.009) and not for subsequently remembered stimuli (EMMs ±SEMs: 0.13 ±0.032% and 0.15 ±0.029%, p=0.67). The percent signal change was greater for the subsequently remembered than the subsequently forgotten stimuli in the patients only (p<0.001) and not in the controls (p=0.35). The interaction between subsequent memory, group and testing time was not significant (p=0.92) and there was no main effect of group (p=0.11).

In the equivalent analysis for the right hippocampus, the only effect to reach significance was the main effect of subsequent memory ($F_{(1,20)}$ = 10.76, p = 0.004), with greater percent signal change for the subsequently remembered (EMM ±SEM: 0.15 ±0.032%) than the subsequently forgotten (EMM ±SEM: 0.093 ±0.027%) stimuli. The interaction between subsequent memory and group did not reach significance (p = 0.097). Again, the interaction between subsequent memory, group and testing time was not significant (p=0.45) and there was no main effect of group (p=0.31).

5.3.2.2.1.2.1. Relationship between the neural data and long-term forgetting

As discussed later in this chapter, the main task of this experiment was not sensitive to ALF. Behavioural deficits were seen on the Early memory test and the forgetting thereafter was not accelerated. As a result, the relevance for ALF of the encoding-related brain activity difference remains unclear from these data alone. Therefore, the relationship between the neural data and forgetting over the long-term (between early and delayed tests) on the word tasks was investigated. In the patient group, there was a significant negative correlation between the percent signal change in the left hippocampus for stimuli that were subsequently forgotten on the Early test and the percent forgotten between 30 minutes and twelve hours in the word-pair associates task that was discussed in Chapter 2 ($r=-0.718$, $p=0.019$, see Figure 5.12), i.e. the lower the percent signal change, the greater the long-term forgetting in the word-pair associates task. In the control participants, the degree of left hippocampal activity at the stage of encoding for these subsequently forgotten stimuli was not significantly related to long-term forgetting in the word-pair associates task ($r=-0.332$, $p=0.29$, see Figure 5.12).

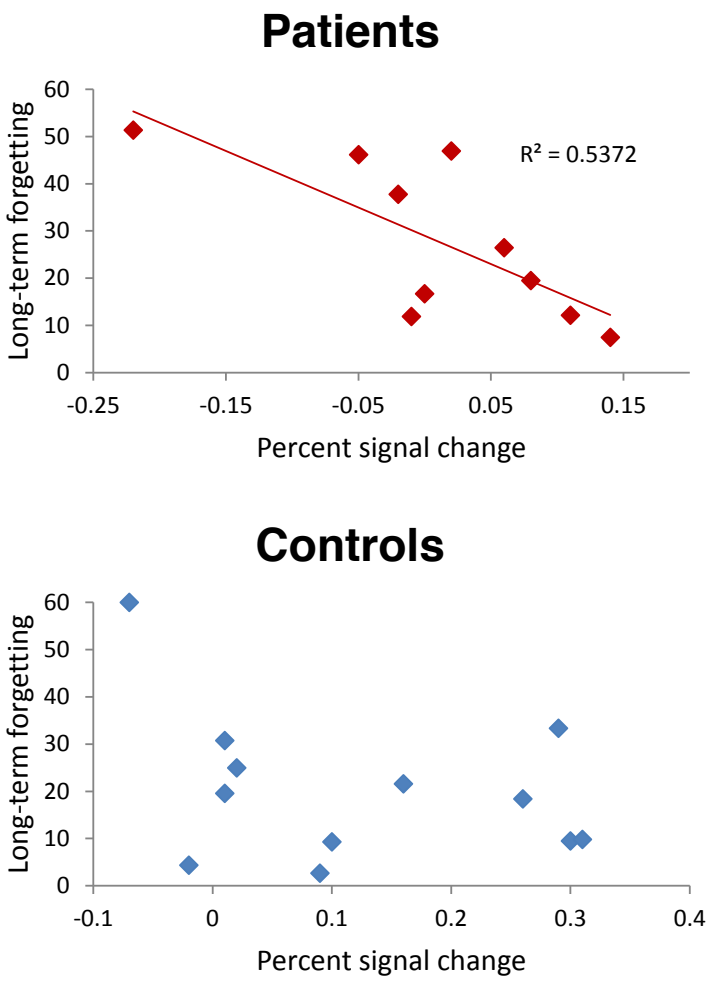


Figure 5.12. The relationship between percent signal change in the left hippocampus for stimuli subsequently forgotten on the Early test of the main task and forgetting between 30 minutes and twelve hours on the word-pair associates task in the patients and controls. In the patients, there was a significant negative correlation (r= -0.718, p=0.019). There was no significant correlation between these variables in the controls (r= -0.332, p=0.29).

5.3.2.2.2. Repeated test analyses

5.3.2.2.2.1. Whole brain analysis

The brain areas that were significantly more active for stimuli that were subsequently remembered on both the Early and Late(B) tests than for stimuli that were remembered on the Early test only, and forgotten on the Late(B) test, are displayed in Figure 5.13. There is only one cluster. It is situated in the left medial temporal lobe, over the hippocampus and the posterior parahippocampal gyrus.

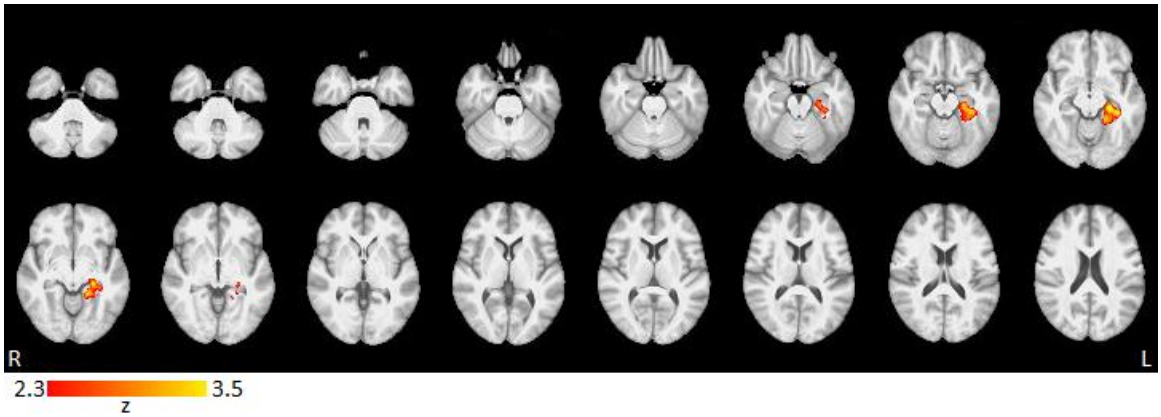


Figure 5.13. Brain areas that were significantly more active for stimuli that were subsequently remembered on both the Early and Late(B) tests than for stimuli that were subsequently remembered on the Early test only, and forgotten on the Late(B) test. The cluster is in the left medial temporal lobe, over the hippocampus and the posterior parahippocampal gyrus.

No significant group differences were found at the whole-brain level.

5.3.2.2.2.2. Hippocampus ROIs

Figure 5.14 displays the percent signal change in the left and right hippocampi associated with stimuli that were subsequently remembered on both the Early and Late(B) tests (Remembered Remembered, RR) and stimuli that were subsequently remembered on the Early test only, and not the Late(B) test (Remembered Forgotten, RF).

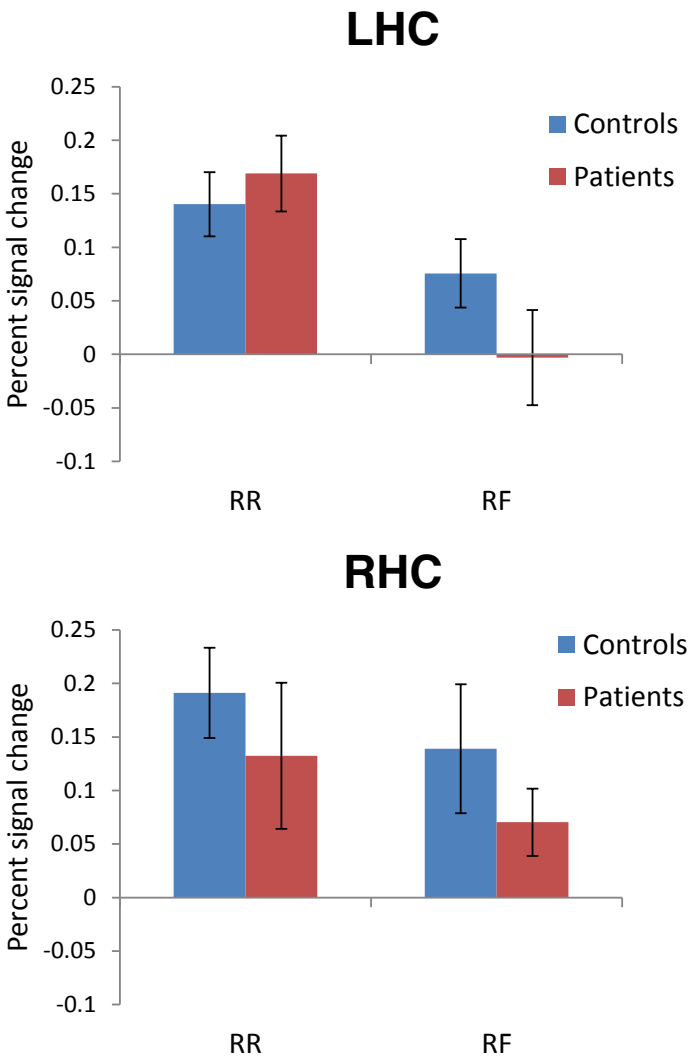


Figure 5.14. The percent signal change in the left (top) and right (bottom) hippocampi associated with stimuli that were subsequently remembered on both the Early and Late(B) tests (RR) and stimuli that were subsequently remembered on the Early test only, and not the Late(B) test (RF). RR stimuli were associated with more activity in the left hippocampus than RF stimuli. This effect only reached significance in the patients.

For the left hippocampus, an ANOVA with percent signal change as the dependent variable, memory performance persistence as the within-subjects factor and group as the between-subjects factor was performed. It produced a significant main effect of memory performance persistence ($F_{(1,19)}$ = 21.11, $p<0.001$), with more activity associated with RR (EMM ±SEM: 0.16 ±0.023%) than RF (EMM ±SEM: 0.036 ±0.027) stimuli. The interaction between memory performance persistence and group was

marginally significant ($F_{(1,19)}$ = 4.34, p=0.051). The difference between RR and RF reached significance in the patients only (RR: 0.17 ±0.035%, RF: -0.003 ±0.040%, p<0.001) and did not quite reach significance in the controls (RR: 0.14 ±0.030%, RF: 0.076 ±0.035%, p=0.070). While the response in the left hippocampus for RF stimuli was significantly greater than 0 in the controls ($t_{(11)}$ = 2.36, p=0.038), this was not the case for patients (p=0.95).

In the equivalent analysis for the right hippocampus, no effects reached significance.

5.3.2.2.2.2.1. Relationship between the neural data and long-term forgetting

In the patient group, the percent signal change in the left hippocampus for stimuli that were subsequently remembered on the Early test but forgotten on the Late(B) test (i.e. RF stimuli) showed a significant negative correlation with the percent of words forgotten between 30 minutes and one week on the RAVLT word-list task (r=-0.884, p=0.019, see Figure 5.15), i.e. the lower the percent signal change, the greater the long-term forgetting in the word-list task. In the control participants, the degree of left hippocampal activity at the stage of encoding for these stimuli was not significantly related to long-term forgetting in the word-list task (r= 0.368, p=0.24, see Figure 5.15). The correlation was significantly different in the two groups (Fisher's Z = 2.67, p<0.01). As the credibility of the correlation in the patients might be considered somewhat questionable, given that it contains only 6 data points, the significant positive correlation between the percent signal change and the raw score on the 1-week test is also presented (r = 0.953, p=0.003), to lend additional weight to the relationship between encoding-related brain activity and memory performance over the long-term. Again, this relationship was not found in the controls (r = -0.503, p=0.095), and the correlation was significantly different in the two groups (Fisher's Z = -3.63, p<0.01).

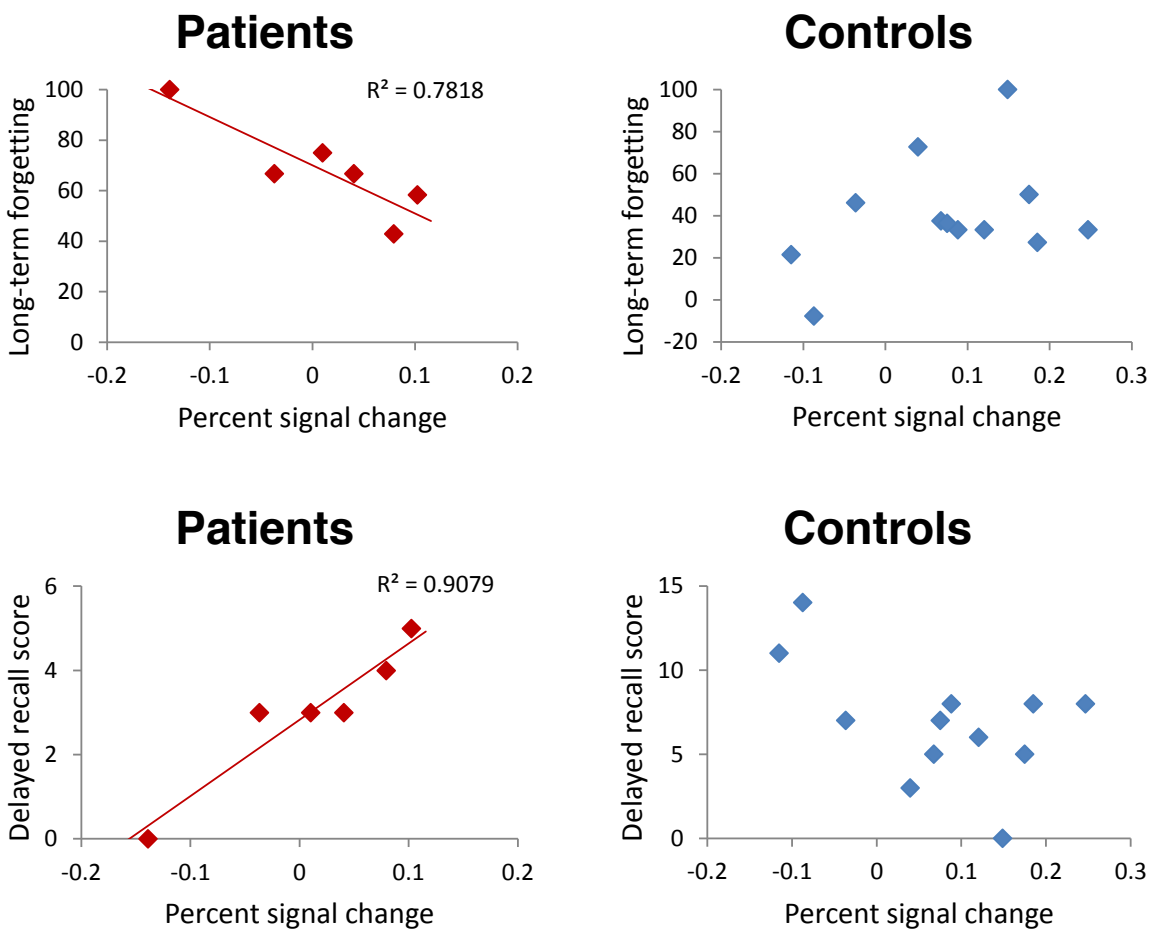


Figure 5.15. The relationship between forgetting over the long-term and the percent signal change in the left hippocampus for stimuli subsequently remembered on the Early test but not the Late(B) test. Percent signal change correlated negatively with forgetting between 30 minutes and one week on the word-list recall task in the patients (top left, r=-0.884, p=0.019). In the controls (top right) the correlation was not significant (r= 0.368, p=0.24), and significantly differed from that in the patients (Fisher's Z = 2.67, p<0.01). Percent signal change correlated positively with word-list recall score at one week in the patients (bottom left, r = 0.953, p=0.003). In the controls (bottom right), the correlation was not significant (r = -0.503, p=0.095), and was significantly different from that in the patients (Fisher's Z = -3.63, p<0.01).

5.4. Discussion

This experiment revealed differences in brain activity at the stage of encoding in TEA patients who report symptoms suggestive of ALF compared to healthy controls that relate to their subsequent memory performance.

5.4.1. Major findings

The main task of this experiment was not sensitive to ALF as it is traditionally reported; the patients did not exhibit normal early performance and abnormally poor delayed performance. Instead, they performed significantly more poorly than the controls on the first memory test, which was approximately 40 minutes after encoding, and they did not perform significantly more poorly than the controls on the equivalent test after four days.

There was also a group difference in response bias: the control participants had a greater bias to respond 'new' in the early and late(A) tests than the patients. This group difference in response bias may reflect group differences in attitudes towards one's own memory. Unless a stimulus elicits a relatively strong memory-related response, healthy people might be inclined to declare the stimulus new, while patients, who are aware that they have memory problems, may not demand that they experience such a strong memory-related response before declaring a stimulus old. There were also group differences in confidence ratings. The patients made fewer high confidence correct rejections than the controls. The patients made more high and medium confidence false alarms than the controls. In the controls, there were more high and medium confidence new responses than other kinds of responses for the foil stimuli. This was not the case in the patients. It is not surprising that there were group differences in false alarms, given the group difference in response bias. However, it is perhaps surprising that the group difference reached significance for high and medium

confidence false alarms, but not for low confidence false alarms. It may be the case that the patients experienced a relatively strong memory-related response for some foil stimuli as a result of a diminished ability to resolve feature ambiguity between foils and encoded stimuli (e.g. Bussey et al., 2005), as discussed below.

However, while the main task of this experiment failed to detect ALF, the RAVLT word-list task, like the word-pair associates task discussed in Chapter 2, was shown to be sensitive to long-term retention deficits in TEA ALF patients. The patients were already performing significantly more poorly than the controls after 30 minutes, but they also performed significantly more poorly than the controls after one week, and the percent of words forgotten between 30 minutes and one week was greater in the patients than the controls.

Due to recruitment problems and testing space constraints for the sleep experiment that accompanied the MRI scan, the number of participants that it was possible to test during the doctoral period was limited. Nevertheless, robust activations were observed in response to novel vs. familiar blocks. These were found in a number of brain regions, including the medial temporal lobes and the fusiform cortex, the inferior frontal gyrus and the ventromedial frontal pole, the retrosplenial cortex and visual cortical areas. These results are similar to those found in the studies on which the blocked component of this experiment's design was based (e.g. Filippini et al., 2009; Voets et al., 2009), but the frontal lobe activation was more marked. The difference was significantly greater for the patients than the controls for some brain areas, including the posterior division of the superior temporal gyrus and planum temporale in the right hemisphere, and the insular/central operculum and the pre- and post- central gyri bilaterally. In the healthy participants, these areas were deactivated for novel blocks compared to familiar blocks. However, in the patients, they were

activated for novel blocks compared to familiar blocks. This difference is difficult to interpret. Interestingly, the same areas have also been identified as more active in people with unusual APOE genotypes than in controls for a similar contrast (subsequently remembered novel items>familiar items, Trachtenberg et al., 2012). Akin to the results presented here, these areas were found to be deactivated for the experimental contrast in control participants, and activated for the people with unusual APOE genotypes. These unusual APOE genotypes predispose the carriers to future neurological disease, and the findings were interpreted as reflecting a failure to disengage non-task related brain areas during encoding. The people with unusual APOE genotypes were thought to be using less specialised networks to perform the task and to have less distinct functional boundaries between the medial temporal lobe memory system and the rest of the brain.

A whole-brain analysis across all participants showed that the subsequently remembered stimuli were associated with more activity in ventral occipitotemporal regions, including the fusiform cortex, than the subsequently forgotten stimuli. The fusiform cortex has been shown to be more active for subsequently remembered than forgotten stimuli in many previous studies (e.g. Garoff, Slotnick, & Schacter, 2005; Kirchhoff, Wagner, Maril, & Stern, 2000; Wagner et al., 1998). However, no significant clusters were found in the medial temporal lobes, prefrontal regions or the dorsal posterior parietal cortex in the current experiment, which many have been a result of limited power due to a relatively small number of participants.

The whole-brain analyses (in which multiple comparisons corrections were made for every voxel in the brain) did not yield significant subsequent-memory group differences. However, hippocampus ROIs revealed interesting results. The stimuli that the patients went on to forget were associated with reduced activity in the left hippocampus compared to the stimuli that were subsequently

remembered, and compared to the subsequently forgotten stimuli in the controls. The percent signal change in the left hippocampus associated with stimuli that were subsequently forgotten in the early test was negatively correlated with forgetting between 30 minutes and twelve hours in the word-pair associates task. This means that the degree of hippocampal hypoactivity for subsequently forgotten stimuli was correlated with long-term forgetting. The correlation was absent in the control group.

Across all participants, stimuli that were subsequently persistently, as compared to only transiently, remembered were associated with activity in the left medial temporal lobe. In the patients, the percent signal change in the left hippocampus for transiently remembered stimuli was not significantly different from zero and, across individuals, it correlated negatively with forgetting between 30 minutes and one week in the word-list recall task. This means that the less positive the change in left hippocampal activity for subsequently transiently remembered stimuli, the greater the forgetting over the course of a week. This correlation was non-significant in the control group and was significantly different between the groups.

5.4.2. Interpretation and future work

The nature of the experimental design somewhat complicates the interpretation of the memory performance persistence effect in the medial temporal lobe. The same foils were used in the repeat of the recognition test four days later, which means that the participants were no longer distinguishing old from new stimuli, but old from old. Accurate performance on the repeat test may have relied upon the ability to retrieve the learning context (the scanner vs only the post-scan testing room). Therefore this contrast of subsequently persistently vs. transiently remembered stimuli is not a clean measure of memory durability, and might be related to source memory (which

may be a function of the hippocampus, Davachi, Mitchell, & Wagner, 2003). Nevertheless, there was a difference in activity in the left hippocampus at the point of encoding between subsequently persistently and transiently remembered stimuli in the patients, and the degree of activity associated with the latter predicted ALF over one week.

It should be noted that the patients had a significantly lower d' than the controls in the repeat recognition test, in spite of normal performance on the discrimination between as-yet-untested target stimuli and novel foils. This is perhaps unsurprising given that other patient groups with compromised hippocampal function have been shown to have particular problems with remembering where and when they learnt a piece of information (e.g. Vargha-Khadem et al., 1997).

