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Effects of Aging on Sleep-Dependent Consolidation of Declarative Memory

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A Dissertation Presented

by

BENGI BARAN

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EFFECTS OF AGING ON SLEEP-DEPENDENT CONSOLIDATION OF DECLARATIVE MEMORY

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ABSTRACT

EFFECTS OF AGING ON SLEEP-DEPENDENT CONSOLIDATION OF DECLARATIVE MEMORY

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Sleep plays a critical role in memory consolidation. However, aging is associated with changes in sleep architecture and memory impairments. The goal of the present study was to identify age-related changes in the memory function of sleep by investigating sleep-dependent changes in neural activation patterns during memory retrieval in young and older adults. Healthy young (21-29 years) and older (62-74 years) adults were trained on a declarative word-pair learning task. Recall was tested 5 hr later while undergoing functional magnetic resonance imaging (fMRI). Participants completed this testing procedure twice, separated by 1 week; once following a mid-day nap and once following continuous wakefulness in a counter-balanced order. Sleep was recorded by polysomnography for the naps and subsequent nocturnal intervals. It was found that napping, as compared to wakefulness, was associated with decreased hippocampal activation and decreased hippocampo-frontal co-activation in young adults. Specifically, slow wave sleep (SWS) in the young adult naps was associated with better memory retention ($r = .61$, $p = .035$) and decreased hippocampal activation ($r = -.71$, $p = .01$) lending support to the two-stage model of memory consolidation (McClelland, McNaughton & O'Reilly, 1995). On the other hand, sleep-dependent neural reorganization

patterns were different in the older adult group. Following a nap, retrieval still required hippocampal activation and hippocampo-frontal co-activation (adjusted R^2 = .701, F(1,10) = 22.08, p = .002). Furthermore, in contrast to a SWS-dependent decrease in anterior cingulate cortex (ACC) activation in young adults for successful retrieval (r = -.61, p = .037), ACC activation in older adults was increased when retrieval was tested following a nap compared to wakefulness, and was not significantly associated with measures of SWS. This suggests that successful retrieval following a nap required allocation of error monitoring processes in older adults. In summary, the present study shows that the efficiency with which systems level consolidation takes place in the first sleep opportunity following learning of a declarative memory task changes in healthy aging. Slow wave sleep-dependent reactivation processes may be disrupted, leaving memory traces at a more labile state of storage that requires additional allocation of cognitive control processes.

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GENERAL INTRODUCTION

Sleep that knits up the raveled sleave of care
The death of each day's life, sore labour's bath
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast. ~William Shakespeare, Macbeth

Sleep is an essential behavior. Humans spend about one third of their life sleeping. Although sleep habits and patterns change through human development, the need for sleep always remains critical. Sleep deprivation interferes with endocrine function (Beck, 1981; Späth-Schwalbe, Gofferje, Kern, Born & Fehm, 1991), impairs attention and vigilance, slows cognitive processing speed, and impairs memory (Rogers, Dorrian & Dinges 2003).

Although the question "Why do we sleep" still does not have a conclusive answer, several theories, not mutually exclusive, have been put forward to explain the function of sleep. For instance, it has been suggested that sleep evolved for energy conservation (Berger & Phillips, 1995), that sleep serves a tissue restorative function (Adam & Oswald, 1977), and that sleep enhances immune function (Brown, Pang, Husband & King, 1989). The present study focuses on the cognitive function of sleep. Since the first report by Jenkins and Dallenbach (1924) of better item recall following a night of sleep relative to an equivalent time awake, researchers have identified active processes that take place during sleep that lead to more efficient cognitive functioning. Accordingly, the cognitive function of sleep is to consolidate newly coded labile memory traces into more stable neural representations (Stickgold, Hobson, Fosse & Fosse, 2001). In fact, performance improvements on several memory tasks are greater if learning is followed by a period of sleep (Stickgold, 2005). Studies published in the last 10 years have provided evidence for

sleep-dependent memory consolidation at the behavioral, molecular and physiological level (Walker, 2005).

Memory impairments are the most common health complaints among older adults. Sleep disturbances are known to impair cognitive functioning in healthy individuals (Durmer & Dinges, 2005). Therefore, age-related changes in sleep may be a potential contributor to memory problems in aging. Population-based studies report the prevalence of memory complaints to be 25-50% among older adults (Blazer, Hays, Fillenbaum & Gold, 1997; Jonker, Geerlings & Schmand, 2000; Ponds, Commissaris & Jolles, 1997). Neuropsychological studies of aging confirm that older adults perform more poorly on tests of memory (Nyberg, Bäckman, Erngrund, Olofsson & Nilsson, 1996; Park et al., 1996).

Elderly constitute a growing proportion of the United States population. Based on 2009 census information, 12% of the US population is 65 years or older. By 2030, this number is projected to reach 19% (Administration on Aging, Department of Health and Human Services). The growth in the elderly population highlights the significance of research on physical and mental health in old age. One of the central aims of aging research is to identify factors that may account for age-related cognitive decline and customize intervention methods that target these factors. The present study considers whether sleep may be the target of such an intervention.

Sleep duration and quality decrease in old age (Buysse et al., 1992). Although subjective estimates of the amount of sleep needed may be similar between young and older adults, as revealed by similar self-reported total sleep time in large-scale surveys (Foley, Ancoli-Israel, Britz & Walsh, 2004), aging may reduce the ability to obtain the

needed sleep. Alternatively, however, some have suggested that older adults may have a reduced sleep need (Klerman & Dijk, 2008). Changes in duration and quality of sleep may interfere with the cognitive function of sleep, and thus, alter sleep-dependent memory consolidation in older adults (Pace-Schott & Spencer, 2011). Furthermore, it has been suggested that understanding this process in healthy older adults is the essential step to investigating the relationship between sleep and memory in neurodegenerative diseases such as Alzheimer's disease (Harand et al., 2012).

Identifying age-related changes that influence the memory function of sleep has important clinical and social implications. However, only a handful of studies have focused on this aim. The present study is an investigation of the memory function of sleep in aging. With a cross-sectional comparison between young and older adult groups, age-related changes in the memory function of sleep were investigated focusing on sleep physiology and neural activation patterns.

A. Sleep-Dependent Memory Consolidation

Adult nocturnal sleep consists of approximately 90 min cycles that transition between two phases: Rapid eye movement (REM) and non-rapid eye movement (nREM) sleep. Non-rapid eye movement sleep is divided into three distinct stages: nREM1, nREM2, and slow wave sleep (SWS, also known as nREM3). The different stages of sleep that cycle throughout the night are each defined by distinct electrophysiological activity patterns. In addition to brain activity, eye movements and muscle tone change with each transition between REM and nREM sleep. Rapid eye movement sleep is widely known as 'dream sleep' as individuals are likely to report that they were dreaming if woken from this sleep stage. Although dreaming may occur during nREM as well, dreaming in the

conventional sense (i.e. dreams with a narrative structure, emotional and bizarre content, and sensory-motor hallucinations) occurs exclusively during REM sleep (Hobson, Stickgold & Pace-Schott, 1998).

The standard method used for monitoring and staging sleep is polysomnography (PSG), a montage of electroencephalography (EEG), electromyography (EMG) and electrooculography (EOG) used to record brain activity, muscle tone, and eye movements respectively. Polysomnographically recorded sleep is typically plotted in a hypnogram that shows how sleep progresses across different stages as a function of time. Figure 1 shows what a hypnogram of a healthy adult may look like. With the onset of sleep, brain activity begins to slow and theta activity emerges in the EEG (Silber et al., 2007). Slow rolling eye movements may accompany this stage. The transition from nREM1 to nREM2 sleep is marked by the appearance of two distinct EEG events in the PSG record: K-complexes and sleep spindles which emerge in a phasic fashion. Slow wave sleep is the deepest stage and is marked by highly synchronous delta activity (0.5-4 Hz) in the EEG. Rapid eye movement sleep is identified by the emergence of rapid eye movements, a significant decrease in muscle tone, and desynchronized, high frequency activity in the gamma range in the EEG. The high frequency EEG activity and rapid eye movements appear almost as awake activity physiologically. Changes in electrophysiology throughout the sleep period are accompanied by changes in neurotransmitter concentrations. Acetylcholine levels are highest during REM sleep. On the other hand, monoamine concentrations increase during SWS (Pace-Schott & Hobson, 2002). While adults usually go through four or five sleep cycles within the course of one night, the duration of each stage within a cycle changes

throughout the night (Carskadon & Dement, 2011). Early night sleep cycles are dominated by SWS whereas late night sleep cycles are rich in REM.

Cerebral blood flow is a measure of neural activity and can be detected by positron emission tomography (PET). Using this imaging method researchers have revealed that patterns of neural activation change significantly across sleep stages. Whereas activity in the thalamic and limbic regions is decreased during SWS sleep, activity in these regions and the occipital cortex is increased during REM sleep (Braun et al., 1998). Regional cerebral blood flow during REM sleep is positively correlated with activity in the amygdala suggesting that cortico-amygdaloid projections are activated during REM sleep (Maquet et al., 1996). As such, physiological and chemical changes that occur during different stages of sleep modulate the direction of communication between cortical and subcortical regions and allow for information processing to take place during sleep.

Memory consolidation is hypothesized to reflect the transfer of fresh and labile memory traces into more permanent and stable representations that require changes both at the synaptic level (i.e. formation of new synapses) and at the systems level (i.e. cortical or hippocampo-cortical reorganization). Accumulating evidence suggests that this process is sleep-dependent (Stickgold, 2005; Walker, 2005). Sleep-dependent memory consolidation may be quantified by comparing changes in performance across sleep and wake intervals. For example, when participants learn a task in the evening and recall is probed 12 hr later following a night of sleep, participants perform better on a variety of tasks relative to a 12 hr intersession interval spent awake (e.g. Stickgold, 2005).

Despite the physiologically complex nature of sleep, one may argue that better memory following sleep as compared to daytime wake is a passive effect, attributable to a

lack of interference from waking activities. However, evidence counters this argument. The amount of time spent in a certain sleep stage correlates significantly with the degree of performance enhancement on a given task. For instance, individuals who spend more time in nREM2 sleep perform better on a motor sequence learning task the next day (Walker, Stickgold, Alsop, Gaab & Schlaug, 2005). On the other hand, SWS enhances performance on a word-pair learning task (e.g. Baran, Wilson & Spencer, 2010; Gais & Born, 2004; Plihal & Born, 1997). One would not expect to see such associations between physiological measures of sleep and memory performance if sleep's benefit on memory merely reflected a passive protection from interference.

Another line of evidence suggesting that sleep has an active role in memory consolidation comes from studies that use control groups that are tested 24 hr after learning. If a daytime wake interval is associated with decreased memory performance due to interference from daily activities and sleep passively protects from this interference, performance after a 24 hr interval should be worse as these individuals will be faced with a longer retention interval, and hence more interference. However, on a declarative memory task, participants who are tested after a 24 hr intersession interval perform similar to a group with a 12 hr interval with sleep and significantly better than a group with a 12 hr interval of continuous daytime wake (Ellenbogen, Hulbert, Stickgold, Dinges & Thompson-Schill, 2006). This finding suggests that sleep has an active effect on memory consolidation that persists to the next day, and cannot be explained by lack of interference.

The effects of sleep on memory consolidation are not limited to nocturnal sleep. Even brief daytime naps are shown to enhance memory performance in young adults. This effect was first demonstrated with a simple perceptual task. Performance on a visual

discrimination test deteriorated significantly over an afternoon interval spent awake. On the contrary, for those participants who napped for 60 or 90 min, speed of performance was either protected or improved. More importantly, nap dependent improvements were similar to overnight improvements (Mednick, Nakayama & Stickgold, 2003). This nap benefit is has been shown for declarative (Tucker et al., 2006; van der Helm, Gujar, Nishida & Walker, 2011) and procedural (Backhaus & Junghanns, 2006) memory tasks as well.

Sleep-related changes in behavior (i.e. better task performance) are accompanied by quantifiable changes in the brain in young adults. Systems level reorganization following sleep can be examined using functional magnetic resonance imaging (fMRI). With fMRI researchers are able to detect the magnitude, location and timing of changes in blood flow. Such hemodynamic responses are quantified by blood-oxygen-level-dependent (BOLD) contrasts that reveal functional (i.e. task-dependent) brain activity. Sleep-dependent functional reorganization has largely been studied for procedural memory. For a motor sequence learning task, sleep following task acquisition (as compared to daytime wake) was found to be associated with decreased activation in the premotor, primary motor, prefrontal, and insular cortices; and increased activation in the striatum, hippocampus, and the cerebellum (Debas et al, 2010; Fischer, Nitschke, Melchert, Erdmann & Born, 2005; Walker et al., 2005). In other words, sleep following procedural learning increases task-related activation in brain regions associated with faster and more accurate motor output, and better stimulus-to-response mapping but decreases task related activation in brain regions associated with effortful monitoring (Walker et al., 2005).

While less work has been done on sleep-related neural changes for the declarative domain, it is well established that a period of sleep alters retrieval related neural activation. Takashima and colleagues (2006) tested the long-term effects of a mid-day nap on neural activation for a picture recognition task at four different time points: following a delay of 1, 2, 30, and 90 days. For the first delay interval, the amount of time spent in SWS correlated positively with recognition performance and negatively with hippocampal activity during correct recognition. This implies that, starting at day 1, SWS was associated with transfer of memories from the labile storage in the hippocampus to a more permanent representation in the cortex. In fact, over the course of time, recognition was associated with a decrease in hippocampal activation coupled with a corresponding increase in ventromedial prefrontal cortex activation. This finding suggests that through the process of sleep-dependent memory consolidation, neural representations of memories become independent of the hippocampus and are transferred to cortical areas.

The mechanism proposed to underlie the transfer of memory traces from the hippocampus to the cortex is *neural reactivation*. Using single-cell recording methods, researchers were able to demonstrate that hippocampal firing patterns recorded during waking exploration are replayed during off-line periods (i.e. between practice sessions when the animal is not actively engaged in learning). Place cells in the hippocampus fire only when the animal is in a specific location in the environment. As such, a maze running trial would result in a unique firing sequence of the place cells. In their seminal work, Wilson and McNaughton (1994) showed that this firing pattern is replayed during SWS in the rat hippocampus. That is, although the animal was resting, the hippocampus was "practicing" that day's learning experience. Importantly, the temporal sequence for the

neuronal activation is maintained during sleep-dependent replay of spatial exploration behavior in the rat (Skaggs & McNaughton, 1996). Neural replay occurring during sleep that retains the spatial and temporal properties of the waking experience is regarded as the neural basis of a memory trace (O'Neill, Pleydell-Bouverie, Dupret & Csicsvari, 2010).

Albeit with less temporal and spatial precision, SWS-related replay has been demonstrated in humans. In a study of spatial route learning, participants learned to navigate through a three-dimensional virtual city (Peigneux et al., 2004). Regional cerebral blood flow was measured with PET in three conditions: during nocturnal sleep before training, during training, and during nocturnal sleep following training. The researchers found that hippocampal activation patterns while learning the spatial navigation task were very similar to hippocampal activation during SWS the following night. Furthermore, better task performance correlated positively with the amount of hippocampal activation during SWS. This SWS-dependent replay has also been triggered experimentally. Rasch and colleagues (2007) presented participants with an odor cue during acquisition of a declarative spatial memory task in which participants were asked to learn the locations of 15 card pairs of everyday objects on a 6 x 5 array. The same odor cue or an odorless vehicle was presented again during early-night SWS, late-night REM sleep, or during a wake period. Spatial memory was significantly enhanced only when the odor cue was presented during SWS. In a subsequent experiment, the researchers used fMRI to specifically examine how changes in brain activity during SWS relate to enhanced memory performance. Following learning, participants underwent functional imaging and were either given an opportunity to sleep or they remained awake. During the functional imaging session, the same odor cues were presented intermittently. Odor-on

periods activated the left hippocampus. This activation was significantly stronger if the participants were in SWS. Odor-related hippocampal activation was weaker and more transient during wake periods. The results of the behavioral study coupled with the imaging evidence suggest that the odor acted as a contextual cue to reactivate the hippocampus and enhance memory consolidation during SWS. A similar enhancement effect has also been demonstrated using sound cues (Rudoy, Voss, Westerberg & Paller, 2009).

Based on the evidence reviewed in this section, it can be concluded that sleep enhances memory consolidation, and retention after an interval of sleep is associated with a different pattern of neural activation as compared to retention after an equal period of daytime wake. This implies that, through processes of reactivation and reorganization, sleep alters neural representations of memory traces.

B. Age-Related Changes in Sleep

1. Age-Related Changes in Nocturnal Sleep

Aging is associated with decreased subjective sleep quality even in the context of excellent physiological and psychological health (Buysse et al., 1992). Although young and older adults may have similar self-reports of ideal sleep duration, older adults may have difficulty obtaining this ideal amount of sleep (Neikrug & Ancoli-Israel, 2010). In fact, PSG-monitored sleep data suggests an age-related decline in sleep duration in older adults (van Cauter, Lepoult & Plat, 2000), and a meta-analysis reveals a significant negative correlation between age and total sleep time in a combined sample of 3577 participants between 5-102 years of age (Ohayon, Carskadon, Guilleminault & Vitiello, 2004). In addition to changes in total sleep time, quality of sleep also decreases with age.

Older adults are more likely to experience frequent awakenings in the middle of the night. Such awakenings may, in turn, decrease sleep efficiency (i.e. the proportion of total sleep time to total time in bed; Ohayon et al., 2004).

Furthermore, aging is associated with changes in sleep architecture. PSG studies on older adults reveal reduced SWS duration, lower percentage of SWS, and decreased delta activity (Lombardo et al., 1998; van Cauter et al., 2000). Older adults also spend significantly less time in REM sleep and more time in the lighter stages of sleep, nREM1 and nREM2 (Ohayon et al., 2004). Importantly, although the duration of nREM2 sleep increases, quality of this sleep stage decreases: Sleep spindles, which are characteristic of nREM2 sleep, decrease in number, density, amplitude and duration in older adults (Nicolas, Petit, Rompré & Montplaisir, 2001; Wei, Riel, Czeisler & Dijk, 1999).

Older adults often experience a shift in the sleep-wake rhythm: Sleep onset is earlier in the evening and wake times are very early in the morning (Weitzman et al., 1981). Age-related shifts in sleep-wake rhythms are caused by physiological changes such as disruption of core body temperature rhythms and decreased melatonin secretion (Moe, Prinz, Vitiello, Marks & Larsen, 1991; Neikrug & Ancoli-Israel, 2010; Shochat, Martin, Marler & Ancoli-Israel, 2000). As a consequence of this shift in the sleep-wake rhythm, older adults are more likely to experience daytime sleepiness. Daytime sleepiness may be further exacerbated by external influences such as reduced exposure to daylight (Ancoli-Israel et al., 1997).

