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A Neuroimaging Investigation of the Effects of Age and Sleep on Pattern Separation

Christopher Robert Doxey

A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy
in Neuroscience

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ABSTRACT

A Neuroimaging Investigation of the Effects of Age and Sleep on Pattern Separation

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Doctor of Philosophy
In Neuroscience

Effective memory representations must be specific to prevent interference between episodes that may overlap in terms of place, time, or items present. Pattern separation, a computational process performed by the hippocampus overcomes this interference by establishing non-overlapping memory representations. This project explores pattern separation and how it is impacted by age and sleep.

Experiment 1. Structures of the medial temporal lobe (MTL) are known to be involved in declarative memory processes. However, little is known about how age-related changes in MTL structures, white matter integrity, and functional connectivity affect pattern separation processes in the MTL. In the present study, we used magnetic resonance imaging (MRI) to measure the volumes of MTL regions of interest, including hippocampal subfields (dentate gyrus, CA3, CA1, and subiculum) in healthy older and younger adults. Additionally, we used diffusion tensor imaging to measure white matter integrity for both groups. Finally, we used functional MRI to acquire resting functional connectivity measures for both groups. We show that, along with age, the volume of left CA3/dentate gyrus predicts memory performance. Differences in fractional anisotropy and the strength of resting functional connections between the hippocampus and other cortical structures implicated in memory processing were not significant predictors of performance. As previous studies have only hinted, it seems that the size of left CA3/dentate gyrus contributes more to successful discrimination between similar mnemonic representations than other hippocampal sub-fields, MTL structures, and other neuroimaging correlates. Accordingly, the implications of aging and atrophy on lure discrimination capacities are discussed.

Experiment 2. Although it is widely accepted that declarative memories are consolidated during sleep, the effects of sleep on pattern separation have yet to be elucidated. We used whole-brain, high-resolution functional neuroimaging to investigate the effects of sleep on a task that places high demands on pattern separation. Sleep had a selective effect on memory specificity and not general recognition memory. Activity in brain regions related to attention, visual acuity, and visual recall demonstrated an interaction between sleep and delay. Surprisingly, there was no effect of sleep on hippocampal activity using a group-level analysis. To further understand the role of the hippocampus on our task, we performed a representational similarity analysis. We investigated whether hippocampal activity associated with looking at novel stimuli correlated more with similar-looking (lure) stimuli or repeated stimuli. Results indicate that while a single night's sleep does not significantly impact hippocampal responses, the hippocampus does treat lure stimuli similarly as it does novel stimuli.

Keywords: pattern separation, sleep, hippocampus, fMRI, DTI

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CHAPTER 1: Literature Review

Cognitive neuroscience continues to ask the question, "How are memories formed and retrieved?" Though the molecular processes by which this occurs remain largely unanswered, the structures of the medial temporal lobe (MTL), including the hippocampus and the adjacent cortex (the parahippocampal cortex, the entorhinal cortex, and the perirhinal cortex) have been well established in their associations with long-term declarative memory (Squire, Stark, & Clark, 2004). Declarative memories are conscious memories for facts and events. Prior literature has demonstrated that the hippocampus is involved with the encoding and consolidation of these memories (C. E. L. Stark, Bayley, & Squire, 2002; Tulving, 2002).

Models of Declarative Memory

The hippocampus receives input from every sensory modality and has specifically been implicated in the encoding of object (Stern et al., 1996), face (Haxby et al., 1996), verbal (Davachi & Wagner, 2002), and auditory (Saykin et al., 1999) stimuli into long-term memories. In addition, the hippocampus supports the retrieval of these various memories (Giovanello, Schnyer, & Verfaellie, 2004; Kirwan & Stark, 2004; Maguire & Mummery, 1999; Maguire, Vargha-Khadem, & Mishkin, 2001; Riedel et al., 1999; Treves & Rolls, 1992). Some of the data associated with these implications have come through a wide variety of methods including neuropsychological case studies (Milner, 1972; Nestor, Fryer, & Hodges, 2006), animal studies (Hampton & Murray, 2002; Zola-Morgan, Squire, & Mishkin, 1982), and neuroimaging studies (Kirwan & Stark, 2004; Petersson, Elfgren, & Ingvar, 1997).

Neuropsychological cases provide substantial evidence that declarative memory processes rely heavily on the intact and properly functioning hippocampus (Milner, 1972; Nestor et al., 2006). Patient H.M. had bilateral hippocampal lesions yet could exhibit motor learning and

verbal priming. Importantly, he could immediately recall a list of a few words, but he could not repeat a list of words after a delay of only a few minutes, indicating that his bilateral hippocampal damage was associated with the specific recall of words (Milner, 1972). Nestor and associates (2006) studied patients with semantic dementia and Alzheimer's disease using magnetic resonance imaging (MRI) techniques and discovered a significant correlation between the volumes of MTL structures and the patients' ability to perform tasks testing their episodic and semantic declarative memories. Specifically, those patients who performed relatively poorly also had smaller MTL volumes compared to controls.

Animal models provide additional evidence that declarative memory relies heavily on MTL structures. Zola-Morgan and associates (1982) lesioned the MTL of monkeys and tested their ability to execute a delayed response memory task. Monkeys who had their temporal stems removed were compared against monkeys who had their amygdala and hippocampus removed bilaterally. Included also in the comparisons were controls that did not receive surgery. Monkeys that lacked a hippocampus and amygdala (and possibly portions of adjacent structures) performed poorly on the memory task compared to the other two experimental groups. Another experiment tested monkeys and their ability to perform a variety of memory tasks with or without perirhinal cortex (Hampton & Murray, 2002). The perirhinal cortex provides the majority of input, via the entorhinal cortex, to the hippocampus (Squire et al., 2004). The lesioned monkeys, compared to controls, performed poorly on tasks that involve remembering and discriminating between pictures of specific everyday objects.

Neuroimaging studies further indicate that MTL structures are essential for declarative memory processes. For example, a study on declarative memory using positron emission tomography (PET) and statistical parametric mapping suggests that performance on a declarative

memory task correlates strongly with MTL activity (Petersson et al., 1997). In this task, participants were shown various abstract designs and asked to replicate them from memory while in a PET scanner in two repeating blocks. The experimenters found significantly more activity in the MTL when participants had a second exposure to the stimuli (and subsequently performed better on a trained recall task) compared to the first time they were asked to recall the stimuli. A study using functional MRI (fMRI) and a face-name association paradigm also points to activity in the hippocampus and MTL region as being correlated with making declarative memories (Kirwan & Stark, 2004). In this paradigm, the participants were placed in an MRI scanner during a study and testing phase while blood oxygen level dependent (BOLD) signal was measured. In fMRI, such a signal is assumed to be associated with brain activity since a change in neural activity in a particular area corresponds with a change in blood flow to that area (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). In the first phase, the participants were asked to remember a set of pictures of random faces associated with a specific name. They were later tested on these specific face-name pairs mixed with lures (same picture, but different name, or vice versa) and novel face-name pairs. The analysis revealed significantly more activity in the right hippocampus, right parahippocampal gyrus, and left amygdala when comparing items remembered or partially remembered during the study phase to items forgotten. Similar activity correlated with the same comparison made of the testing phase. Such significant BOLD signal could mean that these specific areas in the MTL are heavily involved with declarative memory tasks such as the face-name pairing task.

Pattern Separation

The hippocampus receives input from all sensory modalities, but particularly for our purposes activity in the hippocampus corresponds with an individual's ability to recall specific

facts from visual information (Felleman & Van Essen, 1991). This ability to discriminate between details of visual stimuli depends on the computational processes of pattern separation and pattern completion. In pattern separation, memory representations are established that allow individuals to successfully recall specific details of previously viewed stimuli and discriminate between similar-looking stimuli. This process is important in order to compare between very similar, but distinct memory representations. In pattern completion, a previously-stored memory representation may be reactivated from degraded or noisy cues, allowing individuals to clump memories that have similar aspects into one single representation. This process is useful in that it facilitates the retrieval of degraded or incomplete memory representations. Researchers have proposed computational models of declarative memory in which the unique structure and function of the hippocampus plays an important role in this type of memory processing (Norman & O'Reilly, 2003; Schacter, Norman, & Koutstaal, 1998; Yassa & Stark, 2011). The following are only a few examples of impactful studies performed to test these specific regions and their involvement in declarative memory processes, specifically pattern separation.

Human and animal studies have tested the role of the hippocampus in pattern separation processing. Viskontas and associates (2006) studied human hippocampal and parahippocampal regions using *in vivo* electrophysiology. The authors found that while the majority of hippocampal cells responded to repeated stimuli with decreased firing rates, a subset of cells responded differently by increasing firing rates. These cells that responded differently appeared to be more sensitive to stimulus category (faces vs. scenes), than a novelty effect. The implication here is that hippocampal cells, and perhaps regions of cells, have different roles in mnemonic processing. Vazdarjanova and Guzowski (2004) took a more specific route testing the role of CA3 and CA1 subfields in rodents by performing immediate-early gene brain imaging

techniques to specifically look at activity in CA3 compared to CA1 during a task testing pattern separation. They noted when the stimuli (change in surroundings) were only slightly altered there was correspondingly more overlap of activity in CA3 compared to CA1. When the surroundings were more obviously different, the overlap of activity was significantly greater in CA1 compared to CA3. These data suggest that cells in CA3 exhibit activity corresponding with pattern completion when there are only small alterations in stimuli. When the stimuli are more orthogonal to one another, on the other hand, the cells in CA3 correspond with pattern separation behaviors. Thus, it seems that pattern separation processing occurs in the CA3 region, but only if the change in input is sufficiently large enough. Finally, cells in CA1 have more linear activity and thus do not correspond with preferential activity towards pattern separation or pattern completion. Leutgeb and colleagues (2007a) used electrophysiological recordings in rat DG and CA3 cells and compared activity in an environment-altering paradigm. The recordings indicate that cells in the DG have significantly different activity when the rats were placed in a highly similar environment compared to CA3 cells. This could mean that cells in the DG correspond with more pattern separation behavior compared to CA3. Whereas the activity in CA3 is dependent upon the degree of similarity between memory representations, activity in DG changes dramatically even with small differences in memory representations. A lesion study in which researchers specifically ablated cells in either the DG or CA3 provides additional support for the importance of this region in pattern separation (Hunsaker, Rosenberg, & Kesner, 2008). Rats with lesions in the DG were not as capable at discriminating slight differences in their surroundings when compared to others with lesions only to the CA3 region. Taken together, these studies indicate that the regions in DG (with maybe some important overlap in CA3) are

highly involved with pattern separation whereas other areas of the hippocampus and MTL are likely involved with pattern completion.

How and where pattern separation takes place continues to be a topic studied widely through MRI techniques. These studies indicate that regions in the CA3/DG are key to pattern separation behaviors (Bakker, Kirwan, Miller, & Stark, 2008; Kirwan & Stark, 2007; McHugh et al., 2007; Motley & Kirwan, 2012). Kirwan and Stark (2007) used fMRI techniques and a recognition paradigm to compare hippocampal and parahippocampal activity to cortical activity. Their data revealed significantly more activity in the tail of the left CA1 when participants indicated that they thought a stimulus was the exact same picture they had seen before (when in fact they were two very similar pictures) as compared to correctly identifying "old" and "similar" stimuli. These analyses point to CA1 supporting pattern completion. A study performed by Bakker and associates (2008) also used fMRI to analyze potential structures involved with pattern separation. In this task, participants were shown a series of pictures of random, everyday objects in the MRI scanner. Some of the pictures were repeated during the task while other pictures were very similar to each other. Comparing the activity in the hippocampus between similar-looking pictures and novel or repeated images would potentially provide support for structures involved with pattern separation. The authors' analysis implicates the regions of CA3 and DG as being highly associated with pattern separation. Finally, Motley and Kirwan (2012) used a similar paradigm and fMRI data acquisition, but the "similar" pictures were instead pictures of the exact same object only rotated in space to varying degrees. They compared the activity associated with rotated objects versus the original view, and their analysis added additional evidence that regions in the left hippocampus support pattern separation.

If the hippocampus is so heavily involved with pattern separation memory tasks, it can be assumed that damage to areas that provide input to the hippocampus would also affect these processes. In fact, one hypothesis is that the ability to successfully recall specific memories is dependent on the strength of intact structures that provide input to the hippocampus such as the perirhinal cortex (Hampton & Murray, 2002). In their studies with monkeys, Hampton and Murray performed lesions in the perirhinal cortex and tested the monkeys with a number of memory tasks post-operation. They observed that the lesioned monkeys were able to remember pre-operation stimuli by demonstrating that they recognized stimuli that looked similar to those viewed before operation. These observations indicate that the perirhinal cortex is not needed for pattern completion, and could therefore play a role in pattern separation. Another recent study of the perirhinal cortex compared old rats with young rats using an object recognition task (Burke, Hartzell, Lister, Hoang, & Barnes, 2012). These researchers found a significant effect of age on activity in perirhinal cortex.

These memory processes are important in daily living, and when there are failures in either pattern separation or pattern completion, such failures negatively affect quality of life. We are particularly interested in using MRI imaging methods to examine how age negatively affects pattern separation and how sleep positively affects pattern separation. We also propose to examine how pattern separation processing is affected by sleep. As part of that investigation, we are interested to see if the brain reacts to lure stimuli differently from old or new stimuli, and if sleep alters the associated brain activity. Additionally, we will test whether patterns of hippocampal activity are measurably different between lure, old, and new stimuli. We will see whether activity patterns associated with lure stimuli are more closely related to old or new

stimuli in order to test how the hippocampus responds to lure stimuli. We can then test how sleep might affect these patterns of activity.

CHAPTER 2: Effects of Age on Pattern Separation (Experiment 1)

Unfortunately, with age come changes in memory capacities. In fact, older adults have been observed to perform poorly on pattern separation tasks compared to young adults (Burke, Wallace, Nematollahi, Uprety, & Barnes, 2010; S. M. Stark, Yassa, & Stark, 2010; Toner, Pirogovsky, Kirwan, & Gilbert, 2009).

Burke and collaborators (2010) performed memory experiments using two groups of rats: a young adult group and older adult group. They compared the performance of these rats on a task that challenges pattern separation and observed that older rats behaved in such a way that they treated new (though very similar) stimuli as if they were old stimuli. Initially, when these older rats were given a short delay between stimuli, they performed statistically just as well as the younger rats. When the delay was increased to twenty-four hours, however, the older rats displayed behaviors consistent with pattern completion. Another study used human subjects to compare the memory abilities of older individuals to younger ones (Toner et al., 2009). These investigators used a previously tested paradigm in which they had participants perform a continuous recognition task (Kirwan & Stark, 2007). In this task, a large number of pictures of common, everyday objects are displayed sequentially and participants are asked to remember the pictures they see and simultaneously make a response about whether the shown stimulus is old, new, or similar to a previously viewed stimulus. Toner and colleagues conclude that older individuals are more likely to label a similar-looking stimulus as "old" than their younger counterparts. From these studies, researchers have concluded that older individuals are more likely to perform pattern completion with regards to similar-looking stimuli than younger participants.

The disparity between younger and older populations could be associated with a number of factors, and one of the most prominent hypotheses has to deal with the change in hippocampal and white matter volumes with age. Some studies indicate that atrophy associated with aging of MTL structures correlates with declarative memory performance (Jack et al., 1998; Mummery et al., 2000; D. G. M. Murphy, Decarli, Schapiro, Rapoport, & Horwitz, 1992). Other studies, however, do not describe significant differences in volumes of MTL structures with aging (Decarli et al., 1994; Soininen et al., 1994). A review article (Van Petten, 2004) compared results across fifteen different studies examining hippocampal volumes of a wide age range of adults and noted a significant negative correlation with age and hippocampal volume. Some propose that decreased hippocampal and white matter volumes negatively affect declarative memory behaviors (Brickman, Stern, & Small, 2011; den Heijer et al., 2012). Brickman and collaborators (2011) recruited subjects 65 years of age and older and gave them an object recognition task in which they were shown a pattern and then given a test in which the original pattern was mixed with three distractors. Participants' brains were scanned for volumetric analyses. Analyses revealed a significant positive correlation between DG size and performance on the visual recognition task. In another study, den Heijer and associates (2012) used fMRI and Diffusion Tensor Imaging (DTI) measures to look at structural data from hundreds of older individuals. The participants were tested with a word memory task in which they asked them to memorize a list of words and recall as many words as they could. The older participants performed significantly poorer than their younger counterparts on the declarative memory task. These results were compared with dissociations in hippocampal volumes (in persons older than 65 years of age) as well as DTI measures of white matter integrity. It may be the case that having

fewer hippocampal neurons and poorer hippocampal connections with which to perform pattern separation could lead to a greater bias toward pattern completion behaviors.

Some have hypothesized that the older brain performs pattern completion more often than a younger brain because of a downgrading of neurogenesis in the hippocampus (Koehl & Abrous, 2011; Sahay et al., 2011). These studies compared older rats to younger rats and have observed more neurogenesis occurring in the granular layer of the DG in younger rats. Computational models propose that neurogenesis in the DG is necessary for pattern separation (Clelland et al., 2009; Deng, Aimone, & Gage, 2010; Tronel et al., 2012). Clelland and colleagues (2009) ablated neurogenesis in the DG of rats and noted a significant decrease in pattern separation behaviors when they performed maze and contextual fear experiments. Without the creation of these new neurons, the DG could have more difficulty with the orthoganalization of new, similar memories. Additionally, when neurogenesis is enhanced in the DG, there follows an increase in pattern separation capabilities (Sahay et al., 2011). In their experiment, Sahay and colleagues used transgenic mice that had an enhanced promoter that could effectively turn off a gene involved with apoptosis. These transgenic mice more quickly learned during a contextual conditioning experiment known to be associated with pattern separation. Another hypothesis concerning how neurogenesis is involved with patter separation is that younger neurons in the DG are more plastic than older ones, making them quicker and more likely to alter their activity in response to behavioral stimuli (Clark et al., 2012; Kee, Teixeira, Wang, & Frankland, 2007; Ming & Song, 2011). It could be that memories are created and altered slightly thanks to the plasticity of connections in the hippocampus (Kohman & Rhodes, 2013).

Diffusion Tensor and Functional Connectivity Measures

As mentioned above, the integrity of white matter tracts changes with age and could potentially negatively affect pattern separation processing. Diffusion tensor imaging (DTI) is an MRI technique that captures the directionality of water diffusion (Beaulieu, 2002; Le Bihan et al., 2001). In an isotropic environment, water diffuses randomly and unrestricted in all directions. In an anisotropic environment, such as the brain, water diffusion is restricted by the macrostructure (and microstructure) of myelinated axons and neuron packing density in the white matter and gray matter, respectively. In addition to differentiating white matter from gray matter, DTI can discriminate nuances among white matter populations based on the extent of myelination of axons (Basser, Mattiello, & Le Bihan, 1994; Beaulieu, 2002; Le Bihan et al., 2001). Indeed, it has been suggested that the poor performance of older individuals on declarative memory tasks could be linked with DTI measures of white matter (den Heijer et al., 2012), mean diffusivity, which is a potential measure of demyelination (Basser et al., 1994; Le Bihan & Johansen-Berg, 2012), and fractional anisotropy, which is associated with slow response times (Lebel et al., 2012; Madden et al., 2004) and lower cognitive function (Vernooij et al., 2009).

Additionally, functional connectivity analyses have been used in previous research to investigate cortical connections with the hippocampus (Beckmann, DeLuca, Devlin, & Smith, 2005; Biswal, Yetkin, Haughton, & Hyde, 1995; Lacy & Stark, 2012). Lacy and Stark (2012) had some conflicting results when they analyzed their functional data comparing older with younger populations. In an analysis of fMRI activation, the authors found a significant discrepancy in the strength of functional activity in the MTL between the older and younger participants when the participants underwent an incidental encoding task. Another analysis, in

which they used resting fMRI scans (showing the participants no stimuli and telling them to allow their minds to wander), revealed no significant difference between these two populations. This analysis was correlated through an ANOVA test in which they noted a significant interaction with an incidental encoding task and age. It appears that the question of whether older individuals have different MTL connectivity compared to younger people remains unanswered as of yet. We tested if our data would provide evidence for a correlation between performance on a declarative memory task and functional connectivity activation in an older population. These results were compared to DTI measures in order to investigate whether functional connectivity strengths correlated with corresponding integrity of the white matter connections. Finally, we compared the results from the DTI and functional connectivity analyses with behavioral performance on the pattern separation task.