The TEA ALF patients showed significant behavioural memory deficits at early time-points in some tasks but not others. In the main task of this experiment, the patients showed memory performance deficits on the first recognition test, which was within 40 minutes of encoding. The patients also performed significantly worse than the controls on the Recognition Memory Test for faces (as can be seen in Table 5.2 of the methods section) and on the 30 minutes test of the RAVLT word-list recall task. However, they did not perform significantly more poorly than the controls on other memory tasks, such as the WMS-III logical memory story (see Table 5.2 of the methods section). If ALF is related to unusually low hippocampal activity at the stage of encoding of some memories, why do these patients show deficits within an early time-frame on some tasks but not others?

In light of the fact that the medial temporal lobes (MTL), especially the hippocampus, are thought to be important for discriminating between events with overlapping components and thereby

minimising the effects of interference (e.g. Buckley, Booth, Rolls, & Gaffan, 2001; Bussey & Saksida, 2007; Bussey et al., 2005; Graham et al., 2010; Hardt et al., 2013; Lee et al., 2012; Marr, 1971; O'Reilly & McClelland, 1994; Treves & Rolls, 1994; Warrington & Weiskrantz, 1978; Yassa & Stark, 2011), I am tempted to speculate that the patients have more difficulty discriminating between similar stimuli/experiences, and the timescale over which accelerated forgetting appears depends on how soon such processes are required for normal performance on the task.

In the adapted version of the WMS-III logical memory task that was used in this experiment, the participants were read a short story aloud and asked to immediately recall it, and then asked to recall it again after approximately 30 minutes. It is unlikely that any events would have happened over the course of these 30 minutes that would have shared enough features with the story that the separating function of the MTL would have been required for subsequent accurate story recall. Instead, it is likely that more time would have to pass before the processing of sufficiently similar information occurred as to cause interference in the patients.

However, the RAVLT word-list is made up of common, unrelated individual nouns. The 30 minutes after training were filled with many other cognitive tests and conversations (with the same experimenter, in the same room) which may have involved these words, or semantically related ones, in some cases. If this were the case, the patient might have had difficulty keeping the episode of the word-list distinct from the other episodes that occurred during the next 30 minutes, resulting in impaired recall of the target memories.

When a task involves the encoding of a large number of novel stimuli that have many overlapping features (such as the 50 black and white male faces of the Recognition Memory Test for faces, or the 160 pictures of scenes in the main task of this experiment), these stimuli may interfere with each other during the encoding period in the patients. Furthermore, the foils in the recognition test will most likely share features with encoded stimuli. Therefore poor recognition performance might be expected as soon as memory is tested. In the Recognition Memory Test for faces, the test was immediate. In the main task of this experiment the recognition test was within approximately 40 minutes of the encoding phase, and it is impossible to know how the patients would have performed had the test been immediate.

To test for diminished ability to discriminate between experiences/enhanced susceptibility to interference in TEA patients with ALF, the degree of feature overlap between the information to be encoded, the retroactive interference inputs in the retention interval, and the foils (in the case of recognition memory tasks) could be experimentally manipulated. It is worth noting that patients with medial temporal lobe lesions have been shown to be especially vulnerable to interference (e.g. Cowan et al., 2004; Dewar et al., 2009; Warrington & Weiskrantz, 1978). In fact, patients and animals with lesions in the medial temporal lobes have been shown to have difficulty making perceptual discriminations between stimuli with overlapping features (e.g. Barense, Gaffan, & Graham, 2007; Bartko, Winters, Cowell, Saksida, & Bussey, 2007a; Bartko, Winters, Cowell, Saksida, & Bussey, 2007b; Lee, Barense, et al., 2005; Lee, Bussey, et al., 2005). Therefore, a number of researchers have argued that the medial temporal lobes are not a long-term memory-specific system, but are instead responsible for complex conjunctive representations that support not only long-term memory, but also perception and working memory (e.g. Bussey & Saksida, 2007; Graham et al., 2010; Lee et al., 2012). Research in this field has found evidence to suggest that the hippocampus is particularly important for making difficult discriminations for scenes and spatial

information, while the perirhinal cortex is particularly important for making difficult discriminations for objects and faces. This has led to the proposal that functional subdivisions within the MTL are related to material type (e.g. Graham et al., 2010; Lee, Buckley, et al., 2005), rather than memory processes (e.g. Aggleton & Brown, 1999; Brown & Aggleton, 2001). Given that the TEA ALF patients tested in the current experiment showed performance impairments on the Recognition Memory Task for faces as well as the scene stimuli of the main task, future studies should also interrogate brain activity in the perirhinal cortex during encoding of objects and faces.

In fMRI tasks in healthy people, if the same stimulus is repeatedly presented, many brain areas, including the MTL, will show a diminished response, which is often referred to as the repetition-suppression effect (e.g. Grill-Spector, Henson, & Martin, 2006). When pictures that are similar, but not identical, to previously presented pictures are shown to healthy people, many brain regions show repetition suppression but, notably, parts of the hippocampus do not (Bakker, Kirwan, Miller, & Stark, 2008; Kirwan & Stark, 2007). This indicates that the hippocampus is able to separate these similar stimuli, while other brain regions are not. In the TEA patients with ALF, the diminished hippocampal activity when viewing stimuli that go on to be forgotten might be an indication that these stimuli are, at the time, erroneously processed as though they are repetitions (instead of being encoded as new stimuli) because they share many features with previously encountered stimuli, and the hippocampus is failing to separate the stimuli. It would be interesting to conduct an incidental encoding fMRI experiment with these patients in which the feature overlap between the stimuli is experimentally manipulated to form a range of different degrees of feature ambiguity.

If this is the case, then hippocampal hypoactivity might only be detectable on tasks in which the set of encoding stimuli share many overlapping features. Therefore on other tasks, in which behavioural

memory deficits might not appear until later, this hypoactivity might not be seen, and some other more sensitive measure would be required to detect differences in brain activity between subsequently remembered and subsequently forgotten stimuli. In healthy people, multivariate voxel pattern analysis (MVPA) techniques can be used to identify the patterns of neural activity that correspond to the formation of stimulus-specific memory representations (e.g. Deuker et al., 2013). It may be possible to find evidence for the formation of impoverished hippocampal memory representations (which are highly susceptible to subsequent interference) in TEA ALF patients using MVPA.

An alternative explanation for the results of the current experiment is that the reduced hippocampal activity at the stage of encoding is instead an indication that a sub-standard hippocampal representation is being formed, which would render that memory trace vulnerable to subsequent interference from similar information (which might be other pictures in the encoding set in this situation, but could also be information in the retention interval). If this were true, we might expect to still see this hippocampal hypoactivity even in tasks where the stimuli in the encoding set do not share many overlapping features. It might also imply that only those memories associated with a low level of hippocampal activity are especially vulnerable to interference, rather than all memories. In another experiment, using real-time fMRI and a carefully crafted stimulus set, it might be possible to introduce interference in the retention interval specifically for events that were associated with more or less hippocampal activity at the point of encoding, in order to test this theory.

This latter possibility is perhaps more compatible with the finding that stimuli that are only transiently remembered by the patients are associated with reduced hippocampal activity at encoding compared to stimuli that are persistently remembered. If hippocampal hypoactivity were

an indicator of current catastrophic interference, then one might not expect different levels of hippocampal activity for two classes of stimulus that are both remembered at least initially. However, if the level of hippocampal activity signified representation quality (indicating the robustness of the memory to subsequent interference) then one might expect this difference; some vulnerable representations might not have been interfered with by other stimuli in the set during the encoding period, but might have experienced interference over the next four days e.g. from the foils used in the early recognition test. Furthermore, if the hippocampal hypoactivity were an indicator that the stimulus was being treated as old during the scan, then it is not immediately obvious why the stimulus would not be treated as old on the subsequent memory test (i.e. given a yes rather than a no response).

If accelerated forgetting is caused by increased vulnerability to interference between similar experiences, then why are early memory deficits not seen on all tasks as a result of proactive interference i.e. interference from pre-existing memories that share features with the information being encoded? It might be the case that, in healthy people, the disambiguating function of the hippocampus and its surrounding structures is only critical for avoiding catastrophic interference between new and relatively recent experiences. The slow learning neocortical system might, over time, be able to support the associations between the components of an experience independently of the hippocampus. If TEA ALF patients encode some information relatively normally, and this information does not undergo accelerated forgetting, then it might undergo consolidation processes normally and eventually become independent of the hippocampus over time. If this is the case then, when the patients learn something new, a lack of proper separation between this new memory and related older memories in the hippocampus might not be an issue because the latter would no longer be supported by the hippocampus; perhaps only relatively new memories, which are all currently hippocampus-dependent, would provide a large amount of interference with one another

if hippocampal separation functions were to falter. However, hippocampus-independence may not be permanent; reactivation of old memories might render them dependent on the hippocampus again, at least briefly (e.g. Debiec, LeDoux, & Nader, 2002). The reprocessing of old, related memories, as is proposed to happen during systems consolidation of recently-acquired memories (e.g. McClelland et al., 1995), might result in interference in TEA ALF patients, as discussed in the chapters on slow wave sleep (Chapter 3) and post-encoding rest (Chapter 6).

The results of the current experiment might be interpreted as suggesting that the degree of input from the left hippocampus at the stage of encoding is important for memory performance in TEA ALF patients but not in healthy controls. One possible explanation is that a certain degree of input from the hippocampus at encoding is necessary for adequate pattern separation but that, once this criterion is met, additional hippocampal activity has little impact and other factors determine memory performance.

Another issue to bear in mind is the potential influence of response bias on the neural activity associated with stimuli that have a particular mnemonic fate. As mentioned above, the control participants had a greater bias to respond 'new' than the patients in the early and late(A) tests of the main task of this experiment. A group difference in response bias on the recognition tests used to categorise stimuli as subsequently remembered and forgotten might potentially produce group differences in the neural activity related to subsequent memory. For this reason, the results should be interpreted with some degree of caution.

Another reason to exercise caution in the interpretation of the subsequent memory-related fMRI results is the short duration of the intervals between the events of the fMRI experiment; as the hemodynamic response is relatively slow, the use of short inter-stimulus intervals can make it difficult to disambiguate responses to separate events.

Another consideration is that group differences in brain activity measured with fMRI can potentially be a result of group differences in brain structure. The results of a voxel-based morphometry analysis of these participants' structural images are presented in Chapter 7.

It is possible that the lateralisation observed in these fMRI results is related to the location of the epileptic foci in this patient sample. While precise epileptic focus information is not typically readily available in TEA patients, Table 5.1 indicates that there might be a left vs right bias in the patients of this study. This might account for the group differences in the left, but not the right, hippocampus in this experiment. Another issue to bear in mind in fMRI studies of epileptic patients is the possible effect of epileptic medication on the BOLD response. For instance, there is some evidence that carbamazepine might reduce fMRI activation during memory processing (Jokeit, Okujava, & Woermann, 2001). However, while three of the ten TEA patients in this study were taking carbamazepine, all of these patients were on low doses, and it is not immediately obvious why epileptic medication should affect the BOLD response in the left hippocampus but not the right hippocampus, and only for the stimuli that the patients go on to forget.

In conclusion, this experiment demonstrates for the first time that brain activity at the stage of encoding correlates with forgetting over the long-term in TEA patients who complain of ALF. The

patients exhibited hypoactivity in the left hippocampus for stimuli that went on to be forgotten. This hippocampal activity correlated with long-term forgetting in TEA ALF patients but not in healthy people. Confidence in these interesting results would be increased if they could be replicated in a larger, more gender-balanced, sample. The precise meaning of the reduced hippocampal activity is unclear and should be investigated in further experiments.

6. Brain activity at rest

6.1. Introduction

6.1.1. Background

When we are resting, our brains are not 'at rest'; instead, they are constantly active. This activity is not meaningless noise; functionally related brain regions are coactive during rest. Indeed, many studies have demonstrated that networks of brain regions that commonly work together to achieve certain tasks also have correlated activity during the resting state (e.g. Beckmann, DeLuca, Devlin, & Smith, 2005; Fox & Raichle, 2007).

Resting state networks (RSNs) are most commonly studied using fMRI, and are revealed by looking at the correlation of spontaneous low frequency (<0.1Hz) fluctuations in the blood oxygen level dependent (BOLD) signal between different brain regions. Using a technique called independent components analysis (ICA), it is possible to decompose resting-state data into separate RSNs. Using this data driven approach, RSNs can be automatically isolated from the various noise components in the absence of any a priori specification of brain areas of interest.

The Default Mode Network (DMN) was one of the first RSNs to be discovered. The DMN involves a number of brain areas, including: the anterior medial prefrontal cortex (aMPFC); parts of the medial temporal lobes (MTL); the posterior cingulate cortex (PCC); and inferior, lateral regions of the parietal cortex (Boly et al., 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Greicius, Srivastava, Reiss, & Menon, 2004; Gusnard & Raichle, 2001; Raichle et al., 2001). The DMN is unusual in that it is much more active during the resting state than when we are engaged in most specific tasks (Gusnard & Raichle, 2001; Raichle et al., 2001). The DMN bears a striking resemblance to the network of brain regions involved in episodic memory retrieval.

As discussed by Rugg and Vilberg (2013), the brain areas that participate in episodic memory retrieval include the hippocampus, and other regions of MTL, the retrosplenial cortex/PCC, the aMPFC and the inferior lateral parietal cortex/angular gyrus. The latter area is commonly found in fMRI studies of successful episodic memory retrieval, but the effects of lesions in this area on episodic memory retrieval performance are less clear-cut than for the other regions of the network (Rugg & Vilberg, 2013). Abnormal functional connectivity between regions of this network during the resting state has been found in neurological disorders in which memory deficits are prominent, including Alzheimer's disease (e.g. Wang et al., 2006), amnestic mild cognitive impairment (e.g. Dunn et al., 2014) and temporal lobe epilepsy (TLE) (e.g. Voets et al., 2014). Functional connectivity between the PCC and the hippocampus during rest correlates with memory performance in healthy people (Wang et al., 2010), and predicts memory impairments in neurological disorders (Dunn et al., 2014), including TLE (e.g. McCormick et al., 2014; McCormick, Quraan, Cohn, Valiante, & McAndrews, 2013; Voets et al., 2014).

One possible function of RSNs is to reprocess recently-acquired memories. Indeed, there is evidence that RSNs are changed by learning. For instance, Albert, Robertson and Miall (2009) performed resting-state scans before and after a motor learning task and demonstrated learning-induced changes in a fronto-parietal RSN during rest. Furthermore, learning-induced brain activity during post-learning rest predicts subsequent memory performance (e.g. Deuker et al., 2013; Schultz, Balderston, & Helmstetter, 2012; Tambini et al., 2010; Wang et al., 2012) and has been interpreted as a reflection of memory consolidation processes. Systems consolidation of hippocampus-dependent memories is thought to involve memory reactivation, both of the to-be-consolidated material, and of older, related memories (e.g. McClelland et al., 1995). The functional connectivity of

the network of brain regions involved in episodic memory retrieval that is observed during the resting state might indicate reprocessing of recently-acquired hippocampus-dependent memories.

6.1.2. Aims and hypotheses

This experiment was designed to investigate a) potential abnormalities in the functional connectivity of the network of brain areas involved in episodic memory retrieval during baseline rest in TEA patients who report symptoms suggestive of ALF b) changes in this network in response to learning in patients and controls, and c) the relationship between these changes and subsequent memory performance on the learnt material.

As functional connectivity abnormalities within this network have been found in other patient populations with memory impairments, including TLE, it seems possible that TEA patients who report symptoms suggestive of ALF might also have abnormalities. Such abnormalities might be found in the posterior cingulate cortex or the hippocampus, as functional connectivity between these regions has frequently been reported to be abnormal TLE patients and to predict memory performance (e.g. McCormick et al., 2014; McCormick et al., 2013; Voets et al., 2014).

However, the TLE patients studied in previous resting-state experiments typically had considerably more structural abnormalities, including hippocampal sclerosis, than is usually observed in TEA patients. Importantly, the functional connectivity abnormalities in TLE are related to the patients' structural abnormalities (e.g. Liao et al., 2011; Voets et al., 2012). Furthermore, interictal epileptic discharges are known to affect brain activity in regions of this network (e.g. Fahoum, Zelmann, Tyvaert, Dubeau, & Gotman, 2013; Laufs et al., 2007), and the TLE patients studied in previous

resting-state experiments may have had more epileptic activity than is typical of the relatively mild, and easily treated, epileptic syndrome of TEA. Therefore, resting-state connectivity abnormalities may be more difficult to observe in TEA ALF patients.

The functional connectivity of this memory-retrieval network may increase from pre- to post-encoding rest. In particular, brain regions that were heavily involved in the task might be more coactive with the network during post-encoding rest than during pre-encoding rest. During the task that was performed between the resting scans of the current experiment, the blocks of novel pictures (compared to blocks of familiar pictures) robustly activated the MTL, as shown in the previous chapter. A previous study that used the same task to elicit activity in the MTL found that the posterior parahippocampal gyrus showed the greatest signal increase in response to novel vs. familiar pictures (Voets et al., 2014). As demonstrated in the results section of the current chapter, the peak MTL activity in healthy participants for the novel vs. familiar blocks of the task was in the left posterior parahippocampal gyrus. Accordingly, a memory-task reprocessing account would predict that activity in the posterior parahippocampal gyrus would be more strongly correlated with this memory retrieval network during post-encoding rest than during pre-encoding rest.

ALF has been hypothesised to reflect a memory-consolidation deficit (e.g. Blake et al., 2000; Kapur et al., 1997; Tramoni et al., 2011; Wilkinson et al., 2012), and therefore task-induced increases in connectivity might be deficient in TEA ALF patients. Alternatively, the change in connectivity might be abnormally correlated with subsequent memory performance in the patients. Dewar and colleagues (e.g. Cowan et al., 2004; Dewar et al., 2009) have found evidence that memory performance in amnesic patients benefits greatly from a period of rest immediately after learning, and have interpreted these results as indicating that memory consolidation processes in amnesic

patients are unusually vulnerable to disruption from new sensory inputs (Dewar, Cowan, & Della Sala, 2010). If this were true, and if ALF were caused by a similar problem, the use of this post-encoding rest period for consolidation processes (as might be indicated by increased functional connectivity between the brain regions involved in episodic memory retrieval) might be more beneficial for subsequent memory performance in patients than controls. On the other hand, if brain activity patterns that promote consolidation in healthy people interact abnormally with memories in TEA ALF patients (which is a possible interpretation of the abnormal correlations with SWS discussed in Chapter 3), then learning-induced changes in resting-state brain activity might actually be detrimental, rather than beneficial, in these patients.

6.2. Methods

The study received ethical approval from the Scotland A Research Ethics Committee and written informed consent was obtained from all participants.

6.2.1. Participants

Ten patients (who met the diagnostic criteria for transient epileptic amnesia and reported symptoms suggestive of ALF) and twelve control participants took part in this study. The diagnostic criteria for TEA have been published by Zeman and Butler (2010) and are described in the main introduction to this thesis. The details of the participants involved in this experiment are described in the methods section of Chapter 5.

6.2.2. Procedure and data acquisition

The scanning session began with a structural scan, followed by the first resting-state scan, which lasted six minutes. The participants then took part in a memory-encoding task (which is discussed in

Chapter 5), which was followed by a second six-minute resting-state scan. As discussed in Chapter 5, there were two subsequent memory tests for the learnt material. The first test (*Early*), which was for half of the learnt material, was administered shortly after the participants left the scanner (approximately 40 minutes after encoding). The second occurred four days later, and was composed of two parts: a test for the as yet untested half of the learnt material (*Late(A)*), and a repeat of the first test (*Late(B)*).

The participants were asked to look at a white fixation cross, presented against a black background, for the duration of the resting-state scans.

The fMRI sequence used for each resting-state scan was identical to that used for the encoding task scans in Chapter 5. The structural scans described in Chapter 5 were also used in the analyses in the current chapter.

6.2.3. Localisation of peak MTL activity during the task

To identify the location of peak MTL activity in response to novel vs. familiar blocks during the task, a binary mask of the MTL was first created from the combination of the left and right hippocampi and the posterior parahippocampal gyri from the Harvard-Oxford cortical and subcortical atlases, and the left and right entorhinal cortex from the Juelich histological atlas, each thresholded such that all voxels with intensity values below 20 were excluded. This MTL mask was used to mask the control participants' mean image for the novel > familiar contrast (which was thresholded using clusters identified by $z>2.3$ and a corrected cluster significance threshold of $p=0.05$). The FSL cluster tool was then used to identify the MNI coordinates of the activity peak.

Chapter 6.

6.2.4. Resting-state data processing and analysis

Like the functional task data (as described in Chapter 5), the resting-state data were analysed using FSL (FMRIB's Software Library, Jenkinson et al., 2012) version 6.00.

6.2.4.1. Preprocessing and registration

The initial data processing steps (including structural image reorienting, structural image brain extraction and functional data preprocessing using FEAT, which involved brain extraction, motion correction, B0 unwarping, spatial smoothing and high pass temporal filtering) were identical to those used in Chapter 5, with a FWHM of 6mm for the spatial smoothing, and a high pass filter cutoff of 150s.

The data were then cleaned using FIX ("FMRIB's ICA-based X-noiseifier", Salimi-Khorshidi et al., 2014), which identifies and removes artefactual components from the data using ICA. The data were then registered to standard space (MNI-152 template), using transformations computed within FEAT (using the settings described in Chapter 5).

6.2.4.2. Analyses

The data from all participants' resting-state scans were concatenated and MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) ICA (Beckmann et al., 2005) was used to decompose the data into 25 spatiotemporal components that were maximally spatially independent. The episodic memory retrieval network was identified (as the component in which activity in the hippocampus, the retrosplenial cortex/PCC and the aMPFC was correlated).

Individual subject maps of this component were estimated using dual regression. This approach regresses group-level spatial maps into each subject's dataset to produce timecourses, and then regresses these time courses into the same dataset to produce subject-level spatial maps. Permutation testing, implemented using Randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014), was then used to perform statistical tests on the subject-level spatial maps. An unpaired t-test design was used to look for potential group differences during baseline rest. A paired t-test design was used look for differences between pre-encoding and post-encoding rest. To investigate possible group differences in the difference between pre- and post-encoding rest, the difference between the pre- and post-encoding maps of the component were computed for each subject, and an unpaired t-test design was run on these difference images. In all cases, Randomise performed 5000 permutations and used cluster-based thresholding ($t>1.7$), corrected for multiple comparisons ($p=0.05$). To display the results of a contrast of interest for which there were significant differences, the t-statistic image was masked (such that only the clusters that survived correction for multiple comparisons were visible) and then superimposed onto the standard brain (MNI-152). The coordinates of the peaks and local maxima in the grey matter are reported in MNI coordinates (mm). To illustrate the nature of significant differences, the mean regression coefficient (indicating degree of coactivation with the component/involvement in the network) across the brain areas for which there was a significant difference were extracted for each participant, and the means (and standard error of the mean, SEM) for each group/condition were plotted.