As summarized above, age-related changes in subjective and objective measures of nocturnal sleep have been documented. Older adults sleep less, spectral power and

duration of SWS and REM decreases, and sleep efficiency continues to decline in aging (Ohayon et al, 2004).

2. Age-Related Changes in Daytime Naps

Prevalence of daytime naps increases with age. Only 10% of individuals 55-64 years of age report napping 4-7 times/week. In contrast, this rate increases up to 24% in individuals 65-84 years of age (National Sleep Foundation, 2003). Whereas this increase may simply be due to retiring from a daily work schedule that would have interfered with napping, others have suggested that the reason is to compensate for reduced quantity and quality of nocturnal sleep (Dautovich et al., 2012). The causal relationship between daytime napping and overnight sleep quality is not quite clear. The common clinical advice to individuals with nocturnal sleep problems is to refrain from naps, which implies that naps may interfere with nocturnal sleep. However, daytime naps had no negative effect on the duration or efficiency of nocturnal sleep in a group of healthy older adults who completed a month long napping regimen (Campbell, Murphy & Stauble, 2005). In fact, napping increased 24 hr total sleep time. Increases in total sleep time were positively related with increases in cognitive performance as evidenced by detailed neuropsychological evaluation before and after the nap intervention. Furthermore, Tamaki and colleagues (2000) reported that brief (<30 min) afternoon naps are associated with better mood and less fatigue compared to a 30 min wake period in older adults. Despite the documented positive effects of napping, the majority of research on older adult naps targets older adults with insomnia or older adults at risk for dementia and explores the relationship between napping and adverse medical outcomes in these special populations

(Asada, Motonaga, Yamagata, Uno & Takahashi, 2000; Campos & Siles, 2000; Foley et al., 2007; Ohayon & Vecchierini, 2002).

In conclusion, aging is associated with a change in napping habits. Frequency of napping increases in individuals 65 years and older. Although naps in older adults may be related with positive outcomes such as increased 24 hr total sleep time and increased evening alertness (Campbell, Murphy & Stauble, 2005; Monk, Buysse, Carrier, Billy & Rose, 2001), no study to date has investigated the architecture of naps in older adults and whether efficiency and sleep stage distributions of naps differ between young and older adult groups. Furthermore, it is well established that naps serve a cognitive function for young adults. Memory performance following a nap period is significantly better than a period of wake (Backhaus & Junghanns, 2006; Mednick et al., 2003; Tucker et al., 2006; van der Helm et al., 2011). Whether naps serve a similar cognitive function in older adults is still unknown.

C. Age-Related Changes in Memory

Older adults often complain about forgetfulness (Blazer et al., 1997; Jonker et al., 2000; Ponds et al., 1997). These subjective complaints are confirmed by objective findings of impaired memory function (Buckner, 2004). Evidence from both longitudinal and cross-sectional studies suggests that functioning in cognitive domains such as processing speed, spatial orientation, inductive reasoning, and numerical and verbal memory start to decline after the age of 55 (Hedden & Gabrieli, 2004; Salthouse & Ferrer-Caja, 2003; Zelinski & Burnight, 1997). However, not all cognitive abilities decline with age. Retention of semantic knowledge as measured by performance on vocabulary tests remains stable in older adults (Nyberg et al., 1996; Piolino, Desgranges, Benali &

Eustache, 2002). Similarly, emotional processing and memory for positive emotional stimuli does not change with aging, with older adults even reported to be superior to young adults in some cases (Carstensen, Fung & Charles, 2003; Mather & Carstensen, 2005).

Age-related changes in cognitive functioning are paralleled, if not predicted, by age-related changes in the brain. The medial temporal lobes, which are critical for memory encoding and retrieval (Squire, 1992), shrink in volume with age. To determine the time course of structural changes in the brain, Raz and colleagues (2004) used structural MRI to measure brain volume in 140 adults (ages 26-82) at two time points separated by 5 years. Along with the hippocampus, structures with the highest mean shrinkage rates from the first to second measurement were the cerebellum, caudate, prefrontal white matter and the inferior temporal cortex. Age-related atrophy estimates for the medial temporal lobes have been found to be similar in both cross-sectional and longitudinal analyses (Scahill, 2003). Furthermore, age-related atrophy in the medial temporal lobes predicts decline in memory performance (Golomb et al., 1996; Rodrigue & Raz, 2004).

Aging also interferes with neural activation patterns. Functional MRI is a valuable method for investigating the effects of aging on task-related activation. Importantly, the hemodynamic response is comparable between young and older adults when cardiovascular risk factors are controlled for (Aizenstein et al., 2004; Huettel, Singerman & McCarthy, 2001). Thus, fMRI can validly be used to investigate whether functional activation changes in aging. Depending on task constraints and brain area under investigation, age-related changes can manifest themselves as increased or decreased activation. Decreased activation can readily be attributed to age-related function loss

especially when activation changes correlate with structural atrophy and decreased task performance. However, there is a challenge in the interpretation of increased activation. If task-dependent activation in a certain brain region is observed only in older adults, this may be a sign of compensation. That is, if age-related increase in activation is compensatory, then it should correlate positively with task performance only in older adults. For instance, compared to a young adult group showing lateralized and clustered activation, older adults showed increased activation in frontal cortex bilaterally while performing tests of verbal and spatial working memory (Reuter-Lorenz et al., 2000). Importantly, this increased activation arose primarily from frontal cortex subregions associated with rehearsal. In other words, older adults were additionally recruiting rehearsal mechanisms to perform better on the working memory tests. In another study, it was found that hippocampal activation while encoding picture stimuli was significantly decreased in older adults compared to young adults (Gutchess et al., 2005). However, the researchers also showed that decreased hippocampal activation correlated with increased middle frontal activation such that those older adults who have the least hippocampal activation recruited the middle frontal regions the most, possibly as a compensatory mechanism.

Even when young and older adults perform similarly on a cognitive task, age-related changes may emerge in neural activation patterns. In a recent review of imaging studies comparing young and older adults, Spreng and colleagues (2010) showed that, across several cognitive domains, when young and older adults perform similarly on the behavioral task, older adults show higher activation in the dorsolateral prefrontal cortex presumably to engage cognitive control mechanisms. On the other hand, young adults

show higher activation in the ventrolateral prefrontal cortex, a region involved in processing of salience and maintenance of information. When task-related activation is compared between age groups for tasks in which young adults outperform older adults, better performance in the young adult groups is characterized with increased left medial temporal and bilateral occipital activation whereas poorer performance in the older adults is characterized by right dorsolateral prefrontal activation. These findings of over and under-recruitment of brain regions while engaging in cognitive processing are taken as evidence for age-related functional reorganization. Importantly, not only the location but also the pattern of activation may change with age. To investigate the nature of age-related differences in activation patterns in the memory network, Morcom and Friston (2012) used a multivariate Bayesian analysis. The behavioral task was a subsequent incidental declarative memory design. Participants were presented with words and were asked to make living/non-living decisions. Outside the scanner, participants completed a surprise recognition test. The findings indicated that even when the level of recollection was matched between young and older adults, prefrontal activation patterns changed with age. Older adults showed more fragmented and bilateral activation, especially in the dorsolateral prefrontal cortex and anterior portions of the inferior frontal gyrus (IFG). In contrast to young adults who showed activation in larger clusters of voxels, activity predictive of better memory in older adults was found in individual and spatially distributed voxels. Importantly, this greater spatial distribution correlated with poorer memory performance. The finding of reduced spatial coherence in activation in older adults led the researchers to conclude that increased prefrontal activation is not necessarily adaptive or compensatory in older adults (Morcom & Friston, 2012).

Age-related changes in cognitive functioning are most prominent for the episodic/declarative memory domain (Grady, 2012), and specifically for tasks that require associative learning. For instance, in a recent fMRI study, young and older adults studied faces paired with names and job titles, and memory was probed with a two-choice recognition task (Tsukiura et al., 2011). Magnitude of hippocampal activation was significantly reduced in older adults. In fact, according to the Associative Deficit Hypothesis, age-related impairments in declarative memory predominantly stem from an inability to merge different units of an episode (Naveh-Benjamin, 2000).

Episodic learning and retrieval requires involvement of the frontal lobes (e.g. Buckner, Logan, Donaldson & Wheeler, 2000; Nolde, Johnson & Raye, 1998). Whereas retrieval tasks are more likely to involve the right frontal lobes, encoding tasks are associated with left frontal activation (Hemispheric Encoding/Retrieval Asymmetry model, HERA; Tulving, Kapur, Craik, Moscovitch & Houle, 1994). However, it is not uncommon to observe left frontal activation during recall or recognition, and is, therefore, interpreted as a sign of further encoding of poorly learned items at time of retrieval (Andreasen et al., 1995; Buckner, Koutstaal, Schacter, Wagner & Rosen, 1998). Aging may be associated with changes in the lateralization of frontal involvement in episodic learning. According to the Hemispheric Asymmetry Reduction in Older Adults model (HAROLD; Cabeza, 2002) prefrontal activation during cognitive processing is less lateralized in older adults. Whereas retrieval success may be associated with right frontal activation in young adults as reviewed above, frontal activation is bilateral in older adults (Dolcos, Rice & Cabeza, 2002).

As summarized in this section, age-related impairments in declarative memory are associated with functional and structural changes in the prefrontal cortex, frontal white matter and the hippocampus (Kalpouzos et al., 2009; Salat et al., 2005). Importantly, even when memory performance is matched between young and older adults, encoding and retrieval processes are disparate at the neural level. Depending on task requirements, older adults may show compensatory activation in cortical regions associated with cognitive control, error monitoring, verbal rehearsal or visual processing. Besides this beneficial over-activation in older adults, retrieval-related activation may be more spatially fragmented, connectivity within the memory retrieval network may be reduced, and functional lateralization may be diminished.

D. Present Study

The scope of the present study is to investigate the neural and physiological basis of sleep-dependent consolidation of declarative memory in healthy older adults. As reviewed in the preceding sections, aging is associated with memory impairment as well as changes in quantity and quality of sleep. Changes in sleep and memory may both emerge as a manifestation of a general aging trajectory, due to changes in neurochemistry, neurophysiology or brain volumetry (Hornung, Danker-Hopfe & Heuser, 2005). In order to reach systems-level conclusions about aging trajectories, one should investigate whether age-related changes in sleep architecture are associated with changes in the neural mechanism of sleep-dependent memory consolidation in older adults.

Recently, we tested young (18-30 years), middle-aged (35-50 years) and older adults (55-70 years) on two different tasks: a procedural motor sequence learning task (serial reaction time task; SRT) and a declarative word-pair recall task (Wilson, Baran,

Pace-Schott, Ivry & Spencer, 2012). Performance on both tasks was probed at two delay intervals, after a 12 hr interval that included overnight sleep, and after a consecutive 12 hr interval that included continuous daytime wake. The order of interval type was counterbalanced across participants. While sleep enhanced performance in the SRT task for the young adults, no such effect was observed in the middle-aged and older adult groups. The failure of older adults to obtain sleep benefit on the procedural SRT task has been confirmed by other reports (Fogel et al., 2013; Siengsukon & Boyd, 2009; Spencer, Gouw & Ivry, 2007). On the other hand, the effects of sleep on retention of the word-pair task was similar across participants; all three age groups experienced less forgetting following sleep as compared to wake. This suggests that, at the behavioral level, sleep benefits performance of older adults for a declarative task but not for a procedural task. This dissociation may imply that aging exerts its effects on sleep-dependent memory consolidation in a task-dependent fashion.

Sleep-dependent declarative memory consolidation in older adults has been probed with verbal memory tasks other than word pair recall. Aly and Moscovitch (2010) compared retention of stories and personal events over intervals of sleep and wake in young (19-29 years) and older (69-80 years) adults. Although recall was significantly worse in the older adult group, the sleep benefit for both types of declarative tasks was similar between young and older adults.

Neither Wilson and colleagues (2012) nor Aly and Moscovitch (2010) included a physiological measure of sleep. Scullin (2012) compared word-pair recall following 12 hr intervals consisting of overnight sleep or daytime wake, or a 24 hr interval that included both a night of sleep and daytime wake. Young adults in the 12 hr sleep group performed

better than the 12 hr wake and 24 hr groups. However, there was no such interval type effect for older adults. In other words, sleep did not benefit performance of older adults on a declarative word-pair learning task. The discrepancy between this study and others may partly be explained by differences in the design. Prior to probing delayed recall, Scullin (2012) introduced another word list to participants and obtained immediate recall measures for this list. This manipulation, aimed at controlling for time of day effects on encoding, may have introduced retroactive interference (e.g. Ellenbogen et al., 2006). In this study, sleep was monitored by use of a commercially available, single-electrode device (Zeo system; Zeo Inc.). Amount of SWS predicted task acquisition performance in the preceding session for young adults but not for older adults. Contrary to previous research, SWS did not predict overnight improvements in word-pair recall performance in young adults. Notably, this correlation was significant but negative for older adults. As the author notes, an important limitation of this study was that sleep physiology measurement relied on a single-electrode system that may not be as accurate as PSG (Scullin, 2012). Furthermore, a validation study revealed that this single electrode system has only moderate overall agreement with the standard PSG procedure (Griessenberger, Heib, Kunz, Hoedlmoser & Schabus, 2012). The authors concluded that the Zeo system is especially weak at detecting wake after sleep onset and arousals and cannot distinguish between light stages of sleep. Such limitations did not allow Scullin (2012) to investigate the effects of NREM2 sleep and sleep spindles on memory performance and whether age-related changes in sleep quality interfered with sleep-dependent memory consolidation in the older adult group.

Although not directly testing sleep-dependent memory consolidation, a recent study on long-term retention of word-pair learning, suggests that age-related changes in sleep quality may be responsible for decreased memory retrieval (Mary, Schreiner & Peigneux, 2013). Whereas encoding and short-term retention of word-pair learning in older adult participants in this study were similar to that of young adults, recall after a 7-day interval was greatly reduced and was negatively correlated with number of self-reported intra-sleep awakenings in the older adult sample. Thus, the authors concluded that age-related changes in sleep quality contribute to memory impairments.

The relationship between aging and impaired declarative memory may be direct or alternatively, may be mediated by age-related changes in sleep. Two recently published studies from the same lab (Mander et al., 2013a; 2013b) investigated whether SWS and sleep spindles modulate learning and retention of declarative memories. In one of these studies, the authors investigated the role of sleep spindles on subsequent learning. Whereas age itself was not directly associated with decreased learning performance for a face-name pair task, age-related reduction in spindle density was associated with reduced hippocampal activation during encoding, which, in turn, was associated with learning impairments (Mander et al., 2013a). In a separate study, over-sleep retention of a word-pair learning task was reduced in older adults compared to young adults. Through a mediation analysis, the authors found that age-related decrease in medial prefrontal (mPFC) gray matter volume was associated with disrupted EEG power of slow wave sleep, defined as slow wave activity (SWA) which, in turn, was associated with decreased overnight memory retention (Mander et al., 2013b). In summary, the researchers concluded that decreased nocturnal SWA (mediated by prefrontal atrophy) was

responsible for decreased overnight memory retention. This investigation, however, relies solely on an age-group comparison. Both groups of participants were tested only after an offline period of sleep, and decreased overnight memory retention in this case was defined as less memory retention and less hippocampal activation in older adults compared to young adults. Since, neural activation following a wake period is not investigated, the study fails to answer whether sleep-dependent neural reorganization takes place in aging.

Associative learning requires binding of two semantically unrelated concepts, and in addition to the hippocampus (Cameron, Yashar, Wilson & Fried, 2001), requires involvement of frontal lobes (Nolde, Johnson & Raye, 1998). Whereas right frontal activation is associated with retrieval success, left frontal activation is observed when memory strength is low (Andreasen et al., 1995; Buckner et al., 1998). Furthermore, as an integrated system, inferior regions of the frontal cortex (i.e. IFG) are associated with selection of associations between items, and middle frontal regions (i.e. middle frontal gyrus, MFG) are associated with generation of associations (Woodward, Meier, Cairo & Ngan, 2006). Given that lateralization and specific location of frontal activation is associated with memory strength, sleep may modulate frontal activation patterns for retention of associative learning. Through the process of sleep-dependent memory consolidation, retrieval attempts may elicit less competition among candidate associations and may involve less error monitoring and thus, require less involvement of these frontal regions.

As reviewed in the previous sections, at the neural level, consolidation is associated with transfer of memory traces from labile storage in the hippocampus to more permanent storage in the cortex, and this process preferentially takes places over sleep

(e.g. Takashima et al., 2006). Given that aging interferes with declarative memory functioning (Buckner, 2004) and alters physiological properties of sleep (Ohayon et al., 2004), an important question, therefore, is whether aging changes the mechanisms of sleep-dependent memory consolidation. This question is partly addressed by Mander and colleagues (2013a; 2013b). Their findings suggest that, as a consequence of age-related tissue damage, propagation of delta waves during sleep is disrupted in older adults. This may prevent memory consolidation and neural reorganization processes to take place during sleep as they do so in healthy young adults. However, we (Wilson et al., 2012) and others (Aly & Moscovitch, 2010) observe that memory performance in older adults is better after a period of sleep as compared to daytime wake. In order for retrieval efficiency to be better following sleep in older adults, some form of sleep-dependent memory consolidation does take place. Thus, the goal of the present study is to determine whether sleep-dependent neural reorganization is similar between young and older adults, and if not, to investigate whether there any compensatory processes that may aid in memory consolidation and retrieval in the aging brain.

If the mechanism of sleep-dependent memory consolidation is similar between young and older adults, retrieval should elicit sleep-dependent decrease in hippocampal activation and hippocampo-frontal connectivity in both age groups. Furthermore, retrieval should elicit less competition among cues and should require less effortful error monitoring. If, on the other hand, aging interferes with consolidation processes, older adults may need to recruit additional cognitive systems (e.g. error monitoring) to cope with challenging memory retrieval demands. Furthermore, it is still unknown whether daytime naps have a memory consolidation function in older adults. Thus, the present

study combines PSG, functional and structural brain imaging and neuropsychological evaluation methods to determine which brain areas play an active role in sleep-dependent reorganization of memory traces during sleep and whether these sleep-dependent memory consolidation mechanisms are affected by healthy aging.

Objectives of the present study. The present study focuses on one primary and one ancillary aim regarding nap-dependent consolidation of declarative memory in healthy older adults.

Primary Aim: To investigate whether daytime naps are sufficient to serve a memory consolidation function in older adults, resulting in systems level neural reorganization in the memory retrieval network.