Hypotheses

We aimed to replicate previous findings associated with older adults and their performance on declarative memory tasks (Toner et al., 2009) using the same paradigm. We expected to observe that our older group would perform poorly in this task compared to a younger group in that these older individuals likely have a greater bias towards pattern completion when shown a lure object.

We expected to find a correlation with volumes of specific MTL structures (hippocampal subregions CA1, CA3, and DG, the parahippocampal cortex, the perirhinal cortex, and entorhinal cortex) and performance on the continuous recognition task. The current research is less than definitive in this regard in that some have found significant positive correlations with hippocampal volume and declarative memory performance (Brickman et al., 2011) whereas others have not (Van Petten, 2004). Another hypothesis is that if hippocampal volumes are

significantly correlated with pattern separation performance, it is likely that volumes of other brain regions that provide input to the hippocampus (such as those listed above) will also correlate with performance.

Relatively little has been done to investigate the relationship between pattern separation performance and functional or structural connectivity in older populations. We, therefore, used DTI methods to investigate the integrity of white matter, and asked if such is related to pattern separation performance. Our hypothesis was that poor performance on pattern separation tasks is correlated with poor integrity of white matter connections (lower FA values) in various areas of the cortex. We, therefore, compared FA values in the genu, body and splenium of the corpus callosum, the fornix, cingulum, inferior fronto-occipital fasciculus, superior, middle, and inferior temporal gyrus white matter, internal capsule, and cerebral peduncle. We predicted that the older group would have significantly lower FA values, and that these values would predict pattern separation performance.

Further, we wanted to investigate whether resting functional connectivity measures also predict pattern separation performance. We expected that areas associated with episodic memory encoding and retrieval (prefrontal, precuneus, anterior and posterior cingulate, retrosplenial, fusiform, and cuneus) would have different resting connectivity between the two groups, and that the older group would have significantly lower connectivity between these areas. The functional connectivity measures were compared with task performance, and we hypothesized that the functional connectivity would also be positively related to pattern separation performance.

Methods

Participants and Baseline Testing

Thirty-seven older participants (21 female; mean age = 70.9; SD = 6.89; range = 57-83) were recruited from the community via fliers. Out of those 37 individuals, 21 were scanned and tested at the University of Utah at the Utah Center for Advanced Imaging Research (UCAIR) using a Siemens TIM Trio 3T MRI scanner, and the other 16 were scanned and tested at Brigham Young University at the BYU MRI Research Facility (BYU MRI RF) also using a Siemens TIM Trio 3T MRI scanner. Additionally, 20 younger individuals (10 female; mean age = 22; SD = 2.34; range = 18-26) were scanned and tested at the BYU MRI RF. All participants were self-reported to be free of neurological and psychiatric illnesses. Data from one male participant in the older adult group were excluded due to incidental neurological findings. The Institutional Review Boards at the University of Utah and Brigham Young University approved the research, and all participants gave written informed consent prior to participation. The older groups were matched in age and sex and did not differ on behavioral performance. All results of comparisons of MRI measures (see below) between younger and older groups were similar when considering just those participants tested on the same MRI scanner (i.e., at the BYU MRI RF) as when collapsing data across the two older groups. A subset of participants received additional baseline testing such as blood pressure and psychological testing. For the psychological testing, we used a test of premorbid conditioning, which was standardized along with the WAIS-IV and is used to obtain an estimate of intellectual function (e.g. IQ). The Rey Auditory Verbal Learning Test (RAVLT) was given to assess memory capacities. Including these measures did not improve model fits so they were not included in the final analyses. Consequently, the data presented below is collapsed across MRI scanners.

Stimuli and Behavioral Procedure

Participants completed a continuous recognition task similar to previous studies (Holden, Toner, Pirogovsky, Kirwan, & Gilbert, 2013; Kirwan & Stark, 2007; Toner et al., 2009). Stimuli and procedures were identical to those used by Toner and colleagues (2009). Testing was carried out on a laptop computer using the Psychophysics Toolbox for Matlab (Matlab version 7.9). Briefly, outside the MRI scanner, participants were presented with color photographs of every-day objects, one at a time in a pseudorandom order. As the task progressed, repeats and "lures" were shown after a variable delay. The repeats were identical to a previously viewed object, while the "lures" looked very similar (but not identical) to a previously viewed object (Figure 2.1). Participants were asked to indicate whether the image was "old", "similar", or "new" via button press. The task further consisted of 6 blocks with 108 trials in each block (648 trials total). Repeats and lures were separated from target stimuli by 10-40 stimuli.

Figure 2.1: Examples of Related Lure Stimulus Pairs.

Twenty-one older participants (scanned and tested at the UCAIR) performed a self-paced version of the continuous recognition task (i.e., stimuli were displayed until the participants

made a button-press response). For the remaining participants, the task was timed (3 seconds per stimulus with a 0.5 second inter-trial interval, based off the average reaction time of the self-paced version). Task performance did not differ between both older groups performing the self-paced or timed version of the task ($F(1,52) = 1.826$, $p = 0.182$).

MRI Procedures

Imaging was performed with 3T Siemens Tim Trio scanners at both UCAIR and BYU MRI RF. Each participant contributed a standard-resolution structural scan, a high-resolution structural scan, a DTI scan, and a resting fMRI scan. Each scanner had the same operating system software version and the same imaging protocols were followed at both facilities.

Standard-resolution structural MRI images were acquired using a T1-weighted magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) sequence with the following parameters: TE = 2.08 ms, flip angle = 8°, slices = 128, slice thickness = 1.20 mm, matrix size = 192 ×192, voxel size = 1.15 ×1.15 × 1.20 mm, field of view = 220.8 ×220.8 mm.

High-resolution structural MRI images were acquired using a T2-weighted sequence with the following parameters: TE = 64 ms, flip angle = 173°, slices = 19, slice thickness = 3 mm, matrix size = 512 × 512, voxel size = 0.391 × 0.391 × 3 mm, field of view = 200 × 200 mm. High-resolution structural images were aligned with the long axis of the hippocampus and positioned to cover the whole hippocampus.

Diffusion tensor MRI scans were obtained using the following parameters: TR = 7000 ms, TE = 91 ms, matrix size = 128 × 128, voxel size = 2.00 × 2.00 × 2.50, *b*-value = 1000 s/mm^2, total acquisition time = 6 min 4 s. The diffusion gradient directions were taken from the six edges of a cube in *q* space.

Resting fMRI images were acquired using a gradient-echo, echo-planar, T2-weighted pulse sequence with the following parameters: TR = 2500 ms, 155 TRs, TE = 28 ms, flip angle = 90°, matrix size = 64×64, field of view = 220 mm, total acquisition time = 6 min 27 s. Thirty-five oblique axial slices (slice thickness, 3.0 mm) were acquired parallel with the corpus callosum, and were interleaved. The first four TRs acquired were discarded to allow for T1 equilibration. While in the scanner, participants were asked to open their eyes and allow their thoughts to wander during the resting fMRI scan. Incidental head motion of the participants while in the scanner was corrected during preprocessing. For the resting fMRI data, TRs in which the head rotated more than .3° or moved .3 mm in any direction relative to the previous TR were discarded (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012).

Volumetrics

Individual whole brain and MTL ROI volumes were obtained by manual segmentation of the standard-resolution structural scan using the program Analysis of Functional NeuroImages (AFNI) (Cox, 1996). The ROIs were drawn following guidelines from Insausti et al. (1998), using the same procedures as in previous studies (Pruessner et al., 2000; Yassa & Stark, 2009; Yassa et al., 2010; Zeineh, Engel, Thompson, & Bookheimer, 2003). Our ROIs included the temporal polar, parahippocampal, entorhinal, and perirhinal cortices. Two researchers performed the segmentations, and final volumetric analyses were based on the area of overlap between the two segmentations. Additionally, we calculated the Dice Similarity Coefficient (DSC) (Dice, 1945) as a measure of inter-rater similarity as it takes into account the 3-dimensional structure of the volumes (Kasiri, Kazemi, Dehghani, & Helfroush, 2013). The DSC is computed as the volume of the overlap between the two raters divided by the volumes of each of the independent raters as given in this formula: $2|A \cap B| / (|A| + |B|)$. Values of the DSC vary from 0 to 1, with

good agreement represented by scores ≥.7 (Bartko, 1991; Zijdenbos, Dawant, Margolin, & Palmer, 1994). For the MTL tracings, mean DSC was .72, (range = .60 – .81).

Similarly, two researchers performed manual segmentation of the sub-regions of the hippocampus (CA3/DG, CA1, and subiculum) using the high-resolution structural scans. Again overlapping segmentations were used in the volumetric analyses. These hippocampal tracings were performed following guidelines by Duvernoy's atlas (2005) as has been done in previous studies (Kirwan, Jones, Miller, & Stark, 2007; Kirwan & Stark, 2007). Regions CA3 and DG were traced as one since it is difficult to differentiate these regions using MRI scans alone. Again, we calculated Dice Similarity Coefficients (mean = .67, range = .55 – 79).

Additionally, we manually traced each whole brain using AFNI in order to account for overall brain size in our volumetric analyses. Table 2.1 displays the mean values of each ROI after dividing by total brain volume. We also used FreeSurfer image analysis suite (http://sufer.nmr.mgh.harvard.edu) in order to calculate intracranial volume as another control method to account for differences in brain size (Pengas, Pereira, Williams, & Nestor, 2009). We obtained similar results using either method of correction; therefore the results reported here are based off of the former brain volume correction.

Table 2.1: Mean Volumes of MTL and Hippocampal ROIs. * indicates < 0.05 significance comparing the two groups **indicates < 0.001 significance

ROI	Young (mean % brain volume)	Old (mean % brain volume)
Left CA1	0.2268**	0.1683**
Right CA1	0.2387**	0.1727**
Left CA3/DG	0.1745	0.1603
Right CA3/DG	0.1819*	0.1611*
Left Subiculum	0.1088**	0.0739**
Right Subiculum	0.0991**	0.0738**
Left Hippocampus	0.2005**	0.1547**
Right Hippocampus	0.2115**	0.1492**
Left Temporal Polar Cortex	0.2367**	0.1910**
Right Temporal Polar Cortex	0.2534**	0.2019**
Left Perirhinal Cortex	0.2731	0.2495
Right Perirhinal Cortex	0.2919*	0.2481*
Left Entorhinal Cortex	0.0521*	0.0586*
Right Entorhinal Cortex	0.0667	0.0700
Left Parahippocampal Cortex	0.1611*	0.1260*
Right Parahippocampal Cortex	0.1569**	0.1194**

Diffusion Tensor Imaging

We used the FMRIB Software Library (FSL) (Smith et al., 2004) Diffusion Toolbox (Behrens et al., 2003) to preprocess the DTI data. The data were first corrected for eddy currents and then the brain was extracted using the brain extraction tool (Smith, 2002). We then used

DTIfit to calculate the diffusion tensors and to generate FA images (Rowley et al., 2013). After processing the FA images, we used Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) to create two FA skeletons (one each for younger and older participants). All participants' FA data were aligned into a common space based on age group using the nonlinear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b) which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was processed and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each participant group's aligned FA data were then projected onto this skeleton and the resulting data fed into voxel-wise cross-participant statistics and regression models (see below).

Additionally, we segmented the TBSS skeletons into WM masks following an atlas created by Oishi and colleagues (2011). To create a template for WM regions of interest (ROIs), we performed cross-participant normalization by aligning the standard-resolution structural scans to a study-specific template using the Advanced Normalization Tools software (ANTs; Version 1.9; http://sourceforge.net/projects/advants/) (Avants, Epstein, Grossman, & Gee, 2008; Klein et al., 2009; Lacy, Yassa, Stark, Muftuler, & Stark, 2011; Sanchez, Richards, & Almli, 2012; Yassa et al., 2010). Since the TBSS pipeline uses Talairach alignment, we then transformed this template into Talairach space. Separate templates were created for the younger group and the older group. We traced WM masks onto the ANTs template and overlaid them onto the DTI skeletons. Skeletons were used in our ROI analyses because of the significant differences in white matter volumes between the younger and older groups. As mentioned above, TBSS creates a skeleton by calculating the centers of all tracts in common to the group. By shrinking our ROIs to the white matter skeletons, we decided to take a very conservative approach to the DTI analyses. The ROIs we used included: genu, body, and splenium of the corpus callosum, bilateral

cingulum, fornix, inferior fronto-occipital fasciculus, WM of the superior, middle, and inferior temporal gyrus, internal capsule, and cerebral peduncle. We subtracted the areas that were outside of the TBSS skeleton and thus extracted FA values for each WM ROI within the skeleton. We then extracted the average FA values in each of the ROIs as well as for the whole brain.

We compared FA values obtained from the two scanners in order to rule out any differences in data acquisition and justify combining both of the older groups. Bonferroni post-hoc tests revealed significant differences only in the corpus callosum genu (means = .743, .711; $p < 0.041$) and body (means = .699, .660; $p < 0.019$). Furthermore, we conducted an ANOVA using data from our older subjects. We tested for a possible interaction between brain region and scanner. Indeed, the test did not reveal a significant region × scanner interaction ($F(16) = 1.69$, $p > .1$).

Resting fMRI

We performed a seed-based correlation analysis of the resting fMRI data as has been performed in previous studies (von dem Hagen, Stoyanova, Baron-Cohen, & Calder, 2013). To select seed regions, we performed cortical reconstruction and volumetric segmentation with the FreeSurfer image analysis suite (Reuter, Schmansky, Rosas, & Fischl, 2012). This pipeline results in the parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004). The hippocampal seed was taken from the volumetric analysis described above. For our cortical ROIs, we chose the posterior cingulate cortex, retrosplenial cortex, inferior frontal opercular region, the supramarginal region, superior parietal, and parieto-occipital regions as these areas have been implicated in episodic memory retrieval (Cabeza & Nyberg, 2000). We performed correlation analyses on the average time courses

between each cortical ROI. This gave us R-values for each connection. In order to compare these correlations between groups, we calculated Fisher's Z-transformation of each R-value and used these values in a regression model (to be discussed below).

Results

Behavioral

Figure 2.2 depicts the proportion of responses from the continuous recognition task. These results were consistent with those of Toner and colleagues (2009). Behavioral performance was similar for the older group and the younger group for repeated and novel stimuli. The two groups performed differently, however, in response to lure stimuli. The older group was more likely to label a lure stimulus as "old" (mean(standard deviation) = .450 (.158)) than the younger group (m(sd) = .277 (.111); $t(55) = 4.442$, $p < .0001$). The younger group was more likely to label a lure stimulus as "similar" (m(sd) = .582 (.157)) than the older group (m(sd) = .351 (.186); $t(55) = -4.715$, $p < .0001$). Furthermore, we tested whether differences in behavioral performance were correlated with sex. A two-tailed independent samples test revealed no such difference between males (m(sd) = .384 (.213)) and females (m(sd) = .474 (.206); $t(51) = -1.559$, $p > .1$).

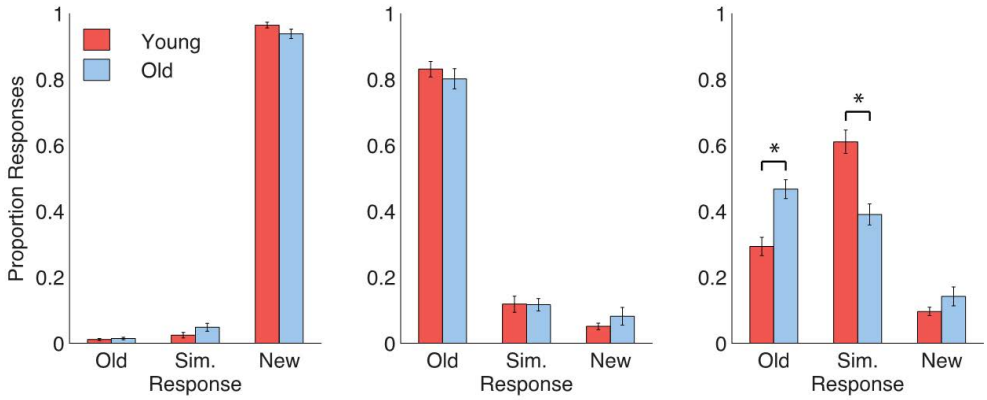

Figure 2.2. Proportion of Responses to New, Old, and Lure Stimuli. The younger and older groups did not differ in behavioral responses to new and old stimuli. When comparing responses to lure stimuli, however, the old group was significantly more likely to call a lure stimulus "old" ($p < .0001$). The younger group was more likely to call a lure stimulus "similar" ($p < .0001$).

Regression Analyses

We calculated a pattern separation score for each participant based on the proportion of lure stimuli called "similar" corrected by the proportion of "similar" responses to novel stimuli. Upon calculating scores for all participants, one participant in the older group was a significant outlier in that performance was at least two standard deviations lower than the mean. Accordingly, this individual's data were not included in the following regression analyses. We tested separate multiple regression models to determine if hippocampal subregion volumes, overall MTL volumes, DTI measures of WM integrity, or hippocampal functional connectivity predicted scores on the memory task. Further, we hypothesized that laterality of the hippocampus could play a role in pattern separation processing (Motley and Kirwan, 2012), so we analyzed volumetric and functional connectivity data for left and right sides separately. For every regression model, we first entered age as a regressor in order to isolate the contribution of sub-region volume from general effects of age on memory task performance.

Including data from two scanners, although identical in model, software, and protocol, can be problematic, so we initially only included data from the BYU MRI RF scanner in our

regressions. We then include data from the UCAIR scanner in order to increase the number of older subjects.

Volumetrics

We first conducted multiple regression analyses on hippocampal sub-region volumes because these were our primary regions of interest for the volumetric investigations. We included volumes of CA3/DG, CA1, and subiculum as regressors for left and right hippocampus models. Aside from age, (beta = -.45, t = -2.13, $p < .05$) left CA3/DG volume (beta = .43, t = 2.24, $p < .05$) was the only regressor that significantly predicted behavioral score (Figure 2.3). Multiple regression analyses of right hippocampal sub-regional volumes and our MTL cortical regions of interest (split into right and left sides) did not reveal any significant predictors of behavioral scores.

Including data from the UCAIR scanner, again age (beta = -.50, t = 3.05, $p < .005$) and left CA3/DG volume were the only regressors that predicted behavioral performance (beta = .33, t = 2.03 $p < .05$).

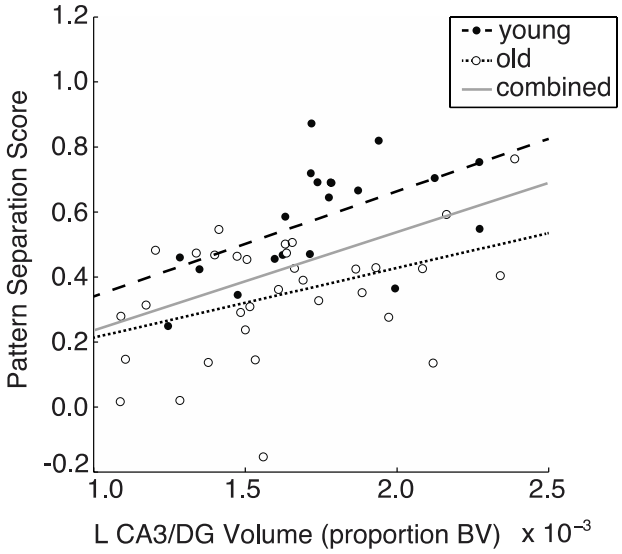

Figure 2.3: Scatter Plot of Left CA3/DG Volumes and Pattern Separation Scores. Volumes calculated as proportion of total brain volume. Volume of left CA3/DG predicts pattern separation score in a linear fashion. Our two groups are overlayed but separated by color. Included are separate regression lines for the two groups (young above and old below) and the regression line of all the data points (middle).