As shown in the results section, the left posterior parahippocampal gyrus (the site of peak MTL activation during the task) was more coactive with the network during rest after, compared to before, the task. To investigate the extent to which increased involvement of the left posterior parahippocampal gyrus with this network during rest related to subsequent memory performance, a mask of the left posterior parahippocampal gyrus was generated from the Harvard-Oxford cortical

atlas (thresholded such that voxels with a value below 20 were excluded from the mask) and the mean regression coefficients in this area were extracted for pre- and post-encoding rest for each participant. The over-task change in connectivity was calculated as the post-encoding coactivation minus the pre-encoding coactivation, and this variable was correlated with d' on the subsequent memory tests (as calculated in the results section of Chapter 5), using two-tailed Pearson tests, in each group. Fisher's Z-transformation was used to compare the correlations in the two groups.

6.3. Results

6.3.1. Localisation of peak MTL activity during the task

Figure 6.1 displays the MTL-masked results of the novel > familiar task contrast for the healthy participants. The peak MTL activity for this contrast was in the left posterior parahippocampal gyrus (z=6.11, -28, -42, -12).

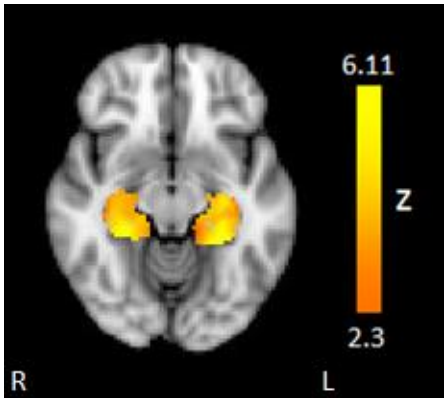


Figure 6.1. MTL activity in response to novel vs. familiar task blocks in healthy participants. The peak activity was in the left posterior parahippocampal gyrus (z=6.11, -28, -42, -12). A similar peak was also observed in the right posterior parahippocampal gyrus (z=5.66, 28, -36, -14).

6.3.2. Analysis of the resting-state data

The ICA produced one component in which activity in the hippocampus, retrosplenial cortex/PCC and aMPFC was correlated. This component, which constitutes a functionally connected network of areas thought to participate in episodic memory retrieval, is displayed in Figure 6.2.

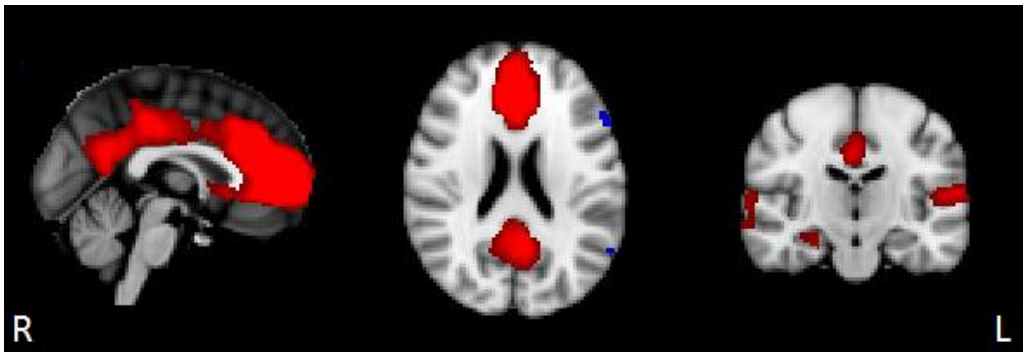
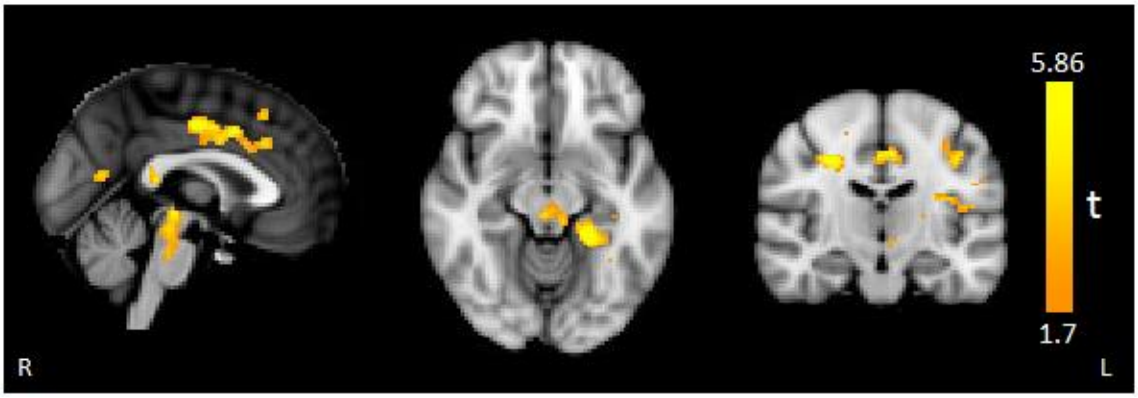


Figure 6.2. The component from the ICA in which activity in the hippocampus, retrosplenial cortex/PCC and aMPFC was correlated. This constitutes a functionally connected network of areas thought to participate in episodic memory retrieval. The brain areas that significantly participated in the network are shown in red (while blue indicates anti-correlation with the network). Brighter colours indicate larger z scores.

Unpaired t-test analyses were used to look for group differences in this network during baseline (pre-encoding) rest. However, no significant differences were found.

Paired t-test analyses revealed that some brain areas were significantly more coactive with this network after, compared to before, the encoding task. These areas are shown in Figure 6.3. Peaks and local maxima fall in the anterior cingulate cortex (t= 4.56, -2, -8, 42; t= 4.11, -2, -4, 40), the left angular gyrus (t= 5.47, -40, -58, 16) and the left posterior parahippocampal gyrus (t= 4.4, -22, -30, -24). There were no brain areas that were significantly more coactive with the component before, compared to after the encoding task. There were no significant group differences in the difference between pre- and post-encoding rest.



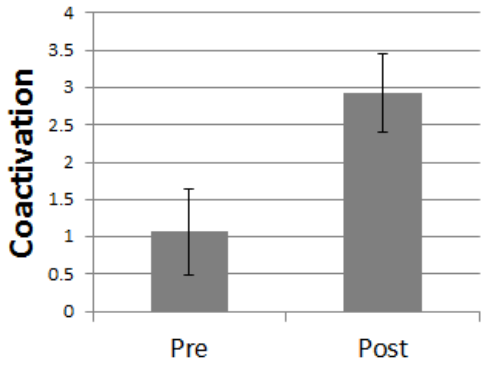


Figure 6.3. Regions that were significantly more coactive with the episodic memory retrieval network (see Figure 2) after, compared to before, the encoding task. These areas include the cingulate cortex (predominantly the anterior part), the left angular gyrus and the posterior parahippocampal gyrus of the left MTL. The bar chart shows the nature of this difference: on average, these areas were more positively associated with the network after the task than before the task.

Intriguingly, the extent to which the left posterior parahippocampal gyrus increased its coactivation with the memory network (from before to after the encoding task) correlated negatively with d' on the Early memory test (r= -0.664, p=0.036, see Figure 6.4a) and with d' on the Late(B) memory test

(r= -0.733, p=0.016, see Figure 6.4b) in the patients, i.e. both of the tests on which they had a significantly lower d' than the controls, as shown in Chapter 5. In contrast, these relationships were positive and non-significant in the controls (r = 0.290, p=0.36 and r = 0.421, p=0.17, respectively). Fisher's transformation analyses revealed that these correlations were significantly different in the two groups (z = 2.18 ($p<0.05$) for d' on the Early test, and z = 2.75 ($p<0.01$) for d' on the Late(B) test).

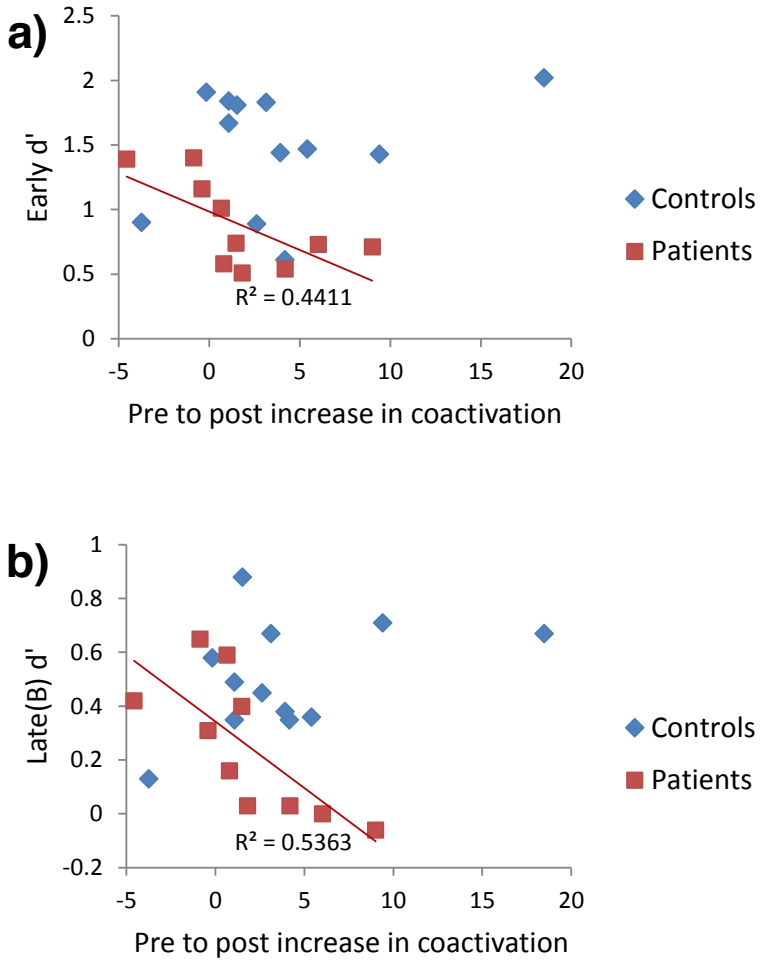


Figure 6.4. Correlations between the over-encoding-task change in coactivity of the left posterior parahippocampal gyrus with the episodic memory retrieval network and performance on the subsequent memory tests. Significant correlations are marked with a line of best fit. In the patients, the increase in coactivation correlated negatively with d' on the Early test (a) and with d' on the Late(B) test (b). These two correlation coefficients were significantly different from the equivalent ones in the control group, which were positive and non-significant.

6.4. Discussion

It was hypothesized that the network of brain areas involved in episodic memory retrieval would show a learning-induced increase in connectivity during post-encoding rest, perhaps especially with an area that was strongly activated during the learning task, reflecting post-encoding memory reprocessing. Indeed, an over-task increase in connectivity between a network of episodic memory retrieval-related regions and the MTL area of peak activity during the task (the left posterior parahippocampal gyrus) was observed. Interestingly, this change in resting-state connectivity was negatively associated with subsequent memory performance in TEA ALF patients. This was not the case in the control group, and there were significant group differences in this respect.

In the control participants, the corresponding brain-behaviour relationships were positive, but did not reach significance. This is perhaps unsurprising. As discussed in the main introduction to this thesis, the primary functions of systems consolidation in healthy people are thought to be the integration of recently-acquired memories with pre-existing related memories, the extraction of invariants, and the reorganisation of the memory trace. One would not necessarily expect systems consolidation to result in substantially improved performance on an item recognition memory test. In contrast, one might expect such brain activity changes to show significant positive relationships with subsequent relational memory performance, and this would be an interesting area for future research.

The pattern of results in this chapter appears similar to that found in the chapter on slow wave sleep: a post-learning pattern of brain activity associated with memory consolidation appears to be deleterious for memory in these patients. One possible interpretation is that memory consolidation processes interact abnormally with memories in this patient group. According to systems

consolidation theory, the integration of recently-acquired memories with the long-term neocortical store involves the reprocessing of related older memories (e.g. McClelland et al., 1995). If accelerated forgetting in TEA patients is caused by increased interference between similar memories as a result of compromised hippocampal function (as discussed in the previous chapter) then the reprocessing of old memories that share features with recently-acquired memories (that is posited to occur during systems consolidation) might cause interference. Therefore, the greater the post-encoding memory reprocessing, the greater the subsequent memory deficit would be.

The parahippocampal cortex is commonly activated during episodic memory retrieval tasks (Rugg & Vilberg, 2013), and it is thought that this may be due to its central role in the representation of spatial/contextual information (e.g. Diana, Yonelinas, & Ranganath, 2007). This area was strongly activated during the learning task of the current experiment, perhaps because the task involved the encoding of novel scene stimuli.

Learning-induced increases in the memory network's functional connectivity were also observed in other brain areas, including the left angular gyrus. Successful episodic memory retrieval is often associated with activity in the angular gyrus (Rugg & Vilberg, 2013), and some studies have found this activity in the left hemisphere only (e.g. Hayama, Vilberg, & Rugg, 2012).

The increase in functional connectivity between an MTL area that was strongly activated by the learning task and a network of brain regions involved in episodic memory retrieval that was observed in this study suggests that the recently-acquired memories were being retrieved and reprocessed during post-learning rest. However, it would be interesting to attempt to more directly

observe the reactivation of the learnt material, which may be possible using multivariate pattern analysis techniques (e.g. Deuker et al., 2013).

To test the theory that it is the reactivation of related older memories that is detrimental to subsequent memory performance in TEA ALF patients, it would be possible to design a cued replay study in which reactivations of related older memories were experimentally induced after learning, to ascertain whether this is especially deleterious in the patient group.

The interpretation of the over-task changes in resting-state connectivity as having been induced by learning is somewhat complicated by the fact that there was no control task; one could be more confident in this interpretation if such changes were not observed when the intervening task did not involve (successful) learning. Future studies should have control task conditions.

Another recommended addition for future experiments that seek to investigate memory reprocessing by looking at learning-induced changes in RSNs is a memory test immediately after the learning task, before the post-encoding rest period, as well as a post-rest memory test. This would enable the over-task change in connectivity to be correlated with the over-post-learning-rest change in memory performance. Otherwise, it is possible to interpret the individual variability in over-task change in resting connectivity as a reflection of individual variability in learning, rather than an indicator of post-learning reprocessing. However, if this were the case, then one would expect the increases in resting-state connectivity to be positively related to subsequent memory performance. The fact that the relationship was negative in the patients in the current experiment suggests that

the brain activity changes reflected post-encoding neural events that had consequences for memory, rather than just a functionless echo of learning, at least in the patient group.

No group differences in baseline functional connectivity within the network of brain regions involved in episodic memory retrieval were observed in this study. However, the analyses presented here represent only one possible way of exploring the resting-state data, and there are a number of other analyses that might yield interesting results. For instance, a posterior hippocampus seed-based analysis might reveal abnormal connectivity with the posterior cingulate/precuneus, which could potentially predict memory impairments, as has been found in temporal lobe epilepsy (e.g. Voets et al., 2014). There are thought to be multiple memory networks, with different functions, which interact to subserve declarative memory (e.g. Aggleton, 2012), and it is possible that TEA ALF patients have abnormalities in some of these networks, but not others.

In conclusion, an over-learning-task increase in the resting functional connectivity between a task-involved MTL region and a network of brain regions involved in hippocampus-dependent memory retrieval was observed and found to predict poor subsequent memory performance in TEA ALF patients. This was not the case in the control participants, in whom the relationship between this resting-state connectivity change and subsequent memory performance was significantly different. These results may indicate that some aspects of post-learning memory reprocessing are deleterious, rather than beneficial, for these patients, but further studies would be required to verify this interpretation.

7. Brain structure

7.1 Introduction

The relationship between ALF and brain structure is currently unclear. To date, structural MRI studies in TEA patients have not found a neural correlate of ALF (Butler et al., 2013; Butler et al., 2009). Some studies of ALF in temporal lobe epilepsy (TLE) have found greater ALF in patients who have hippocampal structural abnormalities than in patients who have normal hippocampi (e.g. Narayanan et al., 2012), while other studies have found ALF in groups of TLE patients in which hippocampal structural abnormalities are either rare or absent (e.g. Blake et al., 2000; Jansari et al., 2010; Mameniskiene et al., 2006).

The available evidence suggests that hippocampal structure relates to anterograde memory problems over the shorter rather than longer term. For instance, Butler and colleagues (Butler et al., 2013; Butler et al., 2009) found that hippocampal structure correlated with memory performance over 30 minutes, but not with percent forgotten between 30 minutes and three weeks in patients with TEA. In a study of patients with TLE, Wilkinson et al. (2012) found that memory deficits over one hour were associated with hippocampal abnormalities, while memory deficits over six weeks were not. A recent study by Lah and colleagues (2014) revealed that TLE patients with hippocampal lesions show more rapid forgetting than those without; both groups showed normal memory retention at 30 minutes, but the patients with hippocampal lesions showed significant memory deficits at one day, while the patients without hippocampal lesions did not show significant memory deficits until the memory test seven days after learning.

One possible interpretation (e.g. Lah et al., 2014) is that the hippocampus is important for memory performance after relatively short delays but not for memory performance after relatively long

delays. If this were the case, memory deficits over long delays might correlate with extra-hippocampal damage, but there is no evidence for this to date (e.g. Butler et al., 2013; Butler et al., 2009).

An alternative possibility is that inter-individual differences in the timescale over which the anterograde memory impairment typically appears depends on the extent to which hippocampal function is compromised. Hippocampal structure may serve as an indirect measure of hippocampal function; it is likely that patients with hippocampal lesions will have severely impaired hippocampal function. However, presumably it is possible to have some degree of impairment of hippocampal function in the absence of detectable structural pathology. The hippocampus is thought to be critical to our ability to distinguish between similar memories (e.g. Marr, 1971; O'Reilly & McClelland, 1994; Treves & Rolls, 1994; Yassa & Stark, 2011). Therefore, if the hippocampus does not function properly, similar memories will interfere with one another and forgetting will occur. Severely impaired hippocampal function might result in behavioural deficits being detected at the stage of learning or over short time scales. In contrast, less severe impairment of hippocampal function might result in memory problems going undetected until later, once more similar information has been encountered, or more similar pre-existing memories have been reactivated during the process of systems consolidation (e.g. McClelland et al., 1995).

Previous structural MRI studies in TEA (Butler et al., 2013; Butler et al., 2009) have used magnet strengths of only 1.5T. It is possible that scanners of greater field strength may be required to detect structural correlates of ALF. Furthermore, the choice of ALF measure may have reduced the chances of finding a structural correlate. These studies used a composite score of the percent forgotten between 30 minutes and three weeks on multiple memory tests. According to the literature

reviewed above, especially the study by Lah et al. (2014), hippocampal structure may relate to ALF over a shorter time period than three weeks. Furthermore, as discussed in Chapter 5 of this thesis, the rate of forgetting, or the time scale over which memory deficits are detected, might vary depending on the nature of the task.

In this study, I looked for structural neural correlates of ALF in TEA patients reporting symptoms suggestive of ALF using voxel-based morphometry based on structural images acquired with a 3T MRI scanner. Analyses were performed for the whole brain and for an *a priori* region of interest – the left hippocampus, based on the results of Chapter 5 of this thesis. The ALF measure used in this study was derived from a word-list task on which the group of patients showed significantly greater forgetting between 30 minutes and one week compared to the control participants.

Chapter 7.

7.2. Methods

The study received ethical approval from the Scotland A Research Ethics Committee and written informed consent was obtained from all participants.

7.2.1. Participants

Ten patients (who met the diagnostic criteria for transient epileptic amnesia and reported symptoms suggestive of ALF) and twelve control participants took part in this study. The diagnostic criteria for TEA have been published by Zeman and Butler (2010) and are described in the main introduction to thesis. The details of the participants involved in this study are described in the methods section of Chapter 5.

7.2.2. ALF measure

The ALF measure was the percent retained between 30 minutes and one week on an adapted version of the RAVLT. The task procedure and the results for this word-list task are described in Chapter 5. As detailed in Chapter 5, three patients had to be excluded from the word-list analyses.

7.2.3. MRI data acquisition

As described in Chapter 5, high resolution structural images were acquired using a T1-weighted MEMPRAGE sequence (van der Kouwe et al., 2008) (slice orientation: sagittal, TR: 2530ms, 4 TEs: 1.69ms, 3.55ms, 5.41ms and 7.27ms (the average image was used), flip angle: 7^{o}, field of view: 256mm, slice thickness: 1mm, voxel size: 1x1x1mm, acquisition time: 6minutes and 3 seconds).

7.2.4. MRI data analysis

The MRI data were analysed using FSL (FMRIB's Software Library, Jenkinson et al., 2012; Smith et al., 2004) version 6.00. The structural images were reoriented using fslreorient2std, and then brain extracted using fsl_anat. FSLVBM (Douaud et al., 2007; Good et al., 2001) was used to perform voxel-based morphometry, as described below. The brain-extracted images were segmented into grey matter, white matter and cerebrospinal fluid images. The grey matter images from the ten patients and the first ten control participants were registered to MNI 152 standard space using non-linear registration (Andersson et al., 2010). The registered images were then averaged and flipped along the x-axis, creating a left-right symmetrical study-specific template. All subjects' grey matter images were then non-linearly registered to the study-specific template. The registered images were modulated to compensate for the contraction/enlargement that occurred as a result of the non-linear component of the registration: each voxel was multiplied by the Jacobian of the warp field (Good et al., 2001). The modulated registered images were smoothed using an isotropic Gaussian kernel with a sigma of 2mm.

Permutation testing, implemented using Randomise (Winkler et al., 2014), was then used to perform statistical tests on the smoothed modulated registered grey matter images. Unpaired t-test designs were used to look for group differences in structure. Covariate analyses were used to look for brain areas in which grey matter correlated with long-term memory retention. To perform these covariate analyses, the mean long-term memory retention score across all participants involved in the analysis was calculated and then subtracted from each participant's long-term memory retention score. These demeaned long-term memory retention values were then used as an explanatory variable (EV) in the general linear model. A significant effect of the covariate's contrast indicates a positive linear relationship between the grey matter in that brain area and long-term memory retention. This was done separately for the patient and control groups. To look for brain areas in which the

relationship between structure and long-term retention was significantly different in the two groups, a 'two groups with continuous covariate interaction' design was used. This design has four EVs: one identifies the control participant scans, one identifies the patient scans, one contains the covariate (long-term retention) information for each control participant (after the mean across all participants has been subtracted), and one contains the covariate information for each patient (after the mean across all participants has been subtracted). The parameter estimates for the two groups' covariate EVs are then contrasted. In all cases, Randomise performed 5000 permutations and used cluster-based thresholding ($t>1.7$), corrected for multiple comparisons ($p=0.05$).

The analyses were first performed for the whole brain's grey matter. The analyses were then restricted to the left hippocampus. The left hippocampus mask used for the latter set of analyses was taken from the Harvard-Oxford subcortical atlas, thresholded such that voxels with an intensity value below 20 were excluded from the mask, binarised, and multiplied with the binary grey matter mask generated by FSLVBM, to ensure that the mask contained only grey matter.