Our previous research indicates that, at the behavioral level, declarative memories are consolidated over nocturnal sleep in older adults (Wilson et al., 2012). The present study investigates whether a daytime nap is associated with a sleep benefit in older adults resulting in observable changes at the behavioral and neural level. Specifically, the goal is to determine whether neural activation patterns associated with successful retrieval following a nap are different when compared to activation following an equal amount of time spent awake. A difference in activation patterns following sleep versus wake would imply that sleep induces long-term changes in the neural representation of memory through consolidation. Slow wave sleep, SWA, nREM2 sleep spindles and sigma power are critical for declarative memory consolidation (e.g. Fogel & Smith, 2011; Gais & Born, 2004) and midday naps rich in SWS and sleep spindles are associated with better consolidation of declarative learning in young adults (e.g. Lau, Tucker & Fishbein, 2010; Rausch et al., 2012). The hypotheses underlying the present study are that (1) following

sleep, retrieval of declarative memory will be associated with more refined and clustered activation that relies less on the medial temporal structures, and (2) measures of SWS and sleep spindles will be associated with more effective sleep-dependent neural reorganization in young adults. Importantly, the present study aims to determine whether sleep-dependent neural reorganization is similar for young and older adults. Memory related activation in older adults is more fragmented, and increased spatial distribution correlates with worse performance (Morcom & Friston, 2012). Therefore, I hypothesize that, contrary to the young adult group, neural activation following sleep will be less clustered and spatially fragmented in older adults. Hippocampo-cortical connectivity would imply that memory retrieval still relies on the hippocampus. I hypothesize that whereas hippocampo-frontal connectivity will be reduced after a nap in young adults (as in Takashima et al., 2006), this connectivity will be stronger in the older adult group.

Ancillary Aim. To investigate whether napping changes overnight sleep architecture.

Although aging may be associated with changes in napping habits, no study to date has investigated whether the nap architecture is similar between young and older adults and whether napping changes the duration, architecture and EEG power of subsequent nocturnal sleep. Although frequency of napping increases in old age, little is known about the relationship between naps and nocturnal sleep. Previous reports suggest that napping increases 24 hr total sleep time and increases evening alertness (Campbell, Murphy & Stauble, 2005; Monk et al., 2001). However, it remains to be investigated whether napping in older adults changes durations and EEG power of sleep stages critical for the memory function of sleep.

CHAPTER 2

EXPERIMENT

A. Method

1. Participants

We recruited 12 young and 12 older healthy adults. Two older adults were not able to complete the first brain scan (due to unanticipated discomfort in the MRI environment), and therefore the final group of participants was composed of 12 young and 10 older adults. Young adults were 21-29 years of age (mean = 23.4, SD = 2.6), and older adults were 62-74 years of age (mean = 66.3, SD = 3.5). All participants were right-handed, and native speakers of English. Exclusion criteria for both young and older adults were as follows:

1. Presence of a current or past neurological or psychiatric diagnosis including depression, stroke, dementia or autoimmune diseases (excluded based on a comprehensive in-house screening form; see Appendix C)
2. Use of medication known to affect cognition or sleep (based on Cooke & Ancoli-Israel, 2011). Stable doses (same dose for > 6 months) were permitted for commonly prescribed medications such as oral contraceptives and hormone replacement therapy
3. Presence of cardiovascular disease or use of medication that may influence blood circulation (blood thinners, decongestants)
4. Habitual nocturnal sleep of less than 5 hr every day
5. Habitual napping regimen of more than twice per week

6. Presence of a sleep disorder as indicated by an in-house questionnaire (questions 9-20 in the screening form; Appendix C)
7. Excessive alcohol consumption (> 10 alcoholic drinks per week)
8. Excessive caffeine consumption (> 10 12-oz caffeinated drinks per week)
9. Obesity as defined by a body mass index of > 30 (Centers for Disease Control and Prevention, 2012).
10. Presence of metal in the body and use of MRI non-compatible glasses or prosthetics.
11. Claustrophobia or discomfort in enclosed spaces.

2. Tasks and Measurements

a. Word-Pair Recall Task

The behavioral task was a word-pair recall task similar to that of Wilson and colleagues (2012). Stimuli consisted of single-syllable, high frequency, and concrete nouns (Donohue & Spencer, 2011). Words were randomly paired to create two lists of 40 cue-target word pairs that were semantically unrelated (e.g., bath-grass, rail-bag). There were four phases to the behavioral task: encoding, immediate recall, delayed recall and 24 hr recall (Figure 2). To avoid learning of a sequence, the order of presentation was random for each cycle of learning or recall. For the encoding phase, participants were presented with a list of 40 word pairs. Each pair was presented for 4 sec with an inter-stimulus interval of 250 msec. Participants were instructed to study each pair of words for subsequent recall and try to form an association between the pairs. Specifically, they were told, “To remember the pairs, it is helpful to think of associations between the pairs. For

instance, if the words were frame-shoe you might try to picture in your mind a framed painting of a shoe" (Wilson et al., 2012).

There was a 5 min break between encoding and the first part of immediate recall during which participants filled out sleep and mood surveys. Recall was prompted by presenting the first word of each pair (i.e. cue word) and asking the participant to remember the target word. The cue word was displayed on a computer screen and participants were instructed to say aloud the target word for that pair. The experimenter typed their response. If their response was incorrect, the correct word was displayed for 750 msec. Participants responded at their own pace. The list was repeated with feedback until performance reached 65% or the list was repeated for five times. The second part of immediate recall was very similar, however no feedback was given regarding accuracy of response. To avoid recency effects there was a 20 min break between the end of immediate recall with feedback and the beginning of the last round. This last round of immediate recall was regarded as the baseline measure of immediate learning performance.

Delayed recall was probed approximately 5 hr (± 30 min) after encoding and took place during MRI scanning. Participants were presented with the cue word for 4 sec and were asked to silently decide whether they can remember the target word. Participants were trained to press one of two keys on a response box to indicate whether or not they recall the target word. Again, there was no feedback regarding accuracy. Upon completion of the MRI session, participants completed the same memory task outside the scanner with procedures identical to the last round of immediate recall.

The twenty-four hour recall phase took place 24 hr after the encoding phase. Similar to the last round of immediate recall and delayed recall, participants were presented with a cue word on a computer screen and were asked to type the target word. The list was presented only once and there was no feedback. Participants completed this phase at their own pace.

b. Actigraphy

Actigraphy was used to provide an accurate and non-invasive measure of sleep and wake habits. The actigraph (Actiwatch Spectrum, Philips Respironics, PA) was worn on the non-dominant wrist, for seven consecutive days to provide a continuous recording of sleep-wake states, activity levels and light exposure via an embedded accelerometer and light sensor. In order to increase the accuracy of light sensor measurements during daytime, participants were instructed to make sure the watch was not covered by clothing.

c. Neuropsychological Testing and Questionnaires

The neuropsychological test battery included a test of verbal memory (California Verbal Learning Test, CVLT-II; Delis, Kramer, Kaplan & Ober, 2000) and subtests of a composite test of executive functioning (Delis Kaplan Executive Function System, D-KEFS; Delis, Kaplan & Kramer, 2001). The Delis Kaplan Executive Function System is a reliable and valid tool sensitive to the assessment of executive functioning in healthy young and older adults as well as clinical populations (Delis, Kramer, Kaplan & Holdnack, 2004). The subtests utilized in this study included Trail Making, Stroop color-word interference and verbal fluency tests.

Several questionnaires were administered to gauge sleep habits, chronotype and mood. The Pittsburg Sleep Quality Index (PSQI) surveys habitual sleep quality estimates

from the preceding 30 days (Buysse, Reynolds, Monk, Berman & Kupfer, 1989) and is a reliable and valid tool for young and older adult populations (Grander, Kripke, Yoon & Youngstedt, 2006; Spira et al., 2012). Individual differences in temporal preferences (i.e. functioning better in the mornings or evenings) are generally referred to as chronotype (Roenneberg, Wirz-Justice & Merrow, 2003). The Morningness-Eveningness Questionnaire (MEQ) provides information about chronotype (Horne & Ostberg, 1976) and can validly be used in aging populations (Taillard, Philip, Chastang & Bioulac, 2004). The Beck Depression Inventory (BDI-II) provides a valid and reliable measure of depression (Beck, Ward, Mendelson, Mock & Erbaugh, 1961; Segal, Coolidge, Cahill & O'Riley, 2008). Furthermore, participants were administered sleepiness and mood scales at each session. Stanford Sleepiness Scale (SSS) is a reliable and valid tool used to quantify progressive steps in sleepiness based on subjective rating (Hoddes, Dement & Zarcone, 1972). The Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988) is a questionnaire consisting of 10 negative and 10 positive emotion words; participants rate to what extent they feel each of these emotions at the time of testing. It has been shown that PANAS is a reliable and valid measure of affect in a large non-clinical sample of individuals 18-90 years of age (Crawford & Henry, 2004). Participants were also asked to fill out an in-house sleep and daily activities survey which was used to monitor nocturnal sleep, naps, and adherence to experimental protocols (i.e. no strenuous exercise, no caffeine or alcohol consumption during testing days).

d. Magnetic Resonance Imaging Data Acquisition

All brain imaging data were acquired using a 3T Philips Achieva scanner housed at University of Massachusetts Medical School Advanced MRI Center. Stimuli were

presented with the Presentation software (Neurobehavioral Systems Inc., Albany, CA) and projected on a screen at the back of the room. Participants viewed the screen via a mirror rigidly attached to the head coil. At the beginning of the functional run participants were instructed that the memory task would start shortly. For each trial, the first word of the pair was presented for 4 sec. Participants were asked to report a memory decision ('remember' vs. 'do not remember') using two MRI-compatible, one-button response boxes that were held in each hand. Each trial was followed by a 14 sec fixed inter-stimulus-interval in order to reach optimal experimental design for event-related functional imaging (Dale, 1999). The functional run started with two practice trials to familiarize participants with the response button decision procedure.

Echo planar imaging (EPI) data were acquired (FA = 80°, TE = 30 ms, TR = 2500 ms) as 43 interleaved axial T2-weighted slices yielding a voxel size of 3 mm x 3 mm x 3 mm. EPI scans were preceded by 2 preparatory scans. Anatomical scans were acquired as high resolution T1 weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) volumes (1 mm x 1 mm x 1 mm voxel size; FA = 3°, TR = 8.3 ms, TE = 3.75 ms, slice thickness = 1 mm, 181 slices).

e. Polysomnography

Sleep was monitored by PSG for the nap and two nocturnal sleep intervals. An ambulatory PSG device (Grass Technologies, Astro-Med Inc., RI) with 6 EEG channels (F_1, F_2, C_3, C_4, O_1 and O_2), 2 EMG channels (submental) and 2 EOG channels (ROC, LOC) was used. Electrode placement and sleep scoring adhered to the American Academy of Sleep Medicine specifications (Iber, Ancoli-Israel, Chesson & Quan, 2007).

B. Procedures

Study procedures are illustrated in Figure 3. Prospective participants completed a screening via phone to determine eligibility to participate (Appendix C). Eligible participants were scheduled to attend an initial session approximately 7 days before the study. This initial session served three primary purposes: familiarize the participants with the study procedures and eligibility criteria, complete the neuropsychological testing phase, and provide qualifying participants with wrist actigraphs and sleep diaries to record daily activities for 7 consecutive days prior to study initiation.

Participants were tested over 4 sessions within a span of 9 days. The first two sessions took place on day 1 and day 2. Sessions 3 and 4 took place one week later, on days 8 and 9. For each of the two-day testing bouts, encoding of the word-pair task was followed by either a nap or a wake period. The nap and wake conditions were counterbalanced such that half of the participants completed the wake condition and the other half completed the nap condition on Session 1. List order was also counterbalanced such that, for instance, half of the participants who started with the nap condition studied List 1 first. All other testing procedures across these two-day testing bouts were identical.

Session 1 started at 11 a.m. (± 1 hr) with the first two phases of the memory task: encoding and immediate recall for List 1. This took place in a quiet room in the participant's own place of residence. The behavioral task was followed by an instructed interval of nap or wake. For the nap condition, PSG electrodes were applied and participants were given an opportunity to nap for a maximum of 2 hr in a quiet bedroom in their place of residence. Two participants (both young adults) chose to take their nap in an

on-campus lab bedroom. For the wake condition participants refrained from any strenuous mental or physical exercise.

Delayed recall for List 1 was tested in the imaging facility. The brain imaging phase started with training and MRI safety screening. Then, participants were taken to the scanning room and were fitted with sound attenuating earplugs and headphones before being positioned supine in the scanner. The participant's head was positioned inside a standard head coil. Foam cushions were placed inside the head coil and under the legs to reduce movement and increase comfort. Participants were given a squeeze-bulb to signal the technician to stop the scanner at any time they felt uncomfortable. To minimize discomfort inside the scanner, participants were presented with relaxing nature scenes except for the functional scans during which participants completed the delayed recall test. On the same night, nocturnal sleep was monitored by PSG. Experimenters arrived at the participant's house 1-2 hr before their regular bedtime to apply the PSG electrodes.

Session 2 took place approximately 24 hr after the beginning of Session 1. Experimenters arrived at the participant's house to collect PSG equipment and to test participants on 24 hr recall. Participants were tested in a quiet room.

The same two-day testing bout was repeated on days 8 and 9. Accordingly, each participant underwent brain imaging twice, following a nap and following continuous daytime wake. The imaging sessions were scheduled for 4 pm (± 1 hr) and started exactly at the same time on both days for each participant to avoid any possible circadian confound on brain activation.

C. Data Analysis

1. Word-pair recall task

Given that recall is probed at three time points (i.e. immediate, delayed and 24 hr), the primary measure of memory retention reflects change in recall from the last testing phase to the current phase. Accordingly,

5 hr Intersession change = Delayed recall (% correct) – Last round of immediate recall (% correct)

24 hr Intersession change = 24 hr recall (% correct) – Delayed recall (% correct)

In order to determine whether a mid-day nap was associated with better memory performance, 5 hr intersession change was compared using a 2 x 2 multivariate ANOVA with condition as the within subjects factor (nap vs. wake) and age group as the between subjects factor (young vs. older). Only the words that the participants judged as 'remembered' during the MRI scanning phase and that they could correctly recall in the subsequent test outside the scanner were identified as correct recall trials (i.e. Hits) to ensure reliability of the initial memory judgment (e.g. Meltzer & Constable, 2005). Twenty-four hour intersession change score reflects whether overnight sleep following a nap provides a further sleep benefit and was analyzed with a similar 2 x 2 multivariate ANOVA with condition as the within subjects factor and age group as the between subjects factor.

2. Actigraphy

Physical activity and light exposure were continuously measured in 15 sec epochs. Lights on and lights off periods were determined by corroborating event markers from actigraphs and sleep diary data. Within the rest periods, sleep and wake onsets were

analyzed automatically using the Actiware 5 software (Philips, Respironics). For instances where event markers and diary data provided by the participant were inconsistent, lights on and off periods were scored manually based on criteria proposed by Acebo and colleagues (2005). Variability in sleep and wake onset were derived by calculating the variance of sleep and wake onset times over the course of the week of actigraphy assessment. The watches automatically detected periods during which the watch was off the wrist, and those periods were excluded from activity analysis. Activity levels were measured for each of the 7 consecutive days by averaging activity counts per minute for wake periods the actigraphy was worn. Standard deviation of daily average activity levels was used as the measure of variability of activity levels. Light exposure (measured in lux) was averaged for wake periods across the 7 days.

3. Neuropsychological Testing

For the CVLT encoding efficiency was measured by the total number of correctly recalled words across the 5 trials for List A. Memory retention for List A was measured as the total number of words correctly recalled at the short delay free recall, long delay free recall, long delay cued recall phases and as the number of hits for the recognition portion.

Measures of executive function from the DKEFS were phonemic verbal fluency (average of the total number of words that start with the letters F, A and S), semantic verbal fluency (average of the total number of words that belong to the categories animal and boys' names), trail making (total time for condition 4 minus average of total time for conditions 2 and 3) and Stroop (total time for color naming minus total time for word reading).

4. Magnetic Resonance Imaging

Functional data were preprocessed and analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 7.7. Raw blood oxygen level dependent (BOLD) images were realigned and corrected offline for slice-timing acquisition. The images were normalized to the Montreal Neurological Institute (MNI) template. The resultant voxel size was 2 mm x 2 mm x 2 mm, and spatial smoothing was completed with a 6 mm isotropic Gaussian kernel prior to modeling the data. All trial types were modeled as events convolved with the canonical hemodynamic response function and inserted in the general linear models (GLM). A high pass filter with a cut-off of 128 sec was applied to remove slow signal drifts from the GLM. Analyses focus on hits (i.e. yes responses during functional imaging that were confirmed by correct recall outside the MRI scanner). Unless otherwise noted, all analyses follow a threshold of $p < .05$ FWE, controlling for multiple comparisons. All whole brain analyses were restricted to at least 5 five contiguous voxels.

Region of interest (ROI) analyses included the hippocampal formation (bilateral hippocampi and hippocampal gyri) given the structure's critical role in learning and memory (e.g. Squire, Stark & Clark, 2004); bilateral anterior cingulate cortex (ACC) given its role in monitoring errors and competition among candidate items in associative learning (Bush, Luu & Posner, 2000; Raichle et al., 1994). Regions of interest were extracted anatomically using the WFU Pickatlas ver. 2.5 (Lancaster et al., 1997; 2000; Maldjian, Laurienti, Kraft & Burdette, 2003) implemented in SPM8. Signal intensity in the ROIs was measured by calculating two interrelated parameter estimates: contrast values (defined as the effect size of the t test), and % signal change (defined as the mean

BOLD signal specific to a type of event as a percentage of the mean of the whole brain signal) using the Marsbar toolbox (ver. 0.43; Brett et al, 2002).

Cortical parcellation and volume segmentation for anatomical data were performed automatically with Freesurfer ver. 4.5 (http://surfer.nmr.mgh.harvard.edu) installed on an iMac workstation. For each participant grey and white matter volume and hippocampal volume were calculated for the right and left hemispheres. Measures of cortical thickness and mean curvature were compared between young and older adults for the right and left parahippocampal gyrus and ACC.

5. Sleep Architecture

Measures of interest for polysomnographically recorded naps and nocturnal sleep can be summarized in three groups: sleep quality measures, sleep stage distributions, and EEG spectral power. Measures of sleep quality included sleep latency, total sleep time (TST), wake after sleep onset (WASO), and sleep efficiency. Measures of sleep stage distributions included the following: nREM1 (%time in nREM1), nREM2 (%time in nREM2, density of nREM2 spindles), SWS (% time in SWS) and REM (% time in REM and REM density.

Rapid eye movements were scored visually and defined as rapid deflections in the EOG signal that are > 25μV and occur in < .5 sec. Rapid eye movement density was calculated by dividing the total number of REMs with total number of minutes spent in REM sleep. For the nap period, sleep spindles were scored visually based on a frequency criterion of 12-16 Hz and a minimum duration criterion of 0.5 sec. Spindle density was calculated by dividing the total number of spindles with total number of minutes spent in nREM2 sleep.

In order to carry out spectral analysis EEG data for naps and nocturnal sleep were imported to Brain Products Analyzer software (Version 2.4) along with sleep staging notations and filtered between 0.3 – 35 Hz. Data were first segmented to the sleep stage of interest (i.e. SWS or nREM2) and divided into 4 sec epochs. Following manual artifact rejection on individual channels, a fast-Fourier transform was applied using a Hanning window with 10% overlap and utilizing variance correction. Analyses on SWA focused on a relative spectral power between 0.5 – 4 Hz. Analyses on sigma power included power density on frequencies in the 12-16 Hz range during nREM2 sleep. All power analyses are reported in power density (μV^2/Hz).