DTI

We next conducted multiple regression analyses for the FA values within our WM regions of interest. When we only included data from participants tested on one scanner, none of our ROIs were significant predictors of performance. When we included all of our data in the DTI model, the results indicated that the splenium (beta = -.48, t = -2.15, p = .039) and white matter of the left inferior temporal gyrus (beta = .90, t = 2.07, p = .046) were significant predictors behavioral performance. Figure 2.4 shows some of the masks used for these ROIs.

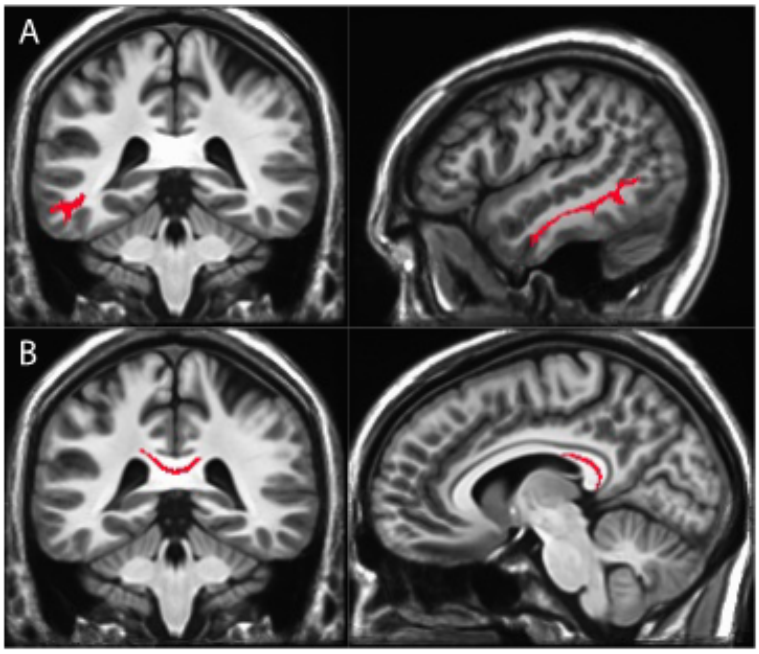

Figure 2.4: Depictions of the White Matter Masks Used in Our Fractional Anisotropy Analysis. These are skeletons obtained from the TBSS pipeline discussed in the text. A) Coronal and sagittal views of the left inferior temporal gyrus white matter mask and B) coronal and sagittal views of the splenium.

Resting fMRI

Finally, we asked if functional connectivity of the hippocampus predicted performance on our task. Accordingly, we included z-normalized correlation coefficients between the hippocampus and each of our cortical ROIs as regressors in our models. These values provide an estimate of functional strength between two regions. Interestingly, none of the resting functional connections were significant predictors of performance. With both the left and right hippocampus connectivity models, age was a significant predictor of behavioral performance (beta = -.80, $t = -4.86$, $p < .0001$ and beta = , -.77, $t = -3.59$, $p < .01$, respectively).

Our results were unchanged when we included data from the UCAIR scanner. Again, none of the resting functional connections significantly predicted performance on our task. Age,

however, remained a significant predictor for both the left hippocampus and right hippocampus models (beta = -.61, t = -4.51, $p < .0001$; beta = -.56, t = -3.68, $p < .001$).

Discussion

This study examined the neural predictors of behavioral performance on a task that taxes pattern separation in young and older adults. In order to more fully understand the disparity in performance between these two groups, we measured hippocampal volumes (including subfields) and MTL volumes, we measured white matter integrity, and we measured the strength of resting connectivity through functional analyses. These measures were used to predict behavioral performance on the mnemonic discrimination task. Our results indicate that the size of the CA3/DG region of the left hippocampus is the strongest predictor of memory discrimination performance other than age. Our results also indicate that the diffusion in white matter tracts and the strength of resting functional connections do not significantly predict performance on our task.

Volumetrics

The dentate gyrus and CA3 region have been previously implicated to be essential for pattern separation processing in both electrophysiological and fMRI studies (Bakker et al., 2008; Leutgeb et al., 2007a; McHugh et al., 2007). Leutgeb et al. (2007b) provided electrophysiological evidence that the dentate gyrus and CA3 work together to orthogonalize firing patterns occurring in CA3. Bakker et al. (2008) provided fMRI evidence that activity in the CA3/DG region is biased towards pattern separation, and that activity in other areas of the hippocampus and MTL is biased toward pattern completion. Though we did not measure activity in these subfields, our results are in line with these previous studies in that computations important for pattern separation behaviors likely take place in CA3/DG. Here, we demonstrate

that volumes, not just activity, of the left CA3/DG play a significant role in pattern separation processes. Volume of the left, but not the right, CA3/DG predicted pattern separation performance in our task. The left hippocampus has been associated with verbal memory (Pereira et al., 2010; Powell et al., 2007), and particularly with object names (Dellarocchetta & Milner, 1993), while the right hippocampus plays a significant role in spatial memory (Maguire, Frackowiak, & Frith, 1997). We did not follow-up with the participant about strategies they used during the task, so we cannot make definitive claims about whether participants relied on explicit verbal or spatial strategies when completing the task. One possibility is that participants used a verbal strategy, to remember the objects in the task, especially since the objects are commonplace and are not necessarily altered in space. If this is the case, participants might rely more on pattern separation computations of the left hippocampus for this task, so one would expect the left CA3/DG to predict task performance more than the right. Consistent with this interpretation, a previous study used a similar paradigm, but participants were required to make a spatial decision about repeated objects (whether they were rotated from their originally presented orientation) (Motley and Kirwan, 2012). This previous study indicated greater evidence of spatial pattern separation processes in the right hippocampus compared to the left.

Another noteworthy aspect of our results is that the volume of left CA3/DG, although a strong predictor of performance, was not significantly different between older and younger groups on average. This is significant in the context of age being another predictor of performance. One possibility is that in addition to hippocampal-dependent pattern separation processes, the behavioral task relies on other processes that are affected by age. Indeed, while CA3/DG volume was a significant predictor of behavioral performance across groups, age was also a strong predictor, indicating that other factors besides hippocampal sub-field volumes

affect mnemonic discrimination. One such factor could be differences in attention, which has been hypothesized to be negatively affected by age (N. A. Murphy & Isaacowitz, 2008). Consistent with previous studies of age-related memory decline (Stark et al., 2010; Holden et al., 2012), there was more variability in memory performance in the group of older adults than in the younger group. Future research may wish to focus on factors that predict memory discrimination performance beyond hippocampal sub-region volumes.

Previous research has shown that differences in hippocampal sizes affect differences in memory capacities in normal aging (Golomb et al., 1996), though the precise reasons remain unclear (Van Petten, 2004). Some studies demonstrate positive associations with hippocampal volume and memory performance, while others demonstrate a negative relationship. Accordingly, Van Petten (2004) concluded that hippocampal volumes do not necessarily predict memory performance. Such seems to be the case with our investigation of hippocampal volumes. Although the volume of the CA3/DG subregion predicted performance, overall hippocampal volumes did not. It could be that since the dentate gyrus comprises only a small portion of the total human hippocampal volume, the volume of the hippocampus does not reliably predict performance on a mnemonic discrimination task such as that described here because variations in the volume of CA3/DG are masked by variations in the overall volume of the hippocampus.

An interesting implication of these findings is in connection with studies on environmental effects on hippocampal size. One study, measuring hippocampal volumes of twins, argues that the size of the hippocampus depends much more on the effects of environment than on genetic factors (Sullivan, Pfefferbaum, Swan, & Carmelli, 2001). Another study investigated the effects of exercise on the hippocampus of older adults (Erickson et al., 2011) and found that aerobic exercise increased the size of the anterior hippocampus and that such an

increase was correlated with improved memory performance. These studies did not differentiate between hippocampal subfields, and further research is warranted on the effects of environmental factors on CA3/DG volumes. If performance on a task that challenges pattern separation relies, at least partly, on the size of CA3/DG, then those who are successful agers could therefore have improved memory performance not because of their genes, but because of environmental factors like exercise.

DTI

Hippocampal pathology is correlated with WM pathology of the medial temporal lobe, and such corresponds with memory deficits (Bronen et al., 1991; Insausti, Annese, Amaral, & Squire, 2013). In addition, differences in memory capacities are associated with differences in the integrity of the corpus callosum. Visual object recognition is significantly hindered in patients with tumors involving the splenium (Rudge & Warrington, 1991). Our hypothesis, therefore, was that a difference in performance on our task would be predicted by the differences in FA of the WM, but our results did not correspond with our prediction. This could be because although measures of FA are typically associated with indications of WM integrity, this may not be the most accurate description (Jones, Knosche, & Turner, 2013). In many studies, a decrease in FA is associated with poor memory performance (Charlton et al., 2006; McDonald et al., 2008), but there are some indications that differences in FA does not always correspond to differences in cognition or memory (Engvig et al., 2012; Wilde et al., 2012). The Envig et al. (2012) study included splitting an older population into two groups; one group received training on a mnemonic strategy and the other was a control. Those who received training indeed performed better and their performance was correlated with an increase in FA in specific ROIs. The control group, however, had no correlation between FA and memory performance.

A recently published study performed similar DTI analyses on behavioral pattern separation (Bennett, Huffman, & Stark, 2014). Their results indicate that the fornix significantly predicts pattern separation performance, which brings to question why the present study did not obtain the same results. There are a number of reasons as to this apparent disparity. One such reason is likely due to a difference in population size (110 in the former study, as compared to our 54). Another reason is that the former research group used tract-based computations in skeleton-wise analyses and probabilistic fiber tracking in separate tractography analyses. The masks chosen for tractography analyses are accordingly different than those used in the present study. As a consequence, our fornix mask was likely much smaller than that used in the former study. In conjunction with that which was previously discussed, we chose to use our DTI skeletons to shrink our white matter tracts in order to take a conservative approach. We took this approach because tracts like the fornix are particularly susceptible to damage and shrinkage with age. This conservative approach has one limitation in that we included only a small portion of the white matter tracts. Finally, there were slight differences in statistical analyses. When we performed the same skeleton-wise analyses, we obtained almost identical results in that the fornix, splenium, and left inferior temporal gyrus WM were highly correlated with behavioral performance ($p < 0.001$) and that the fornix accounted for most of the variance caused by age ($B = -231$, $p < 0.0001$).

Resting fMRI

We hypothesized that resting functional connectivity measures could predict performance, but we did not obtain those results. There is a fundamental difference between resting-state functional connectivity and functional connectivity associated with an engaging task. Resting-state analyses tend to result in increased hemodynamic responses in the default

mode network (DMN) (Raichle et al., 2001), while task-based functional connectivity analyses result in hemodynamic responses associated with a variety of cortical areas, depending on the task. A limitation of the current study is that we did not obtain functional connectivity measurements while participants performed a memory discrimination task. Because we asked the participants to let their minds wander, we would expect that the activity we measured to be localized in the DMN (Mason et al., 2007), and not necessarily in brain regions typically used for the task. It is difficult to make assumptions about a relationship between DMN strength and the ability to perform a memory task. However, previous research does seem to indicate that resting-state and task-based paradigms are both correlated with performance on a memory task (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006). Future research measuring connectivity during a task that taxes pattern separation processes is needed to elucidate these findings. Ideally, comparing functional connectivity at rest with activity during the task would further answer this question.

Conclusions

Our study used a variety of imaging methods in order to understand the changes associated with aging that are likely to be associated with poor memory discrimination performance. We used separate regression models with *a priori* hypotheses in order to identify the factors that predicted behavioral performance. Our results indicate that differences in left medial temporal lobe structures are associated with differences in behavioral performance. Better performance is associated with larger CA3/DG of the left hippocampus. These conclusions add to the current debate about brain structures potentially implicated in pattern separation processing.

In addition to understanding how pattern separation processes are affected negatively by aging, we wanted to examine how pattern separation processes are positively affected by sleep. This was the context for our next experiment.

CHAPTER 3: The Effects of Sleep on Pattern Separation (Experiment 2)

Memory works through three main sub-processes, which include encoding, consolidation, and retrieval (Diekelmann, Wilhelm, & Born, 2009). Encoding first occurs simultaneously with an event, while consolidation typically occurs after the event and is important for delayed retrieval. Sleep has an enhancing effect on memory and learning, and it is likely through enhanced consolidation. Indeed, research has shown that sleep enhances memory whether the interval of sleep is 8 hours long, 1-2 hours, or even 6 minutes long (Diekelmann & Born, 2010). These enhancing effects of sleep have been tested in the consolidation of declarative (Maquet et al., 2000) as well as non-declarative (Peigneux et al., 2003) sequence learning. In both of these experiments, researchers used a serial reaction time task and positron emission topography (PET) imaging during learning as well as during sleep. They found that the same areas activated during the task were activated during REM sleep, indicating that consolidation for procedural memory, as well as the implicit rules underlying such a task, likely takes place during REM sleep.

One of the first studies on sleep consolidation of declarative memories found that items were better remembered after sleep than if a person was awake for the same amount of time (Jenkins & Dallenbach, 1924). The authors concluded that these effects of sleep might be due to its protection against daytime interference. A recent study provides a similar conclusion, where subjects performed significantly better on a word-pair memory test after sleep (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). More interestingly, this study used an interference/no-interference condition where sleep had an even more enhancing effect for the group that was given an interference word list. In other words, the consolidation that occurred during sleep preferentially improved performance when interference was introduced compared to when the subjects did not receive interference. Further research indicates that sleep overcomes

interference that occurs during normal daytime activities (Gaab, Paetzold, Becker, Walker, & Schlaug, 2004). In this study, subjects were given an auditory memory task either in the morning or in the evening. Twelve hours later, the subjects were tested again, and it was discovered that performance was significantly improved for the group that had slept between testing intervals. In addition, when subjects were tested another 12 hours later, both groups performed similarly. In effect, sleep helped the subjects' memory overcome the effects of interference equally regardless of the length of interference interval.

Exactly how consolidation occurs during sleep remains a mystery, though there are two prevailing theories for the mechanisms of sleep-dependent consolidation, which are not necessarily mutually exclusive (Diekelmann & Born, 2010). One such theory is the synaptic homeostasis hypothesis (Tononi & Cirelli, 2006). According to this hypothesis, learning during wakefulness results in the recruitment and strengthening of synapses. During sleep, however, these connections are downgraded, or pruned back in order to make them more energetically efficient. Sleep, therefore, paradoxically improves learning by downscaling the overcompensating strengthening of synapses that occurs during the day. Studies have shown that wakefulness increases gene expression of proteins that lead to the strengthening of synapses, whereas sleep has no such effect on these genes (Cirelli, Gutierrez, & Tononi, 2004; Cirelli & Tononi, 2000).

The downgrading of synapses has been tested in animal models (Kudrimoti, Barnes, & McNaughton, 1999). Activity during a rodent exploration task was recorded and correlated with activity during the first 10, 20, and 30 minutes of sleep. The researches noted that the activity was highly correlated during the first 10 minutes of sleep, but by 30 minutes, the correlation was

similar to the activity seen before the task. This seems to indicate that a significant downgrading of activity occurs during sleep.

Though the synaptic homeostasis hypothesis indicates that a downgrading of synapses occurs during sleep, evidence also suggests that the expression of proteins required for synaptic plasticity is increased during the early hours of sleep (Aton et al., 2009; Seibt et al., 2012). This means that the mechanism for sleep consolidation must also account for an increase in synaptic plasticity in addition to the identified synaptic pruning.

Another theory for the mechanism for sleep-dependent consolidation is the active system consolidation hypothesis (McClelland, McNaughton, & O'Reilly, 1995). According to this hypothesis, activity in the hippocampus during wakefulness runs in parallel with activity in the neocortex during sleep (Diekelmann & Born, 2010). Evidence for this view can be found in a recent study on the effects of sleep on motor learning (Yang et al., 2014). These researchers found a significant increase in dendritic spine formation reduction in dendritic spine formation associated with deprivation of REM sleep and that additional training or subsequent sleep could not compensate for such an effect. The hypothesis further argues that slow wave sleep is a time when events of the day (declarative memories) are in a sense relived as they are passed from the hippocampus to the outlying cortex. In a series of experiments (Ji & Wilson, 2007; Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999; Pavlides & Winson, 1989; Wilson & McNaughton, 1994), rodents were allowed to explore an area while place cells were recorded. When the animal was in slow wave sleep, it was found that the same population of neurons in the hippocampus and cortex fired. Not only did the same cells fire, but they also fired in the same sequence as they had during exploration. Diekelmann and Born (2010) point out that one might assume from

experiments like these that slow wave sleep might be linked with initializing long-term potentiation in order to help with consolidation.

Though the literature typically argues that sleep helps with memory performance for most kinds of memory processes, some data indicate that sleep does not enhance consolidation for familiarity (Drosopoulos, Wagner, & Born, 2005). In this study, performance improved for recollection after sleep compared to a similar period of wakefulness, whereas familiarity was not affected. On the other hand, a different study used a word recognition test and a remember/know paradigm, and the results indicate that sleep enhances both recollection and familiarity to a similar degree (Daurat, Terrier, Foret, & Tiberge, 2007). It would seem that sleep may or may not have an enhancing effect on different memory processing, depending on the type of task utilized in the study. This is intriguing when considering that little has been done to test how sleep affects the specific process of pattern separation. One of our aims is to test whether or not sleep affects brain activity on a task that taxes pattern separation. We will do so using a high-resolution functional imaging method known as multi-band imaging.

Multi-band Imaging

Multi-band imaging is a recently developed scanning technique that increases the spatial and temporal resolution of standard fMRI measures (Moeller et al., 2010). Using this technique, researchers are able to acquire multiple slices simultaneously distributed through the brain in order to decrease volume acquisition time. A difficulty with acquiring functional and diffusion imaging for the whole brain is the amount of time it takes to scan the entire brain while maintaining a high signal to noise ratio (Van Essen & Ugurbil, 2012). In conventional scanning, maintaining the same field of view while increasing the spatial resolution requires decreasing the temporal resolution and vice versa. Multi-band acquisition overcomes these issues by acquiring

multiple slices at the same time. Using multi-band, researchers have significantly decreased acquisition time while simultaneously increasing statistical power of both functional and diffusion weighted imaging (Feinberg et al., 2010; Setsompop et al., 2012). Indeed, a comparison of resting state fMRI between a more conventional TR of 2.5 s and multiplexed-EPI TR of 0.4 s showed a stark contrast between the two methods in that the multi-band images showed resting state networks with much greater clarity (Feinberg & Yacoub, 2012). Decreasing the TRs to this extent also provides much greater temporal resolution, which could have interesting applications in fMRI paradigms. Using this technique, researchers have been able to image the whole brain in under 100 ms at 2.5 mm isotropic resolution (Feinberg et al., 2010). Unfortunately, fMRI is inherently limited by the sluggish hemodynamic response, but the rapid acquisition time provides a more accurate picture of this response and functional networks.

Because multi-band imaging is a novel technique, very little functional research has been done with humans using this technique. Some have used it to map out resting functional connectivity networks (Feinberg et al., 2010; Smith et al., 2012). There are currently no published studies that have used multi-band to image functional measures from a more task-based paradigm. It can be assumed that task-based fMRI studies will similarly be improved from the benefits of multi-band imaging, including improved statistics, improved filter from physiological noise, and movement artifacts (Feinberg & Setsompop, 2013).

Hypotheses

Though much research has been performed on the effects of sleep on declarative memory, to date there is little about the effects of sleep on pattern separation. We tested how hippocampal and general brain activity is altered during a task that challenges pattern separation following a delay that contains sleep compared to a waking delay.