Given the positive correlation between left hippocampus grey matter and long-term memory retention obtained in the current study (see the results section below), it was important to test whether structural differences could account for the functional activation results reported in Chapter 5. Therefore, some reanalyses were performed. To provide the left hippocampus grey matter covariate that was used in these analyses, the mean value within the left hippocampus mask described above was extracted from each subject's smoothed modulated registered grey matter image. The ANOVA from Chapter 5 that used percent signal change in the left hippocampus as the dependent variable and which produced a significant interaction with group (i.e. the ANOVA in section 5.3.2.2.1.2. with testing time (two levels: Early and Late(A)) and subsequent memory (two

levels: remembered and forgotten) as the within-subjects factors and group as the between-subjects factor) was repeated, incorporating grey matter in the left hippocampus as a covariate. The pairwise comparisons were also repeated, to investigate whether the patients still had significantly reduced percent signal change in the left hippocampus for subsequently forgotten stimuli compared to control participants once left hippocampus grey matter was included in the analysis. Furthermore, the correlation between long-term forgetting on the word-pair associates task and the percent signal change in the left hippocampus for stimuli subsequently forgotten in the Early test was repeated, this time as a partial correlation that controlled for grey matter in the left hippocampus.

7.3. Results

7.3.1. Whole-brain analyses

No significant group differences in grey matter were found at the whole-brain level. Nor were there any significant effects for the covariate analyses, indicating that no brain regions were identified for which grey matter significantly covaried with long-term memory retention, once corrections for comparisons for every grey matter voxel in the brain were performed.

7.3.2. Left hippocampus analyses

When the analyses were restricted to the left hippocampus, there were still no significant group differences in grey matter. However, areas were found in which grey matter significantly correlated with long-term memory retention in the patient group. These areas are shown in Figure 7.1.

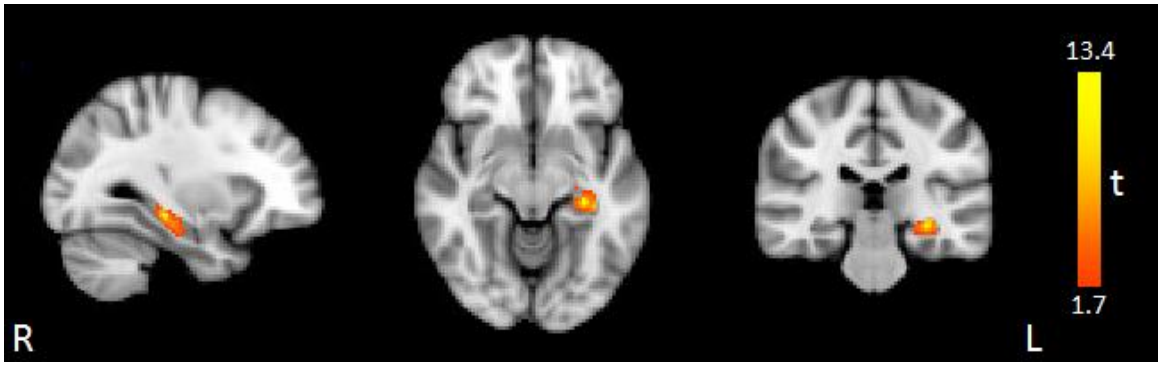


Figure 7.1. Brain areas within the left hippocampus for which grey matter significantly correlated with long-term memory retention in the patient group.

No significant results were found for the controls. Indeed, areas were found for which the relationship between grey matter and long-term memory retention was significantly greater in the patients than the controls. These areas are shown in Figure 7.2. There were no areas for which the relationship was greater in the controls than the patients.

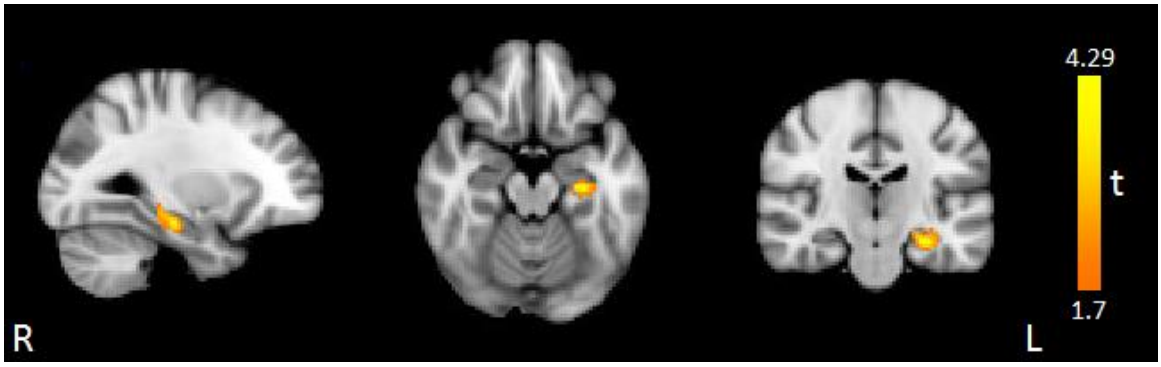


Figure 7.2. Brain areas within the left hippocampus for which the relationship between grey matter and long-term memory retention was significantly greater in the patient group than the control group.

For illustrative purposes, Figure 7.3 plots long-term memory retention against left hippocampus grey matter.

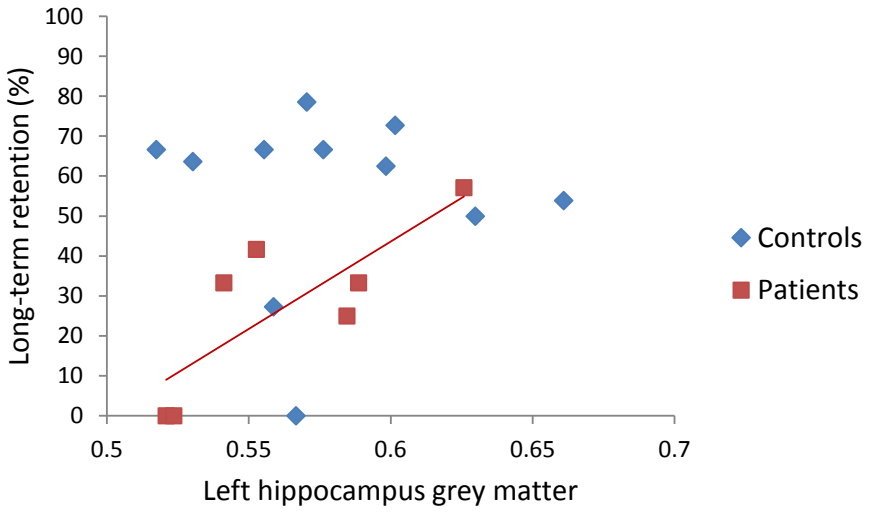


Figure 7.3. Long-term memory retention plotted against left hippocampus grey matter. Long-term memory retention was measured as the percent retained between 30 minutes and one week on the RAVLT word-list recall task. The brain measure reflects the mean grey matter value within the full left hippocampus mask in each participant. In this figure, neither variable is demeaned.

The finding that structural variability in the left hippocampus predicted long-term memory retention in the patients raised some questions about whether the functional MRI results presented in Chapter 5 could be explained by hippocampal structure.

The ANOVA from Chapter 5 that used percent signal change in the left hippocampus as the dependent variable and which produced a significant interaction between group and subsequent memory was therefore repeated, incorporating grey matter in the left hippocampus as a covariate. The interaction between group and subsequent memory remained significant ($F_{(1,19)} = 11.37$, $p=0.003$), as did the significant difference between the groups in the pairwise comparison for the percent signal change associated with subsequently forgotten stimuli (estimated marginal mean (EMM) ±SEM in the controls: 0.13 ±0.033%, EMM ±SEM in the patients: 0.022 ±0.029, $p=0.013$). It remained the case that the difference in percent signal change between subsequently remembered and forgotten stimuli was significant in the patients only ($p<0.001$) and not in the controls ($p=0.43$). Figure 7.4 displays the adjusted means and SEMs produced by this ANOVA.

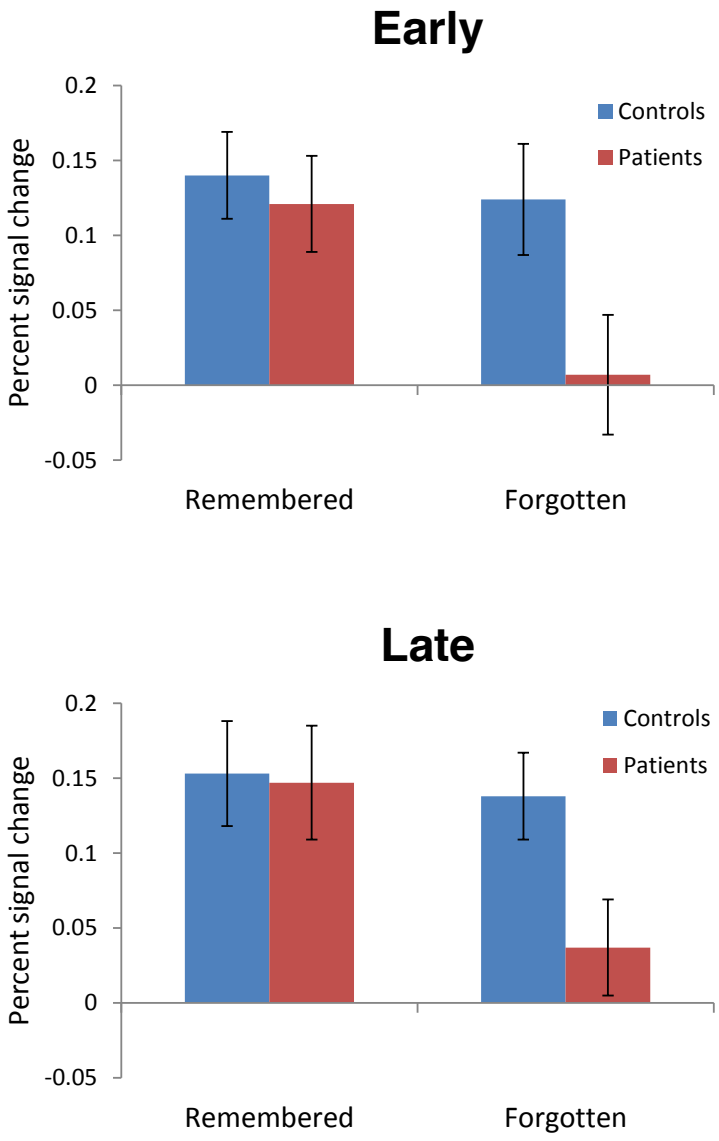


Figure 7.4. Mean percent signal change in the left hippocampus for stimuli subsequently remembered and forgotten in the Early and Late(A) tests of the main task of Chapter 5, adjusted for left hippocampus grey matter. The error bars represent the standard error of the mean. The interaction between group and subsequent memory remained significant, as did the group difference in the percent signal change for subsequently forgotten stimuli.

A partial correlation was used to demonstrate that the correlation in patients between long-term forgetting on the word-pair associates task and the percent signal change in the left hippocampus for stimuli subsequently forgotten on the Early test of the picture encoding task remained significant when controlling for left hippocampus grey matter ($r = -0.715$, $p=0.030$). Figure 7.5 displays this

correlation. The unstandardized residuals from the linear regression in which left hippocampal grey matter is used to predict long-term forgetting on the word-pair associates task is plotted against the unstandardized residuals from the linear regression in which left hippocampal grey matter is used to predict the percent signal change in the left hippocampus for stimuli that go on the be forgotten in the Early test of the picture encoding task.

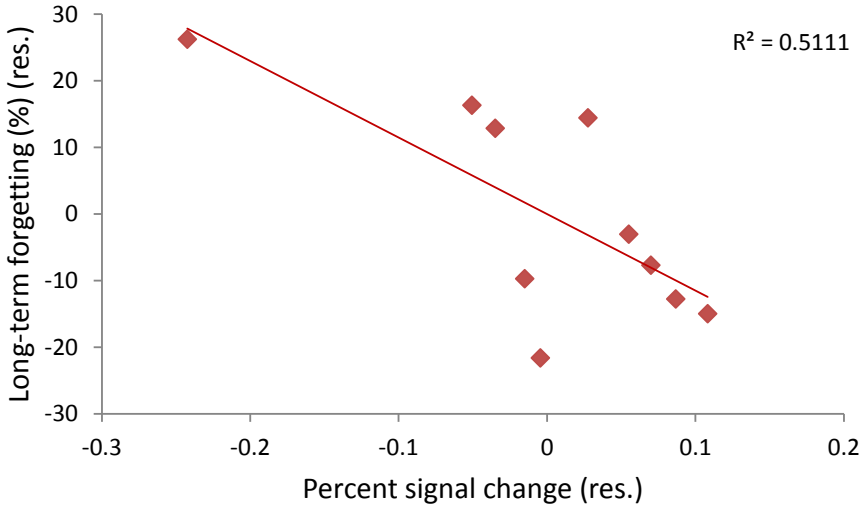


Figure 7.5. The significant partial correlation between the percent signal change in the left hippocampus for stimuli that went on to be forgotten in the Early test of the picture encoding task and long-term forgetting on the word-pair associates task (i.e. percent forgotten between 30 minutes and twelve hours), when controlling for left hippocampus grey matter.

7.4. Discussion

This study is the first to find a structural neural correlate of accelerated long-term forgetting in TEA or indeed any other epileptic syndrome. In the patients, but not the control participants, grey matter in regions of the left hippocampus was found to correlate with long-term retention on a word-list task in which the patient group showed significantly poorer long-term retention than the controls.

The results of this study suggest that researchers looking for a structural neural correlate of ALF might do well to use an MRI scanner with a high field strength, and to use a single, rather than a composite, measure of ALF over the medium (rather than very long) term.

While this is a novel and exciting finding, the results should be interpreted with caution, as the sample size was small. The study should be replicated in a larger, more gender-balanced, sample before we can be confident in the results. However, it should be noted that the lack of significant group differences in grey matter is not cause for suspicion; while VBM has previously been used to detect neural correlates of memory retention over short intervals in TEA patients, it has failed to detect significant group differences in grey matter between these patients and healthy controls (Butler et al., 2009).

For a number of reasons, the results of this study should not be interpreted as an indication that the neural basis of ALF is structural rather than functional. Firstly, measures of structure are relevant to behavioural disorders only insofar as they relate to function. Secondly, as demonstrated in the results section, functional abnormities during encoding that correlate with forgetting over the long-term have been identified in this patient group, which cannot be entirely accounted for by the

structural changes identified in the VBM analysis. Another important consideration is that the hippocampus does not operate in isolation. Memory processes require the coordinated activity of many brain regions. The finding that hippocampal grey matter correlates with ALF simply means that hippocampal functional problems likely contribute to the memory impairment; it does not mean that this is the end of the story.

The ALF measure used in this study concerned memory retention over one week. As there was only one delayed memory test, the temporal profile of forgetting is not clear. It is possible that that an experiment spanning a longer time period, with more delayed tests, would reveal that hippocampal structure correlates with accelerated forgetting over the relatively short term, but not with accelerated forgetting over longer time-periods.

It might be argued that the fact that this patient group has shown significant memory impairments on early tests in some tasks (including the 30 minutes test of the word-list task that was used to provide a measure of long-term forgetting in the current study, as shown in Chapter 5) means that they do not truly have ALF, and that these results would not be found in a patient group with pure ALF. This is certainly possible, and the study should be repeated a group of patients who exhibit entirely normal performance on early memory tests in a large range of tasks. However, I think that there is currently limited evidence to suggest that accelerated forgetting over the longer term is a qualitatively different disorder from accelerated forgetting over the shorter term. I would predict that patients who show accelerated forgetting over the long term in the context of normal early memory performance on a large range of tasks would still have some degree of functional hippocampal impairment, as might be detectable in functional imaging studies. Furthermore, if my hypothesis is correct, it should be possible to observe memory impairments over short times scales

in most ALF patients with a carefully designed task; if the time scale over which the anterograde memory deficit appears in an ALF patient depends not only on the functional integrity of the hippocampus but also the hippocampal demands of the task, then a task with very high pattern separation demands should produce early memory deficits in most patients. This would, of course, have important clinical ramifications, as it would make it possible to diagnose ALF patients who show normal performance on standard neuropsychological tests with anterograde memory problems within the time frame of a normal consultation.

This study is the first to find a structural correlate of accelerated long-term forgetting, and it lends weight to the theory that the hippocampus plays a role in this memory disorder. However, in light of the contradictory findings in previous studies and the small sample size, the results should be interpreted with caution, and the study should be replicated in a larger group.

8. General Discussion

The aim of my doctoral research was to investigate which memory stages are disrupted in ALF in TEA patients, and to shed light on the neural basis of the memory impairment. Many researchers have proposed that ALF reflects a deficit in memory consolidation, perhaps specifically during sleep. An alternative possibility is that patients with ALF suffer from an encoding abnormality that usually goes undetected until delayed memory tests. These candidate explanations of ALF are not mutually exclusive; encoding and consolidation deficits could interact.

8.1. Findings

The explanation of ALF most commonly suggested in the literature is a deficit in sleep-dependent memory consolidation (e.g. Butler et al., 2009; Holmes & Lenck-Santini, 2006; Jansari et al., 2010; Muhlert et al., 2011; Sud et al., 2014; Tramoni et al., 2011; Urbain et al., 2011; Zeman et al., 2013). However, the first experimental chapter of this thesis provided evidence against this hypothesis. In the word-pair associates task used in this experiment, sleep was found to benefit memory retention in TEA patients with ALF, and this benefit was no smaller in magnitude than that seen in healthy controls. Indeed, while the patients showed significantly worse memory retention than the controls over twelve hours of wakefulness, this was not the case over a period of twelve hours that contained a night of sleep. The patients were matched to the controls on learning rate, initial retention, and the effect of time of day on cognitive performance. These data reveal that sleep may benefit memory retention in TEA ALF patients just as much as it does in healthy people. The results also show that it is not necessary for the retention interval to contain sleep in order for ALF to be seen, and that memory deficits can be observed within twelve hours of encoding. These results are compatible with those of another very recent experiment in TEA ALF patients; Hoefeijzers et al.

(2014) found that memory deficits can be detected within three to eight hours of wakefulness after encoding, and they observed no further forgetting over the first post-encoding night of sleep.

However, sleep-dependent consolidation processes do not appear to be normal in this patient group. While slow wave sleep (SWS) is thought to play an active positive role in the consolidation of medial temporal lobe (MTL)-dependent memory in healthy people, it appears to have a negative influence on memory retention in TEA ALF patients. Chapter 3 of this thesis revealed significant negative correlations in the patient group between SWS on the post-learning night (amount of SWS, and power in the slow oscillation frequency range) and the benefit of that sleep for memory retention over twelve hours.

In healthy people, systems consolidation is thought to be achieved through the reactivation of recently-acquired memory traces in the MTL, interleaved with the reactivation of pre-existing related memories (McClelland et al., 1995). It has been proposed that this process might happen preferentially during SWS, triggered by neocortical slow oscillations (e.g. Born et al., 2006; Marshall & Born, 2007). However, there is also evidence for memory reactivations during the waking state (e.g. Deuker et al., 2013; Karlsson & Frank, 2009; Staresina et al., 2013; Tambini & Davachi, 2013). Chapter 6 of this thesis showed that encoding leads to increases in the resting connectivity of the network of brain regions involved in episodic memory retrieval, consistent with the notion that memories are reactivated during post-encoding rest. Intriguingly, the greater the learning-induced increase in connectivity between this memory retrieval network and the area of peak MTL activity during the encoding task (the left posterior parahippocampal gyrus), the *poorer* the subsequent memory performance in the TEA ALF patients.

Therefore, it appears that brain activity patterns conducive to memory consolidation in healthy people might be detrimental for memory retention in TEA ALF patients. One possible explanation is that memory consolidation processes interact abnormally with memories in TEA ALF patients because their memories are abnormally formed. Chapter 5 provides evidence consistent with the idea that memories may not be formed entirely normally in TEA ALF patients. The patients showed reduced activity in the left hippocampus at the stage of encoding for stimuli that they went on to forget. Furthermore, this brain activity correlated with forgetting over the long-term.

Chapter 7 also revealed a correlation between left hippocampus grey matter and a measure of long-term memory retention in the TEA ALF patients. In principle, these structural changes may have contributed to the differences in brain activity recorded with fMRI that were presented earlier in the thesis. The re-analyses in Chapter 7 demonstrate that the structural changes identified using voxel-based morphometry did not entirely account for the encoding-related brain activity results reported in Chapter 5.

Together, the results presented in this thesis suggest that both the formation and the post-encoding processing of MTL-dependent memories may be compromised in TEA ALF patients.

8.2. Interpretation

One intriguing hypothesis compatible with the pattern of results in this thesis is that TEA ALF patients (who are thought to have epileptic foci in the MTL, as discussed in the main introduction) have a diminished capacity to distinguish between similar stimuli/events.

Brain structures within the MTL are thought to be critical to our ability to form representations that allow us to distinguish between similar stimuli/events (e.g. Bussey & Saksida, 2007; Graham et al., 2010; Marr, 1971; O'Reilly & McClelland, 1994; Treves & Rolls, 1994; Yassa & Stark, 2011). MTL function might be compromised in TEA ALF patients, resulting in a diminished capacity to distinguish between similar stimuli/events, ultimately causing memory impairments. According to this hypothesis, performance deficits in TEA ALF patients usually go undetected until delayed tests because the functional impairment is relatively subtle, and the studied materials are usually sufficiently unique so as to be retrieved accurately by these patients initially. However, information that shares many overlapping features with elements of the study set will ultimately be processed, resulting in retrieval deficits. This information might be new sensory stimuli, or it might be pre-existing memories that are re-processed during systems consolidation of the study set. This hypothesis is not dissimilar to one of the explanations offered by Graham et al. (2010) for delay-dependent deficits in temporal lobe amnesics.

This hypothesis generates a number of predictions, which could be experimentally tested. Firstly, it predicts that TEA ALF patients should be especially vulnerable to interference. TEA ALF patients show a large benefit of sleep for memory retention, which does not appear to be driven by SWS. This benefit may be due to the reduced processing of interfering information that occurs during sleep compared to wakefulness. However, susceptibility to interference should be directly tested. This could be achieved by manipulating the degree of feature overlap between the information to be encoded, the additional inputs in the retention interval, and the foils (in the case of recognition memory tasks). It is worth noting that patients with medial temporal lobe lesions have been shown to be especially vulnerable to interference (e.g. Cowan et al., 2004; Dewar et al., 2009; Warrington & Weiskrantz, 1978).