Univariate ANOVAs were used to compare nap architecture between young and older adult groups. Nocturnal sleep measures were compared with 2 x 2 repeated measures ANOVAs with condition as the within subjects factor (nocturnal sleep following a nap vs. continuous daytime wake) and age group as the between subjects factor (young vs. older).

Based on previous literature (Fogel & Smith, 2011; Gais & Born, 2004, Holz et al., 2012; Mander et al., 2013), a priori hypotheses focus on measures of sleep that are shown to be critical for declarative memory consolidation and include measures of SWS (%SWS and SWA) and measures of nREM2 sleep spindles (spindle density and sigma power). The relationship of these sleep measures with behavioral performance (i.e. intersession change in recall following a nap) were investigated with Pearson's correlation coefficients.

The relationship between naps and brain activation was investigated by focusing on two cognitive functions: long-term memory retention (hippocampus) and error monitoring (ACC). Pearson's correlation coefficients were calculated between activation

for each of the ROIs and measures of sleep (%SWS, SWA, spindle density and sigma power) bilaterally for young and older adult groups.

D. Results

1. Participant Characteristics

a. Sleep Habits and Mood as Measured by Questionnaires

Chronotype, as measured by total score on the MEQ, did not differ between young and older adult groups, $F(1,20) = 3.24$, $p = .089$. However, consistent with previous literature (Weitzman et al., 1981), older adults were more likely to be morning types (young adults: moderately morning type = 2, moderately evening type = 3, neither type = 7; older adults: moderately morning type = 7, moderately evening type = 1, neither type = 2). Notably, none of the participants were extreme morning or extreme evening chronotypes. Furthermore, habitual sleep quality, as measured by the PSQI was similar between young and older adults, $F(1,20) = 1.45$, $p = .243$.

Level of sleepiness at time of testing was measured subjectively by the SSS. Repeated measures ANOVAs with condition (nap vs. wake) as the within subject factor and age group as the between subjects factor revealed that young and older adults rated their sleepiness levels similarly for the nap and wake conditions at the time of encoding (main effect of condition: $F(1, 20) = .01$, $p = .912$; main effect of age group: $F(1, 20) = 2.87$, $p = .146$; age group x condition interaction: $F(1, 20) = 1.01$, $p = .327$), at delayed recall (main effect of condition: $F(1, 20) = 1.66$, $p = .212$; main effect of age group: $F(1, 20) = 2.98$, $p = .10$; age group x condition interaction: $F(1, 20) = .71$, $p = .408$), and at 24 hr recall (main effect of condition: $F(1, 20) = .15$, $p = .699$; main effect of age group: $F(1, 20) = 1.68$, $p = .210$; age group x condition interaction: $F(1, 20) = .15$, $p = .699$).

Positive and negative mood was measured by the PANAS. A 2 x 2 x 2 repeated measures ANOVA with condition (nap vs. wake) and valence (positive vs. negative mood) as within subjects factors and age group (young vs. old) as the between subjects factor revealed no significant main effect of condition, $F(1, 20) = .66$, $p = .427$ but a significant main effect of age group, $F(1, 20) = 14.08$, $p = .001$, overall older adults rated the intensity of their mood higher. There was no significant interaction between condition and age group, $F(1, 20) = .15$, $p = .705$ or between condition and valence, $F(1, 20) = .37$, $p = .035$, and no 3-way interaction, $F(1, 20) = .11$, $p = .752$. Notably, the interaction between valence and age group was significant, $F(1, 20) = 5.12$, $p = .035$, the difference between young and older adult mood measures were largely driven by positive mood. Intensity of depressive symptoms measured by BDI were very low (young adults mean = 2.33, SD = 1.72; older adults mean = 2.40, SD = 1.95) and similar between young and older adults, $F(1, 20) < .01$, $p = .933$. Levene's test did not indicate unequal variances for any of the mood and sleep habit measures reported above, $p > .12$.

In sum, young and older adult groups were similar in measures of subjectively rated sleep habits. None of the participants were extreme morning or evening chronotypes, and there were no significant differences between young and older adults in terms of chronotype. Subjectively rated habitual sleep quality was similar across groups. Furthermore, level of sleepiness at time of testing did not differ across sessions or between age groups. Finally, results on subjective mood measures suggest that mood in both groups was similar on the day participants took a nap and the day they stayed awake. However, overall mood ratings were higher for older adults and this difference was more evident for positive affect.

b. Sleep Habits as Measured by Actigraphy

Sleep and daily activities were measured over a 7-day period prior to starting the experiment. Sleep habits, as objectively measured by actigraphy were similar between the young and older adult groups. There was no significant difference across the age groups in terms of total sleep time, $F(1,20) = 3.14$, $p = .092$. Notably, TST was slightly higher in the older adult group (on average older adults got 473.7 min of sleep whereas young adults got 425 min of sleep per night). Importantly, there were no notable age-group differences for other measures of sleep onset and duration such as sleep onset time variability, $F(1,20) = 1.19$, $p = .288$, wake onset time variability $F(1,20) = 1.35$, $p = .259$; wake after sleep onset (WASO), $F(1,20) = .003$, $p = .958$ or sleep latency, $F(1,20) = .96$, $p = .340$. Furthermore, young and older adults in this sample were similar in terms of average activity levels, $F(1,20) = 2.58$, $p = .124$, or variability in activity levels, $F(1,20) = 1.22$, $p = .284$. White light exposure during wake periods was also similar between the young and older adults, $F(1,20) = .66$, $p = .425$. Levene's test did not indicate unequal variances for any of the actigraphy measures reported above, $p > .09$.

Actigraphy allowed for an objective comparison of sleep confirmed that there were no significant differences between young and older adult groups. Furthermore, activity levels and daylight exposure during wake periods were also similar between young and older adults.

c. Neuropsychological Functioning

Neuropsychological tests included measures of episodic memory and executive functioning. Summaries of scores are presented in Table 1. California Verbal Learning Test - II scores were significantly different between the age groups. Specifically,

performance of older adults was significantly worse for encoding (i.e. sum of correctly recalled words across 5 trials), $F(1,20) = 12.36$, $p = .002$; short delay free recall, $F(1,20) = 11.65$, $p = .003$; long delay (20 min) free recall, $F(1,20) = 7.45$, $p = .013$; long delay recall cued by category names, $F(1,20) = 4.66$, $p = .043$ and for long delay recognition, $F(1,20) = 6.62$, $p = .018$. Notably, however, none of the CVLT performance measures in the older adult group were below age norms (Paolo, Tröster & Ryan, 1997). For measures of executive functioning, an age-related change in performance was observed only for the Stroop test, $F(1,20) = 5.89$, $p = .025$ suggesting a decrease in cognitive inhibition abilities. On the contrary, cognitive flexibility as measured by the Trail Making test, and verbal fluency (i.e. phonemic or semantic) were similar between young and older adults.

d. Structural Brain Imaging

The sum of the volumes of brain structures identified by a segmentation process was significantly smaller for older adults, $F(1,20) = 5.13$, $p = .035$. Given that the volume of each structure would scale with head size of that individual, volumetric analyses were corrected for head size. Compared to young adults, older adults had significantly decreased (normalized) volume for cerebral gray matter in the right, $F(1,20) = 17.01$, $p = .001$, but not the left hemisphere, $F(1,20) = 2.27$, $p = .147$. Similarly, normalized hippocampal volume was significantly smaller for the right, $F(1,20) = 9.78$, $p = .005$ but not the left hemisphere, $F(1,20) = 2.87$, $p = .106$ in the older adult group. Additionally, older adults had smaller hippocampal gyrus volume for both right, $F(1,20) = 6.21$, $p = .022$ and the left hemispheres, $F(1,20) = 8.48$, $p = .009$. Parahippocampal gyrus thickness and mean curvature measures were similar for the young and older adult groups, all ps $> .10$.

Cortical thickness and mean curvature were compared for rostral and caudal ACC. Thickness of the caudal ACC was similar between groups for the right hemisphere, $F(1,20) = .22$, $p = .646$, but smaller in the older adult group for the left hemisphere, $F(1,20) = 10.34$, $p = .004$. In contrast, for the rostral ACC, cortical thickness was smaller for older adults on the right, $F(1,20) = 26.89$, $p < .001$ but not on the left, $F(1,20) = .86$, $p = .363$. Mean curvature of the caudal and dorsal ACC was similar between young and older adult groups on both hemispheres, all ps > .17.

2. Nap-Dependent Memory Consolidation

a. Behavioral Results

All participants reached the criterion of > 65% accuracy. On average older adults completed 3.95 rounds of practice to reach this criterion whereas young adults completed 2.12 rounds. A 2 x 2 repeated measures ANOVA with number of rounds as the dependent variable revealed a significant main effect of age $F(1,20) = 23.78$, $p < .001$. Neither the main effect of condition (nap vs. wake), $F(1,20) = 2.34$, $p = .134$, nor the interaction between condition and age group, $F(1,20) = 0.65$, $p = .802$, were significant.

Once participants reached criterion accuracy, immediate recall was tested for one last time without feedback and this measure is considered the primary measure of immediate recall (i.e. baseline memory performance). With a 2 x 2 repeated measures ANOVA, it was found that the main effect of age was significant; overall older adults performed worse (older adults mean = 77.13, SD = 8.95; young adults mean = 86.56, SD = 6.59), $F(1,20) = 8.09$, $p = .010$. The main effect of condition was significant, $F(1,20) = 5.91$, $p = .025$ (nap day mean = 84.55, SD = 10.65; wake day mean = 80, SD = 9.09), perhaps a random effect since participants were randomly assigned to start with the nap or

wake manipulation. The interaction between condition and age group was not significant, $F(1,20) = 1.38$, $p = .254$.

Similar to previous research (e.g. Wilson et al., 2012) performance decreased from immediate to delayed recall for both conditions in both age groups. Intersession change in recall was calculated as delayed recall minus immediate recall and is plotted on Figure 4. A 2 x 2 repeated measures ANOVA revealed, surprisingly, no main effect of condition, $F(1,20) = 0.54$, $p = .819$ nor age group x condition interaction, $F(1,20) = 0.58$, $p = .455$. The main effect of age was significant, $F(1,20) = 5.62$, $p = .028$ (older adults mean = -8.25, SD = 7.98; young adults mean = -2.19, SD = 3.58).

Hits (defined as "yes" judgments for the delayed recall test during brain imaging accompanied by correct recall outside the scanner) were compared between young and older adults for the nap and wake conditions. A 2x2 repeated measures ANOVA revealed no significant main effect of condition, $F(1,20) = 0.89$, $p = .355$ nor age group x condition interaction, $F(1,20) = 2.47$, $p = .131$. The main effect of age was significant, $F(1,20) = 8.57$, $p = .008$ (older adults mean = 62, SD = 15.50; young adults mean = 76.97, SD = 7.93).

In sum, it took more trials for older adults to reach criterion and older adults performed worse on both immediate and delay intervals. Surprisingly, no effect of napping on recall was observed at the behavioral level.

b. Nap Architecture

The nap manipulation was successful for all participants. Nap PSG was not recorded for one older adult participant due to equipment malfunctioning. Total nap time ranged between 47.5 – 118 min for the young adults and between 38.3 - 99 min for the

older adults with no significant group difference, $F(1,19) = 2.52$, $p = .129$. Nap characteristics are summarized in Table 2 (Levene's test did not indicate unequal variances for any of the measures, $p > .05$). All young adults entered SWS but only half of the young adult naps included REM sleep. When sleep quality measures were compared between young adults who reached REM and those who did not, neither nap efficiency, $F(1,10) = 1.89$, $p = .199$, nor TST, $F(1,10) = .03$, $p = .863$, were different. Similarly, percentage of time spent in SWS, $F(1,10) = .53$, $p = .485$, and REM sleep, $F(1,10) = 1.37$, $p = .269$, did not differ between young adults who reached REM and those who did not. Three older adults did not have any SWS and none of the older adults had any REM sleep. Notably, there were no significant age group differences for sleep quality, sleep stage distribution, sleep spindles, or spectral power measures (Table 2). As expected, density of visually scored sleep spindles correlated strongly with spectral power in the sigma frequency range ($r = .79$, $p < .001$).

c. Associations of Memory with Nap Architecture

To investigate the relationship between nap physiology and memory retention following a nap, correlation coefficients were calculated between the intersession change in recall scores and SWS and sleep spindle measures. Percentage of time spent in SWS correlated significantly and positively with intersession change in recall across the nap period ($r = .61$, $p = .035$) for the young adult group. As can be seen in Figure 5, those young adults with more SWS retained better memory after the nap period but this relationship was not significant for older adults ($r = .08$, $p = .829$). To test whether the correlation coefficients between intersession change in recall and SWS were different between young and older adults, a new regression model was calculated with intersession

change in recall as the dependent variable and age group (young = 1, older = 0), the product of age group and percentage of time spent in SWS, and percentage of time spent in SWS as the independent variables. The product of age group and percentage of time spent in SWS is the variable that tests the null hypothesis that the regression coefficients for young and older adults are equal. Notably, this coefficient was not significant ($\beta = .18$, $t(20) = .38$, $p = .706$) suggesting that the correlation coefficients for the relationship between change in recall and time spent in SWS during the nap were not significantly different between young and older adults. Slow wave activity was not significantly associated with change in recall for either young ($r = .36$, $p = .276$) or older adult groups ($r = .01$, $p = .994$). Neither of the sleep spindle measures predicted recall performance in young (spindle density: $r = .09$, $p = .771$; sigma power: $r = .17$, $p = .626$) or older adults (spindle density: $r = -.36$, $p = .346$; sigma power: $r = -.48$, $p = .189$).

d. Functional Brain Imaging

As reported in the previous section, age-group differences were detected for brain volume measures. Although previous reports suggest that age-related structural atrophy may confound interpretation of activation differences in direct comparisons of young and older adult groups (e.g. Maillet & Rajah, 2013), this is not a limitation for the present study since all group level functional imaging analyses were run separately for young and older adult groups. Broad activation patterns relating to successful recall for the nap and wake conditions were investigated with separate GLMs. Within subjects comparisons were included to determine areas that show higher activation following a nap (nap>wake) and areas that show higher activation following wake (wake>nap).

For young adults, successful retrieval of word-pairs following a mid-day nap yielded significant peak activations in the left inferior parietal lobule and the right superior parietal lobule, bilateral anterior cingulate cortex (ACC), right superior frontal gyrus, right middle occipital gyrus, right thalamus, right putamen, left insula, left caudate and right anterior and posterior cerebellum (Table 3). In contrast, retrieval following wake activated a broad network of frontal regions including the MFG and ACC extending bilaterally; left inferior parietal lobule, right inferior occipital gyrus, left putamen and bilateral cerebellum (Table 4). Pairwise comparison of these activation patterns ($p < .001$, uncorrected) revealed that frontal cortical areas were more activated following wake than a nap for young adults with two clusters around the left MFG and left ACC (Table 5). Regions that were activated more in the nap condition included the left middle-occipital gyrus, right IFG, right insula and left precentral gyrus (Table 5).

For the older adult group, brain activation for successful retrieval was more fragmented and limited to smaller cluster sizes. Retrieval following a mid-day nap was associated with activation in several frontal cortical regions including the right precentral gyrus, right MFG, right ACC, left middle frontal and left medial frontal gyri (Table 6). Similarly, retrieval following wake was associated with frontal cortical activation with clusters in the left medial frontal and superior frontal gyri, and right ACC (Table 7). A pairwise comparison of these activation patterns ($p < .001$, uncorrected) revealed that older adults activate the left parahippocampal gyrus more following wake than a nap (Table 8). On the contrary, regions that were associated with increased activation following a nap than wake included a neighboring cluster in the parahippocampal gyrus, a

broad network of frontal cortical regions including the middle frontal, superior frontal and ACC as well as the fusiform gyrus (Table 8).

i. Regions of Interest

As stated in the previous section, for both age groups, recall following a nap was associated with significantly different activation patterns than when recall was tested following wakefulness in the same group of participants. To further decompose the effects of napping on neural activation, ROIs were extracted for regions critical for associative learning (i.e. hippocampal structures for memory and ACC for error monitoring).

Activation in bilateral hippocampi and hippocampal gyri were compared across the nap and wake conditions for young and older adult groups. No hippocampal region was found to be activated more following a nap compared to wake for young adults. However, a seed region in the right parahippocampal gyrus in the young adult group was activated more following wake than a nap (12, -38, 8). For older adults, both contrasts revealed clusters of activation in the left parahippocampal (peak for nap>wake: -16, -18, -24, Brodmann's area [BA] 28; peak for wake>nap: -22, -38, -8; BA 36; Figure 6). Notably, the peak for the nap>wake contrast was slightly more posterior and caudally located than the peak for wake>nap. Whereas increased hippocampal activation was only seen for the Wake condition in young adults, both wake and nap contrasts were associated with increased hippocampal activation in older adults.

Based on the finding that hippocampal activation was modulated by napping, it may be predicted that sleep alters hippocampo-prefrontal connectivity. The method chosen for functional connectivity analysis was pairwise ROI correlations given that the fMRI measure of interest is BOLD deflections from baseline and there is only one event-related

condition (i.e. successful recall hits). To investigate hippocampo-prefrontal co-activations, signal change within the right and left hippocampal and DLPFC ROIs for each participant were compared (e.g. Payne & Kensinger, 2011). This analysis yielded two different patterns of connectivity for the nap and wake conditions for young adults. Whereas there was no functional co-activation between the hippocampus and the DLPFC during memory retrieval following a nap, signal change in the right DLPFC was predicted by signal change in the right parahippocampal region following wake (adjusted R^2 = .25, F(1,10) = 4.62, p = .05).

In contrast functional co-activation between the hippocampus and the DLPFC were similar across the nap and wake conditions for older adults. For the nap condition, signal change in the right DLPFC was significantly predicted by signal change in the right hippocampus (adjusted R^2 = .701, F(1,10) = 22.08, p = .002). Similarly, for the wake condition signal change in the right DLPFC was predicted by right hippocampal and right parahippocampal activation (adjusted R^2 = .496, F(1,10) = 5.43, p = .038), and signal change in the left DLPFC was predicted by left hippocampal and left parahippocampal activation (adjusted R^2 = .526, F(1,10) = 5.98, p = .03). Figure 7 shows functional co-activation between the hippocampus and DLPFC for the right hemisphere for young and older adults.

Anterior cingulate cortex ROIs were extracted in order to investigate the effects of napping on the efficiency of memory search (i.e. monitoring competition among items). For the young adult group, pairwise comparisons within the ACC ROI revealed no significant voxels that were activated more following a nap than wake. On the contrary, a region with a peak on left ACC that extended bilaterally (0, -10, 30) was more active

following wake. For older adults, whereas a posterior cluster of right ACC was more active for the nap condition (4, -14, 30; Brodmann's area [BA] 24) a more anterior cluster was more active for the wake condition (2, 42, 6; BA 32).