We used multi-band imaging to obtain functional measures during the pattern separation task. Previous studies indicate that improved pattern separation performance is associated with differential activation in the CA3/DG region (Bakker et al., 2008; Fujii, Saito, Yanaka, Kosaka, & Okazawa, 2014). Also, the Bakker study (2008) concluded that pattern completion behavioral bias is associated with differential activation in CA1, the subiculum the entorhinal and perirhinal cortices. Our hypothesis, therefore, was that sleep would result in greater activation of the CA3/DG region when participants perform the task after they have slept compared to those participants who have not slept between testing sessions. We also expected to find increased activity in CA1, subiculum, and nearby MTL cortices to be associated with performing the task after having been awake during the day compared to performing the task after having slept.

We expected to see statistically different hippocampal activity when a participant looks at a lure stimulus compared to an old stimulus. Additionally, we hypothesized that hippocampal activity during lure stimulus presentation would be more similar to novel stimulus presentation. Because we acquired functional images using multi-band, we were able to study the whole brain and its involvement in pattern separation processes, which has not been performed to this scale. We hypothesized that areas of the frontal lobe would be correlated with pattern completion behaviors and that areas of the MTL will support pattern separation behaviors. We intended to quantify these differences using our fMRI data.

Methods

Participants and Behavioral Procedures

We recruited 52 (30 female; mean age = 22.6; SD = 2.56; range = 18-28) student participants from BYU campus via fliers or word of mouth. We recruited participants between ages 18-30 to control for possible age-related differences both in learning and in white matter

structure (Camara, Bodammer, Rodriguez-Fornells, & Tempelmann, 2007). Each participant was thoroughly screened for MRI safety and gave a self-report on whether they had any psychological or neurological conditions including traumatic brain injuries. The research was approved through the BYU Institutional Review Board and participants provided written informed consent. Participants were assigned into one of two groups in a within-subjects design. One group was assigned to a sleep test condition while the others were in a wake group. In the sleep condition, participants were assigned to study in the evening and those in the wake group were assigned to study in the morning. Of the 52 participants, five were excluded from analysis due to not following directions during testing or to scanner issues.

We used a variant of the pattern separation task used in previous studies (Doxey & Kirwan, 2015; Holden et al., 2013; Kirwan & Stark, 2007; Toner et al., 2009). In this variation, the participants performed separate study and test blocks rather than a continuous recognition task (see Figure 3.1). During the study phase, participants were shown a series of pictures of everyday objects as in Experiment 1, but in this case all images were novel and participants were asked to make an "indoor" or "outdoor" response based on whether the object viewed is typically found indoors or outdoors. Participants were told that their memory on these objects would be tested in detail and to pay attention to and study the stimuli as best as they could. This phase consisted of 3 blocks of 131 stimuli each, with a total of 393 stimuli, and took place outside the scanner. Stimuli were presented for 3 seconds with an inter-trial interval of 500ms. The task, therefore, lasted about 20 minutes.

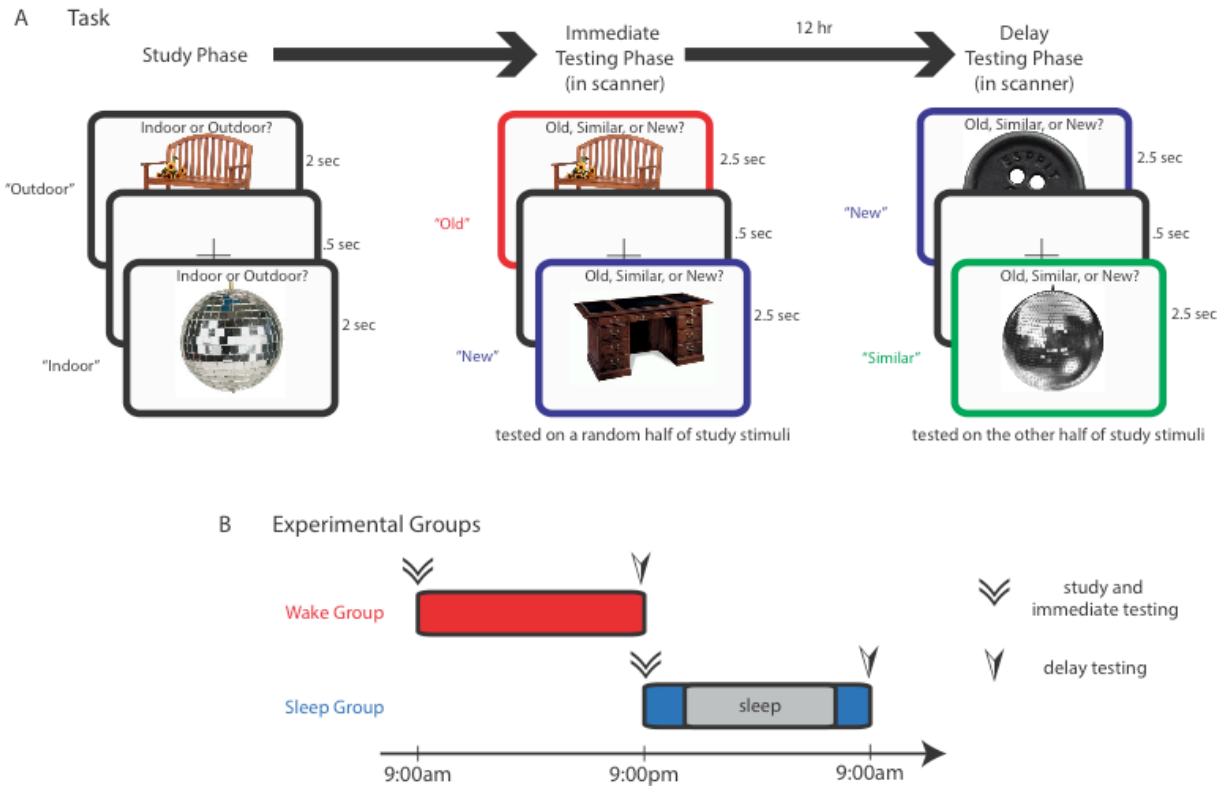

Figure 3.1: Depiction of the Study Protocol. (A) Participants first completed a study portion in which they were shown random pictures of everyday objects and asked to make a judgment as to whether the object was typically found indoors or outdoors. They were then immediately tested on half of the studied stimuli, and tested again 12 hours later on the other half of studied stimuli. Here, participants indicated whether the tested stimulus was a repeat ("old"), lure ("similar"), or novel ("new"). (B) Participants were divided into two groups – wake and sleep. Those in the wake group performed study and immediate testing phases in the morning and were asked to go about their normal daily activities (without napping) before returning in the evening for the delay test. Those in the sleep group performed study and immediate testing phases in the evening and were asked to get a normal night's sleep before returning the following morning.

Each participant was tested with immediate and delay testing phases. These testing phases were identical in format in which participants were tested on half of the stimuli presented during the study phase. After the study phase, participants were immediately brought into the scanner for fMRI acquisition and the first testing phase. The stimuli for testing phases consisted of pictures of common objects. Some of the pictures were the exact same as during the study phase (repeats), some pictures were very similar to those previously viewed (lures), and some pictures were completely novel (foils). We tested participants' memory for the pictures by asking

them to make a response to each object via button press with an MRI-safe button box. They were asked to respond to repeats as “old”, lures as “similar”, and foils as “new”. This task was split into 3 blocks (per testing phase) with 109 stimuli per block. There were a total of 58 repeat, 108 lure, and 161 foil items in the immediate phase, while the delay phase consisted of 52 repeat, 112 lure, and 163 foil items. Stimuli were presented in a pseudorandom order, but blocks were randomized. Stimuli were presented for 2.5 seconds with a 500 ms inter-trial interval, and participants were asked to respond while the each stimulus was presented. Those trials in which participants failed to respond during stimulus presentation were discarded. Furthermore, trials in which participants made more than one response were discarded. As a baseline for the fMRI analyses, we used a random half of the foil trials, which consisted of images shown only once and which did not have any corresponding lure or repeated stimuli. This kind of baseline has been used before when performing fMRI investigations of pattern separation (Bakker et al., 2008; Motley & Kirwan, 2012). While participants performed the task, we tracked brain activity using a multi-band EPI sequence.

In the delay testing phase, participants were tested following a 12 hr delay. For those participants in the sleep group, they were asked to go home and have a normal night’s sleep, and to return the following morning for final testing. Participants in the wake group completed initial testing in the morning and were asked to go about their normal activities during the day and to return the following night for final testing. Each participant was given an ActiGraph to monitor sleep/activity. ActiGraphs provide data on physical activity, sleep time, awakenings, etc. Furthermore, the wake group was asked to not nap during the day, and only one gave verbal report as to having taken a nap. This participant’s data was not excluded due to behavioral performance being within one standard deviation of the mean.

MRI Acquisition and Processing

All MRI scans were performed on a Siemens 3T Tim Trio scanner using a 32-channel head coil at the BYU MRI Research Facility. Structural images were acquired using a T1-weighted MPRAGE sequence with the following parameters: TR = 20 ms, TE = 4.92 ms, slices = 192 interleaved, voxel size = 1.0 × 1.0 × 1.0 mm, FOV = 256 mm, flip angle = 25°, total acquisition time = 8:55 min. While participants performed the task, we tracked brain activity using a multi-band EPI sequence with the following parameters: multi-band factor = 8, TR = 875 ms (374 TRs), TE = 43.6 ms, slices = 72 interleaved, voxel size = 1.8 × 1.8 × 1.8 mm, FOV = 180 mm, flip angle = 55°, total acquisition time = 5:30 min. Slices were acquired parallel with the long axis of the hippocampus and the volume was positioned to cover the entire cortex. The first five volumes acquired were discarded to allow for T1 equilibration.

Imaging data were analyzed using the Analysis of Functional Neuroimages (AFNI) suite of programs (Cox, 1996). Structural images were co-registered to the functional scans. Functional data scans were corrected for incidental head motion and blurred with a 4 mm (full width half maximum) Gaussian filter. TRs in which there was a significant motion event (>.6 mm translation and/or >.3° rotation) were excluded from further analysis. Spatial normalization for group analyses was done using the Advanced Normalization Tools (ANTs) (Avants et al., 2008; Klein et al., 2009), which uses diffeomorphic mapping to calculate a transformation from individual structural scans to a model template based on voxel intensities.

Behavioral vectors were created that coded for response types of interest in the first level regression analysis. Vectors coded for trials where participants correctly identified a foil as "new" (correct rejection or CR), correctly identified a repeat as "old" (Hit), correctly identified a lure as "similar" (lure correct rejection or LureCR), and incorrectly identified a lure as "old"

(lure false alarm or LureFA). All other possible responses to stimuli were included in the first level regression model but not included in further analyses. Half the CR trials were randomly assigned to serve as the functional baseline in fMRI analyses. This kind of baseline has been used before when performing fMRI investigations of pattern separation processes (Bakker et al., 2008; Motley & Kirwan, 2012). The fMRI model also included vectors that coded for scan run, scanner drift, and motion, which included three rotational vectors (pitch, yaw, and roll) and three translational vectors (x, y, and z). The resulting beta coefficients were entered into group-level analyses as described below. We corrected for multiple comparisons using the AFNI ClustSim program, which uses Monte Carlo simulations to calculate the appropriate clusters of voxels that are large enough to be statistically significant (Forman et al., 1995; Xiong, Gao, Lancaster, & Fox, 1995). Using a voxel-wise threshold *p*-value of < .005 the calculated minimum cluster threshold was 42 voxels.

Because we had *a priori* hypotheses about the role of the hippocampus in performing this task, we performed analyses on hippocampal subfields using segmentations based on the high-resolution structural scans. A rater blind to participant group assignment followed established protocols to perform manual segmentations of CA3/DG, CA1, and subiculum sub-regions (Bakker et al., 2008; Doxey & Kirwan, 2015; Duvernoy, 2005). Another rater, also blind to group assignment, performed the same segmentations to establish inter-rater reliability. Manual segmentations were then co-registered to functional space. Because of the small size of our regions of interest, and due to the degree of down sampling occurring during co-registration, the segmentations taken from our two raters were not overlapped. We performed statistical analyses on both segmentations individually and report effects that were common to both raters.

In order to understand the differential effects of sleep on activity patterns in the hippocampus, we created a hippocampal mask using our ANTs normalized template. The mask was back-transformed into subject space using individual ANTs transformations, which was then resampled to the resolution of the functional scans. Representational similarity was calculated for Foils-Lures, Foils-Repeats, and Lures-Repeats comparison pairs of stimuli types by calculating the voxel-by-voxel correlations of activation for hippocampal voxels associated with each pair. Correlation coefficients were z-transformed to obtain a representational similarity score for each participant.

Results

Behavioral

The distribution of behavioral responses during the immediate phase is depicted in Figure 3.2A, and behavioral performance during the delay phase is depicted in Figure 3.2B. A 2 (group) × 2 (phase) × 9 (response type) ANOVA revealed significant main effects of phase ($F(1,45) = 18.8$, $p < .0001 = .00008$) and response ($F(8,38) = 614$, $p < .0001$), as well as significant phase × response ($F(8,38) = 61.8$, $p < .0001$) and group × phase × response ($F(8,38) = 2.65$, $p < .05$) interactions. See Table A.3 for post-hoc analysis of responses. Additionally, we performed a 2 (group) × 2 (phase) ANOVA with the LureFA and LureCR response types separately, which revealed a main effect of phase ($F(1,47) = 98.7$, $p < .0001$) and a significant group × phase interaction ($F(1,47) = 10.3$, $p < .01$) for LureCR response types, but no significant main effects or interactions associated with LureFAs (see Figures 3.2C and 3.2D).

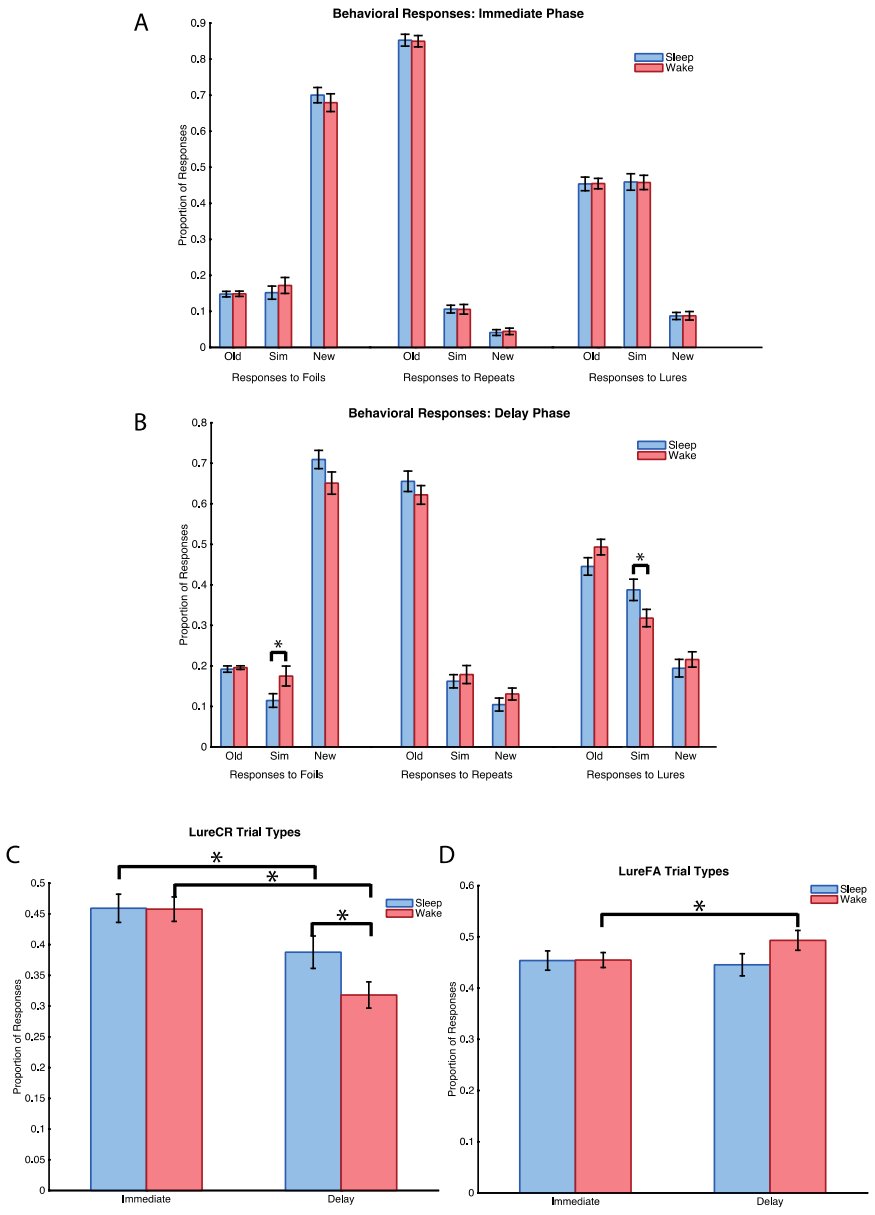

Figure 3.2: Behavioral Responses. (A) Depiction of the proportion of responses to foils, repeats, and lures during the immediate phase and (B) during the delayed phase. Significant differences between groups were only found in the delay phase in proportion of "similar" responses to foils and lures. Participants in the sleep group had better overall performance as they were less likely to respond to a foil as being similar, but more likely to label a lure as similar. (C) LureCR responses changed over time, but were also different between groups. (D) LureFA responses only changed over time in the wake group. * indicates $p < .05$

Since our groups were not matched for the time of day in which they were tested, we tested for time of day effects by comparing the distribution of responses in the immediate test condition between the two groups. There was no main effect of group ($F(1,45) = .048$, $p = .83$).

We calculated "pattern separation scores", as we did in Experiment 1, based on the proportion of "similar" responses to lure items and correcting for a "similar" response bias using the following formula: p("sim" | lure) – p("sim" | repeat). Each participant received a pattern separation score for each testing phase. We also calculated "recognition memory scores" based on the proportion of "old" responses to repeat items and correcting for "old" response bias using the following formula: p("old" | repeat) – p("old" | new). Figure 3.3 shows the change in both pattern separation and recognition memory scores over the 12-hour delay period.

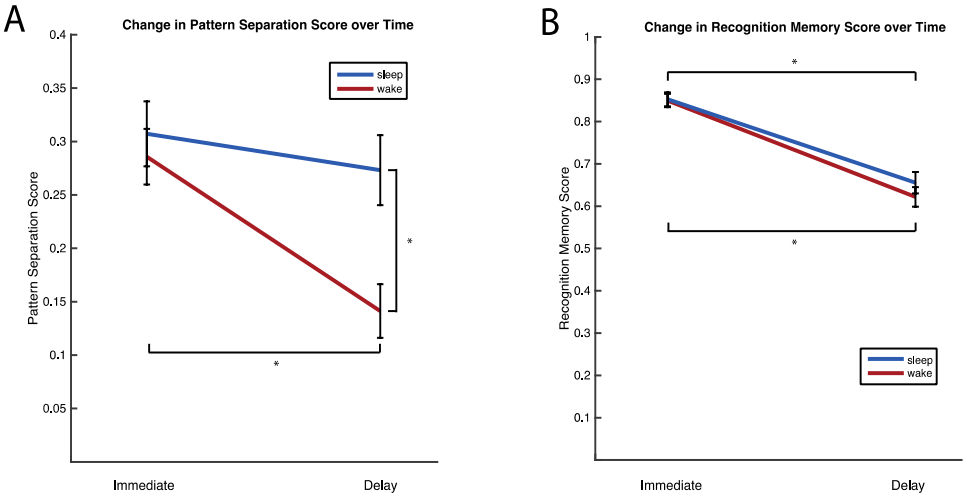

Figure 3.3: Changes in Pattern Separation and Memory Scores Between Testing Phases. (A) Pattern separation scores are relatively unchanged between immediate and delay testing phases if sleep is part of the 12hr delay. Scores do significantly decrease between phases if the 12hr delay is during daytime activities. Between groups, immediate scores are statistically similar, but delay scores are significantly different. (B) Recognition memory scores are affected similarly in both groups. Whether a participant slept or not, there is a similarly significant drop in performance after 12 hours. * indicates $p < .05$

A 2 × 2 analysis of variance (ANOVA) of pattern separation scores using group (sleep vs. wake) as a between-subjects factor and phase (immediate vs. delay) as a within-subjects factor

revealed a main effect of phase ($F(1,47) = 34.2$, $p < .0001$) as well as a phase × group interaction ($F(1,47) = 12.9$, $p < .001$). Further analysis of pattern separation scores between immediate and delay phases indicated no significant difference over time for the sleep group ($t(23) = 1.73$, $p = .10$), but a significant decrease over time for the wake group ($t(24) = 6.27$, $p < .0001$). Analysis of pattern separation performance between groups indicated no differences on the immediate test ($F(1,47) = .289$, $p = .59$), but significant differences on the delay test ($F(1,47) = 10.05$, $p < .005$) (see Figure 3.3A).