Secondly, given sufficient feature overlap within the study set, it should be possible to observe anterograde memory problems in TEA ALF patients within short time intervals. This would have important clinical ramifications. Standard tests are typically not sensitive to anterograde memory problems in patients with ALF, and so these patients' memory problems often go undetected by clinicians. The early memory deficits on the Recognition Memory Test for faces and on the scene encoding task presented in Chapter 5 are consistent with the idea that early anterograde memory problems will be seen in TEA ALF patients when there is a high degree of feature overlap between the study set stimuli. However, feature overlap between the stimuli in the study set should be systematically manipulated in future experiments. Given that patients and animals with lesions in the MTL have been shown to have difficulty making perceptual discriminations between stimuli with overlapping features (e.g. Barense et al., 2007; Bartko et al., 2007a, 2007b; Lee, Barense, et al., 2005; Lee, Bussey, et al., 2005), it might even be possible to observe perceptual or working memory deficits in TEA ALF patients, given sufficient feature overlap.

The perceptual discrimination experiments referred to above have provided evidence to suggest that the hippocampus is particularly important for making difficult discriminations for scenes and spatial information, while the perirhinal cortex is particularly important for making difficult discriminations for objects and faces. In Chapter 5 of this thesis, a group of TEA ALF patients were shown to underperform on the Recognition Memory Test for faces, which formed part of their neuropsychological test battery. TEA ALF patients might suffer from an impairment of perirhinal cortex function and this should be investigated in future experiments. One study has detected perirhinal cortex atrophy at the group level in TEA ALF patients (Butler et al., 2013).

Another prediction generated from the hypothesis outlined above is that there might be a relationship between encoding-related brain activity and susceptibility to interference. If so, then patients with more abnormal brain activity at encoding would be more vulnerable to interference. It might be the case that, within an individual TEA ALF patient, some information is encoded normally while other information is encoded abnormally, and only the abnormally encoded information is especially vulnerable to interference. This possibility could be investigated using real-time fMRI and a carefully crafted stimulus set to introduce interference in the retention interval specifically for events that were associated with more or less hippocampal activity at the point of encoding.

Furthermore, if brain activity patterns conducive to memory consolidation in healthy people interact abnormally with memories in TEA ALF patients because their memories are abnormally formed, then encoding-related abnormalities might predict the negative effect of these brain states.

The hypothesis suggests that SWS and post-encoding memory reprocessing during rest have a negative influence on memory performance in TEA ALF patients because the systems consolidation that occurs during these brain states involves the reactivation of pre-existing memories that share features with the encoded material. To test the theory that it is the reactivation of related older memories that is detrimental to memory performance in TEA ALF patients, it would be possible to design a cued replay study in which reactivations of related older memories were experimentally induced after learning, to ascertain whether this is especially deleterious in the patient group. Another possible explanation (which is not incompatible with the aforementioned interpretation) for the detrimental effect on memory of SWS and post-encoding memory reprocessing during rest in TEA ALF patients, is that these brain states promote epileptic activity that has adverse consequences for memory. Epileptic discharges might disrupt the synaptic weights in MTL memory traces. This

could potentially render the memories even more vulnerable to interference, and would contribute to problems with memory retention. Fitzgerald et al. (2013) found a relationship between ALF and interictal epileptic discharges during the retention interval in a group of epilepsy patients. However, it is worth noting that there was no evidence of epileptic activity during the TEA sleep study presented in this thesis.

A better understanding of ALF might help with the development of therapies. If the hypothesis outlined here is correct, then slow wave suppression might improve memory retention. Furthermore, given that exercise stimulates hippocampal neurogenesis (e.g. van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999), which enhances pattern separation function (e.g. Sahay et al., 2011), an exercise intervention might help to reduce ALF.

In summary, both memory formation and post-encoding memory reprocessing appear to be unusual in TEA ALF patients. Information that was ultimately forgotten was found to be associated with reduced brain activity in the left hippocampus at the stage of encoding. Furthermore, brain activity patterns associated with memory reprocessing appeared to have a negative, rather than positive, influence on subsequent memory. The precise explanation for these effects, and how they interact, remains to be determined in future experiments.

References

Abraham, W. C. (2008). Metaplasticity: tuning synapses and networks for plasticity. *Nature Reviews Neuroscience, 9*(5), 387-387.

Achermann, P., & Borbely, A. A. (1997). Low-frequency (< 1 Hz) oscillations in the human sleep electroencephalogram. *Neuroscience, 81*(1), 213-222.

Aggleton, J. P. (2012). Multiple anatomical systems embedded within the primate medial temporal lobe: implications for hippocampal function. *Neurosci Biobehav Rev, 36*(7), 1579-1596.

Aggleton, J. P., & Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci, 22*(3), 425-444; discussion 444-489.

Agranoff, B. W., Davis, R. E., & Brink, J. J. (1966). Chemical studies on memory fixation in goldfish. *Brain Res, 1*(3), 303-309.

Albert, N. B., Robertson, E. M., & Miall, R. C. (2009). The resting human brain and motor learning. *Curr Biol, 19*(12), 1023-1027.

Alger, S. E., Lau, H., & Fishbein, W. (2012). Slow wave sleep during a daytime nap is necessary for protection from subsequent interference and long-term retention. *Neurobiol Learn Mem, 98*(2), 188-196.

Ally, B. A., Gold, C. A., & Budson, A. E. (2009). An evaluation of recollection and familiarity in Alzheimer's disease and mild cognitive impairment using receiver operating characteristics. *Brain Cogn, 69*(3), 504-513.

Aly, M., & Moscovitch, M. (2010). The effects of sleep on episodic memory in older and younger adults. *Memory, 18*(3), 327-334.

Anderson, J. R. (1983). Retrieval of information from long-term memory. *Science, 220*(4592), 25-30.

Anderson, M. C. (2003). Rethinking interference theory: Executive control and the mechanisms of forgetting. *Journal of Memory and Language, 49*(4), 415-445.

Anderson, M. C., Bjork, R. A., & Bjork, E. L. (1994). Remembering can cause forgetting: retrieval dynamics in long-term memory. *J Exp Psychol Learn Mem Cogn, 20*(5), 1063-1087.

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2010). Non-linear registration, aka spatial normalisation. *FMRIB technical report TR07JA2*.

Atkinson, R. C., & Juola, J. F. (1974). Search and decision processes in recognition memory. In D. H. Krantz, R. C. Atkinson, R. D. Luce & P. Suppes (Eds.), *Contemporary developments in mathematical psychology: I. Learning, memory and thinking* (pp. xiii, 299). Oxford, England: W. H. Freeman.

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: A proposed system and its control processes. *Psychology of learning and motivation, 2*, 89-195.

Axmacher, N., Elger, C. E., & Fell, J. (2008). Ripples in the medial temporal lobe are relevant for human memory consolidation. *Brain, 131*(Pt 7), 1806-1817.

Backhaus, J., Born, J., Hoeckesfeld, R., Fokuhl, S., Hohagen, F., & Junghanns, K. (2007). Midlife decline in declarative memory consolidation is correlated with a decline in slow wave sleep. *Learn Mem, 14*(5), 336-341.

Bailey, C. H., & Chen, M. (1989). Time course of structural changes at identified sensory neuron synapses during long-term sensitization in Aplysia. *J Neurosci, 9*(5), 1774-1780.

Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science, 319*(5870), 1640-1642.

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

Barr, W. B., Goldberg, E., Wasserstein, J., & Novelly, R. A. (1990). Retrograde amnesia following unilateral temporal lobectomy. *Neuropsychologia, 28*(3), 243-255.

Barrett, T. R., & Ekstrand, B. R. (1972). Effect of sleep on memory. 3. Controlling for time-of-day effects. *J Exp Psychol, 96*(2), 321-327.

Bartko, S. J., Cowell, R. A., Winters, B. D., Bussey, T. J., & Saksida, L. M. (2010). Heightened susceptibility to interference in an animal model of amnesia: impairment in encoding, storage, retrieval--or all three? *Neuropsychologia, 48*(10), 2987-2997.

Bartko, S. J., Winters, B. D., Cowell, R. A., Saksida, L. M., & Bussey, T. J. (2007a). Perceptual functions of perirhinal cortex in rats: zero-delay object recognition and simultaneous oddity discriminations. *J Neurosci, 27*(10), 2548-2559.

Bartko, S. J., Winters, B. D., Cowell, R. A., Saksida, L. M., & Bussey, T. J. (2007b). Perirhinal cortex resolves feature ambiguity in configural object recognition and perceptual oddity tasks. *Learn Mem, 14*(12), 821-832.

Bartsch, T., & Butler, C. (2013). Transient amnesic syndromes. *Nat Rev Neurol, 9*(2), 86-97.

Battaglia, F. P., Benchenane, K., Sirota, A., Pennartz, C. M., & Wiener, S. I. (2011). The hippocampus: hub of brain network communication for memory. *Trends Cogn Sci, 15*(7), 310-318.

Bazil, C. W. (2000). Sleep and epilepsy. *Curr Opin Neurol, 13*(2), 171-175.

Bazil, C. W., & Walczak, T. S. (1997). Effects of sleep and sleep stage on epileptic and nonepileptic seizures. *Epilepsia, 38*(1), 56-62.

Beckmann, C. F., DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci, 360*(1457), 1001-1013.

Bell, B. D., & Giovagnoli, A. R. (2007). Recent innovative studies of memory in temporal lobe epilepsy. *Neuropsychol Rev, 17*(4), 455-476.

Ben-Yakov, A., & Dudai, Y. (2011). Constructing realistic engrams: poststimulus activity of hippocampus and dorsal striatum predicts subsequent episodic memory. *J Neurosci, 31*(24), 9032-9042.

Bendor, D., & Wilson, M. A. (2012). Biasing the content of hippocampal replay during sleep. *Nat Neurosci, 15*(10), 1439-1444.

Bergin, P. S., Thompson, P. J., Fish, D. R., & Shorvon, S. D. (1995). The effect of seizures on memory for recently learned material. *Neurology, 45*(2), 236-240.

Blake, R. V., Wroe, S. J., Breen, E. K., & McCarthy, R. A. (2000). Accelerated forgetting in patients with epilepsy: evidence for an impairment in memory consolidation. *Brain, 123 Pt 3*, 472-483.

Bland, B. H. (1986). The physiology and pharmacology of hippocampal formation theta rhythms. *Progress in neurobiology, 26*(1), 1-54.

Bliss, T. V., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol, 232*(2), 331-356.

Blumenfeld, R. S., & Ranganath, C. (2006). Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *J Neurosci, 26*(3), 916-925.

Bódizs, R., Kántor, S., Szabó, G., Szûcs, A., Erõss, L., & Halász, P. (2001). Rhythmic hippocampal slow oscillation characterizes REM sleep in humans. *Hippocampus, 11*(6), 747-753.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T. T., . . . Laureys, S. (2008). Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? *Ann N Y Acad Sci, 1129*, 119-129.

Bonnici, H. M., Chadwick, M. J., Lutti, A., Hassabis, D., Weiskopf, N., & Maguire, E. A. (2012). Detecting representations of recent and remote autobiographical memories in vmPFC and hippocampus. *J Neurosci, 32*(47), 16982-16991.

Bonnici, H. M., Chadwick, M. J., & Maguire, E. A. (2013). Representations of recent and remote autobiographical memories in hippocampal subfields. *Hippocampus, 23*(10), 849-854.

Bontempi, B., Laurent-Demir, C., Destrade, C., & Jaffard, R. (1999). Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature, 400*(6745), 671-675.

Borbely, A. A., & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *J Biol Rhythms, 14*(6), 557-568.

Born, J., Rasch, B., & Gais, S. (2006). Sleep to remember. *Neuroscientist, 12*(5), 410-424.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Making memories: brain activity that predicts how well visual experience will be remembered. *Science, 281*(5380), 1185-1187.

Broadbent, N. J., & Clark, R. E. (2013). Remote context fear conditioning remains hippocampus-dependent irrespective of training protocol, training-surgery interval, lesion size, and lesion method. *Neurobiol Learn Mem, 106*, 300-308.

Broadbent, N. J., Squire, L. R., & Clark, R. E. (2006). Reversible hippocampal lesions disrupt water maze performance during both recent and remote memory tests. *Learn Mem, 13*(2), 187-191.

Brown, G. D., Neath, I., & Chater, N. (2007). A temporal ratio model of memory. *Psychol Rev, 114*(3), 539-576.

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat Rev Neurosci, 2*(1), 51-61.

Bryant, P. A., Trinder, J., & Curtis, N. (2004). Sick and tired: Does sleep have a vital role in the immune system? *Nat Rev Immunol, 4*(6), 457-467.

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

Bussey, T. J., & Saksida, L. M. (2007). Memory, perception, and the ventral visual-perirhinal-hippocampal stream: thinking outside of the boxes. *Hippocampus, 17*(9), 898-908.

Bussey, T. J., Saksida, L. M., & Murray, E. A. (2005). The perceptual-mnemonic/feature conjunction model of perirhinal cortex function. *Q J Exp Psychol B, 58*(3-4), 269-282.

Butler, C., van Erp, W., Bhaduri, A., Hammers, A., Heckemann, R., & Zeman, A. (2013). Magnetic resonance volumetry reveals focal brain atrophy in transient epileptic amnesia. *Epilepsy Behav, 28*(3), 363-369.

Butler, C. R., Bhaduri, A., Acosta-Cabronero, J., Nestor, P. J., Kapur, N., Graham, K. S., . . . Zeman, A. Z. (2009). Transient epileptic amnesia: regional brain atrophy and its relationship to memory deficits. *Brain, 132*(Pt 2), 357-368.

Butler, C. R., Graham, K. S., Hodges, J. R., Kapur, N., Wardlaw, J. M., & Zeman, A. Z. (2007). The syndrome of transient epileptic amnesia. *Ann Neurol, 61*(6), 587-598.

Butler, C. R., & Zeman, A. (2008a). A case of transient epileptic amnesia with radiological localization. *Nat Clin Pract Neurol, 4*(9), 516-521.

Butler, C. R., & Zeman, A. Z. (2008b). Recent insights into the impairment of memory in epilepsy: transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment. *Brain, 131*(Pt 9), 2243-2263.

Buzsaki, G. (1989). Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience, 31*(3), 551-570.

Buzsaki, G. (1998). Memory consolidation during sleep: a neurophysiological perspective. *J Sleep Res, 7 Suppl 1*, 17-23.

Buzsaki, G. (2002). Theta oscillations in the hippocampus. *Neuron, 33*(3), 325-340.

Cajal, S. R. Y. (1894). The Croonian Lecture: La fine structure des centres nerveux. *Proceedings of the Royal Society of London, 55*(331-335), 444-468.

Cantero, J. L., Atienza, M., Stickgold, R., Kahana, M. J., Madsen, J. R., & Kocsis, B. (2003). Sleep-dependent theta oscillations in the human hippocampus and neocortex. *J Neurosci, 23*(34), 10897-10903.

Carr, V. A., Viskontas, I. V., Engel, S. A., & Knowlton, B. J. (2010). Neural activity in the hippocampus and perirhinal cortex during encoding is associated with the durability of episodic memory. *J Cogn Neurosci, 22*(11), 2652-2662.

Cermak, L. S., & O'Connor, M. (1983). The anterograde and retrograde retrieval ability of a patient with amnesia due to encephalitis. *Neuropsychologia, 21*(3), 213-234.

Cherdieu, M., Reynaud, E., Uhlrich, J., Versace, R., & Mazza, S. (2014). Does age worsen sleep-dependent memory consolidation? *J Sleep Res, 23*(1), 53-60.

Clark, R. E., Broadbent, N. J., & Squire, L. R. (2005a). Hippocampus and remote spatial memory in rats. *Hippocampus, 15*(2), 260-272.

Clark, R. E., Broadbent, N. J., & Squire, L. R. (2005b). Impaired remote spatial memory after hippocampal lesions despite extensive training beginning early in life. *Hippocampus, 15*(3), 340-346.

Clark, R. E., Broadbent, N. J., & Squire, L. R. (2007). The Hippocampus and Spatial Memory: Findings with a Novel Modification of the Water Maze. *The Journal of Neuroscience, 27*(25), 6647-6654.

Clemens, Z., Molle, M., Eross, L., Barsi, P., Halasz, P., & Born, J. (2007). Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. *Brain, 130*(Pt 11), 2868-2878.

Clemens, Z., Weiss, B., Szucs, A., Eross, L., Rasonyi, G., & Halasz, P. (2009). Phase coupling between rhythmic slow activity and gamma characterizes mesiotemporal rapid-eye-movement sleep in humans. *Neuroscience, 163*(1), 388-396.

Cohen, A., Ivry, R. I., & Keele, S. W. (1990). Attention and structure in sequence learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 16*(1), 17.

Coltheart, M. (1981). The MRC psycholinguistic database. *Q J Exp Psychol, 33*(4), 497-505.

Contreras, D., & Steriade, M. (1995). Cellular basis of EEG slow rhythms: a study of dynamic corticothalamic relationships. *J Neurosci, 15*(1 Pt 2), 604-622.

Coughlan, A., K., Oddy, M., J., & Crawford, J. R. (2007). *BIRT Memory and Information Processing Battery (BMIPB)*. London: Brain Injury Rehabilitation Trust.

Cowan, N., Beschin, N., & Della Sala, S. (2004). Verbal recall in amnesiacs under conditions of diminished retroactive interference. *Brain, 127*(Pt 4), 825-834.

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2006). Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. *J Neurosci, 26*(47), 12186-12197.

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2010). Components of recognition memory: Dissociable cognitive processes or just differences in representational complexity? *Hippocampus, 20*(11), 1245-1262.

Craik, F. I., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. *Journal of verbal learning and verbal behavior, 11*(6), 671-684.

Curran, T. (1997). Higher-order associative learning in amnesia: evidence from the serial reaction time task. *J Cogn Neurosci, 9*(4), 522-533.

Damasio, A. R., Eslinger, P. J., Damasio, H., Van Hoesen, G. W., & Cornell, S. (1985). Multimodal amnesic syndrome following bilateral temporal and basal forebrain damage. *Arch Neurol, 42*(3), 252-259.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Curr Opin Neurobiol, 16*(6), 693-700.

Davachi, L., Mitchell, J. P., & Wagner, A. D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc Natl Acad Sci U S A, 100*(4), 2157-2162.

Davidson, M., Dorris, L., O'Regan, M., & Zuberi, S. M. (2007). Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. *Epilepsy Behav, 11*(3), 394-400.

Davis, H. P., Small, S. A., Stern, Y., Mayeux, R., Feldstein, S. N., & Keller, F. R. (2003). Acquisition, recall, and forgetting of verbal information in long-term memory by young, middle-aged, and elderly individuals. *Cortex, 39*(4-5), 1063-1091.

Davis, H. P., & Squire, L. R. (1984). Protein synthesis and memory: a review. *Psychol Bull, 96*(3), 518-559.

De Koninck, J., Lorrain, D., Christ, G., Proulx, G., & Coulombe, D. (1989). Intensive language learning and increases in rapid eye movement sleep: evidence of a performance factor. *International Journal of Psychophysiology, 8*(1), 43-47.

Deak, M. C., Stickgold, R., Pietras, A. C., Nelson, A. P., & Bubrick, E. J. (2011). The role of sleep in forgetting in temporal lobe epilepsy: a pilot study. *Epilepsy Behav, 21*(4), 462-466.

Debiec, J., LeDoux, J. E., & Nader, K. (2002). Cellular and systems reconsolidation in the hippocampus. *Neuron, 36*(3), 527-538.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: Psychological Corporation.

Derry, C. P., & Duncan, S. (2013). Sleep and epilepsy. *Epilepsy Behav, 26*(3), 394-404.

Deuker, L., Olligs, J., Fell, J., Kranz, T. A., Mormann, F., Montag, C., . . . Axmacher, N. (2013). Memory consolidation by replay of stimulus-specific neural activity. *J Neurosci, 33*(49), 19373-19383.

Dewar, M., Cowan, N., & Della Sala, S. (2010). Forgetting due to retroactive interference in amnesia: Findings and implications. In S. Della Sala (Ed.), *Forgetting*. New York: Psychology Press.

Dewar, M., Garcia, Y. F., Cowan, N., & Della Sala, S. (2009). Delaying interference enhances memory consolidation in amnesic patients. *Neuropsychology, 23*(5), 627-634.

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

Diekelmann, S., Biggel, S., Rasch, B., & Born, J. (2012). Offline consolidation of memory varies with time in slow wave sleep and can be accelerated by cuing memory reactivations. *Neurobiol Learn Mem, 98*(2), 103-111.

Diekelmann, S., Buchel, C., Born, J., & Rasch, B. (2011). Labile or stable: opposing consequences for memory when reactivated during waking and sleep. *Nat Neurosci, 14*(3), 381-386.

Diekelmann, S., Wilhelm, I., & Born, J. (2009). The whats and whens of sleep-dependent memory consolidation. *Sleep Med Rev, 13*(5), 309-321.

Dijk, D. J., Beersma, D. G., & Daan, S. (1987). EEG power density during nap sleep: reflection of an hourglass measuring the duration of prior wakefulness. *J Biol Rhythms, 2*(3), 207-219.

Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., . . . James, A. (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain, 130*(Pt 9), 2375-2386.

Drosopoulos, S., Schulze, C., Fischer, S., & Born, J. (2007). Sleep's function in the spontaneous recovery and consolidation of memories. *J Exp Psychol Gen, 136*(2), 169-183.

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram? *Annu Rev Psychol, 55*, 51-86.

Dunn, C. J., Duffy, S. L., Hickie, I. B., Lagopoulos, J., Lewis, S. J., Naismith, S. L., & Shine, J. M. (2014). Deficits in episodic memory retrieval reveal impaired default mode network connectivity in amnestic mild cognitive impairment. *Neuroimage Clin, 4*, 473-480.

Dupret, D., O'Neill, J., Pleydell-Bouverie, B., & Csicsvari, J. (2010). The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nat Neurosci, 13*(8), 995-1002.

Durrant, S. J., Taylor, C., Cairney, S., & Lewis, P. A. (2011). Sleep-dependent consolidation of statistical learning. *Neuropsychologia, 49*(5), 1322-1331.

Ebbinghaus, H. (1885/1964). *Memory: A contribution to experimental psychology*. Oxford: Dover.

Ego-Stengel, V., & Wilson, M. A. (2010). Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus, 20*(1), 1-10.

Ellenbogen, J. M., Hu, P. T., Payne, J. D., Titone, D., & Walker, M. P. (2007). Human relational memory requires time and sleep. *Proc Natl Acad Sci U S A, 104*(18), 7723-7728.

Ellenbogen, J. M., Hulbert, J. C., Jiang, Y., & Stickgold, R. (2009). The sleeping brain's influence on verbal memory: boosting resistance to interference. *PLoS One, 4*(1), e4117.

Ellenbogen, J. M., Hulbert, J. C., Stickgold, R., Dinges, D. F., & Thompson-Schill, S. L. (2006). Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. *Curr Biol, 16*(13), 1290-1294.