Functional imaging findings, in summary, reveal that retrieval-related activation is modulated by napping, and whereas a nap is associated with reduced hippocampal activation and hippocampo-prefrontal connectivity for retrieval success, and reduced ACC activation for error monitoring in young adults, no such modulation was observed in the older adult group.

e. Associations of Memory-Related Brain activation with Nap Architecture

In order to investigate whether nap-dependent changes in brain activation are attributable to SWS and nREM2 spindles, the relationship between nap physiology and retrieval related signal intensity in the ROIs was investigated separately for the young and older adult groups.

Slow wave sleep duration predicted better post-nap memory retention in young adults, and it was negatively related to hippocampal activation during successful recall. Importantly, this SWS related decrease in hippocampal involvement during recall in young adults was evident bilaterally (left hippocampus: r = -.71, p = .010; right hippocampus: r = -.55, p = .067). Figure 8 shows that this relationship was observed not only for time spent in SWS but also for spectral power of SWA for young adults and was evident for both frontal (Fig 6b; r = -.58, p = .012) and central channels (r = -.55, p = .079). A similar but weaker relationship was observed for older adults. Time spent in SWS was associated with decreased retrieval related activation on the left hippocampus (Figure 9; r = -.62, p = .078).

Analyses regarding sleep spindles revealed that sigma power was associated with decreased activation in right hippocampus (frontal: r = -.66, p = .020; central: r = -.5, p = .079) for young adults. On the contrary, for older adults there was no relationship between hippocampal activation and spindle density or sigma power (all ps > .25).

As reported in the previous section, retrieval success was associated with robust and bilateral activation in ACC in both age groups (i.e. Tables 3, 4, 6 and 7). Voxel-wise comparisons of the nap and wake conditions revealed that the strength of ACC activation was modulated by the nap manipulation only for young adults (i.e. increased activation after a wake period in young adults, no significant condition effect in older adults). This may suggest that, following a nap, retrieval required less involvement of ACC in young adults, possibly due to reduced competition among items and stronger cue-target relationships. In fact, decreased ACC activation for young adults was associated with more time spent in SWS (r = - .61, p = .037) and higher SWA (frontal: r = -.73, p = .008; central: r = -.64, p = .035) during the nap for young adults. Such a relationship was not observed in the older adult group (Figure 10). Spindle density or sigma power measures did not predict ACC activation in either young or older adult groups.

3. The Interaction Between Naps and Nocturnal Sleep

a. Effects of Napping on Nocturnal Sleep Architecture

In order to determine whether taking a nap during the day changes nocturnal sleep characteristics, sleep quantity and quality measures were compared with 2 x 2 repeated measures ANOVAs. Table 9 shows nocturnal sleep duration and sleep stage distributions for young and older adult groups. For the dependent measure of total sleep time, there was no significant main effect of condition (nap night vs. wake night), $F(1,18) = .39$, p = .538;

no significant main effect of age group, F(1,18) = .14, p = .718 and no condition by age group interaction, F(1,18) = .44, p = .517 suggesting no effect of a mid-day nap on nocturnal sleep duration. For sleep latency, there was no significant main effect of condition, F(1, 18) = 1.01, p = .328 but a trend-level main effect of age group, F(1,18) = 3.87, p = .065 with older adults taking longer to fall asleep. Notably, there was no significant interaction, F(1,18) = .47, p = .501; irrespective of presence of a nap older adults had longer nocturnal sleep latencies. In contrast, napping increased WASO, F(1,18) = 7.05, p = .016. The main effect of age on WASO was significant, F(1,18) = 5.02, p = .038, and there was a trend level condition by age group interaction, F(1,18) = 3.92, p = .063. Wake after sleep onset was higher in the older adult group and taking a nap increased nocturnal WASO for all participants; however, this effect was more pronounced for older adults. Sleep efficiency, by definition, is strongly correlated with WASO. Accordingly, for the efficiency measure there was a significant main effect of condition, F(1,18) = 5.95, p = .025; a marginal main effect of age group, F(1,18) = 4.16, p = .056 and a trend level condition by age group interaction, F(1,18) = 3.85, p = .065 suggesting that the magnitude of the effect of napping on reducing sleep efficiency was higher for older adults .

Similar repeated measures ANOVAs were run to investigate the effects of napping on nocturnal sleep stage distributions in young and older adults. For nREM1, there was a marginal main effect of condition, F(1,18) = 4.09, p = .058; a trend-level main effect of age group, F(1,18) = 3.54, p = .076 and a trend level condition by age group interaction, F(1,18) = 3.78, p = .068. Whereas time spent in nREM1 was similar for both sessions in the young adult group, nREM1 was increased following a nap in the older adult group. For

nREM2 main effects for neither condition, $F(1,18) = .47$, $p = .502$ nor age group, $F(1,18) = .30$, $p = .588$ were significant. However the interaction between condition and age group was significant, $F(1,18) = 8.51$, $p = .009$, suggesting that nocturnal nREM2 was decreased following a nap only for older adults (Table 9). No effects were observed for SWS (main effect of condition: $F(1,18) = 1.43$, $p = .247$; main effect of age group: $F(1,18) = 2.17$, $p = .158$; condition by age group interaction: $F(1, 18) = .39$, $p = .541$) or REM sleep (main effect of condition: $F(1,18) = .09$, $p = .768$; main effect of age group: $F(1,18) = .57$, $p = .459$; condition by age group interaction: $F(1,18) = .59$, $p = .449$).

Next, spectral power of nocturnal sleep was analyzed in order to determine whether taking a mid-day nap influences delta waves of SWS and sigma waves of nREM2 sleep (Table 10). Repeated measures ANOVA with power density of delta waves on frontal channel revealed a significant main effect of age group, $F(1,18) = 15.87$, $p = .001$ with reduced SWA in the older adult group. Neither the main effect of condition, $F(1,18) = .54$, $p = .470$ nor the condition by age group interaction, $F(1,18) = .81$, $p = .381$, were significant. A similar age-related reduction in SWA was observed for the central channels, $F(1,18) = 15.94$, $p = .001$. There was no significant effect of condition, $F(1,18) = 1.65$, $p = .215$ or condition by age group interaction, $F(1,18) = 1.48$, $p = .239$ for central SWA. Power density analyses within the sigma range yielded a different pattern. Unlike delta, sigma in this sample was not influenced by age. A repeated measures ANOVA with sigma power on the frontal channels revealed no main effect of condition, $F(1,18) = .16$, $p = .691$; no main effect of age group, $F(1,18) = .35$, $p = .564$ and no condition by age group interaction, $F(1,18) = .01$, $p = .911$. Sigma power on the central channels also yielded no

main effect of condition, F(1,18) = .55, p = .468; no main effect of age group, F(1,18) = .04, p = .838 and no condition by age group interaction, F(1,18) = .01, p = .925.

In summary, taking a mid-day nap affected nocturnal sleep in various ways for young and older adults. Overall, taking a nap increased WASO and decreased sleep efficiency for all participants but this effect was significantly more pronounced for older adults. Furthermore, time spent in light sleep (i.e. nREM1) was increased following a nap in the older adult group. On the contrary, napping had no effect on sleep stage distributions for SWS or REM sleep. Spectral analyses revealed that SWA (delta power) was greatly reduced in older adults. However, a mid-day nap had no effect on SWA. Spectral power on the spindle frequency (i.e. sigma power) was similar between young and older adults and was not affected by napping.

b. Effects of Nocturnal Sleep on Memory

In order to determine whether the overnight interval was associated with further changes in memory consolidation, the relationship between overnight changes in recall and sleep physiology were investigated for both of the overnight intervals: following a mid-day nap or continuous wake. Overnight change in recall was calculated by subtracting delayed recall score from the 24 hr recall score. A 2 x 2 repeated measures ANOVA with the 24 hr overnight change score as the dependent variable revealed no main effect of condition, $F(1, 20) = .08$, $p = .785$; no main effect of age group, $F(1, 20) = 2.11$, $p = .162$ and no condition by age group interaction, $F(1, 20) = .26$, $p = .613$. As can be seen in Figure 11, this intersession change in recall was smaller in magnitude and highly variable in both groups. In fact, one sample t-tests revealed that the 24 hr intersession change in recall score was not different from zero for either the young adult group (nap: t(12) = -

1.39, p = .191; wake: t(11) = -.39, p = .701) or the older adult group (nap: t(9) = .71, p = .494; wake: t(9) = .67, p = .520). As such, there was no reliable change in memory performance from delay to 24 hr retention intervals in either age group.

Next, the relationship between overnight changes in memory and nocturnal sleep characteristics were investigated. For the night preceded by a mid-day nap, those older adults with more nocturnal SWS, performed better the next morning, r = .68, p = .044. The relationship between overnight changes in memory and nocturnal SWS following a nap was negative for young adults, r = -.65, p = .032. Given that SWS during the nap period predicted better performance, it might be speculated that SWS-dependent declarative memory consolidation already took place in the young adult group. However, when SWS duration for the nap was partialed out, the relationship between overnight changes in memory and nocturnal SWS was still significant, = -.64, p = .045. There was no significant relationship between nocturnal sleep for the wake condition and 24 hr intersession change in recall for either young or older adult groups.

CHAPTER 3

DISCUSSION

The present study provides evidence that sleep is a unique period during which memory consolidation and systems level reorganization takes place, and that aging interferes with the efficiency of this mechanism. In a sample of healthy young adults, it was observed that electrophysiological properties of a mid-day nap predict better long-term memory retention, and more efficient retrieval-related brain activation. Specifically, sleep following learning in young adults is associated with decreased hippocampal activation and decreased hippocampo-frontal co-activation, which may be interpreted as initial signs of transfer of memory storage from the hippocampus to the neocortex. Importantly, it was found that this process depends largely on SWS and to a lesser extent on sleep spindles. Although the duration and architecture of naps were similar between young and older adults, the pattern of nap-dependent neural reorganization was different in the older adult group. Following a nap, retrieval still required hippocampal activation and hippocampo-frontal co-activation. Furthermore, successful retrieval required cognitive control and error monitoring processes as evidenced by increased ACC and MFG activation following a nap as compared to wakefulness in the older adult group.

A. Nap-Dependent Neural Reorganization

As predicted, longer duration of SWS in the nap was associated with reduced forgetting of word-pairs from baseline to a delay interval in the young adult group. At the neural level, napping was associated with reduced hippocampal activation. Specifically, EEG power of SWS (i.e. delta) and nREM2 spindles (i.e. sigma) were negatively correlated with hippocampal activity. Furthermore, napping in young adults was

associated with reduced co-activation between the hippocampus and dorsolateral prefrontal regions.

The finding of SWA and sigma-related decrease in hippocampal involvement during retrieval provides evidence that systems level neural reorganization in the episodic memory network takes place as early as the first sleep opportunity following learning. This finding lends support to the two-stage model of memory consolidation. Accordingly, memory consolidation preferentially takes place via sleep-dependent reactivation (McClelland, McNaughton & O'Reilly, 1995) that eventually results in transfer of memory traces from labile storage in the hippocampus to more permanent storage in the necortex (Buzsáki, 1998). During active wake, new memories and their contextual properties are coded in the hippocampal system. Subsequently during sleep, SWA in the neocortex initiates a cortico-hippocampal dialogue. Sharp wave ripples are fast depolarizing EEG events that occur during wakefulness and SWS, and have been shown to accompany neural reactivation of new learning that preceded sleep (Nadasdy et al., 1999; Wilson & McNaughton, 1994). Simultaneous co-occurrence of SWA in the neocortex and sharp waves in the hippocampus provides the mechanism by which the reactivated new memory representations are transferred to neocortical regions for long-term storage (Inostroza & Born, 2013). Furthermore, sleep spindles, which are generated in the thalamus and spread to the cortex play a crucial role in memory consolidation. New learning increases spindle activity (Fogel & Smith, 2006; Gais, Mölle, Helms & Born, 2002; Holz et al., 2012) and remarkably, spindle propagation following learning is higher in cortical regions that play a critical role in learning that particular task (Nishida & Walker, 2007).

An important highlight of the present study is that sleep-dependent neural reorganization patterns are different between young and older adults. Unlike young adults, nap-dependent reduction in hippocampo-frontal co-activation was not seen in the older adult group. Irrespective of whether recall was preceded by a nap, approximately 50% of activation in the dorsolateral regions of the frontal cortex was predicted by hippocampal activation in older adults. Notably, although overall older adults performed worse on the declarative memory task, neural activation patterns for successful retrieval in older adults still *were* different following a nap than continuous wake. Napping was associated with greater activation in frontal regions including ACC, MFG and superior frontal gyrus. This suggests that, a mid-day nap does indeed induce some long-term changes in the neural representation of memory for older adults. However, memory retrieval still relies largely on hippocampal activation and fronto-hippocampal co-activation.

The present finding that aging is associated with changes in sleep-dependent neural reorganization is in line with previous animal research. Studies on spatial memory in rats (e.g. maze navigation learning) show that neuronal firing patterns in the CA1 subfield of the hippocampus are significantly correlated between learning and subsequent rest episodes (e.g. Wilson & McNaughton, 1994) providing evidence for sleep-dependent replay of episodic learning. However, it has been shown that aging interferes with hippocampal replay. Specifically, it was found that the temporal order of neural reactivation was diminished in older rats (Gerrard, Burke, McNaughton & Barnes, 2008). In other words, although aged rats show preserved hippocampal reactivation following learning, the temporal sequence of neuronal firing was lost and this impairment, in turn, correlated with decreased spatial memory performance.

It may be speculated that age-related changes in sleep-dependent neural reorganization are caused by age-related changes in SWS-mediated neural reactivation. Although it is not possible to measure hippocampal neuronal replay akin to animal studies in healthy human subjects, advents in brain imaging methods such as simultaneous EEG-fMRI (Deuker et al., 2013) or EEG-MEG (Bang, Khalilzadeh, Hämäläinen, Watanabe & Sasaki, 2013) makes it possible to investigate neural activation patterns during sleep. Using such methods will allow for comparing learning-dependent neural activation during sleep in young and older adults.

The age-group differences observed in nap-dependent neural reorganization cannot be explained by an age-related deficit in the ability to nap. All young and older participants were successfully able to nap according to instructions. With the exception of REM duration, nap architecture, sleep stage duration, quality and EEG power measures were similar between young and older adults. Whereas 50% of the young adults had some REM sleep, none of the older adults entered this stage. Importantly, memory performance and SWS duration were similar between young adults who had REM and those who did not. Duration of nREM sleep in naps is modulated by prior wakefulness, with longer prior wakefulness being positively associated with SWS duration (Dijk, Beersma & Daan, 1987). On the other hand, REM sleep follows a circadian variation. Propensity for REM sleep has an acrophase in the early morning (Endo et al., 1981), and given that naps in this study started between 12:00-13:00, it does not come as a surprise that REM was rare in young adults and was absent in older adults who are likely to have an advanced circadian phase (Weitzman et al., 1981).

Even though duration and power of SWS in the older adult naps was not significantly different from that of young adults, the relationship between SWS and memory-related neural activation was altered. Slow wave sleep duration was not associated with better memory performance in older adults. However, SWS was associated with a relative decrease in left hippocampal activation. Although retrieval still relies largely on hippocampo-frontal co-activation, the finding of SWS dependent decrease in hippocampal activation suggests that some degree of nap-dependent memory consolidation occurs in aging. In support of this, Wilson and colleagues (2012) found no difference between overnight consolidation of declarative learning for young and older adults. Furthermore, it was found that in a combined sample of individuals with mild cognitive impairment and healthy older adults nocturnal SWA was positively associated with change in recall performance for semantically associated word-pairs (Westerberg et al., 2012).

Analysis of functional imaging data revealed that, irrespective of condition and age group, recall of associative learning yielded activation in a broad network of structures including inferior parietal and occipital cortex, putamen, and the cerebellum. Declarative memory retrieval requires activation of a broad network of structures engaging in visual, verbal and motor processes, and activation is modulated by mental search and monitoring demands (Daselaar et al., 2009; Henson, Shallice & Dolan, 1999; Kim, 2010; Konishi, Wheeler, Donaldson & Buckner 2000; Reas, Gimbel, Hales & Brewer, 2011; Shallice et al., 1994). Inferior parietal lobule is a multi-modal processing region that plays a critical role in comprehension of verbal material (e.g. Price, 1998), and is densely connected with the hippocampus and the cerebellum (Clower et al., 2001). Thus, the brain areas that are

commonly activated across conditions correspond to regions that play primary roles in visual processing, reading, verbal comprehension and simple motor movement (i.e. button press).

Within-subject comparisons of retrieval-related brain activation when tested following a mid-day nap relative to continuous wake yielded regionally specific and significant differences in brain activation. Notably, even under identical circadian and experimental conditions, we observe differences in brain activation patterns within participants. This emphasizes the critical role of sleep in the intervening interval. In young adults, napping was associated with increased activation in right IFG. Conversely, when compared to napping, wakefulness was associated with increased frontal activation in bilateral ACC and left MFG. Previous research confirms that both IFG and MFG play a critical role in declarative encoding and retrieval (Woodward et al., 2006), however, with a critical difference of function between the structures. Inferior frontal gyrus is commonly activated in tasks that require semantic associations and relates to working memory functioning. Furthermore, right prefrontal regions are activated more during successful remembering than left frontal regions (Tulving et al., 1994). With respect to a word-pair recall task, the role of IFG activation is the selection of the most suitable associations among competing alternatives that relate two concepts best (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). Middle frontal gyrus, on the other hand, may play a role earlier in associative learning that corresponds to testing scenarios and generation of relational associations. In support of this functional distinction, in a study that manipulated memory performance by controlling rounds of practice during encoding, low memory performance compared to high performance, was associated with increased bilateral MFG

activity (Montaldi et al., 2001). Another functional imaging investigation further revealed that hippocampo-MFG connectivity was associated with *generation* of semantic relationships whereas hippocampo-IFG connectivity was associated with *selection* of semantic relationships (Woodward et al., 2006). Seen in this light, increased left MFG activation following wake may correspond to online attempts for making associations (i.e. further encoding attempts at time of retrieval) whereas increased right IFG activation following napping in young adults may correspond to retrieval of already formed associations. Notably, in older adults middle frontal regions were active in both nap and wake conditions.

Word-pair recall in this study was associated with robust activation in the anterior cingulate regions in both age groups. However, sleep modulated ACC activation in significantly different ways for young and older adults. In young adults, napping was associated with decreased ACC activation compared to wakefulness. In stark contrast, for older adults ACC was more active following napping. As part of the limbic system, ACC has traditionally been associated with emotional processing. However, ACC consists of two major subdivisions: a dorsal cognitive division including Brodmann's areas 24 and 32, and a more rostral-ventral affective division including Brodmann's areas 25 and 33 (Devinsky, Morrell, & Vogt, 1995; Vogt et al., 1992). Notably, the clusters of activation observed in this task are within the boundaries of the cognitive subdivision of ACC.