Interestingly, we did not find a similar trend with recognition memory performance. A similar 2 × 2 ANOVA, but using recognition memory scores, revealed a significant main effect of phase ($F(1,47) = 314$, $p < .0001$), driven by decreased performance in the delay condition (p's $< .0001$), but no main effect of group ($F(1,47) = .476$, $p = .494$) or phase × group interaction ($F(1,47) = 1.63$, $p = .208$) (see Figure 3.3B). Sleep, therefore, seems to have a selective effect on memory specificity only, and not recognition memory in general.

Additionally, we tested possible effects of sleep on reaction times. Specifically, we examined reaction times when participants correctly identified repeat, foil, and lure stimuli (Hits, CR, and LureCR, respectively), as well as when participants incorrectly identified lure stimuli as "old" (LureFA). Independent samples t-tests revealed no differences between groups or between testing phases in all four categories of behavioral responses. Finally we performed regression analyses to test whether reaction times could predict pattern separation performance. A stepwise linear regression included three significant variables in the delay model. Reaction times for both CR and LureCR negatively predicted behavioral performance (CR $\beta = -0.468$, $p < 0.05$; LureCR $\beta = -0.656$, $p < 0.0001$), while reaction times for LureFA positively predicted pattern separation performance ($\beta = 0.936$, $p < 0.0001$).

Imaging

The effects of sleep and delay on neural activity were examined by conducting a 2 × 2 ANOVA on the whole-brain fMRI data using group (sleep, wake) and phase (immediate, delayed) as fixed factors. Activity (in steps) and sleep (in minutes) were included in the model as covariates. In order to avoid a voxel selection bias, we identified regions that demonstrated a significant group × phase interaction and then interrogated these regions for differential effects of stimulus type. We identified eight regions of interest (ROIs) where there was a significant group × phase interaction: right inferior temporal gyrus, left post central sulcus, right lingual gyrus, right insula, right fusiform gyrus, left lingual gyrus, left inferior parietal lobule, and right inferior parietal lobule (see Figure 3.4 and Table 3.1). We further interrogated the interaction effect for specific response types in these functionally-defined ROIs. When considering only CR trials, the group × phase interaction was significant only in the right fusiform gyrus and left lingual gyrus (see Table 3.1 and Table A.2). The interaction was significant in every region for LureFA, LureCR, and Hit trials, indicating that the interaction between group and phase was strongest for Lure and Repeat stimuli. Figure 3.5 depicts the common patterns of activation for the eight ROIs. Comparing brain activity in these regions between groups, we only found significant differences between groups in the immediate phase in the left lingual gyrus for LureFA trials (see Table A.1). Of particular note, the right inferior temporal gyrus and left inferior parietal lobule had significantly different activity between groups during the delay phase for LureFA and LureCR trials, but not for Hits and CRs. These results indicate that out of all the regions that are affected by the interaction of sleep and delay, the change in activity over time in only the right inferior temporal gyrus and left inferior parietal lobule is related to the difference in behavioral response to lure stimuli.

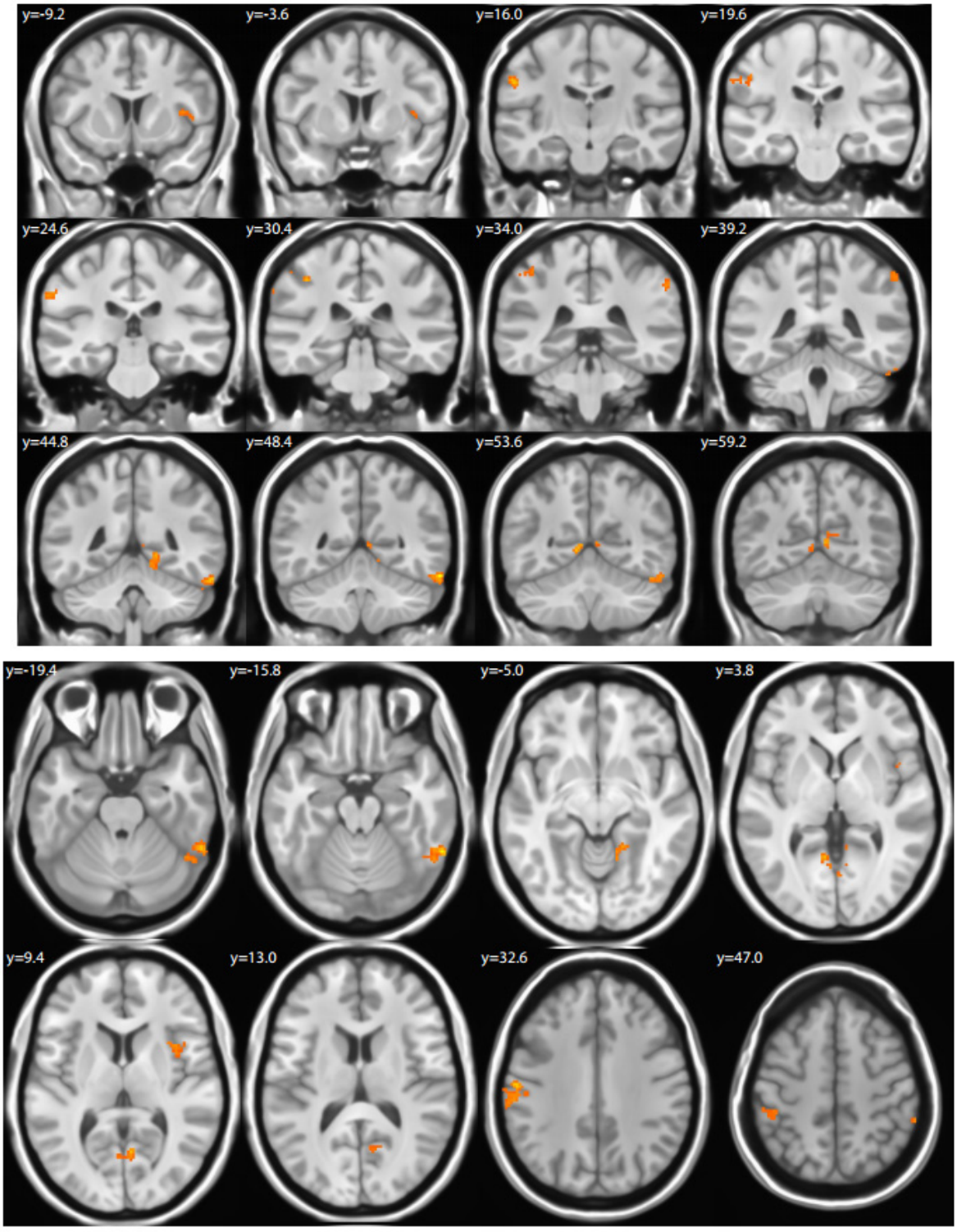

Figure 3.4: Brain Regions Demonstrating a Group × Phase Interaction**.** Regions where there was a significant group × phase interaction included right inferior temporal gyrus, left post central sulcus, right lingual gyrus, right insula, right fusiform gyrus, left lingual gyrus, left inferior parietal lobule, and right inferior parietal lobule. The left side of the brain is on the left of the image.

Table 3.1: Functional Clusters Relating to the Group × Phase Interaction.

Region	# voxels	Peak x	Peak y	Peak z	LureFA F (1,44)	p	LureCR F (1,44)	p
R inferior temporal gyrus	136	-50.4	41.1	-26.9	12.5	< .01	8.78	< .01
L post central gyrus	134	52.2	15.9	27.1	10.7	< .01	26.4	< .0001
R lingual gyrus	85	-3.6	66.3	.1	10.3	< .01	10.2	< .01
R insula	79	-43.2	-9.3	3.7	15.2	< .001	11.7	< .001
R fusiform gyrus	53	-16.2	42.9	-10.7	12.6	< .001	8.45	< .01
L lingual gyrus	45	7.2	55.5	-1.7	13.5	< .001	5.33	< .05
L inferior parietal lobule	45	36	28.5	39.7	13.1	< .001	16.9	< .001
R inferior parietal lobule	44	-54	33.9	34.3	5.05	< .05	4.05	.05

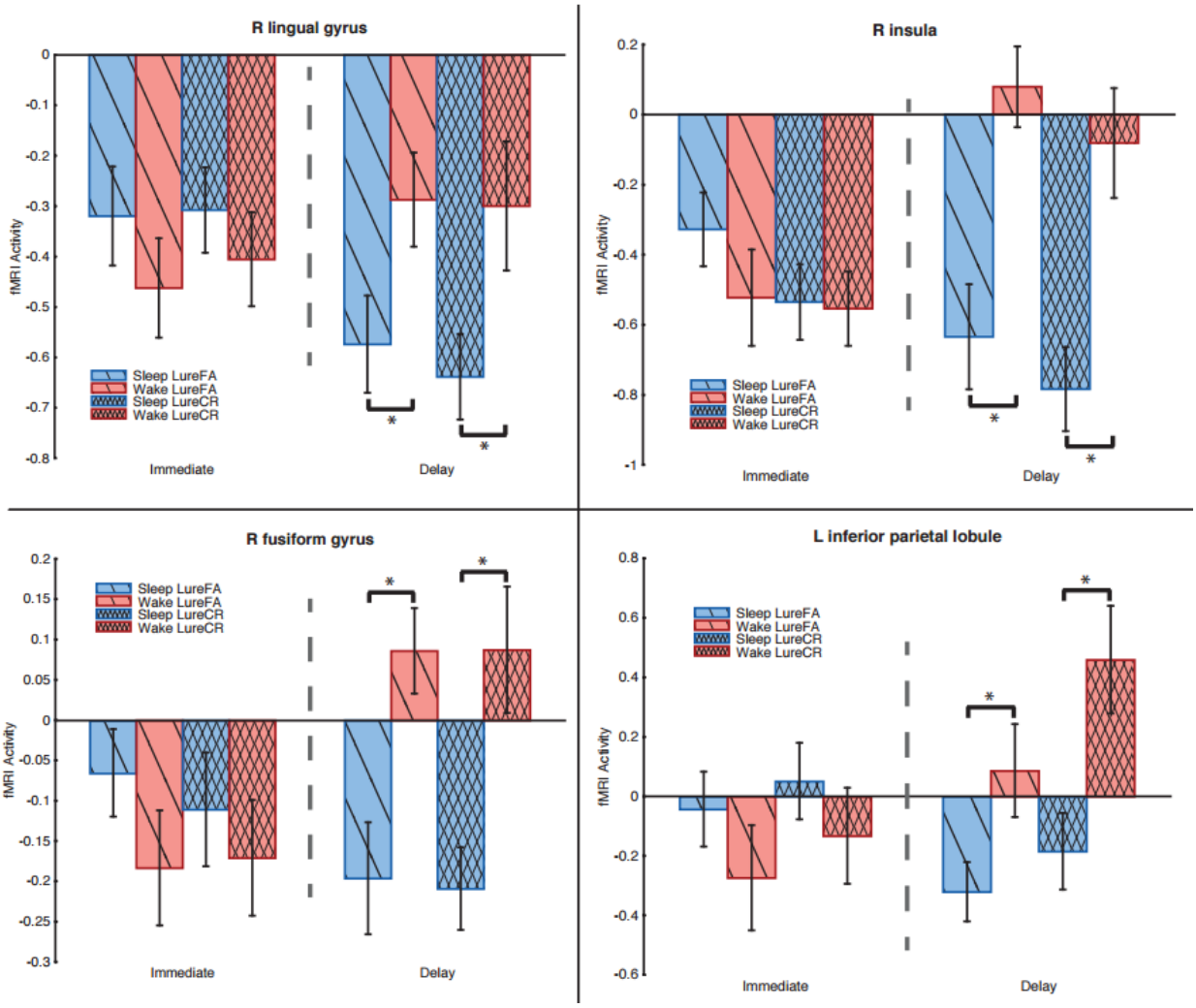

Figure 3.5: Depiction of the Group × Phase Interaction in fMRI Activation. These are representative samples of fMRI activity for LureCR and LureFA response types during the immediate and delay phases. The significant interaction is driven by differences between groups during the delay phase in these regions. The observed pattern of activity is that the wake group is associated with increased activity for lure stimuli in the delay phase compared to the sleep group. * indicates $p < .05$

We performed a 2 (group) × 2 (phase) × 4 (trial type) repeated measures ANOVA on the activation within sub-regions of the hippocampus (CA3/dentate gyrus [DG], CA1, and subiculum). There were no main effects of sleep on activation in any of the sub-regions, but there was a main effect of trial type in left CA3/DG ($F(3,43) = 6.0$, $p < .01$), left CA1 ($F(3,43) = 4.2$, $p < .05$), right CA1 ($F(3,43) = 6.8$, $p < .001$), and right subiculum ($F(3,43) = 3.8$, $p < .05$), but not in right CA3/DG ($F(3,43) = 2.4$, $p = .08$), or left subiculum ($F(3,43) = 2,5$, $p = .07$). We did note

that right CA3, right CA1, and bilateral subiculum, but not CA1 or left CA3/DG, had significant phase × trial type interactions (see Table 3.2). The three-way interaction was not significant. From these results, we conclude that although activity in these hippocampal sub-regions did change with trial type over time, sleep did not have a direct effect on the variability. Thus, our results indicate that activity in the hippocampus during task performance is similar following a delay, whether it contains sleep or not. A single night's sleep, therefore, has a preservative effect on task performance likely because it helps the process of response selection as mediated by other cortical regions, like those revealed previously.

Table 3.2: Statistics Relating to the Phase × Trial Type and Group × Phase × Trial Type Interactions of Beta Values in all Six Hippocampal Sub-regions. Note that none of the ROIs corresponded with a significant 3-way interaction, while four ROIs exhibited a phase × trial type interaction.

Region	Phase X Trial Type F(3,45)	p	Group X Phase X Trial Type F(1,45)	p
R CA3/DG	4.10	< .05	0.27	0.847
L CA3/DG	1.07	0.368	0.41	0.747
R CA1	5.79	< .001	0.32	0.809
L CA1	2.10	0.103	0.89	0.450
R subiculum	2.84	< .05	0.34	0.798
L subiculum	3.31	< .05	0.87	0.457

To understand the role of the hippocampal subfields in our study, we tested whether functional activity in hippocampal sub-regions predicted behavioral performance. Activity in each sub-region associated with trial type was used as independent variables, and the pattern separation or recognition memory scores were used as dependent variables in linear regression

models. We conducted four regression models with separate delay and immediate analyses on pattern separation and recognition memory performance. Stepwise linear regression results indicated that activity in right CA3/DG associated with LureFA trials during both immediate (β = -.290, $p < .05$) and delay phases (β = .301, $p < .05$) significantly predicted pattern separation scores (see Figure 3.6). The only significant predictor of memory score was activity in right CA3/DG associated with Hit trials during the immediate phase only (β = -.429, $p < .05$). No predictors of recognition memory performance were associated with the delay phase.

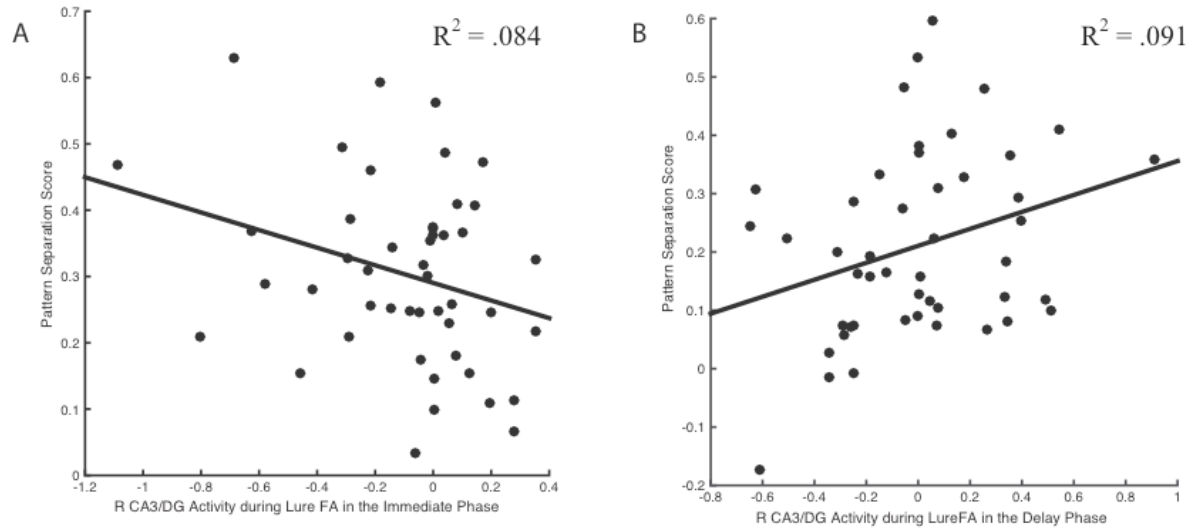

Figure 3.6: Scatter Plots of Right CA3/DG Activity During LureFA Trials on Pattern Separation Scores. (A) In the immediate phase, activity during LureFA trials in right CA3/DG negatively predicts pattern separation scores. (B) In the delay phase, activity during LureFA trials in right CA3/DG positively predicts pattern separation scores

Because we believed the hippocampus to be heavily involved in our task, we extracted patterns of activity in the hippocampus to test how patterns associated with specific stimuli types are related. We hypothesized that brain activity during Lure stimuli presentation would be similar to activity associated with Foils since these are both forms of novel stimuli, and a major role of the hippocampus is to respond to novel stimuli (Kohler, Danckert, Gati, & Menon, 2005; Montaldi, Spencer, Roberts, & Mayes, 2006; Stern et al., 1996).

We conducted a 2 (group) × 2 (phase) × 3 (comparison) repeated measures ANOVA on the representational similarity scores for each comparison (Foils-Lures, Foils-Repeats, Lures-Repeats) within the hippocampal mask. This analysis revealed a significant main effect of phase ($F(1,44) = 7.38$, $p < .01$) and comparison ($F(2,43) = 403$, $p < .0001$), but no main effect of group ($F(1,44) = .015$, $p = .7$). Additionally, we noted a significant phase × comparison interaction ($F(2,43) = 24$, $p < .0001$). This interaction is driven by the significant change in time for the Foils-Lures comparison, as further analysis revealed a significant difference between testing phases for Foils-Lures ($t(45) = 4.98$, $p < .0001$), but no significant differences for Foils-Repeats ($t(45) = 1.59$, $p = .12$) and Lures-Repeats ($t(45) = .858$, $p = .40$), collapsing across groups (see Figure 3.7). Because we were interested in which comparison had the highest correlation, we performed one-tailed t-tests, resulting in the Foils-Lures comparison having the highest correlation compared to Foils-Repeats ($t(45) = 18.6$, $p < .0001$) and Lures-Repeats ($t(45) = 29.4$, $p < .0001$). This confirmed our hypothesis that hippocampal activity associated with the presentation of lure stimuli looks more like the activity associated with the presentation of novel stimuli compared to repeated stimuli.