Ellenbogen, J. M., Payne, J. D., & Stickgold, R. (2006). The role of sleep in declarative memory consolidation: passive, permissive, active or none? *Curr Opin Neurobiol, 16*(6), 716-722.

Elliott, G., Isaac, C. L., & Muhlert, N. (2014). Measuring forgetting: a critical review of accelerated long-term forgetting studies. *Cortex, 54*, 16-32.

Embree, L. M., Budson, A. E., & Ally, B. A. (2012). Memorial familiarity remains intact for pictures but not for words in patients with amnestic mild cognitive impairment. *Neuropsychologia, 50*(9), 2333-2340.

Ergorul, C., & Eichenbaum, H. (2006). Essential role of the hippocampal formation in rapid learning of higher-order sequential associations. *J Neurosci, 26*(15), 4111-4117.

Estes, W. K. (1955). Statistical theory of spontaneous recovery and regression. *Psychological review, 62*(3), 145-154.

Euston, D. R., Tatsuno, M., & McNaughton, B. L. (2007). Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. *Science, 318*(5853), 1147-1150.

Evers, E. A., Klaassen, E. B., Rombouts, S. A., Backes, W. H., & Jolles, J. (2012). The effects of sustained cognitive task performance on subsequent resting state functional connectivity in healthy young and middle-aged male schoolteachers. *Brain Connect, 2*(2), 102-112.

Fahoum, F., Zelmann, R., Tyvaert, L., Dubeau, F., & Gotman, J. (2013). Epileptic discharges affect the default mode network--FMRI and intracerebral EEG evidence. *PLoS One, 8*(6), e68038.

Ferrara, M., Moroni, F., De Gennaro, L., & Nobili, L. (2012). Hippocampal sleep features: relations to human memory function. *Front Neurol, 3*, 57.

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., . . . Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci U S A, 106*(17), 7209-7214.

Fischer, S., & Born, J. (2009). Anticipated reward enhances offline learning during sleep. *J Exp Psychol Learn Mem Cogn, 35*(6), 1586-1593.

Fischer, S., Drosopoulos, S., Tsen, J., & Born, J. (2006). Implicit learning -- explicit knowing: a role for sleep in memory system interaction. *J Cogn Neurosci, 18*(3), 311-319.

Fitzgerald, Z., Thayer, Z., Mohamed, A., & Miller, L. A. (2013). Examining factors related to accelerated long-term forgetting in epilepsy using ambulatory EEG monitoring. *Epilepsia, 54*(5), 819-827.

Fowler, M. J., Sullivan, M. J., & Ekstrand, B. R. (1973). Sleep and memory. *Science, 179*(4070), 302-304.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci, 8*(9), 700-711.

Frey, U., Krug, M., Reymann, K. G., & Matthies, H. (1988). Anisomycin, an inhibitor of protein synthesis, blocks late phases of LTP phenomena in the hippocampal CA1 region in vitro. *Brain Res, 452*(1-2), 57-65.

Gais, S., & Born, J. (2004). Declarative memory consolidation: mechanisms acting during human sleep. *Learn Mem, 11*(6), 679-685.

Gais, S., Lucas, B., & Born, J. (2006). Sleep after learning aids memory recall. *Learn Mem, 13*(3), 259-262.

Gais, S., Molle, M., Helms, K., & Born, J. (2002). Learning-dependent increases in sleep spindle density. *J Neurosci, 22*(15), 6830-6834.

Gallassi, R. (2006). Epileptic amnesic syndrome: an update and further considerations. *Epilepsia, 47 Suppl 2*, 103-105.

Gallassi, R., Morreale, A., Lorusso, S., Pazzaglia, P., & Lugaresi, E. (1988). Epilepsy presenting as memory disturbances. *Epilepsia, 29*(5), 624-629.

Garoff, R. J., Slotnick, S. D., & Schacter, D. L. (2005). The neural origins of specific and general memory: the role of the fusiform cortex. *Neuropsychologia, 43*(6), 847-859.

Gerrard, J. L., Burke, S. N., McNaughton, B. L., & Barnes, C. A. (2008). Sequence reactivation in the hippocampus is impaired in aged rats. *J Neurosci, 28*(31), 7883-7890.

Gilboa, A., Winocur, G., Grady, C. L., Hevenor, S. J., & Moscovitch, M. (2004). Remembering our past: functional neuroanatomy of recollection of recent and very remote personal events. *Cereb Cortex, 14*(11), 1214-1225.

Girardeau, G., Benchenane, K., Wiener, S. I., Buzsaki, G., & Zugaro, M. B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. *Nat Neurosci, 12*(10), 1222-1223.

Goncharova, II, Zaveri, H. P., Duckrow, R. B., Novotny, E. J., & Spencer, S. S. (2009). Spatial distribution of intracranially recorded spikes in medial and lateral temporal epilepsies. *Epilepsia, 50*(12), 2575-2585.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage, 14*(1 Pt 1), 21-36.

Graf, P., & Schacter, D. L. (1985). Implicit and explicit memory for new associations in normal and amnesic subjects. *J Exp Psychol Learn Mem Cogn, 11*(3), 501-518.

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

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A, 100*(1), 253-258.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A, 101*(13), 4637-4642.

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

Grill-Spector, K., Henson, R., & Martin, A. (2006). Repetition and the brain: neural models of stimulus-specific effects. *Trends Cogn Sci, 10*(1), 14-23.

Groen, G., Sokolov, A. N., Jonas, C., Roebling, R., & Spitzer, M. (2011). Increased resting-state perfusion after repeated encoding is related to later retrieval of declarative associative memories. *PLoS One, 6*(5), e19985.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience, 2*(10), 685-694.

Haist, F., Bowden Gore, J., & Mao, H. (2001). Consolidation of human memory over decades revealed by functional magnetic resonance imaging. *Nat Neurosci, 4*(11), 1139-1145.

Halgren, E., Babb, T. L., & Crandall, P. H. (1978). Human hippocampal formation EEG desynchronizes during attentiveness and movement. *Electroencephalogr Clin Neurophysiol, 44*(6), 778-781.

Hardt, O., Nader, K., & Nadel, L. (2013). Decay happens: the role of active forgetting in memory. *Trends Cogn Sci, 17*(3), 111-120.

Hasson, U., Nusbaum, H. C., & Small, S. L. (2009). Task-dependent organization of brain regions active during rest. *Proc Natl Acad Sci U S A, 106*(26), 10841-10846.

Hayama, H. R., Vilberg, K. L., & Rugg, M. D. (2012). Overlap between the neural correlates of cued recall and source memory: evidence for a generic recollection network? *J Cogn Neurosci, 24*(5), 1127-1137.

Hebb, D. (1949). *The organization of behavior*. New York: Wiley.

Heib, D. P., Hoedlmoser, K., Anderer, P., Zeitlhofer, J., Gruber, G., Klimesch, W., & Schabus, M. (2013). Slow oscillation amplitudes and up-state lengths relate to memory improvement. *PLoS One, 8*(12), e82049.

Hoefeijzers, S., Dewar, M., Della Sala, S., Butler, C., & Zeman, A. (2014). Accelerated Long-Term Forgetting Can Become Apparent Within 3-8 Hours of Wakefulness in Patients With Transient Epileptic Amnesia. *Neuropsychology*.

Hoefeijzers, S., Dewar, M., Della Sala, S., Zeman, A., & Butler, C. (2013). Accelerated long-term forgetting in transient epileptic amnesia: an acquisition or consolidation deficit? *Neuropsychologia, 51*(8), 1549-1555.

Hoffman, K. L., & McNaughton, B. L. (2002). Coordinated reactivation of distributed memory traces in primate neocortex. *Science, 297*(5589), 2070-2073.

Holmes, G. L., & Lenck-Santini, P. P. (2006). Role of interictal epileptiform abnormalities in cognitive impairment. *Epilepsy Behav, 8*(3), 504-515.

Holz, J., Piosczyk, H., Feige, B., Spiegelhalder, K., Baglioni, C., Riemann, D., & Nissen, C. (2012). EEG Sigma and slow-wave activity during NREM sleep correlate with overnight declarative and procedural memory consolidation. *J Sleep Res, 21*(6), 612-619.

Howard, D. V., Howard, J. H., Jr., Japikse, K., DiYanni, C., Thompson, A., & Somberg, R. (2004). Implicit sequence learning: effects of level of structure, adult age, and extended practice. *Psychol Aging, 19*(1), 79-92.

Howard, J. H., Jr., & Howard, D. V. (1997). Age differences in implicit learning of higher order dependencies in serial patterns. *Psychol Aging, 12*(4), 634-656.

Howard, M. W., Bessette-Symons, B., Zhang, Y., & Hoyer, W. J. (2006). Aging selectively impairs recollection in recognition memory for pictures: evidence from modeling and receiver operating characteristic curves. *Psychol Aging, 21*(1), 96-106.

Howard, M. W., & Kahana, M. J. (2002). A distributed representation of temporal context. *Journal of Mathematical Psychology, 46*(3), 269-299.

Huber, R., Ghilardi, M. F., Massimini, M., Ferrarelli, F., Riedner, B. A., Peterson, M. J., & Tononi, G. (2006). Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat Neurosci, 9*(9), 1169-1176.

Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature, 430*(6995), 78-81.

Huber, R., Määttä, S., Esser, S. K., Sarasso, S., Ferrarelli, F., Watson, A., . . . Tononi, G. (2008). Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. *The Journal of Neuroscience, 28*(31), 7911-7918.

Hupbach, A., Gomez, R., Hardt, O., & Nadel, L. (2007). Reconsolidation of episodic memories: a subtle reminder triggers integration of new information. *Learn Mem, 14*(1-2), 47-53.

Huppert, F. A., & Kopelman, M. D. (1989). Rates of forgetting in normal ageing: a comparison with dementia. *Neuropsychologia, 27*(6), 849-860.

Iber, C., Ancoli-Israel, S., Chesson, A., & Quan, S. F. (2007). *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specification.* Westchester, IL: American Academy of Sleep Medicine.

Isaac, C. L., & Mayes, A. R. (1999a). Rate of forgetting in amnesia: I. Recall and recognition of prose. *J Exp Psychol Learn Mem Cogn, 25*(4), 942-962.

Isaac, C. L., & Mayes, A. R. (1999b). Rate of forgetting in amnesia: II. Recall and recognition of word lists at different levels of organization. *J Exp Psychol Learn Mem Cogn, 25*(4), 963-977.

Isomura, Y., Sirota, A., Ozen, S., Montgomery, S., Mizuseki, K., Henze, D. A., & Buzsaki, G. (2006). Integration and segregation of activity in entorhinal-hippocampal subregions by neocortical slow oscillations. *Neuron, 52*(5), 871-882.

Izquierdo, I., Schroder, N., Netto, C. A., & Medina, J. H. (1999). Novelty causes time-dependent retrograde amnesia for one-trial avoidance in rats through NMDA receptor- and CaMKII-dependent mechanisms in the hippocampus. *Eur J Neurosci, 11*(9), 3323-3328.

Jackson, O., 3rd, & Schacter, D. L. (2004). Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *Neuroimage, 21*(1), 456-462.

Jacoby, L. L., & Dallas, M. (1981). On the relationship between autobiographical memory and perceptual learning. *Journal of Experimental Psychology: General, 110*(3), 306.

James, W. (1890). The principles of psychology (Vol. I). *New York: Holt*.

Jansari, A. S., Davis, K., McGibbon, T., Firminger, S., & Kapur, N. (2010). When "long-term memory" no longer means "forever": analysis of accelerated long-term forgetting in a patient with temporal lobe epilepsy. *Neuropsychologia, 48*(6), 1707-1715.

Jenkins, J. G., & Dallenbach, K. M. (1924). Obliviscence during sleep and waking. *Am J Psychol*, 605-612.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841.

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *Neuroimage, 62*(2), 782-790.

Ji, D., & Wilson, M. A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat Neurosci, 10*(1), 100-107.

Jokeit, H., Daamen, M., Zang, H., Janszky, J., & Ebner, A. (2001). Seizures accelerate forgetting in patients with left-sided temporal lobe epilepsy. *Neurology, 57*(1), 125-126.

Jokeit, H., Okujava, M., & Woermann, F. G. (2001). Carbamazepine reduces memory induced activation of mesial temporal lobe structures: a pharmacological fMRI-study. *BMC Neurol, 1*, 6.

Jouvet, M. (1969). Biogenic amines and the states of sleep. *Science, 163*(3862), 32-41.

Kapur, N. (1990). Transient epileptic amnesia: a clinically distinct form of neurological memory disorder. *Transient global amnesia and related disorders. New York: Hogrefe and Huber*, 140-151.

Kapur, N., Millar, J., Colbourn, C., Abbott, P., Kennedy, P., & Docherty, T. (1997). Very long-term amnesia in association with temporal lobe epilepsy: evidence for multiple-stage consolidation processes. *Brain Cogn, 35*(1), 58-70.

Karlsson, M. P., & Frank, L. M. (2009). Awake replay of remote experiences in the hippocampus. *Nat Neurosci, 12*(7), 913-918.

Kilpatrick, C., Murrie, V., Cook, M., Andrewes, D., Desmond, P., & Hopper, J. (1997). Degree of left hippocampal atrophy correlates with severity of neuropsychological deficits. *Seizure, 6*(3), 213-218.

Kirchhoff, B. A., Wagner, A. D., Maril, A., & Stern, C. E. (2000). Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *J Neurosci, 20*(16), 6173-6180.

Kirwan, C. B., & Stark, C. E. (2007). Overcoming interference: an fMRI investigation of pattern separation in the medial temporal lobe. *Learn Mem, 14*(9), 625-633.

Korman, M., Doyon, J., Doljansky, J., Carrier, J., Dagan, Y., & Karni, A. (2007). Daytime sleep condenses the time course of motor memory consolidation. *Nat Neurosci, 10*(9), 1206-1213.

Kotagal, P. (2001). The relationship between sleep and epilepsy. *Semin Pediatr Neurol, 8*(4), 241-250.

Kroes, M. C., Tendolkar, I., van Wingen, G. A., van Waarde, J. A., Strange, B. A., & Fernandez, G. (2014). An electroconvulsive therapy procedure impairs reconsolidation of episodic memories in humans. *Nat Neurosci, 17*(2), 204-206.

Kudrimoti, H. S., Barnes, C. A., & McNaughton, B. L. (1999). Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. *J Neurosci, 19*(10), 4090-4101.

Kuhl, B. A., Bainbridge, W. A., & Chun, M. M. (2012). Neural reactivation reveals mechanisms for updating memory. *J Neurosci, 32*(10), 3453-3461.

Lah, S., Mohamed, A., Thayer, Z., Miller, L., & Diamond, K. (2014). Accelerated long-term forgetting of verbal information in unilateral temporal lobe epilepsy: Is it related to structural hippocampal abnormalities and/or incomplete learning? *J Clin Exp Neuropsychol, 36*(2), 158-169.

Landsness, E. C., Crupi, D., Hulse, B. K., Peterson, M. J., Huber, R., Ansari, H., . . . Ghilardi, M. F. (2009). Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. *Sleep, 32*(10), 1273.

Lau, H., Tucker, M. A., & Fishbein, W. (2010). Daytime napping: Effects on human direct associative and relational memory. *Neurobiol Learn Mem, 93*(4), 554-560.

Laufs, H., Hamandi, K., Salek-Haddadi, A., Kleinschmidt, A. K., Duncan, J. S., & Lemieux, L. (2007). Temporal lobe interictal epileptic discharges affect cerebral activity in "default mode" brain regions. *Hum Brain Mapp, 28*(10), 1023-1032.

Lee, A. C., Barense, M. D., & Graham, K. S. (2005). The contribution of the human medial temporal lobe to perception: bridging the gap between animal and human studies. *Q J Exp Psychol B, 58*(3-4), 300-325.

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

Lee, A. C., Bussey, T. J., Murray, E. A., Saksida, L. M., Epstein, R. A., Kapur, N., . . . Graham, K. S. (2005). Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view. *Neuropsychologia, 43*(1), 1-11.

Lee, A. C., Yeung, L. K., & Barense, M. D. (2012). The hippocampus and visual perception. *Front Hum Neurosci, 6*, 91.

Leech, R., Braga, R., & Sharp, D. J. (2012). Echoes of the brain within the posterior cingulate cortex. *J Neurosci, 32*(1), 215-222.

Lehmann, H., Lacanilao, S., & Sutherland, R. J. (2007). Complete or partial hippocampal damage produces equivalent retrograde amnesia for remote contextual fear memories. *Eur J Neurosci, 25*(5), 1278-1286.

Lencz, T., McCarthy, G., Bronen, R. A., Scott, T. M., Inserni, J. A., Sass, K. J., . . . Spencer, D. D. (1992). Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. *Ann Neurol, 31*(6), 629-637.

Leonard, B. J., McNaughton, B. L., & Barnes, C. A. (1987). Suppression of hippocampal synaptic plasticity during slow-wave sleep. *Brain Res, 425*(1), 174-177.

Levy, B. J., & Anderson, M. C. (2002). Inhibitory processes and the control of memory retrieval. *Trends Cogn Sci, 6*(7), 299-305.

Lewis, P., & Kopelman, M. D. (1998). Forgetting rates in neuropsychiatric disorders. *J Neurol Neurosurg Psychiatry, 65*(6), 890-898.

Lewis, P. A., & Durrant, S. J. (2011). Overlapping memory replay during sleep builds cognitive schemata. *Trends Cogn Sci, 15*(8), 343-351.

Liao, W., Zhang, Z., Pan, Z., Mantini, D., Ding, J., Duan, X., . . . Chen, H. (2011). Default mode network abnormalities in mesial temporal lobe epilepsy: a study combining fMRI and DTI. *Hum Brain Mapp, 32*(6), 883-895.

Loftus, G. R. (1985a). Consistency and confoundings: Reply to Slamecka.

Loftus, G. R. (1985b). Evaluating forgetting curves. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 11*(2), 397.

Lux, S., Bindrich, V. N., Markowitsch, H. J., & Fink, G. R. (2013). Medial temporal lobe activation during autobiographical context memory retrieval of time and place and its dependency upon recency. *Neurocase*.

Macdonald, S. W., Stigsdotter-Neely, A., Derwinger, A., & Backman, L. (2006). Rate of acquisition, adult age, and basic cognitive abilities predict forgetting: new views on a classic problem. *J Exp Psychol Gen, 135*(3), 368-390.

Mameniskiene, R., Jatuzis, D., Kaubrys, G., & Budrys, V. (2006). The decay of memory between delayed and long-term recall in patients with temporal lobe epilepsy. *Epilepsy Behav, 8*(1), 278-288.

Mander, B. A., Rao, V., Lu, B., Saletin, J. M., Lindquist, J. R., Ancoli-Israel, S., . . . Walker, M. P. (2013). Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci, 16*(3), 357-364.

Mandler, G. (1980). Recognizing: The judgment of previous occurrence. *Psychological review, 87*(3), 252.

Marr, D. (1971). Simple memory: a theory for archicortex. *Philos Trans R Soc Lond B Biol Sci, 262*(841), 23-81.

Marshall, L., & Born, J. (2007). The contribution of sleep to hippocampus-dependent memory consolidation. *Trends Cogn Sci, 11*(10), 442-450.

Marshall, L., Helgadottir, H., Molle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature, 444*(7119), 610-613.

Martin, R. C., Loring, D. W., Meador, K. J., Lee, G. P., Thrash, N., & Arena, J. G. (1991). Impaired long-term retention despite normal verbal learning in patients with temporal lobe dysfunction. *Neuropsychology, 5*(1), 3.

Martin, S. J., de Hoz, L., & Morris, R. G. (2005). Retrograde amnesia: neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding. *Neuropsychologia, 43*(4), 609-624.

Mary, A., Schreiner, S., & Peigneux, P. (2013). Accelerated long-term forgetting in aging and intra-sleep awakenings. *Front Psychol, 4*, 750.

Matos, G., Andersen, M. L., do Valle, A. C., & Tufik, S. (2010). The relationship between sleep and epilepsy: evidence from clinical trials and animal models. *J Neurol Sci, 295*(1-2), 1-7.

Mayanagi, Y. (1977). The influence of natural sleep on focal spiking in experimental temporal lobe epilepsy in the monkey. *Electroencephalogr Clin Neurophysiol, 43*(6), 813-824.

Mayes, A. R. (1986). Learning and memory disorders and their assessment. *Neuropsychologia, 24*(1), 25-39.

McCarthy, R. A., & Warrington, E. K. (1992). Actors but not scripts: the dissociation of people and events in retrograde amnesia. *Neuropsychologia, 30*(7), 633-644.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol Rev, 102*(3), 419-457.

McCormick, C., Protzner, A. B., Barnett, A. J., Cohn, M., Valiante, T. A., & McAndrews, M. P. (2014). Linking DMN connectivity to episodic memory capacity: What can we learn from patients with medial temporal lobe damage? *Neuroimage Clin, 5*, 188-196.

McCormick, C., Quraan, M., Cohn, M., Valiante, T. A., & McAndrews, M. P. (2013). Default mode network connectivity indicates episodic memory capacity in mesial temporal lobe epilepsy. *Epilepsia, 54*(5), 809-818.

McGaugh, J. L. (2000). Memory--a century of consolidation. *Science, 287*(5451), 248-251.

McGeoch, J. A. (1932). Forgetting and the law of disuse. *Psychological review, 39*(4), 352.

McGeoch, J. A. (1942). *The psychology of human learning*. New York: Longmans, Green.

McGibbon, T., & Jansari, A. S. (2013). Detecting the onset of accelerated long-term forgetting: evidence from temporal lobe epilepsy. *Neuropsychologia, 51*(1), 114-122.

McKenna, P., & Warrington, E. K. (1980). Testing for nominal dysphasia. *Journal of Neurology, Neurosurgery & Psychiatry, 43*(9), 781-788.

McKinney, F., & McGeoch, J. A. (1935). The character and extent of transfer in retroactive inhibition: disparate serial lists. *Am J Psychol*, 409-423.

McNaughton, N., & Morris, R. G. (1987). Chlordiazepoxide, an anxiolytic benzodiazepine, impairs place navigation in rats. *Behav Brain Res, 24*(1), 39-46.

Mednick, S. C., Cai, D. J., Shuman, T., Anagnostaras, S., & Wixted, J. T. (2011). An opportunistic theory of cellular and systems consolidation. *Trends Neurosci, 34*(10), 504-514.

Mednick, S. C., Makovski, T., Cai, D. J., & Jiang, Y. V. (2009). Sleep and rest facilitate implicit memory in a visual search task. *Vision Res, 49*(21), 2557-2565.

Mednick, S. C., McDevitt, E. A., Walsh, J. K., Wamsley, E., Paulus, M., Kanady, J. C., & Drummond, S. P. (2013). The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. *J Neurosci, 33*(10), 4494-4504.