A prominent theory of the function of ACC, which is part of a parallel distributed cingulo-frontal network, highlights the structure's critical role in error detection and monitoring (Bush, Luu & Posner, 2000). Specifically, ACC engages in effortful control when verbal associations are initially generated. In contrast, insula becomes more active

when the associations are more practiced or established (Raichle et al., 1994). Evidence for the error detection and monitoring role of ACC comes from a meta-analysis concluding that ACC activation is modulated by increasing task difficulty and memory demands (Paus, Koski, Caramanos & Westbury, 1998). In fact, the effects of memory strength on brain activation were recently investigated by allowing participants to practice word pairs for different number of rounds (Reas & Brewer, 2013). Specifically, recall of word pairs that participants were allowed to study only once (i.e. low memory strength) was associated with increased ACC activation compared to recall of pairs the participants studied several times (i.e. high memory strength). It can thus be concluded that, for weaker memory traces ACC activation is required in order for retrieval search to be successful since weaker cue-target associations would result in more competition between candidate target items. In fact, results of the present experiment reveal that ACC activation is reduced when learning is followed by a mid-day nap and, duration and EEG power for SWS in the nap predicts this reduced ACC activation for young adults. Slow wave sleep in the nap was associated with better memory retention, making associations between cue and target words stronger. This results in reduced competition among candidate semantic relationships and thus, retrieval is associated with decreased involvement of error monitoring processes.

In the older adult group ACC (BA 24) was found to be more active when recall was preceded by sleep than wakefulness and furthermore, ACC activation was not modulated by SWS. Based on the findings that successful retrieval in older adults following a nap was associated with MFG and ACC activation, it may be concluded that aging is associated with changes in the efficiency with which memories are consolidated

over sleep, thus the aged brain relies more on error monitoring and control processes to successfully execute an effortful retrieval search. In fact, compensatory ACC activation during retrieval in older adults has been reported elsewhere (Martinelli et al., 2013) and has been associated with increased cognitive control (Botvinick, Nystrom, Fissell, Carter & Cohen, 1999; Miller, 2000). However, while increased frontal activation in the middle frontal and anterior cingulate regions may be associated with more effortful retrieval search due to decreased memory strength, one must also address the alternative that memory search demands in older adults might be greater because of richness of semantic networks. In fact, it has been suggested that age-related changes in cognitive functioning may be due to increased knowledge as opposed to a processing deficit (Ramscar, Hendrix, Shaoul, Milin & Baayen, 2014). However, the finding that SWS during the nap was associated with decreased ACC activation during post-nap memory retrieval in young but not older adults suggests that ACC activation was mediated by sleep-dependent memory consolidation.

Recently, Mander and colleagues (2013b) investigated whether age-related changes in long-term retention of declarative memory are associated with disrupted quality of SWS and age-related brain atrophy. Older adults in this study had decreased SWA, decreased gray matter volume in the medial prefrontal cortex and decreased overnight memory retention. Furthermore, the authors found that the effect of age on SWA was mediated by mPFC atrophy and concluded that age-related cortical atrophy may be responsible for disrupted slow wave propagation. Their finding may suggest that the mechanism of sleep-dependent memory consolidation may not be identical between young and older adults. In fact, we found that the process of systems level consolidation

observed in young adults is changed in older adults. Although more time spent in SWS was associated with reduced left hippocampal activation in older adults (Figure 9), successful retrieval still largely relied on hippocampal activation and hippocampo-frontal co-activation. Furthermore, we found that retrieval following a nap requires additional cognitive control processes in older adults. Slow wave sleep-dependent decrease in ACC activation was diminished in aging.

In summary, the present study shows that the efficiency with which systems level consolidation takes place in the first sleep opportunity following learning is reduced in healthy older adults. This may suggest that SWS-dependent memory reactivation processes are disrupted in aging, leaving memory traces at a more labile state of storage that still rely on hippocampal activation and therefore, successful retrieval requires additional allocation of compensatory cognitive control processes. Young and older adults performed similarly in tests of executive functioning that measure cognitive flexibility and verbal fluency. However, older adults in this sample, although scoring higher than age norms, performed worse than young adults on the Stroop interference task suggesting that cognitive inhibition in this group may not be as efficient as young adults. Therefore error monitoring (as executed by ACC) and association generation processes (as executed by MFG) that young adults do not need after a nap, presumably due to sleep-dependent strengthening of cue-target associations, were still recruited in older adults.

B. Strengths and Potential Limitations

As opposed to more traditional functional imaging designs that utilize cognitive subtraction methods (e.g. contrasting memory retrieval with a memory irrelevant task such as Chinese letter identification or word reading), the current design relies on investigation

of a BOLD deflection from baseline during successful recall of associative learning. In discussion of pros and cons of this approach, Reas and colleagues (2011) concluded that deflection from baseline gives information about task engagement and task difficulty effects that are lost when cognitive subtraction is used exclusively. In fact, memory retrieval relies on several processes such as mental search and error monitoring, which are carried out by different but interacting frontal cognitive networks (e.g. Moscovitch, 1992). Implementing a design in which BOLD analysis would rely on subtraction of incorrect trials from correct trials would not have allowed for investigation of such resources that vary with recall success.

The most important methodological strength of the present study is the use of a within-subjects design. This approach allowed for direct comparison of brain activation changes when the same individual is tested after a nap and wakefulness. Unlike previous studies that focus on between group comparisons of sleep-dependent changes in behavior and neural activation (e.g. Fogel et al., 2013; Mander et al., 2013b), all contrasts reported in this study are based on subtractions of the individual's own brain activation patterns. Thus, analyses were robust to any potential effects of age-related atrophy or changes in vasculature on brain activation. Furthermore, at the behavioral level, encoding and recall performance in older adults was reduced compared to young adults. Functional imaging in this study was based on an event-related analysis of successful retrieval and thus, there were fewer events in the older adult group. While this would have been a significant limitation if analyses were based on between group comparisons, within-subject comparisons were reliable and robust to group differences in number of events entered into general linear models.

Another major methodological strength of the present study is that using a nap design to study sleep-dependent neural activation patterns rules out any potential circadian confounds. Previous research suggests that BOLD activation may be influenced by circadian phase (Gorfine & Zisapel, 2009; Vandewalle et al., 2009) and such confounds have been addressed in studies of sleep-dependent memory consolidation (e.g. Payne & Kensinger, 2011). Importantly, functional imaging in the present study started at the same time of the day for the nap and wake sessions for each participant.

The age group differences in the associations of memory performance and brain activation with sleep are not attributable to non-specific effects such as diminished habitual sleep quality or alertness. Sleep habits and circadian rhythmicity as measured subjectively through diaries and questionnaires, and objectively with actigraphy, were similar between young and older adult groups. Based on self-reports, sleepiness at the onset of each behavioral testing session was similar across age groups and conditions.

A potential limitation that needs to be addressed is the lack of significant behavioral effects in either the young or older adult groups. In fact, another functional imaging study that tested memory for word-pairs following a nap also failed to show a behavioral effect of sleep-dependent memory consolidation (Takashima et al., 2009). Durrant and Lewis (2009) note that the major goal in memory consolidation is efficient learning and storage. Thus, sleep-dependent memory consolidation may not necessarily lead to a measurable increase in performance at the behavioral level but may instead be associated with more efficient neural representation of the memory experience.

Another potential limitation is the size and the nature of the participant sample. The present study has a small sample ($n = 22$) that may have resulted in reduced statistical

power to detect age-group differences. Furthermore, safety precautions associated with magnetic resonance imaging restricts study inclusion. For instance, presence of cardiovascular disease and use of blood thinner medication, both of which are highly prevalent in older adults (Sebastian & Tresch, 2000), interfere with the BOLD signal and thus, were included as exclusion criteria for the present study. Similarly, medical conditions such as arthritis that are highly prevalent in aging (Centers for Disease Control and Prevention, 2003) may require surgery involving metal implants (e.g. joint replacement), and older adults with such medical history would not be eligible for MRI studies. Such methodology-related restrictions in participant recruitment may limit the generalizability of the present findings to the general aging population. However, it should be noted that the goal of the present study was to investigate changes associated with *healthy* aging. Previous research shows that such comorbidities like cardiovascular disease and arthritis are associated with increased sleep disturbances that are explained by the presence of comoborbid condition and are not caused by aging (Ancoli-Israel, Ayalon & Salzman, 2008).

C. Age-Related Changes in the Relationship Between Naps and Nocturnal Sleep

In addition to investigating the cognitive function of mid-day naps, the present study design also allowed for comparing the effects of napping on subsequent nocturnal sleep in young and older adults. Perhaps not surprisingly, napping decreased sleep efficiency and increased wake after sleep onset, and the magnitude of this effect was larger for older adults. In relation to longer awakenings, older adults had more nocturnal nREM1 and nREM2 following napping. Importantly, however, SWA and spectral power in the spindle frequency range was unaffected by napping.

Age-related changes in sleep architecture are well documented and include decreased time in REM and SWS, and increased time in nREM1 and nREM2 (Lombardo et al., 1998; Ohayon et al., 2004; van Cauter et al., 2000). In this sample, for both the night following a nap and the night following continuous wakefulness, older adults had increased sleep latency, increased WASO and decreased sleep efficiency but no significant age-related differences were observed for sleep stage distributions. In line with previous research (Mander et al., 2013b; van Cauter et al., 2000), spectral power in the delta band for nocturnal sleep was reduced in older adults compared to young adults. Overall, these findings suggest that, in a sample of healthy older adults who have intact cognitive functioning who have sleep and activity habits not significantly different from young adults taking a mid-day nap increases night awakenings and decreases sleep efficiency.

In conclusion, as the first within-subjects investigation of the effects of sleep on declarative memory-related brain activation in young and older adults, the present study shows that aging is associated with changes in sleep-dependent neural reorganization. Whereas retrieval for a word-pair learning task relies less on hippocampal structures in young adults following a mid-day nap rich in SWS (both in duration and power of delta waves), successful retrieval requires hippocampal activation and hippocampo-frontal co-activation in older adults. Furthermore, strength of the association between word pairs are increased following naps rich in SWS in young adults (as evidenced by positive correlations between SWS duration and post-nap change in memory performance). Thus, retrieval search is associated with less competition among target associations. Therefore, SWS and SWA predict decreased ACC activation in young adults. On the other hand, retrieval following a nap still relies on compensatory error monitoring and semantic

association generation processes in older adults. Importantly, age-related changes in the effects of a mid-day nap on retrieval-related brain activation cannot be explained by age-related changes in sleep habits, ability to nap or circadian influences. As evidenced by self-reports as well as objective measures, sleep habits were similar between young and older adults, there were no significant age-related differences in the nap architecture, and all testing took place at the same time of the day across nap and wake conditions in this sample.

APPENDIX A

TABLES

Table 1. Summary of results for neuropsychological tests for young and older adult groups.

	Young Adults Mean (SD)	Older Adults Mean (SD)	*p**
Episodic Memory			
CVLT: Trials 1-5 Total Correct	62.33 (7.42)	50.0 (9.04)	.002
CVLT: Short Delay Free Recall	14.5 (1.73)	10.4 (3.72)	.003
CVLT: Long Delay Free Recall	14.25 (1.91)	11.5 (2.79)	.013
CVLT: Long Delay Cued Recall	14.42 (1.91)	12.4 (2.46)	.043
CVLT: Recognition Hits	15.67 (.65)	14.30 (1.71)	.018
Executive Functioning			
Phonemic Fluency	16.42 (3.02)	16.03 (5.89)	.846
Semantic Fluency	24.33 (2.36)	20.75 (6.28)	.081
Trail Making (switching - number/letter sequencing)	30.54 (24.65)	47.3 (23.51)	.120
Stroop (color naming – word reading)	24.94 (8.83)	69.92 (63.73)	.025

CVLT, California Verbal Learning Test-II

* *p* values correspond to one-way ANOVAs comparing young and older adults, F(1,20)

Table 2. Nap characteristics for young and older adults.

	Young Adults Mean (SD)	Older Adults Mean (SD)	*p**
TST (min)	85.22 (19.81)	71.78 (18.28)	.129
Sleep Latency (min)	7.42 (3.99)	4.67 (2.9)	.098
WASO (min)	5.37 (6.42)	3.06 (3.19)	.334
Sleep Efficiency (%)	86.67 (9.71)	90.16 (5.73)	.350
nREM1(%)	30.39 (24.45)	49.04 (28.31)	.122
nREM2 (%)	41.91 (17.71)	38.60 (19.15)	.687
SWS (%)	23.14 (12.81)	12.37 (15.0)	.092
REM (%)	4.56 (6.34)	0	
REM latency (min)	52 (20.52)	n/a	
REM density (REMs/REM duration)	11.89 (4.79)	n/a	
Mean SWA on frontal bands (μV^2/Hz)	223.03 (156.33)	129.27 (71.41)	.189
Mean SWA on central bands (μV^2/Hz)	189.94 (152.71)	84.58 (40.83)	.123
Mean Sigma on frontal bands (μV^2/Hz)	2.55 (1.18)	2.35 (2.31)	.807
Mean Sigma on central bands (μV^2/Hz)	2.37 (1.08)	2.61 (2.06)	.746
Spindle density on frontal bands	0.95 (.77)	1.03 (1.42)	.858
Spindle density on central bands	0.76 (.72)	0.86 (.89)	.796

TST, total sleep time; WASO, wake after sleep onset; nREM, non-rapid eye movement sleep, SWS, slow wave sleep; REM, rapid eye movement, SWA, slow wave activity
* *p* values correspond to one-way ANOVAs comparing young and older adults, F(1,19)

Table 3. Functional imaging results for the main effect of napping on successful recall in young adults

Lobe	Gyrus	BA	MNI coordinates	Talairach coordinates	Cluster size
L Parietal Lobe	Inferior parietal lobule	BA 40	-34, -48, 46	-33.6, -44.4, 44.6	95
R Parietal Lobe	Superior Parietal Lobule	BA 7	34, -56, 58	33.6, -51.6, 56.1	15
R Frontal Lobe	Superior Frontal Gyrus	BA 6	2, 12, 56	1.9, 14.2, 50.9	17
R Frontal Lobe	Cingulate gyrus	BA 32	4, 12, 38	3.9, 13.4, 34.3	15
L Frontal Lobe	Cingulate gyrus	BA 32	-8, 20, 34	-7.9, 20.9, 30.3	17
R Occipital Lobe	Middle occipital gyrus	BA 19	34, -91, 13	33.6, -90.6, 12.8	10
Sub lobar	Insula	BA 13	-32, 22, 0	-31.7, 21.3, -1.1	34
Sub lobar	Caudate		-8, 14, -4	-7.9, 13.4, -4	60
Sub lobar	Putamen		20, 16, -8	19.8, 15.2, -7.5	36
Sub Lobar	Thalamus		10, -12, 2	9.9, -11.5, 2.4	16
R posterior cerebellum			38, -66, -22	37.6, -64.9, -15.3	137
R anterior cerebellum			8, -28, -12	7.9, -27.6, -8.7	77

BA, Brodmann's Area; MNI, Montreal Neurological Institute

Table 4. Functional imaging results for the main effect of wakefulness on successful recall in young adults

Lobe	Gyrus	BA	MNI coordinates	Talairach coordinates	Cluster size
L Frontal lobe	Medial frontal gyrus	BA 6	-2, 14, 48	-1.9, 15.7, 43.4	134
R Limbic lobe	Cingulate gyrus	BA 24	6, 6, 34	5.9, 7.4, 30.9	98
L Limbic lobe	Cingulate gyrus	BA 24	-6, 10, 32	-5.9, 11, 28.9	
L Parietal lobe	Inferior parietal lobule	BA 40	-36, -48, 44	-35.6, -44.5, 42.8	25
R Occipital Lobe	Inferior occipital gyrus	BA 18	34, -96, -8	33.7, -93.3, -2.1	23
Sub lobar	Putamen		-24, 8, 10	-23.8, 8.2, -8.8	131
R posterior cerebellum			36, -64, -28	35.6, -63.3, -20.4	134
L anterior Cerebellum			-34, -54, 32	-33.7, -53.7, -24.2	139

BA, Brodmans's Area; MNI, Montreal Neurological Institute

Table 5. Functional imaging results for paired-sample t-tests comparisons in young adults

Lobe	Gyrus	BA	MNI coordinates	Talairach coordinates	Cluster size
Regions showing greater activation following a nap (Nap > Wake)					
L Occipital Lobe	Middle Occipital Gyrus	BA 18	-24, -92, -2	-23.8, -89.2, 2.8	39
R Frontal Lobe	Inferior Frontal Gyrus	BA 45	52, 26, 2	51.5, 25.3, 0.6	27
Sub Lobar	Insula	BA 13	38, 20, 18	37.6, 20.2, 15.6	8
L Frontal Lobe	Precentral Gyrus	BA 4	-64, -10, 28	-63.4, -8.4, 26.2	6
Regions showing greater activation following wake (Wake > Nap)					
L Limbic Lobe	Cingulate Gyrus	BA 24	-2, -10, 28	-2, -8.4, 26.2	36
L Frontal Lobe	Middle Frontal Gyrus	BA 11	-26, 34, -20	-25.7, 32.1, -18.4	9

BA, Brodmans's Area; MNI, Montreal Neurological Institute

Table 6. Functional imaging results for the main effect of napping on successful recall in older adults.

Lobe	Gyrus	BA	MNI coordinates	Talairach coordinates	Cluster size
R Frontal Lobe	Precentral Gyrus	BA 4	42, -18, 58	41.8, -14.8, 54.2	9
R Frontal Lobe	Medial Frontal Gyrus	BA 8	2, 24, 50	2, 25.5, 44.8	6
R Limbic Lobe	Anterior Cingulate	BA 24	8, 22, 30	7.9, 22.7, 26.5	6
L Frontal Lobe	Middle Frontal Gyrus	BA 46	-48, 24, 26	-47.5, 24.4, 22.7	8
L Frontal Lobe	Medial Frontal Gyrus	BA 6	-2, 30, 38	-2, 30.8, 33.5	6

BA, Brodmann's Area; MNI, Montreal Neurological Institute

Table 7. Functional imaging results for the main effect of wakefulness on successful recall in older adults

Lobe	Gyrus	BA	MNI coordinates	Talairach coordinates	Cluster size
L Frontal Lobe	Medial Frontal Gyrus	BA 6	0, 32, 40	0, 32.8, 35.2	6
R Limbic Lobe	Cingulate Gyrus	BA 32	8, 14, 44	7.9, 15.6, 39.7	14
L Frontal Lobe	Superior Frontal Gyrus	BA 6	-4, 10, 54	-3.9, 12.2, 49.1	7
L Frontal Lobe	Superior Frontal Gyrus	BA 6	0, 6, 56	0, 8.4, 51.2	5

BA, Brodmann's Area; MNI, Montreal Neurological Institute

Table 8. Functional imaging results paired-sample t-tests comparisons in older adults.