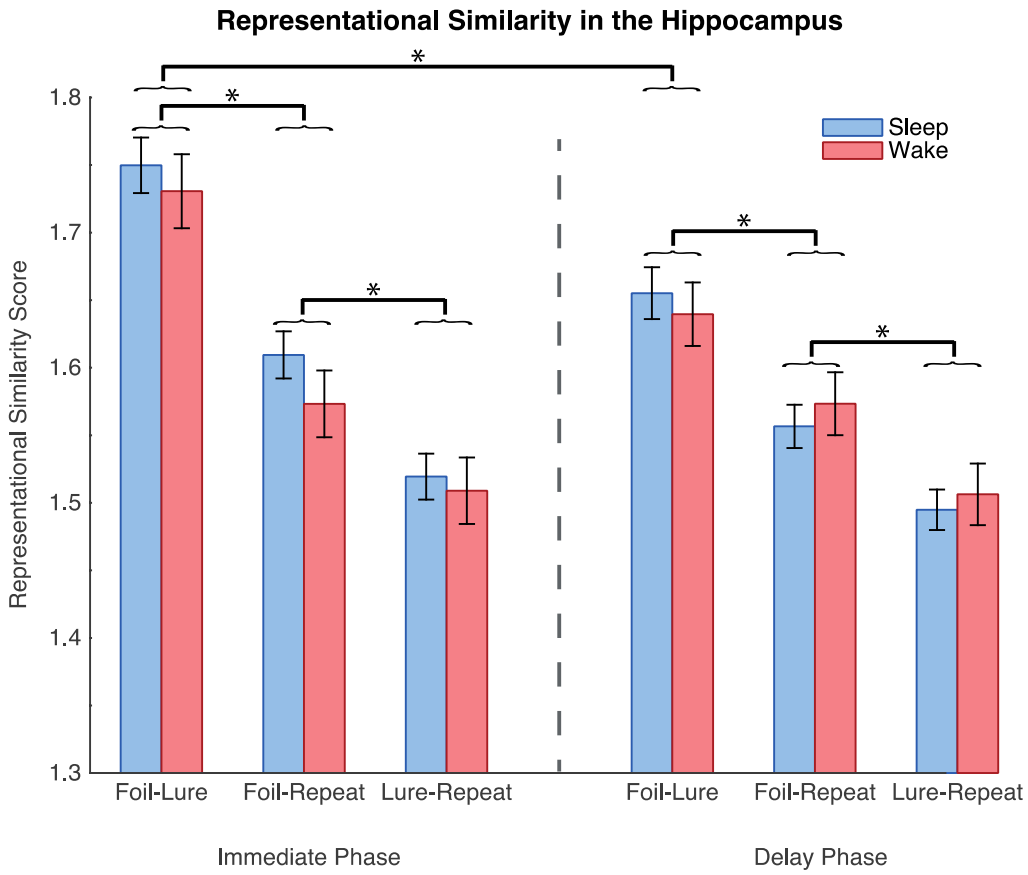

Figure 3.7: Representational Similarity in the Hippocampus is Not Affected by Sleep When Not Accounting for Behavior**.** Analyses revealed significant differences in representational similarity for the three comparisons. Activity associated with Foil trials was most similar to activity associated with Lure trials, indicating that the hippocampus responds similarly to novel stimuli, regardless of behavioral response. This hippocampal response, however, is statistically unaffected by sleep. Interestingly, only the Foils-Lures comparison significantly changes over a 12hr delay. * indicates $p < .0001$

Discussion

We examined the effect of sleep on both behavioral and neural responses in a task that places high demands on pattern separation processes. Behaviorally, we observed a decrease in mnemonic discrimination (i.e., pattern separation scores) following a wake-filled delay but preserved performance when the delay contained sleep. There was no effect of sleep on recognition memory performance. In terms of brain activation, we observed an interaction

between sleep, delay, and stimulus condition in a network of brain regions related to attention, visual acuity, and visual recall (discussed below).

Behavioral Performance

Previous research has indicated that sleep preserves declarative memories from interference when subjects are retested over a 12 hour interval (Ellenbogen et al., 2006). REM sleep, in particular, improves memory discrimination performance retroactively despite the introduction of high interference (McDevitt, Duggan, & Mednick, 2015). These findings are consistent with our observation that sleep seems to have a compensatory effect on interference. The paradigm used here did not introduce explicit interference as in previous studies. Instead, the task involved interference caused by daily activities (including college classes and other activities requiring extensive cognitive resources) and by interference inherent in a difficult mnemonic discrimination task.

Another specific effect sleep has on learning is that it is associated with improved consolidation of explicit memories that are more difficult to encode or that are only weakly encoded (Diekelmann & Born, 2010). In our behavioral task, obtaining a high pattern separation score is much more challenging and computationally intensive compared to obtaining a high recognition memory score. An interesting and novel finding from our results is that sleep does not appear to affect recognition memory in general whilst it does benefit mnemonic discrimination that is dependent on pattern separation. It is reasonable to conclude, therefore, that sleep has a greater effect on pattern separation processing compared to other processes underlying declarative memory.

Voxel-wise Group fMRI Analysis

Neuroimaging results indicate that when a 12hr delay includes sleep, activity in eight brain regions is significantly different compared to a 12hr delay that does not include sleep while undergoing a task that places high demands on pattern separation. These regions include the right inferior temporal gyrus, left post central sulcus, right lingual gyrus, right insula, right fusiform gyrus, left lingual gyrus, and bilateral inferior parietal lobules. Activity in these regions is significantly different between groups during LureFA, LureCR, and Hit response types (with differences between groups in only the fusiform and lingual gyri during CR response types), and this contrast is likely involved with the observed difference in behavioral performance. These findings provide interesting insights to the discussions about pattern separation processes since many of our functional ROIs are part of the default-mode network (DMN) and are implicated in various executive, memory, and visual discrimination processes.

The DMN comprises a set of brain regions that are more active during task-free rest periods than during active task conditions (Raichle et al., 2001). Our observed activations are within (inferior temporal gyrus and inferior parietal lobules) or near (fusiform gyrus and post central sulcus) regions considered to make up the DMN. One implication of the DMN noted in the literature is that the deactivation of this network correlates with the process of switching attention during tasks (Binder et al., 1999; Raichle et al., 2001), and indeed the insula has been implicated to have a role in switching to executive control networks (Sridharan, Levitin, & Menon, 2008; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Our results are consistent with the idea that increased activation of these regions could be associated with decreased task-directed attention. As can be observed in the examples provided in Figure 9, activity during LureFA and LureCR response types in these regions typically is suppressed in the sleep group

compared to the wake group, and this difference in activation is likely associated with differences in behavioral performance. Sleep, therefore, could have a positive effect on memory discrimination performance because it is associated with decreased activity in the DMN, likely related to increased attention during our difficult task.

The lingual gyrus, inferior frontal lobe/insula, and inferior parietal lobule regions have previously been implicated in some executive function processing related to increased activity with response inhibition during Go/NoGo trials compared to simple button pressing associated with Go trials (Menon, Adleman, White, Glover, & Reiss, 2001; Nee, Wager, & Jonides, 2007). This is interesting since our results show an increase in activation associated with the wake group during LureFA and LureCR trials. Deciding whether a lure stimulus is "old" or "similar" is intentionally very difficult, so it is understandable that response inhibition could be taking place as participants quickly go back and forth between these two choices. Indeed, behavioral responses indicate that this decision is extremely difficult as participants in the wake group are more likely to label a lure stimulus as "old" than they are to label it as "similar" (see Fig. 6). Sleep appears to result in decreased activation in brain areas associated with response inhibition, possibly facilitating more accurate recognition decision-making.

Three of our functional ROIs, the inferior temporal gyrus, inferior parietal lobule, and insula, have been implicated in recall through visual cues. Despite often being considered integral for emotional processes, the insula is sometimes activated during memory tasks (Konishi, Wheeler, Donaldson, & Buckner, 2000; Nee et al., 2007). A PET study in which visual categories of studied patterns were used as a condition resulted in increased blood flow to the inferior temporal gyrus and angular gyrus (inferior parietal lobule) compared to a working memory condition (Herath, Kinomura, & Roland, 2001). In one study, the insula was more

activated for cued recall trials compared to free recall, thereby implicating a role in retrieval through an external instead of an internal cue (Fletcher, Shallice, & Dolan, 1998). We used visual cues as part of our experimental design, so one reason for the increase in activity of these areas, associated with the wake group, could be that participants relied more on the visual cues provided during the delayed testing portion as opposed to their internal representation of the stimuli consolidated into long-term memory.

Another important aspect to consider is the high level of discrimination needed to perform well on our task. Extrastriate regions such as the lingual and fusiform gyri have been implicated in discrimination of visual stimuli using tasks that also inherently rely on working memory (Cornette et al., 1998; Schiltz et al., 1999). Although our task is not a test of visual discrimination *per se*, it does challenge participants' ability to discriminate between memories of specific visual stimuli with presented stimuli. This likely requires similar brain areas as the working memory versions performed previously, and it appears that sleep alters the activity of these regions.

Hippocampal Subfields

Our results suggest that the response of right CA3/DG to LureFA trials has the greatest impact on performance outcome, but that this effect is not necessarily enhanced or diminished with sleep. Hippocampal sub-regions perform pattern separation computations regardless of sleep, but these computations have less influence on behavior after a twelve-hour delay. Such results are consistent with the importance of DG in performing pattern separation processing (Bakker et al., 2008; Deng et al., 2010; Leutgeb et al., 2007b). The results of our regression analysis indicate that indeed pattern separation performance relies heavily on activity of the

DG/CA3 region. However, these computations are affected to the greatest degree by time, and not whether an individual has slept or not.

An explanation for the change in slopes of the regression lines (see Figure 3.6) between the immediate and delay phases is unclear, particularly since a regression analysis of our version of a memory discrimination task using high resolution scans is novel to the pattern separation literature. One important factor to consider is the type of consolidation happening during the immediate and delay phases, which could affect DG activity. Recent work indicates that consolidation (a process to transform a memory into a long term memory) and reconsolidation (when a recalled memory again goes through a process of consolidation) are dissociable processes happening in the hippocampus (Lee, Everitt, & Thomas, 2004). It is likely that consolidation is the dominant process occurring during the immediate phase of our study, while reconsolidation is the dominant process during the delay phase. Perhaps less DG activity during the immediate phase helps with performance because the memories are more readily available as opposed to needing to go through a more thorough process of retrieval. Effective retrieval during reconsolidation, on the other hand, could require more neural activity. Of course, such a simple explanation may be insufficient since fMRI does not allow examining pattern separation processes on the cellular level. Well understood is that the DG is extremely complex and unique, as indicated by the evidence that it holds the greatest density of neurons compared to other hippocampal sub-regions (West, Slomianka, & Gundersen, 1991) and is a site for neurogenesis (Kuhn, DickinsonAnson, & Gage, 1996). This complexity could drive heretofore-unknown processes in the DG that change over a 12hr period.

Representational Similarity

The similarity between the overall pattern of activation for Foils and Lures in the hippocampus was greater than the similarity between Foils-Repeats and Repeats-Lures. Interestingly, activity patterns for the sleep group were not significantly different compared to the wake group in either immediate or delay testing phases.

The hippocampus has often been found to be integral for pattern separation processes (Bakker et al., 2008; Clelland et al., 2009; Leutgeb et al., 2007a; McHugh et al., 2007; Rolls & Kesner, 2006; Yassa & Stark, 2011), and this assertion is consistent with our data. As stated above, we hypothesized that brain activity during Lure stimuli presentation would be similar to activity associated with Foils because a major role of the hippocampus is to respond to novel stimuli (Kohler et al., 2005; Montaldi et al., 2006; Stern et al., 1996). This has been found to be true even independent of conscious awareness (Daselaar, Fleck, Prince, & Cabeza, 2006; Kirwan, Shrager, & Squire, 2009). Our results support this notion since we binned individual stimuli types, regardless of behavioral responses.

Limitations and Future Directions

As noted above, one limitation of using non-invasive functional neuroimaging to assess pattern separation processes is that as a cellular computation, pattern separation processing can truly be measured only at the cellular level (Aimone, Deng, & Gage, 2011; Leutgeb et al., 2007a; McClelland et al., 1995; Norman & O'Reilly, 2003; Treves & Rolls, 1994). While high-resolution fMRI gives superb spatial resolution over the whole brain, it cannot measure cellular processes directly. Previous studies, however, indicate that activity in hippocampal sub-regions is associated with differential processing of lure stimuli relative to repeated and novel stimuli (Bakker et al., 2008; Leal, Tighe, Jones, & Yassa, 2014). These studies found increased activity

in CA3/DG when participants correctly identify a lure as "similar." Therefore, though fMRI cannot directly measure pattern separation, behavioral performance can be used to make inferences about regions where pattern separation processing takes place.

This study provides initial insight as to the effects of sleep on neural activity on a task that places high demands on pattern separation. Because we did not test specific sleep states, future studies may wish to examine the effects of REM/non-REM sleep on behavioral performance and on neural activity. Another direction for the future might involve a more longitudinal approach. While it is interesting that we show a single night's sleep had such a dramatic effect on behavioral performance, future studies would need to investigate whether this translates into a long-term effect or not and if the sleep-related changes that we observe in the fMRI activation reflect long-term consolidation effects. Sleep seems to enhance performance on our task by assisting with overcoming interference. A question remains as to whether we would see similar group differences with a delay of 24 hours or longer. If studying a list of items, like in the current study, immediately before sleep has a significant long-term effect, this would provide important implications about optimal study habits in educational settings.

Conclusions

Our results indicate that sleep is important for performing well on memory tasks that are highly cognitively demanding. Various cortical regions are positively affected by sleep such that an increase of activity in these areas is associated with more correctly identifying lure stimuli. Sleep appears to have a preserving effect on memory specificity because it affects general activity in regions involved with attention, visual acuity, and visual recall.

We then took this experiment one step further by testing brain activity during lure stimulus presentation in a multivariate study. Once we find how hippocampal subfield activity

changes with sleep, we can then test how this affects hippocampal activity and brain activity as a whole. We will ask whether a trained computer algorithm can dissociate whole brain and/or hippocampal activity for each type of stimulus. We are particularly interested in whether whole brain activity patterns associated with lure stimulus presentation look more like activity patterns associated with repeat stimulus or old stimulus presentation. Such an analysis could further our understanding of pattern separation processing, especially the subtleties in brain activity associated with lure stimuli compared to new and old stimuli. That is the reasoning behind the following experiment.

REFERENCES

4-side Button Cylinder [Apparatus]. (2014). Philadelphia, PA: Current Designs Inc.

ActiGraph GT3X+ [Apparatus and software]. (2011). Pensacola, FL: ActiGraph.

Aimone, J. B., Deng, W., & Gage, F. H. (2011). Resolving New Memories: A Critical Look at the Dentate Gyrus, Adult Neurogenesis, and Pattern Separation. *Neuron, 70*(4), 589-596. doi:10.1016/j.neuron.2011.05.010

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007a). Non-linear optimisation. *FMRIB technical report TR07JA1*. Retrieved from http://www.fmrib.ox.ac.uk/analysis/techrep

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007b). Non-linear registration, aka Spatial normalisation. *FMRIB technical report TR07JA2*. Retrieved from http://www.fmrib.ox.ac.uk/analysis/techrep

Aton, S. J., Seibt, J., Dumoulin, M., Jha, S. K., Steinmetz, N., Coleman, T., . . . Frank, M. G. (2009). Mechanisms of Sleep-Dependent Consolidation of Cortical Plasticity. *Neuron, 61*(3), 454-466. doi:10.1016/j.neuron.2009.01.007

Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. *Medical Image Analysis, 12*(1), 26-41. doi:10.1016/j.media.2007.06.004

Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. L. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science, 319*(5870), 1640-1642. doi:10.1126/science.1152882

Bartko, J. J. (1991). MEASUREMENT AND RELIABILITY - STATISTICAL THINKING CONSIDERATIONS. *Schizophrenia Bulletin, 17*(3), 483-489.

Basser, P. J., Mattiello, J., & Le Bihan, D. (1994). MR DIFFUSION TENSOR SPECTROSCOPY AND IMAGING. *Biophysical Journal, 66*(1), 259-267.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *Nmr in Biomedicine, 15*(7-8), 435-455. doi:10.1002/nbm.782

Beckmann, C. F., DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society B-Biological Sciences, 360*(1457), 1001-1013. doi:10.1098/rstb.2005.1634

Behrens, T. E. J., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., . . . Smith, S. M. (2003). Characterization and propagation of uncertainty in diffusion-

weighted MR imaging. *Magnetic Resonance in Medicine, 50*(5), 1077-1088. doi:10.1002/mrm.10609

Bennett, I. J., Huffman, D. J., & Stark, C. E. L. (2014). Limbic Tract Integrity Contributes to Pattern Separation Performance Across the LIfespan. *Cerebral Cortex*. doi:10.1093/cercor/bhu093

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Rao, S. M., & Cox, R. W. (1999). Conceptual processing during the conscious resting state: A functional MRI study. *Journal of Cognitive Neuroscience, 11*(1), 80-93. doi:10.1162/089892999563265

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). FUNCTIONAL CONNECTIVITY IN THE MOTOR CORTEX OF RESTING HUMAN BRAIN USING ECHO-PLANAR MRI. *Magnetic Resonance in Medicine, 34*(4), 537-541. doi:10.1002/mrm.1910340409

Brickman, A. M., Stern, Y., & Small, S. A. (2011). Hippocampal Subregions Differentially Associate With Standardized Memory Tests. *Hippocampus, 21*(9), 923-928. doi:10.1002/hipo.20840

Bronen, R. A., Cheung, G., Charles, J. T., Kim, J. H., Spencer, D. D., Spencer, S. S., . . . McCarthy, G. (1991). IMAGING FINDINGS IN HIPPOCAMPAL SCLEROSIS - CORRELATION WITH PATHOLOGY. *American Journal of Neuroradiology, 12*(5), 933-940.