Melton, A. W., & Irwin, J. M. (1940). The Influence of Degree of Interpolated Learning on Retroactive Inhibition and the Overt Transfer of Specific Responses. *Am J Psychol, 53*(2), 173-203.

Mensink, G.-J., & Raaijmakers, J. G. (1988). A model for interference and forgetting. *Psychological review, 95*(4), 434.

Mensink, G.-J. M., & Raaijmakers, J. G. (1989). A model for contextual fluctuation. *Journal of Mathematical Psychology, 33*(2), 172-186.

Mickes, L., Wixted, J. T., & Wais, P. E. (2007). A direct test of the unequal-variance signal detection model of recognition memory. *Psychon Bull Rev, 14*(5), 858-865.

Milner, B. (1966). Amnesia following operation on the temporal lobes. *Amnesia*, 109-133.

Misanin, J. R., Miller, R. R., & Lewis, D. J. (1968). Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science, 160*(3827), 554-555.

Molle, M., Eschenko, O., Gais, S., Sara, S. J., & Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *Eur J Neurosci, 29*(5), 1071-1081.

Molle, M., Marshall, L., Gais, S., & Born, J. (2002). Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. *J Neurosci, 22*(24), 10941-10947.

Molle, M., Yeshenko, O., Marshall, L., Sara, S. J., & Born, J. (2006). Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. *J Neurophysiol, 96*(1), 62-70.

Moroni, F., Nobili, L., Curcio, G., De Carli, F., Fratello, F., Marzano, C., . . . Ferrara, M. (2007). Sleep in the human hippocampus: a stereo-EEG study. *PLoS One, 2*(9), e867.

Muhlert, N., Grunewald, R. A., Hunkin, N. M., Reuber, M., Howell, S., Reynders, H., & Isaac, C. L. (2011). Accelerated long-term forgetting in temporal lobe but not idiopathic generalised epilepsy. *Neuropsychologia, 49*(9), 2417-2426.

Muhlert, N., Milton, F., Butler, C. R., Kapur, N., & Zeman, A. Z. (2010). Accelerated forgetting of real-life events in Transient Epileptic Amnesia. *Neuropsychologia, 48*(11), 3235-3244.

Mulkey, R. M., & Malenka, R. C. (1992). Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron, 9*(5), 967-975.

Müller, G. E., & Pilzecker, A. (1900). Pilzecker Experimentelle Beiträge zur Lehre vom Gedächtnis. *Z. Psychol. Ergänzungsband, 1*, 1-300.

Nadasdy, Z., Hirase, H., Czurko, A., Csicsvari, J., & Buzsaki, G. (1999). Replay and time compression of recurring spike sequences in the hippocampus. *J Neurosci, 19*(21), 9497-9507.

Nadel, L., & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr Opin Neurobiol, 7*(2), 217-227.

Nader, K. (2003). Memory traces unbound. *Trends Neurosci, 26*(2), 65-72.

Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406*(6797), 722-726.

Narayanan, J., Duncan, R., Greene, J., Leach, J. P., Razvi, S., McLean, J., & Evans, J. J. (2012). Accelerated long-term forgetting in temporal lobe epilepsy: verbal, nonverbal and autobiographical memory. *Epilepsy Behav, 25*(4), 622-630.

Nazer, F., & Dickson, C. T. (2009). Slow oscillation state facilitates epileptiform events in the hippocampus. *J Neurophysiol, 102*(3), 1880-1889.

Nelson, H., & Willison, J. (1991). The revised national adult reading test–test manual. *Windsor: NFER-Nelson*.

Nelson, H. E. (1982). *The National Adult Reading Test (NART): Test manual, 1-13*. Windsor: NFER-Nelson.

Nemeth, D., Janacsek, K., Londe, Z., Ullman, M. T., Howard, D. V., & Howard, J. H., Jr. (2010). Sleep has no critical role in implicit motor sequence learning in young and old adults. *Exp Brain Res, 201*(2), 351-358.

Ngo, H. V., Martinetz, T., Born, J., & Molle, M. (2013). Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron, 78*(3), 545-553.

Niki, K., & Luo, J. (2002). An fMRI study on the time-limited role of the medial temporal lobe in long-term topographical autobiographic memory. *J Cogn Neurosci, 14*(3), 500-507.

Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive psychology, 19*(1), 1-32.

O'Reilly, R. C., & McClelland, J. L. (1994). Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. *Hippocampus, 4*(6), 661-682.

Paller, K. A., Kutas, M., & Mayes, A. R. (1987). Neural correlates of encoding in an incidental learning paradigm. *Electroencephalogr Clin Neurophysiol, 67*(4), 360-371.

Paller, K. A., & Wagner, A. D. (2002). Observing the transformation of experience into memory. *Trends Cogn Sci, 6*(2), 93-102.

Pavlides, C., & Winson, J. (1989). Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *J Neurosci, 9*(8), 2907-2918.

Peigneux, P., Laureys, S., Fuchs, S., Collette, F., Perrin, F., Reggers, J., . . . Maquet, P. (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron, 44*(3), 535-545.

Peters, K. R., Ray, L., Smith, V., & Smith, C. (2008). Changes in the density of stage 2 sleep spindles following motor learning in young and older adults. *J Sleep Res, 17*(1), 23-33.

Peyrache, A., Khamassi, M., Benchenane, K., Wiener, S. I., & Battaglia, F. P. (2009). Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. *Nat Neurosci, 12*(7), 919-926.

Piefke, M., Weiss, P. H., Zilles, K., Markowitsch, H. J., & Fink, G. R. (2003). Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain, 126*(Pt 3), 650-668.

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *J Cogn Neurosci, 9*(4), 534-547.

Plihal, W., & Born, J. (1999). Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology, 36*(5), 571-582.

Polyn, S. M., Norman, K. A., & Kahana, M. J. (2009). A context maintenance and retrieval model of organizational processes in free recall. *Psychol Rev, 116*(1), 129-156.

Prehn-Kristensen, A., Goder, R., Fischer, J., Wilhelm, I., Seeck-Hirschner, M., Aldenhoff, J., & Baving, L. (2011). Reduced sleep-associated consolidation of declarative memory in attention-deficit/hyperactivity disorder. *Sleep Med, 12*(7), 672-679.

Prull, M. W., Gabrieli, J. D., & Bunge, S. A. (2000). Age-related changes in memory: A cognitive neuroscience perspective.

Qin, Y. L., McNaughton, B. L., Skaggs, W. E., & Barnes, C. A. (1997). Memory reprocessing in corticocortical and hippocampocortical neuronal ensembles. *Philos Trans R Soc Lond B Biol Sci, 352*(1360), 1525-1533.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682.

Rasch, B., & Born, J. (2007). Maintaining memories by reactivation. *Curr Opin Neurobiol, 17*(6), 698-703.

Rasch, B., Buchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science, 315*(5817), 1426-1429.

Rauchs, G., Feyers, D., Landeau, B., Bastin, C., Luxen, A., Maquet, P., & Collette, F. (2011). Sleep contributes to the strengthening of some memories over others, depending on hippocampal activity at learning. *J Neurosci, 31*(7), 2563-2568.

Reber, P. J., & Squire, L. R. (1994). Parallel brain systems for learning with and without awareness. *Learn Mem, 1*(4), 217-229.

Rechtschaffen, A., & Kales, A. (1968). *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Washington, D.C.: National Institute of Health Publications, U.S. Government Printing Office.

Reed, J., & Johnson, P. (1994). Assessing implicit learning with indirect tests: Determining what is learned about sequence structure. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20*(3), 585.

Reminger, S. L., Kaszniak, A. W., Labiner, D. M., Littrell, L. D., David, B. T., Ryan, L., . . . Kaemingk, K. L. (2004). Bilateral hippocampal volume predicts verbal memory function in temporal lobe epilepsy. *Epilepsy Behav, 5*(5), 687-695.

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Arch. Psychol., 28*, 286-340.

Ribot, T. (1882). *Diseases of memory*. New York: Appleton.

Ritchey, M., Dolcos, F., & Cabeza, R. (2008). Role of amygdala connectivity in the persistence of emotional memories over time: an event-related FMRI investigation. *Cereb Cortex, 18*(11), 2494-2504.

Robertson, E. M., Pascual-Leone, A., & Press, D. Z. (2004). Awareness modifies the skill-learning benefits of sleep. *Curr Biol, 14*(3), 208-212.

Robinson, E. S. (1920). Some factors determining the degree of retroactive inhibition. *Psychological Monographs, 28*(6), i.

Roediger, H. L., Weinstein, Y., & Agarwal, P. K. (2010). Forgetting: Preliminary considerations. In S. Della Sala (Ed.), *Forgetting*. New York: Psychology Press.

Romcy-Pereira, R. N., Leite, J. P., & Garcia-Cairasco, N. (2009). Synaptic plasticity along the sleep-wake cycle: implications for epilepsy. *Epilepsy Behav, 14 Suppl 1*, 47-53.

Rosanova, M., & Ulrich, D. (2005). Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *J Neurosci, 25*(41), 9398-9405.

Rossi, G. F., Colicchio, G., & Pola, P. (1984). Interictal epileptic activity during sleep: a stereo-EEG study in patients with partial epilepsy. *Electroencephalogr Clin Neurophysiol, 58*(2), 97-106.

Rubin, D. C., & Wenzel, A. E. (1996). One hundred years of forgetting: A quantitative description of retention. *Psychological review, 103*(4), 734.

Rudoy, J. D., Voss, J. L., Westerberg, C. E., & Paller, K. A. (2009). Strengthening individual memories by reactivating them during sleep. *Science, 326*(5956), 1079.

Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Curr Opin Neurobiol, 23*(2), 255-260.

Sahay, A., Scobie, K. N., Hill, A. S., O'Carroll, C. M., Kheirbek, M. A., Burghardt, N. S., . . . Hen, R. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature, 472*(7344), 466-470.

Salimi-Khorshidi, G., Douaud, G., Beckmann, C. F., Glasser, M. F., Griffanti, L., & Smith, S. M. (2014). Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. *Neuroimage, 90*, 449-468.

Sammaritano, M., Gigli, G. L., & Gotman, J. (1991). Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. *Neurology, 41*(2 (Pt 1)), 290-297.

Schabus, M., Gruber, G., Parapatics, S., Sauter, C., Klosch, G., Anderer, P., . . . Zeitlhofer, J. (2004). Sleep spindles and their significance for declarative memory consolidation. *Sleep, 27*(8), 1479-1485.

Schacter, D. L., & Tulving, E. (1994). *Memory systems 1994*: MIT Press.

Schendan, H. E., Searl, M. M., Melrose, R. J., & Stern, C. E. (2003). An FMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron, 37*(6), 1013-1025.

Schendan, H. E., Tinaz, S., Maher, S. M., & Stern, C. E. (2013). Frontostriatal and mediotemporal lobe contributions to implicit higher-order spatial sequence learning declines in aging and Parkinson's disease. *Behav Neurosci, 127*(2), 204-221.

Schmidt, M. (1996). *Rey auditory verbal learning test: A handbook*: Western Psychological Services Los Angeles.

Schneider, A. M., & Sherman, W. (1968). Amnesia: a function of the temporal relation of footshock to electroconvulsive shock. *Science, 159*(3811), 219-221.

Schultz, D. H., Balderston, N. L., & Helmstetter, F. J. (2012). Resting-state connectivity of the amygdala is altered following Pavlovian fear conditioning. *Front Hum Neurosci, 6*, 242.

Scullin, M. K. (2013). Sleep, memory, and aging: the link between slow-wave sleep and episodic memory changes from younger to older adults. *Psychol Aging, 28*(1), 105-114.

Shallice, T., & Warrington, E. K. (1970). Independent functioning of verbal memory stores: a neuropsychological study. *Q J Exp Psychol, 22*(2), 261-273.

Shatskikh, T. N., Raghavendra, M., Zhao, Q., Cui, Z., & Holmes, G. L. (2006). Electrical induction of spikes in the hippocampus impairs recognition capacity and spatial memory in rats. *Epilepsy Behav, 9*(4), 549-556.

Shimamura, A. P., Jurica, P. J., Mangels, J. A., Gershberg, F. B., & Knight, R. T. (1995). Susceptibility to Memory Interference Effects following Frontal Lobe Damage: Findings from Tests of Paired-Associate Learning. *J Cogn Neurosci, 7*(2), 144-152.

Shuell, T. J., & Keppel, G. (1970). Learning ability and retention. *Journal of Educational Psychology, 61*(1), 59.

Siapas, A. G., & Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron, 21*(5), 1123-1128.

Sirota, A., Csicsvari, J., Buhl, D., & Buzsaki, G. (2003). Communication between neocortex and hippocampus during sleep in rodents. *Proc Natl Acad Sci U S A, 100*(4), 2065-2069.

Skaggs, E. B. (1925). Further studies in retroactive inhibition. *Psychological Monographs, 34*(Whole No. 161), 1-60.

Skaggs, W. E., & McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science, 271*(5257), 1870-1873.

Slamecka, N. J. (1985). On comparing rates of forgetting: Comment on Loftus (1985).

Slamecka, N. J., & McElree, B. (1983). Normal forgetting of verbal lists as a function of their degree of learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 9*(3), 384.

Smith, M. L., Leonard, G., Crane, J., & Milner, B. (1995). The effects of frontal- or temporal-lobe lesions on susceptibility to interference in spatial memory. *Neuropsychologia, 33*(3), 275-285.

Smith, S. M. (2002). Fast robust automated brain extraction. *Hum Brain Mapp, 17*(3), 143-155.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23 Suppl 1*, S208-219.

Song, S., Howard, J. H., Jr., & Howard, D. V. (2007). Sleep does not benefit probabilistic motor sequence learning. *J Neurosci, 27*(46), 12475-12483.

Spaniol, J., Davidson, P. S., Kim, A. S., Han, H., Moscovitch, M., & Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia, 47*(8-9), 1765-1779.

Sparks, F. T., Lehmann, H., Hernandez, K., & Sutherland, R. J. (2011). Suppression of neurotoxic lesion-induced seizure activity: evidence for a permanent role for the hippocampus in contextual memory. *PLoS One, 6*(11), e27426.

Spencer, R. M., Gouw, A. M., & Ivry, R. B. (2007). Age-related decline of sleep-dependent consolidation. *Learn Mem, 14*(7), 480-484.

Squire, L. R. (1987). The organization and neural substrates of human memory. *Int J Neurol, 21-22*, 218-222.

Squire, L. R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological review, 99*(2), 195.

Squire, L. R., Clark, R. E., & Knowlton, B. J. (2001). Retrograde amnesia. *Hippocampus, 11*(1), 50-55.

Squire, L. R., Cohen, N. J., & Nadel, L. (1984). The medial temporal region and memory consolidation: A new hypothesis. *Weingartner, H. & Parker, ES (editors), Memory Consolidation: Psychobiology of Cognition*, 185-210.

Squire, L. R., Slater, P. C., & Chace, P. M. (1975). Retrograde amnesia: temporal gradient in very long term memory following electroconvulsive therapy. *Science, 187*(4171), 77-79.

Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nat Rev Neurosci, 8*(11), 872-883.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*(5026), 1380-1386.

Staresina, B. P., Alink, A., Kriegeskorte, N., & Henson, R. N. (2013). Awake reactivation predicts memory in humans. *Proc Natl Acad Sci U S A, 110*(52), 21159-21164.

Steriade, M. (2006). Grouping of brain rhythms in corticothalamic systems. *Neuroscience, 137*(4), 1087-1106.

Stevens, W. D., Buckner, R. L., & Schacter, D. L. (2010). Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. *Cereb Cortex, 20*(8), 1997-2006.

Storm, B. C. (2011). The benefit of forgetting in thinking and remembering. *Current Directions in Psychological Science, 20*(5), 291-295.

Sud, S., Sadaka, Y., Massicotte, C., Smith, M. L., Bradbury, L., Go, C., & Weiss, S. K. (2014). Memory consolidation in children with epilepsy: does sleep matter? *Epilepsy Behav, 31*, 176-180.

Sutherland, R. J., O'Brien, J., & Lehmann, H. (2008). Absence of systems consolidation of fear memories after dorsal, ventral, or complete hippocampal damage. *Hippocampus, 18*(7), 710-718.

Takashima, A., Petersson, K. M., Rutters, F., Tendolkar, I., Jensen, O., Zwarts, M. J., . . . Fernandez, G. (2006). Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. *Proc Natl Acad Sci U S A, 103*(3), 756-761.

Talamini, L. M., Nieuwenhuis, I. L., Takashima, A., & Jensen, O. (2008). Sleep directly following learning benefits consolidation of spatial associative memory. *Learn Mem, 15*(4), 233-237.

Tambini, A., & Davachi, L. (2013). Persistence of hippocampal multivoxel patterns into postencoding rest is related to memory. *Proc Natl Acad Sci U S A, 110*(48), 19591-19596.

Tambini, A., Ketz, N., & Davachi, L. (2010). Enhanced brain correlations during rest are related to memory for recent experiences. *Neuron, 65*(2), 280-290.

Tamura, R., Nishida, H., Eifuku, S., Fushiki, H., Watanabe, Y., & Uchiyama, K. (2013). Sleep-stage correlates of hippocampal electroencephalogram in primates. *PLoS One, 8*(12), e82994.

Tononi, G., & Cirelli, C. (2003). Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull, 62*(2), 143-150.

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Med Rev, 10*(1), 49-62.

Trachtenberg, A. J., Filippini, N., Cheeseman, J., Duff, E. P., Neville, M. J., Ebmeier, K. P., . . . Mackay, C. E. (2012). The effects of APOE on brain activity do not simply reflect the risk of Alzheimer's disease. *Neurobiol Aging, 33*(3), 618 e611-618 e613.

Tramoni, E., Felician, O., Barbeau, E. J., Guedj, E., Guye, M., Bartolomei, F., & Ceccaldi, M. (2011). Long-term consolidation of declarative memory: insight from temporal lobe epilepsy. *Brain, 134*(Pt 3), 816-831.

Treves, A., & Rolls, E. T. (1994). Computational analysis of the role of the hippocampus in memory. *Hippocampus, 4*(3), 374-391.

Tucker, M., McKinley, S., & Stickgold, R. (2011). Sleep optimizes motor skill in older adults. *J Am Geriatr Soc, 59*(4), 603-609.

Tulving, E. (1972). Episodic and semantic memory 1. *Organization of Memory. London: Academic, 381*, e402.

Tulving, E., & Arbuckle, T. Y. (1963). Sources of intratrial interference in immediate recall of paired associates. *Journal of verbal learning and verbal behavior, 1*(5), 321-334.

Tulving, E., Schacter, D. L., McLachlan, D. R., & Moscovitch, M. (1988). Priming of semantic autobiographical knowledge: a case study of retrograde amnesia. *Brain Cogn, 8*(1), 3-20.

Tulving, E., & Thomson, D. M. (1973). Encoding specificity and retrieval processes in episodic memory. *Psychological review, 80*(5), 352.

Turner, M. S., Cipolotti, L., Yousry, T., & Shallice, T. (2007). Qualitatively different memory impairments across frontal lobe subgroups. *Neuropsychologia, 45*(7), 1540-1552.

Uchida, S., Maehara, T., Hirai, N., Okubo, Y., & Shimizu, H. (2001). Cortical oscillations in human medial temporal lobe during wakefulness and all-night sleep. *Brain Res, 891*(1-2), 7-19.

Uncapher, M. R., & Rugg, M. D. (2005). Encoding and the durability of episodic memory: a functional magnetic resonance imaging study. *J Neurosci, 25*(31), 7260-7267.

Uncapher, M. R., & Wagner, A. D. (2009). Posterior parietal cortex and episodic encoding: insights from fMRI subsequent memory effects and dual-attention theory. *Neurobiol Learn Mem, 91*(2), 139-154.

Underwood, B. J. (1964). Forgetting. *Sci Am, 210*, 91-99.

Urbain, C., Di Vincenzo, T., Peigneux, P., & Van Bogaert, P. (2011). Is sleep-related consolidation impaired in focal idiopathic epilepsies of childhood? A pilot study. *Epilepsy & behavior, 22*(2), 380-384.

Van Cauter, E., Leproult, R., & Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA, 284*(7), 861-868.

van der Kouwe, A. J., Benner, T., Salat, D. H., & Fischl, B. (2008). Brain morphometry with multiecho MPRAGE. *Neuroimage, 40*(2), 559-569.

van Kesteren, M. T., Fernandez, G., Norris, D. G., & Hermans, E. J. (2010). Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and postencoding rest in humans. *Proc Natl Acad Sci U S A, 107*(16), 7550-7555.

van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A, 96*(23), 13427-13431.

van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci, 2*(3), 266-270.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science, 277*(5324), 376-380.

Villarreal, D. M., Do, V., Haddad, E., & Derrick, B. E. (2002). NMDA receptor antagonists sustain LTP and spatial memory: active processes mediate LTP decay. *Nat Neurosci, 5*(1), 48-52.

Voets, N. L., Adcock, J. E., Stacey, R., Hart, Y., Carpenter, K., Matthews, P. M., & Beckmann, C. F. (2009). Functional and structural changes in the memory network associated with left temporal lobe epilepsy. *Hum Brain Mapp, 30*(12), 4070-4081.

Voets, N. L., Beckmann, C. F., Cole, D. M., Hong, S., Bernasconi, A., & Bernasconi, N. (2012). Structural substrates for resting network disruption in temporal lobe epilepsy. *Brain, 135*(Pt 8), 2350-2357.

Voets, N. L., Zamboni, G., Stokes, M. G., Carpenter, K., Stacey, R., & Adcock, J. E. (2014). Aberrant functional connectivity in dissociable hippocampal networks is associated with deficits in memory. *J Neurosci, 34*(14), 4920-4928.

Vyazovskiy, V. V., Cirelli, C., Pfister-Genskow, M., Faraguna, U., & Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nat Neurosci, 11*(2), 200-208.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., . . . Buckner, R. L. (1998). Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*(5380), 1188-1191.

Wagner, U., Gais, S., Haider, H., Verleger, R., & Born, J. (2004). Sleep inspires insight. *Nature, 427*(6972), 352-355.

Walker, M. P., Brakefield, T., Hobson, J. A., & Stickgold, R. (2003). Dissociable stages of human memory consolidation and reconsolidation. *Nature, 425*(6958), 616-620.

Walker, M. P., & Stickgold, R. (2006). Sleep, memory, and plasticity. *Annu Rev Psychol, 57*, 139-166.

Wang, D. Y., Liu, D. Q., Li, S. F., & Zang, Y. F. (2012). Increased local synchronization of resting-state fMRI signal after episodic memory encoding reflects off-line memory consolidation. *Neuroreport, 23*(15), 873-878.

Wang, L., Laviolette, P., O'Keefe, K., Putcha, D., Bakkour, A., Van Dijk, K. R., . . . Sperling, R. A. (2010). Intrinsic connectivity between the hippocampus and posteromedial cortex predicts memory performance in cognitively intact older individuals. *Neuroimage, 51*(2), 910-917.

Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., . . . Li, K. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. *Neuroimage, 31*(2), 496-504.

Warrington, E. K. (1984). *The recognition memory test*. Windsor, United Kingdom: NFER-Nelson.

Warrington, E. K., & Weiskrantz, L. (1978). Further analysis of the prior learning effect in amnesic patients. *Neuropsychologia, 16*(2), 169-177.

Watkins, M. J., & Watkins, O. C. (1975). A categorically postcategorical interpretation of the modality effect: a reply to Nilsson. *J Exp Psychol Hum Learn, 1*(6), 733-735.

Webb, W. B., & Agnew, H. W., Jr. (1971). Stage 4 sleep: influence of time course variables. *Science, 174*(4016), 1354-1356.

Wechsler, D. (1955). *Manual for the Wechsler Adult Intelligence Scale*. New York: Psychological Corporation.

Wechsler, D. (1997). *Wechsler memory scale III*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence*. San Antonio, TX: Psychological Corporation.

Werk, C. M., Harbour, V. L., & Chapman, C. A. (2005). Induction of long-term potentiation leads to increased reliability of evoked neocortical spindles in vivo. *Neuroscience, 131*(4), 793-800.

Westerberg, C. E., Mander, B. A., Florczak, S. M., Weintraub, S., Mesulam, M. M., Zee, P. C., & Paller, K. A. (2012). Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. *J Int Neuropsychol Soc, 18*(3), 490-500.

Whitlock, J. R., Heynen, A. J., Shuler, M. G., & Bear, M. F. (2006). Learning induces long-term potentiation in the hippocampus. *Science, 313*(5790), 1093-1097.

Wilhelm, I., Diekelmann, S., Molzow, I., Ayoub, A., Molle, M., & Born, J. (2011). Sleep selectively enhances memory expected to be of future relevance. *J Neurosci, 31*(5), 1563-1569.

Wilkinson, H., Holdstock, J. S., Baker, G., Herbert, A., Clague, F., & Downes, J. J. (2012). Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy. *Cortex, 48*(3), 317-332.

Wilson, J. K., Baran, B., Pace-Schott, E. F., Ivry, R. B., & Spencer, R. M. (2012). Sleep modulates word-pair learning but not motor sequence learning in healthy older adults. *Neurobiol Aging, 33*(5), 991-1000.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science, 265*(5172), 676-679.

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage, 92*, 381-397.

Winocur, G., & Moscovitch, M. (2011). Memory transformation and systems consolidation. *J Int Neuropsychol Soc, 17*(5), 766-780.

Wixted, J. T. (1990). Analyzing the empirical course of forgetting. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 16*(5), 927.

Wixted, J. T. (2004). The psychology and neuroscience of forgetting. *Annu Rev Psychol, 55*, 235-269.

Wixted, J. T. (2010). The role of retroactive interference and consolidation in everyday forgetting. In S. Della Sala (Ed.), *Forgetting*. New York: Psychology Press.

Wixted, J. T., & Carpenter, S. K. (2007). The Wickelgren power law and the Ebbinghaus savings function. *Psychol Sci, 18*(2), 133-134.

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage, 14*(6), 1370-1386.

Worsley, K. J. (2001). Testing for signals with unknown location and scale in a χ 2 random field, with an application to fMRI. *Advances in Applied Probability*, 773-793.

Xu, L., Anwyl, R., & Rowan, M. J. (1998). Spatial exploration induces a persistent reversal of long-term potentiation in rat hippocampus. *Nature, 394*(6696), 891-894.

Yang, G., Lai, C. S., Cichon, J., Ma, L., Li, W., & Gan, W. B. (2014). Sleep promotes branch-specific formation of dendritic spines after learning. *Science, 344*(6188), 1173-1178.

Yaroush, R., Sullivan, M. J., & Ekstrand, B. R. (1971). Effect of sleep on memory. II. Differential effect of the first and second half of the night. *J Exp Psychol, 88*(3), 361-366.

Yassa, M. A., & Stark, C. E. (2011). Pattern separation in the hippocampus. *Trends Neurosci, 34*(10), 515-525.

Yonelinas, A. P. (1994). Receiver-operating characteristics in recognition memory: evidence for a dual-process model. *J Exp Psychol Learn Mem Cogn, 20*(6), 1341-1354.

Yonelinas, A. P. (1999). The contribution of recollection and familiarity to recognition and source-memory judgments: a formal dual-process model and an analysis of receiver operating characteristics. *J Exp Psychol Learn Mem Cogn, 25*(6), 1415-1434.

Yonelinas, A. P., Kroll, N. E., Dobbins, I., Lazzara, M., & Knight, R. T. (1998). Recollection and familiarity deficits in amnesia: convergence of remember-know, process dissociation, and receiver operating characteristic data. *Neuropsychology, 12*(3), 323-339.

Yordanova, J., Kolev, V., Wagner, U., Born, J., & Verleger, R. (2012). Increased alpha (8-12 Hz) activity during slow wave sleep as a marker for the transition from implicit knowledge to explicit insight. *J Cogn Neurosci, 24*(1), 119-132.

Zeman, A., & Butler, C. (2010). Transient epileptic amnesia. *Curr Opin Neurol, 23*(6), 610-616.

Zeman, A., Butler, C., Muhlert, N., & Milton, F. (2013). Novel forms of forgetting in temporal lobe epilepsy. *Epilepsy Behav, 26*(3), 335-342.

Zeman, A. Z., Boniface, S. J., & Hodges, J. R. (1998). Transient epileptic amnesia: a description of the clinical and neuropsychological features in 10 cases and a review of the literature. *J Neurol Neurosurg Psychiatry, 64*(4), 435-443.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta psychiatrica scandinavica, 67*(6), 361-370.

Zola-Morgan, S. M., & Squire, L. R. (1990). The primate hippocampal formation: evidence for a time-limited role in memory storage. *Science, 250*(4978), 288-290.

Appendix A: Methodological details for the word-pair associates task

During training, each pair of words was presented (A above B) in lower case, in a white Times New Roman font of size 75 (letters up to 1.6cm in height), against a black background for seven seconds. During training and testing, the 30 pairs were presented in random order. The participants sat at approximately 65cm from the screen and were asked to keep their eyes on the screen at all times.

The participants were instructed to try to remember the words as pairs and were informed about the upcoming test sessions, but were asked to avoid deliberately rehearsing the pairs in the intervals. In order to standardise encoding strategies to the extent possible and to ensure that participants had processed the target words, the participants were instructed to produce a sentence containing the two words (and where possible, no other nouns) and to say this aloud. After the seven-second presentation of each word-pair, a white fixation cross appeared. I sat behind the participants with a silent computer mouse. Once the sentence was complete, I pressed a button. If my button-press occurred after more than two seconds of fixation, it caused the programme to move onto the next pair immediately. If my button-press occurred prior to this stage in the trial, the fixation cross was presented for two seconds between word-pairs.

After all of the pairs had been presented, there was a cued recall test. The cue words were individually displayed in isolation (with a question mark beneath) and the participants were asked to recall the paired associate. The participants were required to say their answer aloud (or pass) and then press the down arrow key to indicate that they had given their final answer. The cue word was presented for three seconds. If the down arrow key had not been pressed within this time, the question mark remained on the screen until it was pressed. The white fixation cross then appeared on the screen. During fixation, I used the silent mouse to record the correctness of the participant's

response. There was an additional 1, 2 or 3 seconds of fixation (randomly selected on each trial) after my response before the next cue word appeared.

If the participants did not reach the 60% criterion on the 30 pairs, they were shown the full set of pairs again, this time for five seconds each. There was a border around the pairs that was green or red depending on the correctness of the latest response for this pair. The participants were asked to re-produce their original sentence upon seeing each pair. They were instructed that if they could not recall their sentence they must produce a new one. After the five-second presentation of each word-pair, a white fixation cross appeared. Once the sentence was complete, I pressed a button on the silent mouse. If my button-press occurred after more than two seconds of fixation, it caused the programme to move onto the next pair immediately. If my button-press occurred prior to this stage in the trial, the fixation cross was presented for two seconds between word-pairs. After all the pairs had been presented, the participants were re-tested on the word-pairs and so on until they scored at least 60% in a test.

A serial reaction time task (SRTT) was performed in the 30 minutes interval between the final training test and the 30mins test. In the SRTT, the participants had to respond as quickly as possible with the appropriate keyboard button to a square flashing up on the screen at one of four possible locations. The SRTT served to standardise activity in the retention interval. Data from the SRTT are presented in Chapter 4. The procedure for the 30mins A-B pair test was identical to that used in the cued recall phases of the training session.

Twelve hours after the beginning of A-B training, participants were trained on A-C word-pairs. The procedure was identical to the first training trial and first (immediate) cued recall test of A-B pair training. There was then a ten minute interval, during which the participants performed additional trials of the SRTT and a short alertness test, before the 12hrs A-B&C pair test. In this test, each cue word was presented alone (with two question marks beneath it). The participants were required to say aloud the two nouns that had previously been paired with the cue word (or pass for one or both of them) and then press the down arrow key to indicate that they had given their final answers. The cue word was presented for three seconds. If the down arrow key had not been pressed within this time, the question marks remained on the screen until it was pressed. A blue fixation cross then appeared. I indicated the correctness of the participant's answers to the computer and 1, 2 or 3 seconds of fixation later (randomly selected), the participants were asked (by the word "When?" appearing on the screen) to indicate when they had learnt each of the paired associates they provided. They pressed the down arrow key once they had given their final answer. I indicated their correctness to the computer and 1, 2 or 3 seconds of fixation later (randomly selected), the participants were asked (with the visual prompt "Sentences?") to try to reproduce the sentence they had used to learn each of the paired associates. When the participants had given their final answers, they pressed the down arrow key once more. The white fixation cross was then presented for three seconds before the next cue word appeared.

Appendix B: Estimating recollection and familiarity

Using confidence-rating data and models of recognition memory, it is possible to derive parameter estimates that are relevant to the memory processes that underlie recognition decisions. However, this is a highly contentious area of research, and therefore the 'correct' way to analyse confidence rating data is unclear. Two prominent competing models are the unequal variance signal-detection theory model (e.g. Mickes, Wixted, & Wais, 2007; Squire, Wixted, & Clark, 2007) and the dual process signal-detection model (e.g. Yonelinas, 1994, 1999; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). The former argues that recognition decisions are governed by a single signal-detection process. However, according to the latter model, a given recognition decision is based on one of two independent memory processes: recollection and familiarity. In this model, recollection is conceived as a discrete, probabilistic process. If the threshold for recollection is not reached, then the decision will be based on familiarity, which is a signal-detection process.

In this appendix, the confidence rating data from Chapter 5 are analysed with reference to a formal dual process signal-detection model called the Yonelinas High Threshold (YHT) model (Yonelinas, 1994). The appeal of this approach is that it allows quantitative estimation of recollection (in addition to a signal-detection process measure). The YHT model estimates recollection and familiarity from receiver operating characteristics (ROC) curves (which are derived from confidence rating data and are explained below), and it is the most widely regarded method for doing so, especially in patient populations and groups of older adults (e.g. Ally, Gold, & Budson, 2009; Embree, Budson, & Ally, 2012; Howard, Bessette-Symons, Zhang, & Hoyer, 2006).

Two control participants and one patient were excluded from these analyses because their recollection and/or familiarity estimates were more than 2 standard deviations away from their group means.

To derive the data points for an ROC curve, each confidence rating is considered in turn. Firstly, the maximum-confidence 'old' rating (i.e. 1, in this experiment) is considered to indicate an 'old' response, while all other ratings are considered to indicate 'new' responses. The hit rate and false alarm rate are calculated accordingly. This constitutes the first data point of the ROC curve. Next, both maximum and medium confidence 'old' ratings (i.e. 1s and 2s) are considered to indicate 'old' responses, while all other responses are considered to indicate 'new' responses, and the hit and false alarm rates are calculated accordingly, producing the second data point. This cumulative process continues until the hit and false-alarm rates are calculated when 1s, 2s, 3, 4s and 5s are considered 'old' responses, and only 6s are considered new responses, which produces the final ROC data point. For illustrative purposes, the average ROC curves in the controls and the patients for the Early and Late(A) tests are shown in Figure B.1.

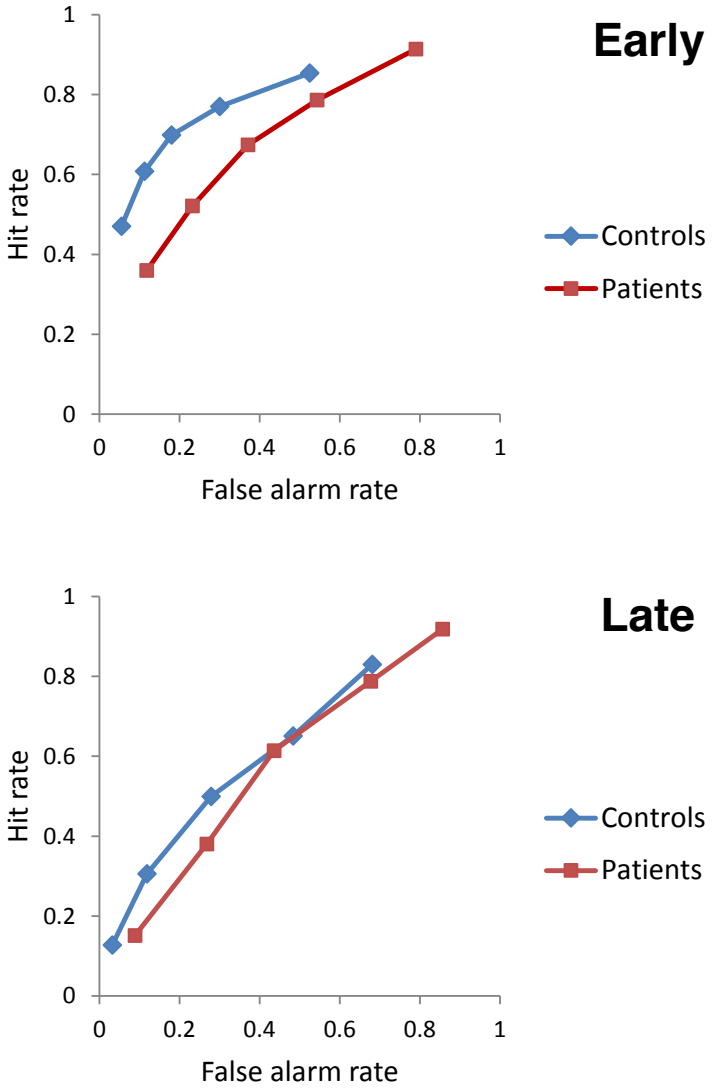


Figure B.1. The average receiver operating characteristics (ROC) curves of the patients and controls for the Early and Late(A) tests.

To produce estimates of recollection and familiarity, ROC curves were generated for each individual participant, for the Early and Late(A) tests separately. Using the procedure originally described by Yonelinas et al. (1998), the Yonelinas Microsoft Excel solver routine (which can be obtained from http://yonelinas.faculty.ucdavis.edu/) was used to calculate estimates of recollection (R) and familiarity (d') from each ROC curve. This involves fitting the model's equations to the observed ROC data to determine the recollection and familiarity values that provide the best account of the data.

This is achieved using a search algorithm that reduces the sum of the squared errors between the predicted and observed data.

The mean (and SEM) across all participants for the sum of the squared errors between the predicted and observed data was 0.0013 ±0.00028 for the Early test and 0.0018 ±0.0028 for the Late(A) test. The fit of the model was not different in the two groups or in the two recognition tests (an ANOVA with the sum of the squared errors between the predicted and observed data as the dependent variable, time as the within-subjects factor and group as the between-subjects factor produced no significant effects). Figure B.2 illustrates the fit of the model to the Early test ROC of an example participant.

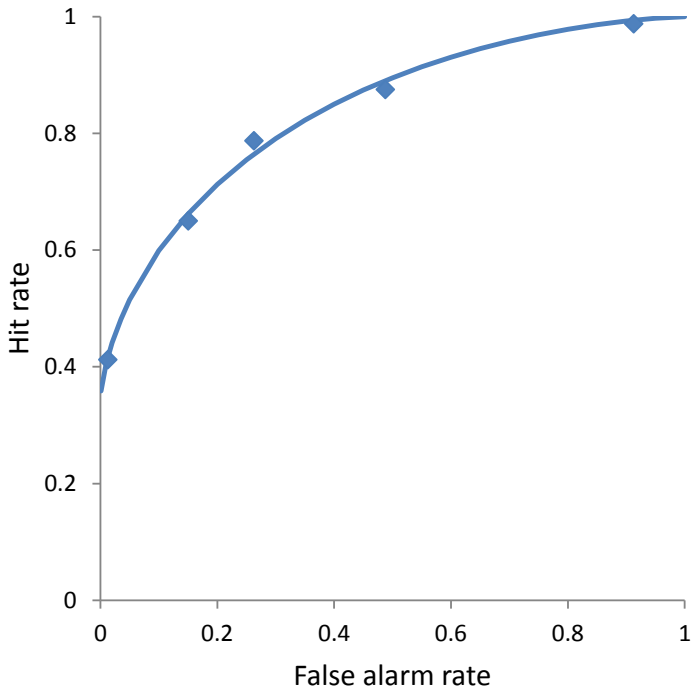


Figure B.2. An illustration of the fit of the Yonelinas High Threshold (YHT) model to the receiver operating characteristics (ROC) curve of a single control participant for the Early test.

Figure B.3 displays the recollection estimates and Figure B.4 displays the familiarity estimates. The recollection estimates were analysed using an ANOVA with time (two levels: Early and Late(A)) as the within-subjects factor and group as the between-subjects factor. There was a significant main effect of group ($F_{(1,17)} = 4.52$, $p=0.048$), with lower recollection estimates in the patients (EMM and SEM: 0.050 ±0.046) than the controls (EMM: 0.19 ±0.044). There was also a significant main effect of time ($F_{(1,17)} = 19.01$, $p<0.001$), with lower recollection estimates in the Late(A) test (EMM: 0.018 ±0.025) than the Early test (EMM: 0.22 ±0.050). However, the interaction between group and time was not significant ($p=0.67$), indicating that time did not have an effect on the difference between patients and controls in terms of recollection. However, it is possible that floor effects in the patients in the Late(A) test prevented detection of an interaction between group and time (see Figure B.3).

The equivalent analysis for the familiarity estimates produced a significant main effect of time ($F_{(1,17)}$ = 13.58, p=0.002), with lower familiarity values in the Late(A) test (EMM: 0.47 ±0.054) than the Early test (EMM: 0.82 ±0.091), but the main effect of group did not quite reach significance (p=0.081). The interaction between time and group was relatively close to significance (p=0.092), in that the p value was less than 0.1. The p value for the comparison between the controls (1.01 ±0.13) and the patients (0.63 ±0.13) for the Early test was 0.050, while that for the comparison between the controls (0.49 ±0.075) and patients (0.45 ±0.079) for the Late(A) test was 0.67. Only the controls (p=0.001), and not the patients (p=0.21), showed a significant decline in familiarity between the Early and Late(A) tests.

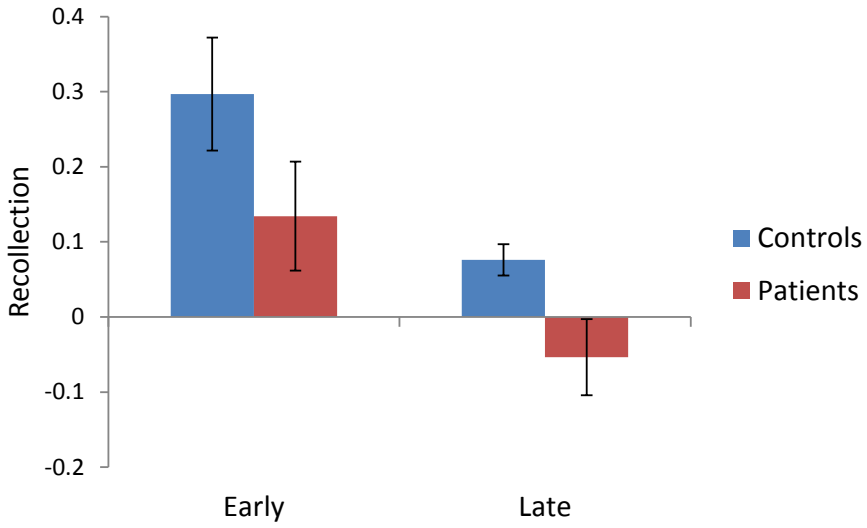


Figure B.3. The recollection (R) estimates for the patients and the controls for the Early and Late(A) recognition tests. Each bar represents a group mean and the error bars represent the SEMs. The estimates were derived from individual participant ROCs using the Yonelinas High Threshold (YHT) model. The recollection estimates were lower in the patients than the controls, and lower in the Late(A) test than the Early test. However, there was no interaction between group and time.

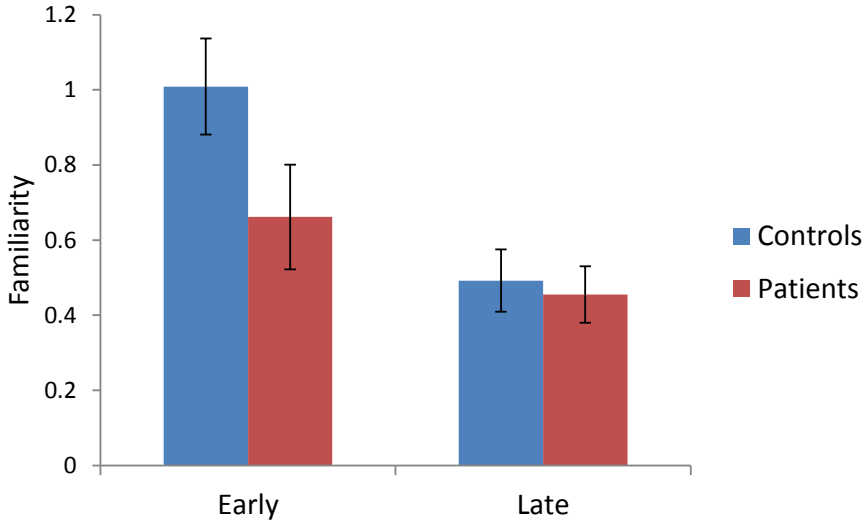


Figure B.4. The familiarity (d') estimates for the patients and the controls for the Early and Late(A) recognition tests. Each bar represents a group mean and the error bars represent the SEMs. The estimates were derived from individual participant ROCs using the Yonelinas High Threshold (YHT) model. The familiarity estimates were lower in the Late(A) test than the Early test. The interaction between time and group was close to significance; p=0.050 for the group comparison in the Early test, while p=0.67 for the group comparison in the Late(A) test, and familiarity declined significantly with time in the control group but not the patient group.