Lobe	Gyrus	BA	MNI coordinates	Talairach coordinates	Cluster size
Regions showing greater activation following a nap (Nap > Wake)					
L Frontal Lobe	Middle Frontal Gyrus	BA 6	-20, -8, 46	-19.8, -5.6, 42.6	62
L Limbic Lobe	Posterior Cingulate	BA 30	-30, -78, 8	-29.7, -75,2, 11	45
R Frontal Lobe	Superior Frontal Gyrus	BA 8	18, 16, 48	17.8, 17.7, 43.3	42
L Limbic Lobe	Parahippocampal Gyrus	BA 28	-18, -20, -28	-17.8, -20.1, -22.5	16
R Occipital Lobe	Fusiform Gyrus	BA 37	38, -54, -6	37.6, -52.6, -2.4	12
L Limbic Lobe	Cingulate Gyrus	BA 24	-22, -20, 46	-21.8, -17.3, 43.2	9
Regions showing greater activation following wake (Wake > Nap)					
L Limbic Lobe	Parahippocampal Gyrus	BA 36	-22, -38, -8	-21.8, -37.1, -4.8	6

BA, Brodmann's Area; MNI, Montreal Neurological Institute

Table 9. Nocturnal sleep characteristics in young and older adults.

Nocturnal sleep following a mid-day nap		
	Young Adults Mean (SD)	Older Adults Mean (SD)
TST	425.41 (51.53)	404. 50 (89.17)
Sleep Latency	4.27 (2.83)	5.83 (2.41)
REM Latency	98.77 (53.59)	109.78 (39.48)
WASO	8.18 (8.43)	38.70(44.08)
Sleep Efficiency	97.02 (2.05)	89.11 (12.57)
NREM1	10.25 (3.65)	15.55 (2.63)
NREM2	52.58 (7.19)	49.91 (8.62)
SWS	18.76 (4.95)	16.63 (5.89)
REM	18.39 (3.87)	17.90 (8.01)
REM density	14.31 (6.84)	12.74 (5.38)
Nocturnal sleep following continuous daytime wake		
	Young Adults Mean (SD)	Older Adults Mean (SD)
TST	425.38 (67.74)	418.97 (79.89)
Sleep Latency	4.37 (2.62)	7.70(6.53)
REM Latency	75.54 (29.03)	130.75 (68.73)
WASO	5.25 (3.58)	31.65 (53.13)
Sleep Efficiency	97.74 (.99)	91.89 (10.08)
NREM1	9.83 (6.28)	12.01 (5.41)
NREM2	47.67 (8.98)	53.90 (8.82)
SWS	22.39 (6.87)	17.83 (5.66)
REM	20.12 (4.65)	16.26 (5.51)
REM density	16.12 (8.12)	9.90 (3.51)

TST, total sleep time; WASO, wake after sleep onset; nREM, non-rapid eye movement sleep, SWS, slow wave sleep; REM, rapid eye movement.

Table 10. Spectral analyses for overnight sleep following a mid-day nap or continuous wakefulness in young and older adults

Nocturnal sleep following a mid-day nap

	Young Adults Mean (SD)	Older Adults Mean (SD)
Mean SWA on frontal channels (μV^2/Hz)	275.82 (111.95)	108.66 (58.17)
Mean SWA on central channels (μV^2/Hz)	184.09 (75.39)	80.09 (37.37)
Mean Sigma on frontal channels (μV^2/Hz)	2.51 (.91)	2.11 (1.98)
Mean Sigma on central channels (μV^2/Hz)	2.39 (.96)	2.27 (2.02)

Nocturnal sleep following continuous daytime wake

	Young Adults Mean (SD)	Older Adults Mean (SD)
Mean SWA on frontal channels (μV^2/Hz)	322.51 (160.85)	105.47 (73.32)
Mean SWA on central channels (μV^2/Hz)	231.34 (114.37)	81.67 (47.31)
Mean Sigma on frontal channels (μV^2/Hz)	2.42 (.59)	1.98 (2.01)
Mean Sigma on central channels (μV^2/Hz)	2.49 (.53)	2.31 (1.98)

APPENDIX B

FIGURES

Figure 1. A hypnogram that shows the normal progression of sleep stages during nocturnal sleep in healthy adults and characteristic EEG patterns associated with each sleep stage.

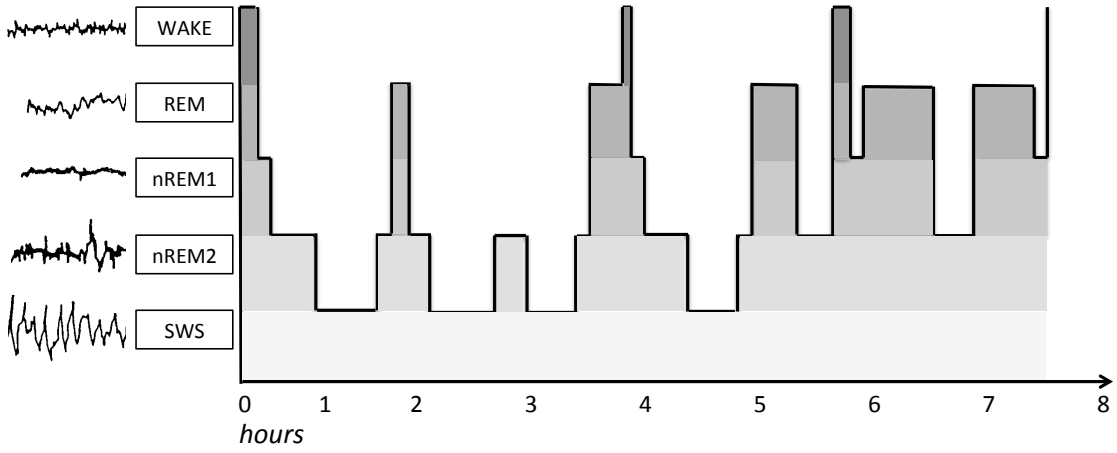


Figure 2. Declarative memory task (figure adapted from Wilson et al., 2012)

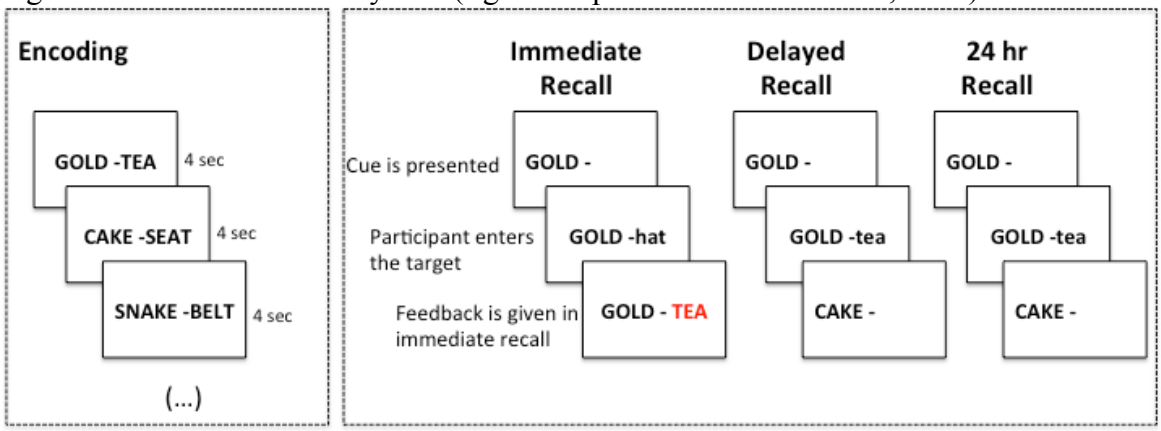


Figure 3. Study procedures

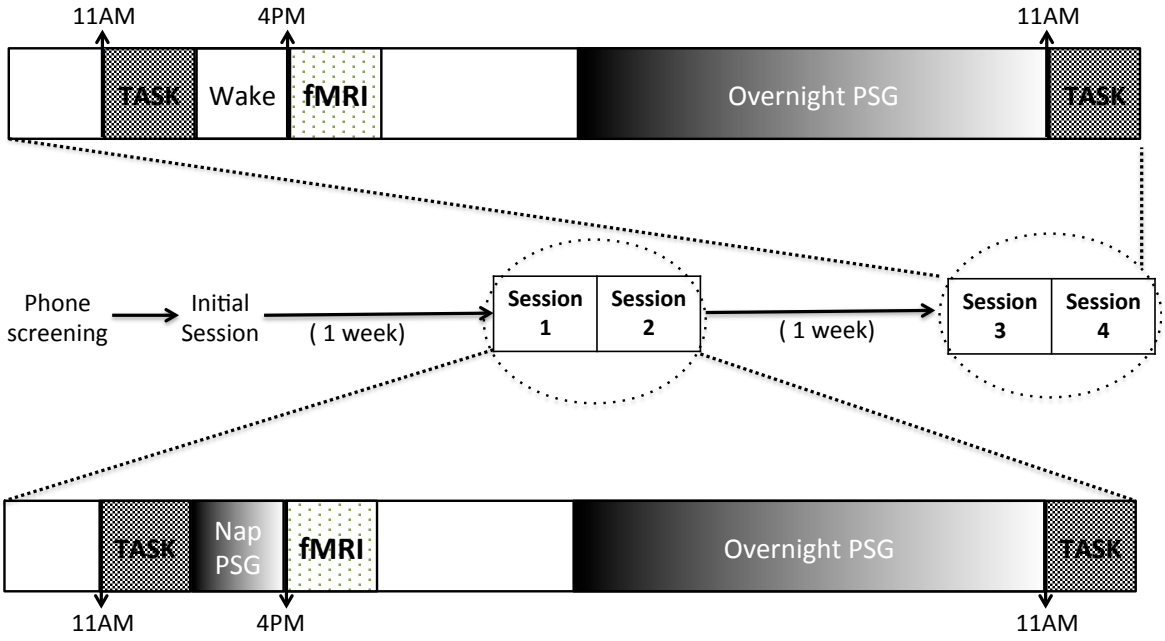


Figure 4. Intersession change in recall for the nap and wake conditions. Error bars represent standard error of the mean.

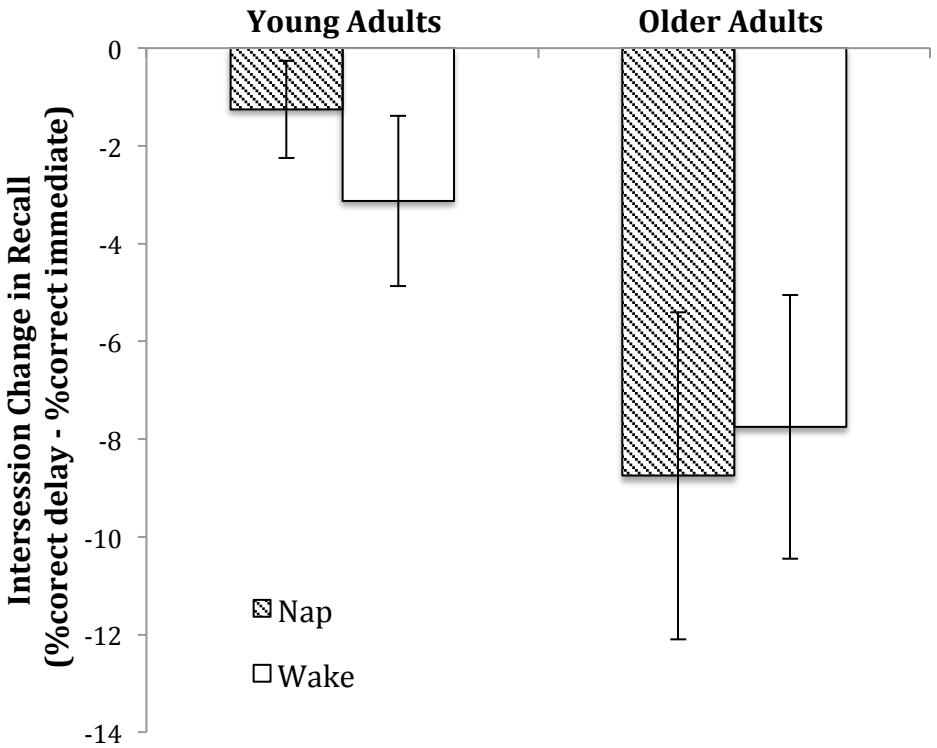


Figure 5. The relationship between percentage of time spent in slow wave sleep and intersession change in recall over a nap period for young and older adults (young: r = .61, p = .035; older: r = .08, p = .829).

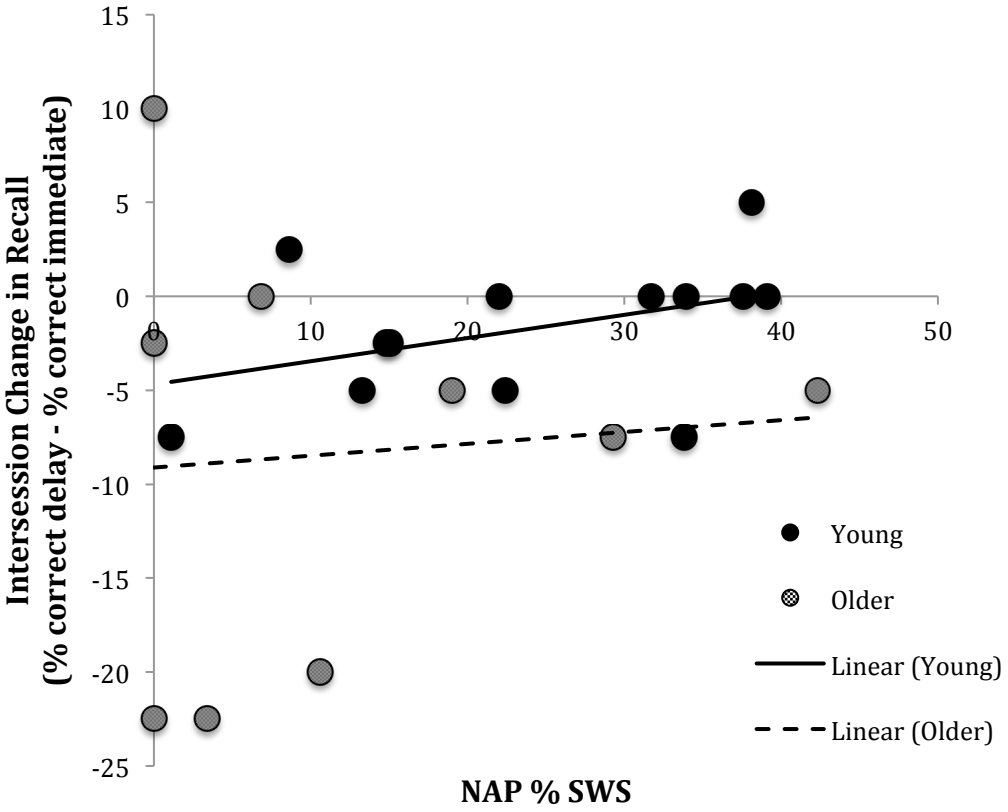


Figure 6. Hippocampal region of interest analysis in older adults. Within-subjects contrasts (paired samples t-test, $p < .05$, FWE) revealed that BA 28 of the left parahippocampal gyrus (MNI coordinates: -16, -18, -24) was activated more following a nap than wakefulness, and BA 36 of the left parahippocampal gyrus (MNI coordinates: -22, -38, -8) was activated more following wakefulness than nap in older adults.

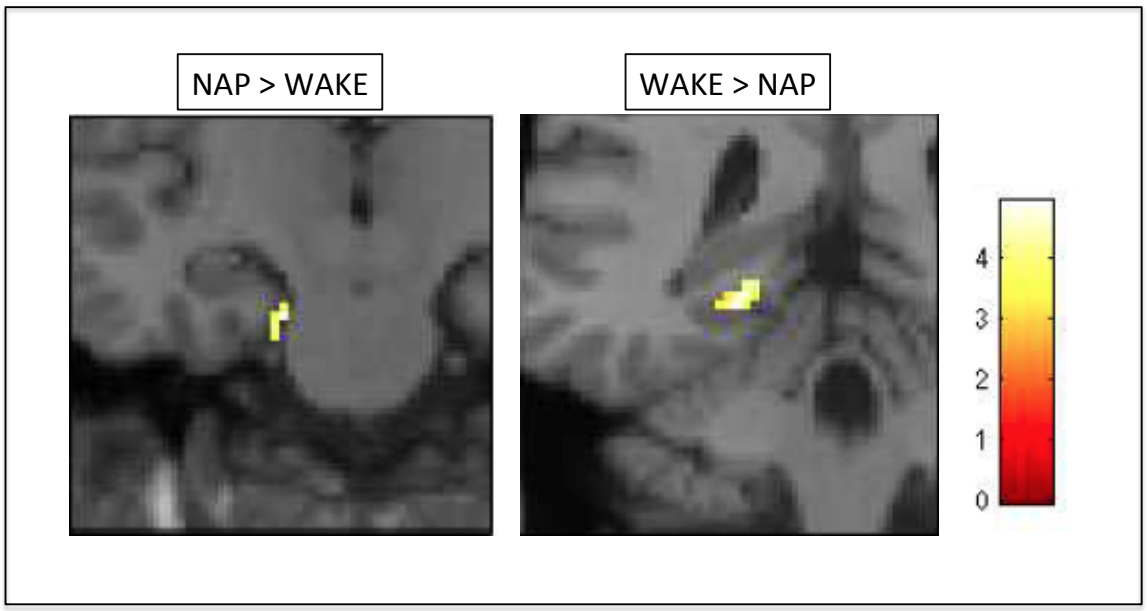


Figure 7. Functional co-activation between the right hippocampus and right dorsolateral prefrontal cortex following a nap for young and older adults. (young: r = .31, p = .335; older: r = .86, p = .002).