Burke, S. N., Hartzell, A. L., Lister, J. P., Hoang, L. T., & Barnes, C. A. (2012). Layer V perirhinal cortical ensemble activity during object exploration: A comparison between young and aged rats. *Hippocampus, 22*(10), 2080-2093. doi:10.1002/hipo.22066

Burke, S. N., Wallace, J. L., Nematollahi, S., Uprety, A. R., & Barnes, C. A. (2010). Pattern Separation Deficits May Contribute to Age-Associated Recognition Impairments. *Behavioral Neuroscience, 124*(5), 559-573. doi:10.1037/a0020893

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience, 12*(1), 1-47. doi:10.1162/08989290051137585

Camara, E., Bodammer, N., Rodriguez-Fornells, A., & Tempelmann, C. (2007). Age-related water diffusion changes in human brain: A voxel-based approach. *Neuroimage, 34*(4), 1588-1599. doi:10.1016/j.neuroimage.2006.09.045

Charlton, R. A., Barrick, T. R., McIntyre, D. J., Shen, Y., O'Sullivan, M., Howe, F. A., . . . Markus, H. S. (2006). White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. *Neurology, 66*(2), 217-222. doi:10.1212/01.wnl.0000194256.15247.83

Cirelli, C., Gutierrez, C. M., & Tononi, G. (2004). Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron, 41*(1), 35-43. doi:10.1016/s0896-6273(03)00814-6

Cirelli, C., & Tononi, G. (2000). Gene expression in the brain across the sleep-waking cycle. *Brain Research, 885*(2), 303-321. doi:10.1016/s0006-8993(00)03008-0

Clark, P. J., Bhattacharya, T. K., Miller, D. S., Kohman, R. A., DeYoung, E. K., & Rhodes, J. S. (2012). New neurons generated from running are broadly recruited into neuronal activation associated with three different hippocampus-involved tasks. *Hippocampus, 22*(9), 1860-1867. doi:10.1002/hipo.22020

Clelland, C. D., Choi, M., Romberg, C., Clemenson, G. D., Jr., Fragniere, A., Tyers, P., . . . Bussey, T. J. (2009). A Functional Role for Adult Hippocampal Neurogenesis in Spatial Pattern Separation. *Science, 325*(5937), 210-213. doi:10.1126/science.1173215

Cornette, L., Dupont, P., Rosier, A., Sunaert, S., Van Hecke, P., Michiels, J., . . . Orban, G. A. (1998). Human brain regions involved in direction discrimination. *Journal of Neurophysiology, 79*(5), 2749-2765.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29*(3), 162-173. doi:10.1006/cbmr.1996.0014

Daselaar, S. M., Fleck, M. S., Prince, S. E., & Cabeza, R. (2006). The medial temporal lobe distinguishes old from new independently of consciousness. *Journal of Neuroscience, 26*(21), 5835-5839. doi:10.1523/jneurosci.0258-06.2006

Daurat, A., Terrier, P., Foret, J., & Tiberge, M. (2007). Slow wave sleep and recollection in recognition memory. *Consciousness and Cognition, 16*(2), 445-455. doi:10.1016/j.concog.2006.06.011

Davachi, L., & Wagner, A. D. (2002). Hippocampal contributions to episodic encoding: Insights from relational and item-based learning. *Journal of Neurophysiology, 88*(2), 982-990. doi:10.1152/jn00046.2002

Decarli, C., Murphy, D. G. M., Gillette, J. A., Haxby, J. V., Teichberg, D., Schapiro, M. B., & Horwitz, B. (1994). LACK OF AGE-RELATED DIFFERENCES IN TEMPORAL-LOBE VOLUME OF VERY HEALTHY-ADULTS. *American Journal of Neuroradiology, 15*(4), 689-696.

Dellarocchetta, A. I., & Milner, B. (1993). STRATEGIC SEARCH AND RETRIEVAL INHIBITION - THE ROLE OF THE FRONTAL LOBES. *Neuropsychologia, 31*(6), 503-524.

den Heijer, T., van der Lijn, F., Vernooij, M. W., de Groot, M., Koudstaal, P. J., van der Lugt, A., . . . Breteler, M. M. B. (2012). Structural and diffusion MRI measures of the hippocampus and memory performance. *Neuroimage, 63*(4), 1782-1789. doi:10.1016/j.neuroimage.2012.08.067

Deng, W., Aimone, J. B., & Gage, F. H. (2010). New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nature Reviews Neuroscience, 11*(5), 339-350. doi:10.1038/nrn2822

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., . . . Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968-980. doi:10.1016/j.neuroimage.2006.01.021

Dice, L. R. (1945). MEASURES OF THE AMOUNT OF ECOLOGIC ASSOCIATION BETWEEN SPECIES. *Ecology, 26*(3), 297-302. doi:10.2307/1932409

Diekelmann, S., & Born, J. (2010). SLEEP The memory function of sleep. *Nature Reviews Neuroscience, 11*(2), 114-126. doi:10.1038/nrn2762

Diekelmann, S., Wilhelm, I., & Born, J. (2009). The whats and whens of sleep-dependent memory consolidation. *Sleep Medicine Reviews, 13*(5), 309-321. doi:10.1016/j.smrv.2008.08.002

Doxey, C. R., & Kirwan, C. B. (2015). Structural and Functional Correlates of Behavioral Pattern Separation in the Hippocampus and Medial Temporal Lobe. *Hippocampus, 25*(4), 524-533. doi:10.1002/hipo.22389

Drosopoulos, S., Wagner, U., & Born, J. (2005). Sleep enhances explicit recollection in recognition memory. *Learning & Memory, 12*(1), 44-51. doi:10.1101/kfg.mu-luebeck.de

Duvernoy, H. M. (2005). *The human hippocampus functional anatomy, vascularization, and serial sections with MRI* (Vol. 3rd ed.): Berlin New York.

Duvernoy, H. M., & SpringerLink (Online service). (2005). *The human hippocampus functional anatomy, vascularization, and serial sections with MRI* (pp. viii, 232 p.). Retrieved from http://dx.doi.org/10.1007/b138576 http://www.loc.gov/catdir/enhancements/fy0662/2004112752-d.html

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. *Current Biology, 16*(13), 1290-1294. doi:10.1016/j.cub.2006.05.024

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, O., Larsen, V. A., & Walhovd, K. B. (2012). Memory training impacts short-term changes in aging white matter: A

Longitudinal Diffusion Tensor Imaging Study. *Human Brain Mapping, 33*(10), 2390-2406. doi:10.1002/hbm.21370

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America, 108*(7), 3017-3022. doi:10.1073/pnas.1015950108

Feinberg, D. A., Moeller, S., Smith, S. M., Auerbach, E., Ramanna, S., Glasser, M. F., . . . Yacoub, E. (2010). Multiplexed Echo Planar Imaging for Sub-Second Whole Brain FMRI and Fast Diffusion Imaging. *PloS one, 5*(12). doi:10.1371/journal.pone.0015710

Feinberg, D. A., & Setsompop, K. (2013). Ultra-fast MRI of the human brain with simultaneous multi-slice imaging. *Journal of Magnetic Resonance, 229*, 90-100. doi:10.1016/j.jmr.2013.02.002

Feinberg, D. A., & Yacoub, E. (2012). The rapid development of high speed, resolution and precision in fMRI. *Neuroimage, 62*(2), 720-725. doi:10.1016/j.neuroimage.2012.01.049

Felleman, D. J., & Van Essen, D. C. (1991). Distributed Hierarchical Processing in the Primate Cerebral Cortex. *Cerebral Cortex, 1*(1), 1-47. doi:10.1093/cercor/1.1.1

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D. H., . . . Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex, 14*(1), 11-22. doi:10.1093/cercor/bhg087

Fletcher, P. C., Shallice, T., & Dolan, R. J. (1998). The functional roles of prefrontal cortex in episodic memory - I. Encoding. *Brain, 121*, 1239-1248. doi:10.1093/brain/121.7.1239

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). IMPROVED ASSESSMENT OF SIGNIFICANT ACTIVATION IN FUNCTIONAL MAGNETIC-RESONANCE-IMAGING (FMRI) - USE OF A CLUSTER-SIZE THRESHOLD. *Magnetic Resonance in Medicine, 33*(5), 636-647. doi:10.1002/mrm.1910330508

Fujii, T., Saito, D. N., Yanaka, H. T., Kosaka, H., & Okazawa, H. (2014). Depressive Mood Modulates the Anterior Lateral CA1 and DG/CA3 During a Pattern Separation Task in Cognitively Intact Individuals: A Functional MRI Study. *Hippocampus, 24*(2), 214-224. doi:10.1002/hipo.22216

Gaab, N., Paetzold, M., Becker, M., Walker, M. P., & Schlaug, G. (2004). The influence of sleep on auditory learning: a behavioral study. *Neuroreport, 15*(4), 731-734. doi:10.1097/01.wnr.0000113532.32218.d6

Giovanello, K. S., Schnyer, D. M., & Verfaellie, M. (2004). A critical role for the anterior hippocampus in relational memory: Evidence from an fMRI study comparing associative and item recognition. *Hippocampus, 14*(1), 5-8.

Golomb, J., Kluger, A., deLeon, M. J., Ferris, S. H., Mittelman, M., Cohen, J., & George, A. E. (1996). Hippocampal formation size predicts declining memory performance in normal aging. *Neurology, 47*(3), 810-813.

Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *Journal of Neuroscience, 26*(51), 13338-13343. doi:10.1523/jneurosci.3408-06.2006

Hampton, R. R., & Murray, E. A. (2002). Learning of discriminations is impaired, but generalization to altered views is intact, in monkeys (Macaca mulatta) with perirhinal cortex removal. *Behavioral Neuroscience, 116*(3), 363-377. doi:10.1037//0735-7044.116.3.363

Haxby, J. V., Ungerleider, L. G., Horwitz, B., Maisog, J. M., Rapoport, S. I., & Grady, C. L. (1996). Face encoding and recognition in the human brain. *Proceedings of the National Academy of Sciences of the United States of America, 93*(2), 922-927. doi:10.1073/pnas.93.2.922

Herath, P., Kinomura, S., & Roland, P. E. (2001). Visual recognition: Evidence for two distinctive mechanisms from a PET study. *Human Brain Mapping, 12*(2), 110-119. doi:10.1002/1097-0193(200102)12:2<110::aid-hbm1008>3.0.co;2-0

Holden, H. M., Toner, C., Pirogovsky, E., Kirwan, C. B., & Gilbert, P. E. (2013). Visual object pattern separation varies in older adults. *Learning & Memory, 20*(7), 358-362. doi:10.1101/lm.030171.112

Hunsaker, M. R., Rosenberg, J. S., & Kesner, R. P. (2008). The Role of the Dentate Gyrus, CA3a,b, and CA3c for Detecting Spatial and Environmental Novelty. *Hippocampus, 18*(10), 1064-1073. doi:10.1002/hipo.20464

Insausti, R., Annese, J., Amaral, D. G., & Squire, L. R. (2013). Human amnesia and the medial temporal lobe illuminated by neuropsychological and neurohistological findings for patient E. P. *Proceedings of the National Academy of Sciences of the United States of America, 110*(21), E1953-E1962. doi:10.1073/pnas.1306244110

Insausti, R., Juottonen, K., Soininen, H., Insausti, A. M., Partanen, K., Vainio, P., . . . Pitkanen, A. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *American Journal of Neuroradiology, 19*(4), 659-671.

Jack, C. R., Petersen, R. C., Xu, Y., O'Brien, P. C., Smith, G. E., Ivnik, R. J., . . . Kokmen, E. (1998). Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology, 51*(4), 993-999.

Jenkins, J. G., & Dallenbach, K. M. (1924). Obliviscence during Sleep and Waking. *The American Journal of Psychology, 35*(4), 605-612. doi:10.2307/1414040

Ji, D. Y., & Wilson, M. A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nature Neuroscience, 10*(1), 100-107. doi:10.1038/nn1825

Jones, D. K., Knosche, T. R., & Turner, R. (2013). White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *Neuroimage, 73*, 239-254. doi:10.1016/j.neuroimage.2012.06.081

Kasiri, K., Kazemi, K., Dehghani, M. J., & Helfroush, M. S. (2013). A hybrid hierarchical approach for brain tissue segmentation by combining brain atlas and least square support vector machine. *Journal of medical signals and sensors, 3*(4), 232-243.

Kee, N., Teixeira, C. M., Wang, A. H., & Frankland, P. W. (2007). Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. *Nature Neuroscience, 10*(3), 355-362. doi:10.1038/nn1847

Kirwan, C. B., Jones, C. K., Miller, M. I., & Stark, C. E. L. (2007). High-resolution fMRI investigation of the medial temporal lobe. *Human Brain Mapping, 28*(10), 959-966. doi:10.1002/hbm.20331

Kirwan, C. B., Shrager, Y., & Squire, L. R. (2009). Medial temporal lobe activity can distinguish between old and new stimuli independently of overt behavioral choice. *Proceedings of the National Academy of Sciences of the United States of America, 106*(34), 14617-14621. doi:10.1073/pnas.0907624106

Kirwan, C. B., & Stark, C. E. L. (2004). Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. *Hippocampus, 14*(7), 919-930. doi:10.1002/hipo.20014

Kirwan, C. B., & Stark, C. E. L. (2007). Overcoming interference: An fMRI investigation of pattern separation in the medial temporal lobe. *Learning & Memory, 14*(9), 625-633. doi:10.1101/lm.663507

Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M. C., . . . Parsey, R. V. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage, 46*(3), 786-802. doi:10.1016/j.neuroimage.2008.12.037

Koehl, M., & Abrous, D. N. (2011). A new chapter in the field of memory: adult hippocampal neurogenesis. *European Journal of Neuroscience, 33*(6), 1101-1114. doi:10.1111/j.1460-9568.2011.07609.x

Kohler, S., Danckert, S., Gati, J. S., & Menon, R. S. (2005). Novelty responses to relational and non-relational information in the hippocampus and the parahippocampal region: A

comparison based on event-related fMRI. *Hippocampus, 15*(6), 763-774. doi:10.1002/hipo.20098

Kohman, R. A., & Rhodes, J. S. (2013). Neurogenesis, inflammation and behavior. *Brain Behavior and Immunity, 27*, 22-32. doi:10.1016/j.bbi.2012.09.003

Konishi, S., Wheeler, M. E., Donaldson, D. I., & Buckner, R. L. (2000). Neural correlates of episodic retrieval success. *Neuroimage, 12*(3), 276-286. doi:10.1006/nimg.2000.0614

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

Kuhn, H. G., DickinsonAnson, H., & Gage, F. H. (1996). Neurogenesis in the dentate gyrus of the adult rat: Age-related decrease of neuronal progenitor proliferation. *Journal of Neuroscience, 16*(6), 2027-2033.

Lacy, J. W., & Stark, C. E. L. (2012). Intrinsic functional connectivity of the human medial temporal lobe suggests a distinction between adjacent MTL cortices and hippocampus. *Hippocampus, 22*(12), 2290-2302. doi:10.1002/hipo.22047

Lacy, J. W., Yassa, M. A., Stark, S. M., Muftuler, L. T., & Stark, C. E. L. (2011). Distinct pattern separation related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable mnemonic similarity. *Learning & Memory, 18*(1), 15-18. doi:10.1101/lm.1971110

Le Bihan, D., & Johansen-Berg, H. (2012). Diffusion MRI at 25: Exploring brain tissue structure and function. *Neuroimage, 61*(2), 324-341. doi:10.1016/j.neuroimage.2011.11.006

Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging, 13*(4), 534-546. doi:10.1002/jmri.1076

Leal, S. L., Tighe, S. K., Jones, C. K., & Yassa, M. A. (2014). Pattern Separation of Emotional Information in Hippocampal Dentate and CA3. *Hippocampus, 24*(9), 1146-1155. doi:10.1002/hipo.22298

Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W., & Beaulieu, C. (2012). Diffusion tensor imaging of white matter tract evolution over the lifespan. *Neuroimage, 60*(1), 340-352. doi:10.1016/j.neuroimage.2011.11.094

Lee, J. L. C., Everitt, B. J., & Thomas, K. L. (2004). Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science, 304*(5672), 839-843. doi:10.1126/science.1095760

Leutgeb, J. K., Leutgeb, S., Moser, M., & Moser, E. I. (2007a). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science, 315*(5814), 961-966. doi:10.1126/science.1135801

Leutgeb, J. K., Leutgeb, S., Moser, M. B., & Moser, E. I. (2007b). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science, 315*(5814), 961-966. doi:10.1126/science.1135801

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*(6843), 150-157. doi:10.1038/35084005

Madden, D. J., Whiting, W. L., Huettel, S. A., White, L. E., MacFall, J. R., & Provenzale, J. M. (2004). Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *Neuroimage, 21*(3), 1174-1181. doi:10.1016/j.neuroimage.2003.11.004

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

Maguire, E. A., & Mummery, C. J. (1999). Differential modulation of a common memory retrieval network revealed by positron emission tomography. *Hippocampus, 9*(1), 54-61. doi:10.1002/(sici)1098-1063(1999)9:1<54::aid-hipo6>3.0.co;2-o

Maguire, E. A., Vargha-Khadem, F., & Mishkin, M. (2001). The effects of bilateral hippocampal damage on fMRI regional activations and interactions during memory retrieval. *Brain, 124*, 1156-1170. doi:10.1093/brain/124.6.1156

Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., . . . Cleeremans, A. (2000). Experience-dependent changes in cerebral activation during human REM sleep. *Nature Neuroscience, 3*(8), 831-836. doi:10.1038/77744

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: The default network and stimulus-independent thought. *Science, 315*(5810), 393-395. doi:10.1126/science.1131295

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. *Psychological Review, 102*(3), 419-457. doi:10.1037/0033-295x.102.3.419

McDevitt, E. A., Duggan, K. A., & Mednick, S. C. (2015). REM sleep rescues learning from interference. *Neurobiology of Learning and Memory, 122*, 51-62. doi:10.1016/j.nlm.2014.11.015

McDonald, C. R., Ahmadi, M. E., Hagler, D. J., Tecoma, E. S., Iragui, V. J., Gharapetian, L., . . . Halgren, E. (2008). Diffusion tensor imaging correlates of memory and language impairments in temporal lobe epilepsy. *Neurology, 71*(23), 1869-1876. doi:10.1212/01.wnl.0000327824.05348.3b

McHugh, T. J., Jones, M. W., Quinn, J. J., Balthasar, N., Coppari, R., Elmquist, J. K., . . . Tonegawa, S. (2007). Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. *Science, 317*(5834), 94-99. doi:10.1126/science.1140263

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, A. L. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping, 12*(3), 131-143. doi:10.1002/1097-0193(200103)12:3<131::aid-hbm1010>3.0.co;2-c

Milner, B. (1972). Disorders of learning and memory after temporal lobe lesions in man. *Clinical neurosurgery, 19*, 421-446.

Ming, G.-l., & Song, H. (2011). Adult Neurogenesis in the Mammalian Brain: Significant Answers and Significant Questions. *Neuron, 70*(4), 687-702. doi:10.1016/j.neuron.2011.05.001

Moeller, S., Yacoub, E., Olman, C. A., Auerbach, E., Strupp, J., Harel, N., & Ugurbil, K. (2010). Multiband Multislice GE-EPI at 7 Tesla, With 16-Fold Acceleration Using Partial Parallel Imaging With Application to High Spatial and Temporal Whole-Brain FMRI. *Magnetic Resonance in Medicine, 63*(5), 1144-1153. doi:10.1002/mrm.22361

Montaldi, D., Spencer, T. J., Roberts, N., & Mayes, A. R. (2006). The neural system that mediates familiarity memory. *Hippocampus, 16*(5), 504-520. doi:10.1002/hipo.20178

Motley, S. E., & Kirwan, C. B. (2012). A Parametric Investigation of Pattern Separation Processes in the Medial Temporal Lobe. *Journal of Neuroscience, 32*(38), 13076-U13378. doi:10.1523/jneurosci.5920-11.2012

Mummery, C. J., Patterson, K., Price, C. J., Ashburner, J., Frackowiak, R. S. J., & Hodges, J. R. (2000). A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. *Annals of Neurology, 47*(1), 36-45.

Murphy, D. G. M., Decarli, C., Schapiro, M. B., Rapoport, S. I., & Horwitz, B. (1992). AGE-RELATED DIFFERENCES IN VOLUMES OF SUBCORTICAL NUCLEI, BRAIN MATTER, AND CEREBROSPINAL-FLUID IN HEALTHY-MEN AS MEASURED WITH MAGNETIC-RESONANCE-IMAGING. *Archives of Neurology, 49*(8), 839-845.

Murphy, N. A., & Isaacowitz, D. M. (2008). Preferences for emotional information in older and younger adults: A meta-analysis of memory and attention tasks. *Psychology and Aging, 23*(2), 263-286. doi:10.1037/0882-7974.23.2.263

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

Nee, D. E., Wager, T. D., & Jonides, J. (2007). Interference resolution: Insights from a meta-analysis of neuroimaging tasks. *Cognitive Affective & Behavioral Neuroscience, 7*(1), 1-17. doi:10.3758/cabn.7.1.1

Nestor, P. J., Fryer, T. D., & Hodges, J. R. (2006). Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage, 30*(3), 1010-1020. doi:10.1016/j.neuroimage.2005.10.008

Norman, K. A., & O'Reilly, R. C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: A complementary-learning-systems approach. *Psychological Review, 110*(4), 611-646. doi:10.1037/0033-295x.110.4.611

Oishi, K., Faria, A., van Zijl, P. C. M., & Mori, S. (2011). *MRI Atlas of Human White Matter* (2nd ed.). 32 Jamestown Road, London NW1 7BY, UK: Elsevier.

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. *Journal of Neuroscience, 9*(8), 2907-2918.

Peigneux, P., Laureys, S., Fuchs, S., Destrebecqz, A., Collette, F., Delbeuck, X., . . . Maquet, P. (2003). Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. *Neuroimage, 20*(1), 125-134. doi:10.1016/s1053-8119(03)00278-7

Pengas, G., Pereira, J. M. S., Williams, G. B., & Nestor, P. J. (2009). Comparative Reliability of Total Intracranial Volume Estimation Methods and the Influence of Atrophy in a Longitudinal Semantic Dementia Cohort. *Journal of Neuroimaging, 19*(1), 37-46. doi:10.1111/j.1552-6569.2008.00246.x

Pereira, F. R. S., Alessio, A., Sercheli, M. S., Pedro, T., Bilevicius, E., Rondina, J. M., . . . Cendes, F. (2010). Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. *Bmc Neuroscience, 11*. doi:10.1186/1471-2202-11-66

Petersson, K. M., Elfgren, C., & Ingvar, M. (1997). A dynamic role of the medial temporal lobe during retrieval of declarative memory in man. *Neuroimage, 6*(1), 1-11. doi:10.1006/nimg.1997.0276

Powell, H. W. R., Richardson, M. P., Symms, M. R., Boulby, P. A., Thompson, P. J., Duncan, J. S., & Koepp, M. J. (2007). Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. *Epilepsia, 48*(8), 1512-1525. doi:10.1111/j.1528-1167.2007.01053.x

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage, 59*(3), 2142-2154. doi:10.1016/j.neuroimage.2011.10.018

Pruessner, J. C., Li, L. M., Serles, W., Pruessner, M., Collins, D. L., Kabani, N., . . . Evans, A. C. (2000). Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: Minimizing the discrepancies between laboratories. *Cerebral Cortex, 10*(4), 433-442. doi:10.1093/cercor/10.4.433

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. *Proceedings of the National Academy of Sciences of the United States of America, 98*(2), 676-682. doi:10.1073/pnas.98.2.676

Reuter, M., Schmansky, N. J., Rosas, H. D., & Fischl, B. (2012). Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage, 61*(4), 1402-1418. doi:10.1016/j.neuroimage.2012.02.084

Riedel, G., Micheau, J., Lam, A. G. M., Roloff, E. V., Martin, S. J., Bridge, H., . . . Morris, R. G. M. (1999). Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nature Neuroscience, 2*(10), 898-905.

Rolls, E. T., & Kesner, R. P. (2006). A computational theory of hippocampal function, and empirical tests of the theory. *Progress in Neurobiology, 79*(1), 1-48. doi:10.1016/j.pneurobio.2006.04.005

Rowley, J., Fonov, V., Wu, O., Eskildsen, S. F., Schoemaker, D., Wu, L. Y., . . . Alzheimer's Dis Neuroimaging, I. (2013). White Matter Abnormalities and Structural Hippocampal Disconnections in Amnestic Mild Cognitive Impairment and Alzheimer's Disease. *PloS one, 8*(9). doi:10.1371/journal.pone.0074776

Rudge, P., & Warrington, E. K. (1991). SELECTIVE IMPAIRMENT OF MEMORY AND VISUAL-PERCEPTION IN SPLENIAL TUMORS. *Brain, 114*, 349-360. doi:10.1093/brain/114.1.349

Rueckert, D., Sonoda, L. I., Hayes, C., Hill, D. L. G., Leach, M. O., & Hawkes, D. J. (1999). Nonrigid registration using free-form deformations: Application to breast MR images. *Ieee Transactions on Medical Imaging, 18*(8), 712-721. doi:10.1109/42.796284

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-U539. doi:10.1038/nature09817

Sanchez, C. E., Richards, J. E., & Almli, C. R. (2012). Age-Specific MRI Templates for Pediatric Neuroimaging. *Developmental Neuropsychology, 37*(5), 379-399. doi:10.1080/87565641.2012.688900

Saykin, A. J., Johnson, S. C., Flashman, L. A., McAllister, T. W., Sparling, M., Darcey, T. M., . . . Mamourian, A. (1999). Functional differentiation of medial temporal and frontal regions involved in processing novel and familiar words: an fMRI study. *Brain, 122*, 1963-1971. doi:10.1093/brain/122.10.1963

Schacter, D. L., Norman, K. A., & Koutstaal, W. (1998). The cognitive neuroscience of constructive memory. *Annual Review of Psychology, 49*, 289-318. doi:10.1146/annurev.psych.49.1.289

Schiltz, C., Bodart, J. M., Dubois, S., Dejardin, S., Michel, C., Roucoux, A., . . . Orban, G. A. (1999). Neuronal mechanisms of perceptual learning: Changes in human brain activity with training in orientation discrimination. *Neuroimage, 9*(1), 46-62. doi:10.1006/nimg.1998.0394

Seibt, J., Dumoulin, M. C., Aton, S. J., Coleman, T., Watson, A., Naidoo, N., & Frank, M. G. (2012). Protein Synthesis during Sleep Consolidates Cortical Plasticity In Vivo. *Current Biology, 22*(8), 676-682. doi:10.1016/j.cub.2012.02.016

Setsompop, K., Cohen-Adad, J., Gagoski, B. A., Raij, T., Yendiki, A., Keil, B., . . . Wald, L. L. (2012). Improving diffusion MRI using simultaneous multi-slice echo planar imaging. *Neuroimage, 63*(1), 569-580. doi:10.1016/j.neuroimage.2012.06.033

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*, 22-33.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143-155. doi:10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., . . . Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31*(4), 1487-1505. doi:10.1016/j.neuroimage.2006.02.024

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*, S208-S219. doi:10.1016/j.neuroimage.2004.07.051

Smith, S. M., Miller, K. L., Moeller, S., Xu, J. Q., Auerbach, E. J., Woolrich, M. W., . . . Ugurbil, K. (2012). Temporally-independent functional modes of spontaneous brain activity. *Proceedings of the National Academy of Sciences of the United States of America, 109*(8), 3131-3136. doi:10.1073/pnas.1121329109

Soininen, H. S., Partanen, K., Pitkanen, A., Vainio, P., Hanninen, T., Hallikainen, M., . . . Riekkinen, P. J. (1994). VOLUMETRIC MRI ANALYSIS OF THE AMYGDALA AND THE HIPPOCAMPUS IN SUBJECTS WITH AGE-ASSOCIATED MEMORY IMPAIRMENT - CORRELATION TO VISUAL AND VERBAL MEMORY. *Neurology, 44*(9), 1660-1668.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience, 27*, 279-306. doi:10.1146/annurev.neuro.27.070203.144130

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America, 105*(34), 12569-12574. doi:10.1073/pnas.0800005105

Stark, C. E. L., Bayley, P. J., & Squire, L. R. (2002). Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learning and Memory, 9*(5), 238-242. doi:10.1101/lm.51802

Stark, S. M., Yassa, M. A., & Stark, C. E. L. (2010). Individual differences in spatial pattern separation performance associated with healthy aging in humans. *Learning and Memory, 17*(6), 284-288. doi:10.1101/lm.1768110

Stern, C. E., Corkin, S., Gonzalez, R. G., Guimaraes, A. R., Baker, J. R., Jennings, P. J., . . . Rosen, B. R. (1996). The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America, 93*(16), 8660-8665. doi:10.1073/pnas.93.16.8660

Sullivan, E. V., Pfefferbaum, A., Swan, G. E., & Carmelli, D. (2001). Heritability of hippocampal size in elderly twin men: Equivalent influence from genes and environment. *Hippocampus, 11*(6), 754-762. doi:10.1002/hipo.1091

Toner, C. K., Pirogovsky, E., Kirwan, C. B., & Gilbert, P. E. (2009). Visual object pattern separation deficits in nondemented older adults. *Learning & Memory, 16*(5), 338-342. doi:10.1101/lm.1315109

Tononi, G., & Cirelli, C. (2006). Steep function and synaptic homeostasis. *Sleep Medicine Reviews, 10*(1), 49-62. doi:10.1016/j.smrv.2005.05.002

Treves, A., & Rolls, E. T. (1992). COMPUTATIONAL CONSTRAINTS SUGGEST THE NEED FOR 2 DISTINCT INPUT SYSTEMS TO THE HIPPOCAMPAL CA3-NETWORK. *Hippocampus, 2*(2), 189-200. doi:10.1002/hipo.450020209

Treves, A., & Rolls, E. T. (1994). COMPUTATIONAL ANALYSIS OF THE ROLE OF THE HIPPOCAMPUS IN MEMORY. *Hippocampus, 4*(3), 374-391. doi:10.1002/hipo.450040319

Tronel, S., Belnoue, L., Grosjean, N., Revest, J. M., Piazza, P. V., Koehl, M., & Abrous, D. N. (2012). Adult-born neurons are necessary for extended contextual discrimination. *Hippocampus, 22*(2), 292-298. doi:10.1002/hipo.20895

Tulving, E. (2002). Episodic memory: From mind to brain. *Annual Review of Psychology, 53*, 1-25. doi:10.1146/annurev.psych.53.100901.135114

Van Essen, D. C., & Ugurbil, K. (2012). The future of the human connectome. *Neuroimage, 62*(2), 1299-1310. doi:10.1016/j.neuroimage.2012.01.032

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia, 42*(10), 1394-1413. doi:10.1016/j.neuropsychologia.2004.04.006

Vazdarjanova, A., & Guzowski, J. F. (2004). Differences in hippocampal neuronal population responses to modifications of an environmental context: Evidence for distinct, yet complementary, functions of CA3 and CA1 ensembles. *Journal of Neuroscience, 24*(29), 6489-6496. doi:10.1523/jneurosci.0350-04.2004

Vernooij, M. W., Ikram, M. A., Vrooman, H. A., Wielopolski, P. A., Krestin, G. P., Hofman, A., . . . Breteler, M. M. B. (2009). White Matter Microstructural Integrity and Cognitive Function in a General Elderly Population. *Archives of General Psychiatry, 66*(5), 545-553.

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a Frontoparietal Control System Revealed by Intrinsic Functional Connectivity. *Journal of Neurophysiology, 100*(6), 3328-3342. doi:10.1152/jn.90355.2008

Viskontas, I. V., Knowlton, B. J., Steinmetz, P. N., & Fried, I. (2006). Differences in mnemonic processing by neurons in the human hippocampus and parahippocampal regions. *Journal of Cognitive Neuroscience, 18*(10), 1654-1662. doi:10.1162/jocn.2006.18.10.1654

von dem Hagen, E. A. H., Stoyanova, R. S., Baron-Cohen, S., & Calder, A. J. (2013). Reduced functional connectivity within and between 'social' resting state networks in autism spectrum conditions. *Social Cognitive and Affective Neuroscience, 8*(6), 694-701. doi:10.1093/scan/nss053

West, M. J., Slomianka, L., & Gundersen, H. J. G. (1991). UNBIASED STEREOLOGICAL ESTIMATION OF THE TOTAL NUMBER OF NEURONS IN THE SUBDIVISIONS OF THE RAT HIPPOCAMPUS USING THE OPTICAL FRACTIONATOR. *Anatomical Record, 231*(4), 482-497. doi:10.1002/ar.1092310411

Wilde, E. A., McCauley, S. R., Barnes, A., Wu, T. C., Chu, Z., Hunter, J. V., & Bigler, E. D. (2012). Serial measurement of memory and diffusion tensor imaging changes within the first week following uncomplicated mild traumatic brain injury. *Brain Imaging and Behavior, 6*(2), 319-328. doi:10.1007/s11682-012-9174-3

Wilson, M. A., & McNaughton, B. L. (1994). REACTIVATION OF HIPPOCAMPAL ENSEMBLE MEMORIES DURING SLEEP. *Science, 265*(5172), 676-679. doi:10.1126/science.8036517

Xiong, J. H., Gao, J. H., Lancaster, J. L., & Fox, P. T. (1995). Clustered pixels analysis for functional MRI activation studies of the human brain. *Human Brain Mapping, 3*(4), 287-301. doi:10.1002/hbm.460030404

Yang, G., Lai, C. S. W., 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. doi:10.1126/science.1249098

Yassa, M. A., & Stark, C. E. L. (2009). A quantitative evaluation of cross-participant registration techniques for MRI studies of the medial temporal lobe. *Neuroimage, 44*(2), 319-327. doi:10.1016/j.neuroimage.2008.09.016

Yassa, M. A., & Stark, C. E. L. (2011). Pattern separation in the hippocampus. *Trends in Neurosciences, 34*(10), 515-525. doi:10.1016/j.tins.2011.06.006

Yassa, M. A., Stark, S. M., Bakker, A., Albert, M. S., Gallagher, M., & Stark, C. E. L. (2010). High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic Mild Cognitive Impairment. *Neuroimage, 51*(3), 1242-1252. doi:10.1016/j.neuroimage.2010.03.040

Zeineh, M. M., Engel, S. A., Thompson, P. M., & Bookheimer, S. Y. (2003). Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science, 299*(5606), 577-580. doi:10.1126/science.1077775

Zijdenbos, A. P., Dawant, B. M., Margolin, R. A., & Palmer, A. C. (1994). MORPHOMETRIC ANALYSIS OF WHITE-MATTER LESIONS IN MR-IMAGES - METHOD AND VALIDATION. *Ieee Transactions on Medical Imaging, 13*(4), 716-724. doi:10.1109/42.363096

Zola-Morgan, S., Squire, L. R., & Mishkin, M. (1982). THE NEUROANATOMY OF AMNESIA - AMYGDALA-HIPPOCAMPUS VERSUS TEMPORAL STEM. *Science, 218*(4579), 1337-1339. doi:10.1126/science.6890713

APPENDIX

Table A.1: Comparison of fMRI Beta Coefficients in the Immediate and Delay Phases.

	Mean Sleep Immediate (SEM)	Mean Wake Immediate (SEM)	t(45)	p	Mean Sleep Delay (SEM)	Mean Wake Delay (SEM)	t(45)	p
R inferior temporal gyrus								
Hit	.091 (.06)	-.037 (.06)	1.888	.14	.013 (.08)	.078 (.06)	-.662	.51
CR	.299 (.08)	.103 (.07)	1.499	.07	-.063 (.06)	.102 (.09)	-1.526	.13
LureFA	.161 (.10)	.032 (.08)	1.050	.30	-.157 (.07)	.169 (.07)	-2.822	.007
LureCR	.267 (.09)	.059 (.06)	1.857	.07	-.146 (.09)	.158 (.09)	-2.424	.02
L post central sulcus								
Hit	-.157 (.06)	-.083 (.10)	-.674	.50	-.239 (.06)	.009 (.09)	-2.236	.03
CR	-.187 (.07)	-.329 (.10)	1.167	.25	-.432 (.10)	-.133 (.13)	-1.832	.07
LureFA	-.342 (.10)	-.578 (.13)	1.465	.15	-.589 (.08)	-.252 (.13)	-2.265	.03
LureCR	-.423 (.09)	-.698 (.11)	1.889	.07	-.746 (.09)	-.285 (.15)	-2.690	.01
R lingual gyrus								
Hit	-.093 (.08)	-.102 (.06)	.086	.93	-.130 (.08)	.086 (.07)	-2.041	.05
CR	-.197 (.08)	-.297 (.07)	.882	.38	-.337 (.09)	-.051 (.09)	-2.229	.03
LureFA	-.320 (.10)	-.462 (.10)	1.023	.31	-.574 (.10)	-.287 (.09)	-2.129	.04
LureCR	-.308 (.08)	-.405 (.09)	.777	.44	-.639 (.08)	-.300 (.13)	-2.243	.03
R insula								
Hit	-.111 (.09)	-.079 (.13)	-.203	.84	-.255 (.08)	.070 (.10)	-2.589	.01
CR	-.137 (.13)	-.226 (.13)	.488	.63	-.501 (.10)	.199 (.13)	-4.220	.001
LureFA	-.327 (.11)	-.523 (.14)	1.138	.26	-.634 (.15)	.079 (.12)	-3.725	.001

LureCR	-.535 (.11)	-.554 (.11)	.122	.90	-.784 (.12)	-.081 (.16)	-3.594	.001
R fusiform gyrus								
Hit	-.021 (.05)	-.036 (.05)	.220	.83	-.050 (.04)	.136 (.04)	-3.112	.003
CR	-.002 (.05)	-.026 (.07)	.352	.73	-.145 (.06)	.132 (.05)	-3.531	.001
LureFA	-.065 (.05)	-.183 (.07)	1.329	.19	-.196 (.07)	.086 (.05)	-3.184	.003
LureCR	-.111 (.07)	-.171 (.07)	.596	.55	-.209 (.05)	.087 (.08)	-3.217	.002
L lingual gyrus								
Hit	-.137 (.06)	-.232 (.08)	.923	.36	-.204 (.08)	-.068 (.08)	-1.208	.23
CR	-.148 (.06)	-.306 (.06)	1.912	.06	-.358 (.08)	-.030 (.07)	-2.987	.005
LureFA	-.180 (.06)	-.400 (.07)	2.418	.02	-.463 (.10)	-.251 (.07)	-1.690	.10
LureCR	-.384 (.08)	-.520 (.09)	1.162	.25	-.585 (.11)	-.365 (.10)	-1.490	.14
L inferior parietal lobule								
Hit	-.024 (.08)	-.095 (.09)	.596	.55	-.157 (.09)	.073 (.09)	-1.838	.07
CR	-.055 (.12)	-.232 (.15)	.948	.35	-.153 (.12)	.148 (.17)	-1.452	.15
LureFA	-.043 (.13)	-.274 (.18)	1.076	.29	-.321 (.10)	.087 (.16)	-2.236	.03
LureCR	.051 (.13)	-.133 (.16)	.899	.37	-.185 (.13)	.460 (.18)	-2.939	.005
R inferior parietal lobule								
Hit	-.334 (.10)	-.309 (.08)	-.194	.85	-.448 (.11)	-.317 (.09)	-.924	.36
CR	-.121 (.10)	-.114 (.13)	-.043	.97	-.759 (.11)	-.222 (.12)	-3.387	.001
LureFA	-.458 (.11)	-.510 (.17)	.269	.79	-.960 (.15)	-.408 (.14)	-2.641	.01
LureCR	-.670 (.13)	-.585 (.14)	-.447	.66	-1.05 (.12)	-.563 (.11)	-2.961	.005

Table A.2: Regions Corresponding to the Group × Phase Interaction. F-values shown for post-hoc analysis of Hits and CRs.

Region	Hit F (1,44)	p	CR F (1,44)	p
R inferior temporal gyrus	6.65	< .05	2.98	.092
L post central gyrus	7.28	< .01	2.39	.130
R lingual gyrus	7.50	< .01	3.83	.057
R insula	12.2	< .01	2.58	.115
R fusiform gyrus	8.23	< .01	5.28	< .05
L lingual gyrus	16.1	< .001	4.32	< .05
L inferior parietal lobule	5.77	< .05	3.29	.077
R inferior parietal lobule	5.40	< .05	.470	.497

Table A.3: Post-hoc Analysis of Group × Phase Interaction of Responses. Analyzing these results with the behavioral response graphs indicates that participants who sleep during the delay are less likely to call a foil "similar", less likely to call a lure "old" and more likely to call a lure "similar" compared to the wake group.

Response	F (1,45)	p
Foils		
Old	.073	.788
Similar	5.45	.024*
New	3.30	.076
Repeats		
Old	1.82	.184
Similar	.843	.363
New	1.46	.233
Lures		
Old	4.10	.049*
Similar	11.4	.002*
New	1.08	.304

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D. Nicholas Top Jr., Kevin G. Stephenson, Christopher R. Doxey, Michael J. Crowley, C. Brock Kirwan, Mikle South (in press). Atypical amygdala response to fear conditioning in autism spectrum disorder, Biological Psychiatry: Cognitive Neuroscience and Neuroimaging

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