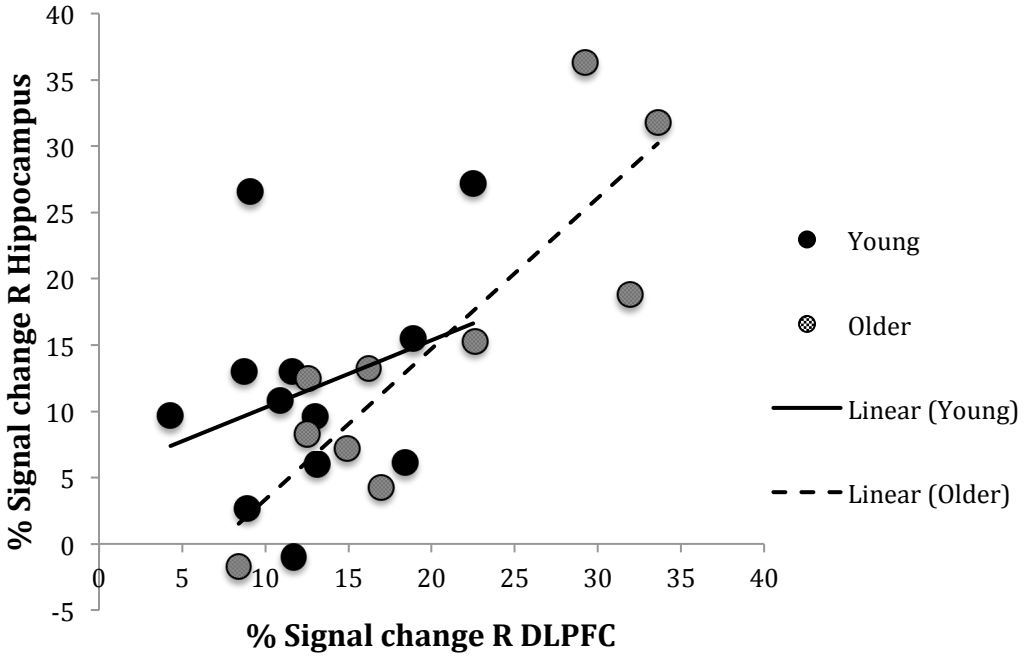
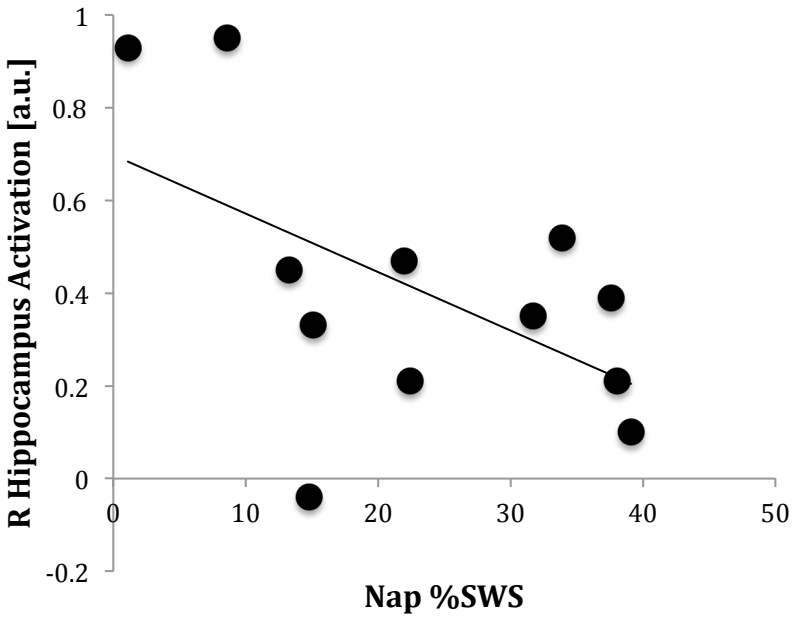


Figure 8. The relationship between hippocampal activation and slow wave sleep in young adults. Percentage of time spent in slow wave sleep during a nap (a) and slow wave activity (b) were negatively correlated with right hippocampus activation strength (contrast value, arbitrary units, a.u.) for successful word-pair recall tested following the nap for young adults (%SWS: r = -.55, p = .067; SWA: r = -.58, p = .012).

A)



B)

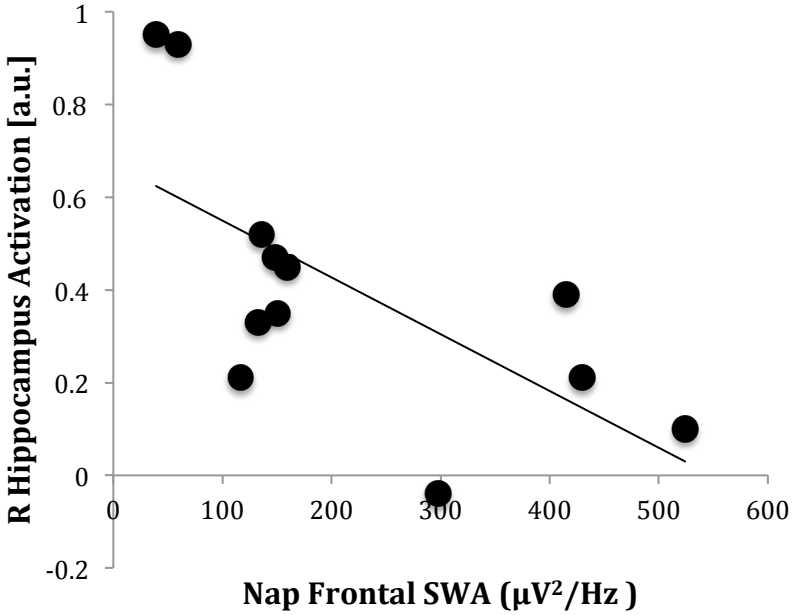


Figure 9. The relationship between percentage of time spent in slow wave sleep during a nap and left hippocampus activation strength (contrast value, arbitrary units, a.u.) for successful word-pair recall tested following the nap in young and older adults (young: r = -.71, p = .010; older: r = -.62, p = .078).

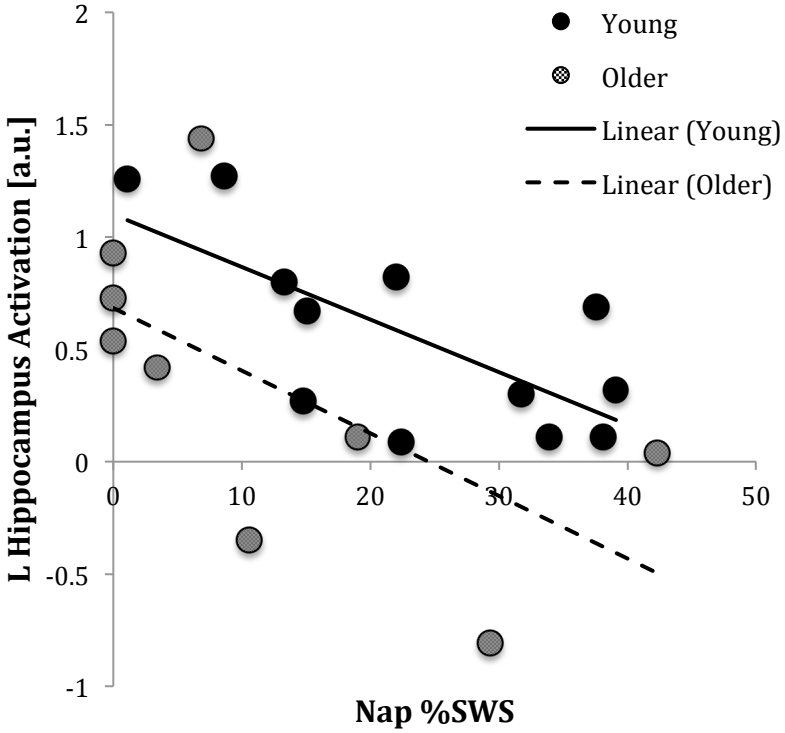
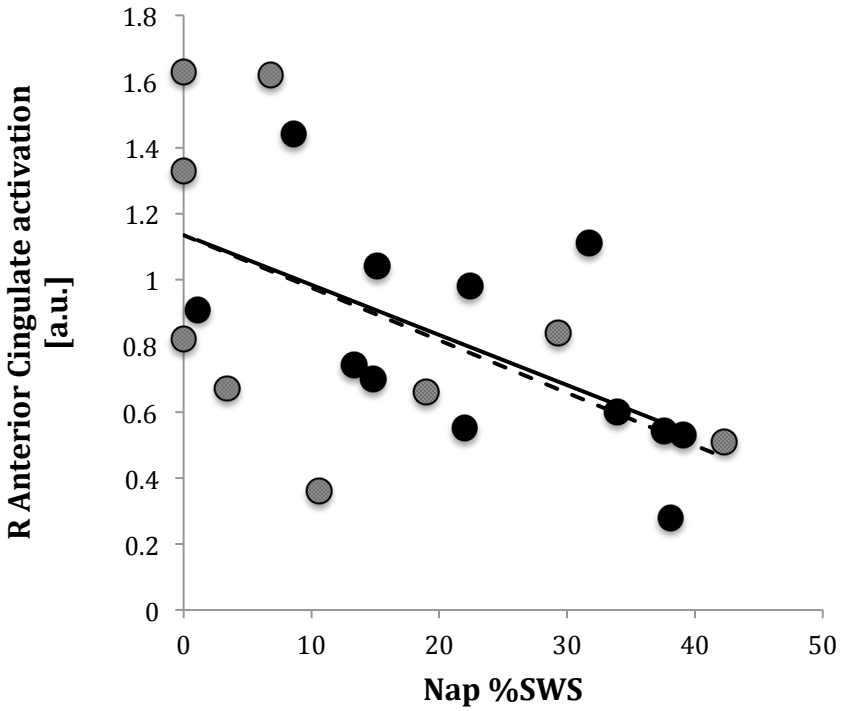


Figure 10. The relationship between right anterior cingulate activation (contrast value, arbitrary units, a.u.) during successful recall and (a) percentage of time spent in slow wave sleep (young: r = -.61, p = .037; older: r = -.51, p = .166) (b) slow wave activity (young: r = -.51, p = .030; older: r = -.15, p = .776) in young and older adults.

A)



B)

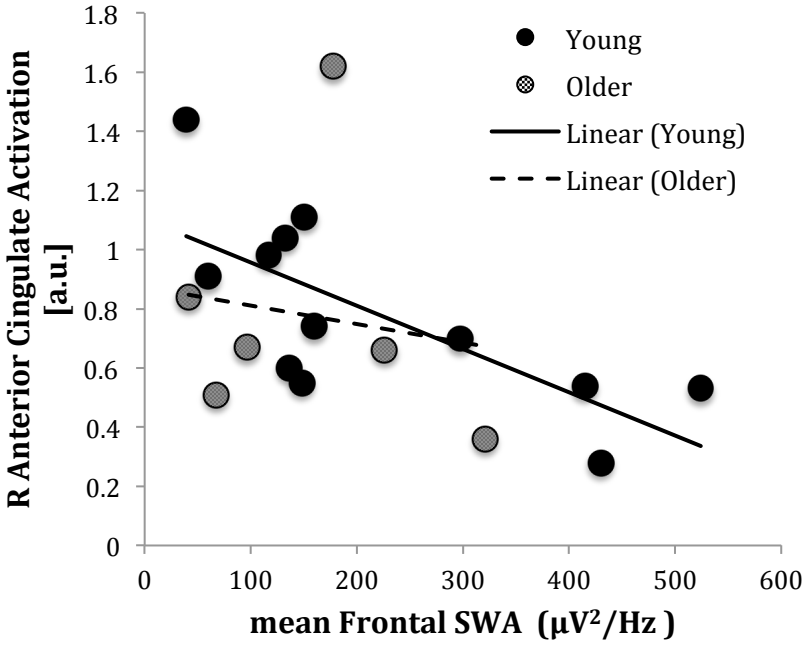
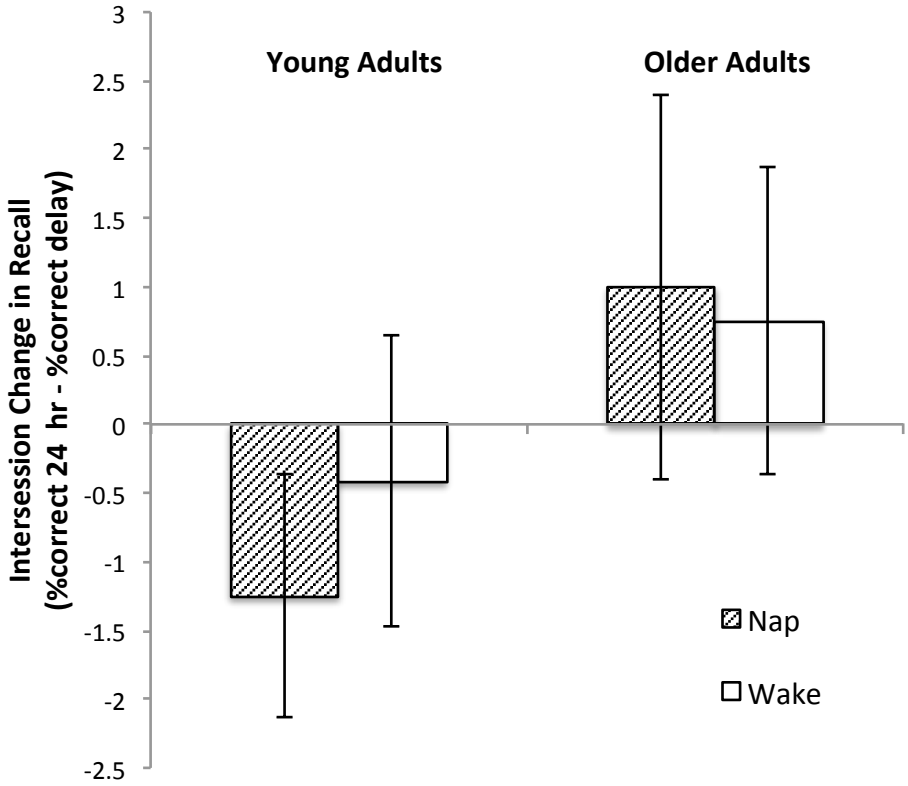


Figure 11. Intersession change in recall from delayed to 24 hr recall sessions for young and older adults. Error bars represent standard error of the mean.



APPENDIX C

PARTICIPANT SCREENING FORM

May I ask you some questions to determine whether you qualify for this experiment? **[Must respond yes]**

1. What is your date of birth? _____

   [Must be between 60-75 years of age]

2. Are you taking any medications which affect your sleep or cognitive functioning? If you are unsure about a medication, please let us know what it is so that we can verify.

List any: _____

[Must not include herbs such as St. John's wort or any of the following- Sonata (Zaleplon), Ambien (Zolpidem), Halcion (Triazolam), Rozerem (Ramelteon), Lunesta (Ezcopiclone)]

If lists oral contraceptives, or hormone replacement therapy medication:

How long have you been on the current dose of this medication? **[Must be for 6 months or longer]**

3. Are you right or left handed? **[Must respond right, ambidextrous not accepted]**
4. Have you ever been diagnosed with a cardiovascular disease or had a heart attack? **[Must respond no]**
5. Have you ever been diagnosed with a sleep disorder (yes or no)? **[Must respond no]**

6. Have you ever been diagnosed with a neurological disease or had a stroke (yes or no)? **[Must respond no]**

7. Have you ever been diagnosed with a psychiatric disease (yes or no)? **[Must respond no]**

8. Do you have normal or corrected-to-normal vision (yes or no)? **[Must respond yes]**

9. On average, what time do you go to bed? On average, what time do you wake up? **[Must indicate average sleep time of 5 hours or greater]**

10. On average, how many naps do you take each week? **[Must indicate fewer than 2 naps/week**

11. Has anyone ever observed you stop breathing when you sleep? **[Must respond no]**

12. Do you awaken gasping or choking? **[Must respond no]**

13. Do you kick or twitch your legs when you sleep? **[Must respond no]**

14. Do you have creepy/crawly feelings, numbness of legs, when you are trying to fall asleep? **[Must respond no]**

15. Do you sit up and scream while asleep or suddenly wake up scared? **[Must respond no]**

16. Do you walk while asleep, with no recall the next day? **[Must respond no]**

17. Do you frequently have frightening nightmare or dreams? **[Must respond no]**

18. Have you felt paralyzed, unable to move, but mentally alert while falling asleep or awakening? **[Must respond no]**

19. How many alcoholic drinks do you average per week? **[Must indicate fewer than 10 drinks/week]**

20. How many cups of coffee do you average per week? **[Must indicate fewer than 10 12-oz drinks/week]**

21. What is your height? What is your weight? **[BMI must be < 30 based on the calculation from http://www.nhlbisupport.com/bmi/]**

22. Do you have claustrophobia or feel discomfort in enclosed spaces that would prevent you from spending 1 continuous hour inside an MRI scanner? **[Must respond no]**

23. Are you pregnant or trying to become pregnant? **[Must respond no]**

24. I will go through various ways you could have metal in your body. Please let me know if any of these apply to you:

- Do you have a pacemaker? Y N

- Have you had a joint replacement? Y N

- Have you had heart surgery? Y N

- Do you wear a hearing aid? Y N

- Have you been in a situation where you may have shrapnel or metal fragments in your body? Y N

- Do you have any body piercings? Can they be removed? Y N

- Any other implants of any sort? Y N

IF THEY QUALIFY FOR THE STUDY, WE WILL GO AHEAD AND SCHEDULE THEM FOR THE INITIAL SESSION IF THEY ARE WILLING TO DO SO RIGHT AWAY, OR GIVE THEM THE OPTION OF LETTING US KNOW AT A LATER TIME (VIA EMAIL OR PHONE).

IF THEY DO NOT QUALIFY:

"Thank you for answering those questions and for your time. At this time, you do not qualify for this particular study. However, there are several other studies conducted through the department that you would qualify for- if you are interested in hearing about those studies, I will let the researchers in charge know, and have them contact you"

APPENDIX D
WORD PAIRS

DESK - LEAF
CHIN - SNAKE
CLUB - EYE
SKY - GLUE
PILL - BOAT
SAND - NAIL
BOY - CUP
LEG - STOVE
EGG - RAIN
FARM - STICK
JAM - TREE
BEACH - DRUM
FLOOR - POLE
HAT - DIRT
FRUIT - MOON
GLOVE - FLY
PARK - HAND
SEED - HOOK
BOOK - SHIP
ROCK - CHEEK
CARD - AIR
BUSH - ROPE
KING - COACH
COAT - SCALE
MAP - CAST
BANK - PAGE
STAIR - INK
AUNT - ZOO
HORN - CAKE
TAIL - BAR
NECK - BOOT
CHAIR - BREAD
MOUSE - BIKE
RAIL - BAG
BELT - PIG
DOOR - KID
AGE - FIRE
CROWN - BEAR
TOWN - CHIP
BLOCK – GIFT
FISH - SKIRT
ICE - DOG

BATH - GRASS
BALL - CLOUD
ARM - BONE
LAMP - PEN
LOCK - GRAY
TENT - BIRD
CAT - BAND
RING - BUS
FOOT - TOY
PET - WALL
GIRL - BELL
JOKE - HIP
MUD - SALT
CHEST - ART
BILL - FORK
DISH - TOE
BED - COAST
CAP - FAN
COAL - LAKE
SUN - CAR
DUST - JOB
HOLE - FLAG
WING - GLASS
GOLD - NOSE
SNOW - WOOD
NUT - CROP
MILK - CHAIN
BODY - TEA
SEA - LID
FACE - ROAD
CLOCK - PRIZE
POOL - MEAT
DAD - BOX
COW - SEAT
SHIRT - CHILD
SACK - HOUSE
HAIR - BAY
BRICK -MOUTH

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