Published in final edited form as:

J Cogn Neurosci. 2016 June ; 28(6): 792–802. doi:10.1162/jocn_a_00938.

Age-related Changes in the Sleep-dependent Reorganization of Declarative Memories

Bengi Baran¹, Janna Mantua¹, and Rebecca M. C. Spencer¹

¹University of Massachusetts

Abstract

Consolidation of declarative memories has been associated with slow wave sleep in young adults. Previous work suggests that, in spite of changes in sleep, sleep-dependent consolidation of declarative memories may be preserved with aging, although reduced relative to young adults. Previous work on young adults shows that, with consolidation, retrieval of declarative memories gradually becomes independent of the hippo-campus. To investigate whether memories are similarly reorganized over sleep at the neural level, we compared functional brain activation associated with word pair recall following a nap and equivalent wake in young and older adults. SWS during the nap predicted better subsequent memory recall and was negatively associated with retrieval-related hippocampal activation in young adults. In contrast, in older adults there was no relationship between sleep and memory performance or with retrieval-related hippocampal activation. Furthermore, compared with young adults, postnap memory retrieval in older adults required strong functional connectivity of the hippocampus with the PFC, whereas there were no differences between young and older adults in the functional connectivity of the hippocampus following wakefulness. These results suggest that, although neural reorganization takes place over sleep in older adults, the shift is unique from that seen in young adults, perhaps reflecting memories at an earlier stage of stabilization.

INTRODUCTION

Sleep enhances memory consolidation in young adults (Stickgold, 2005). Newly acquired declarative memory traces are transformed into more stable neural representations during subsequent slow wave sleep (Inostroza & Born, 2013; Lau, Tucker, & Fishbein, 2010; Tucker et al., 2006; Gais & Born, 2004). Aging, even in the absence of diminished health, is associated with changes in sleep duration and quality (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Buysse et al., 1992). SWS duration and delta activity (0.5–4 Hz) are particularly reduced in older adults (Van Cauter, Leproult, & Plat, 2000; Lombardo et al., 1998). As such, it has been proposed that age-related memory impairments are associated with changes in sleep (Buckley & Schatzberg, 2005; Hornung, Danker-Hopfe, & Heuser, 2005). However, recent studies that examine the effects of aging on declarative memory consolidation have provided conflicting evidence. Although some studies report superior performance in older adults following a 12-hr interval with sleep compared with an

equivalent interval awake (Sonni & Spencer, 2015; Wilson, Baran, Pace-Schott, Ivry, & Spencer, 2012; Aly & Moscovitch, 2010), others show impaired sleep-dependent declarative memory consolidation with aging (Mander et al., 2013; Scullin, 2013).

Models of systems level consolidation posit that the medial-temporal lobes have a critical, albeit temporary, role in retrieval such that with time there is a gradual reorganization of storage of recent memories (Alvarez & Squire, 1994). Evidence for this account comes from patient and animal studies: Insult to the medial-temporal lobes results in temporally graded amnesia whereby recently acquired memories are impaired but remote memories may be spared (Winocur, Sekeres, Binns, & Moscovitch, 2013; Anagnostaras, Maren, & Fanselow, 1999; Squire & Spanis, 1984; Squire, Slater, & Chace, 1975; Scoville & Milner, 1957). Furthermore, neuroimaging studies have revealed that retrieval of declarative memories is associated with a decline in hippocampal activation coupled with an increase in prefrontal activation when measured over 90 days (Takashima et al., 2006, 2009).

SWS is thought to support this reorganization of memories through neural reactivation. Reactivation of newly encoded memories initiates a hippocampo-neocortical dialogue, via slow oscillations, that eventually results in reorganization (Inostroza & Born, 2013). Supporting this, in rodents, hippocampal place cells that were active during spatial learning are reactivated during subsequent non-rapid eye movement (NREM) sleep, and this replay maintains the same firing pattern as initial experience (Lee & Wilson, 2002; Wilson & McNaughton, 1994). Furthermore, re-presenting auditory cues associated with a learned task during NREM sleep triggers selective neural reactivation of memory associated with the cue (Bendor & Wilson, 2012). Such experimentally triggered reactivation through sensory cueing has also been demonstrated in humans. For instance, postsleep memory performance is better if an odor cue that was presented during learning is presented again during SWS (Rasch, Büchel, Gais, & Born, 2007). Odor-on periods during SWS activate the hippocampus. Importantly, sensory cueing benefits memory only if presented during SWS and not during REM sleep or wakefulness. Overall, it is clear that neural mechanisms in SWS activate a cascade that is critical for declarative memory reorganization.

Although the mechanism of sleep-dependent memory reorganization is relatively well defined in healthy young adults, little is known about how declarative memories evolve offline in older adults at the neural level. Given that aging is associated with marked changes in neural engagement at encoding (Gutchess et al., 2005) and changes in sleep physiology (Ohayon et al., 2004; Van Cauter et al., 2000; Lombardo et al., 1998), the difference in retrieval-related activation postsleep compared with postwake may be distinct for older compared with younger adults. The goal of this study was to examine age-related changes in the neural and physiological correlates of sleep-dependent declarative memory consolidation using fMRI and polysomnography (PSG). We tested retention of declarative learning and recall-related brain activation following a midday nap and following continuous wakefulness in young and older adults. We postulated that the mechanism and the timescale of consolidation would differ for young and older adults, yet changes in retrieval-related activation following sleep compared with wake would be present in both groups. Moreover, based on prior studies that suggest that sleep modulates hippocampal-neocortical dialogue in young adults (Wierzyński, Lubenov, Gu, & Siapas, 2009; Siapas & Wilson, 1998) and that

retrieval success is predicted by changes in the functional connectivity of the hippocampus (King, de Chastelaine, Elward, Wang, & Rugg, 2015), we investigated age-related changes in the functional connectivity of the hippocampus during postnap and post-wake memory retrieval. We hypothesized that, if the neural mechanisms underlying sleep-dependent consolidation are similar in young and older adults, connectivity of the hippocampus during postsleep recall would be similar across age groups. Alternatively, if aging alters memory reorganization, then we may see hippocampo-prefrontal decoupling exclusively in young adults. Importantly, by comparing a nap with an equivalent interval of wake, we eliminated the concern of circadian confounds on brain activation that have previously been reported (Gorfine & Zisapel, 2009; Vandewalle et al., 2009).

METHODS

Participants

Healthy young ($n = 13$, ages 18–25 years) and older adults ($n = 13$, ages 60–75 years; Table 1) were recruited from the local community and were paid for their time. Exclusion criteria included diagnosis of neurological, psychiatric, or cardiovascular disease or sleep disorders, use of medication known to affect cognition or sleep (based on Cooke & Ancoli-Israel, 2011), habitual nocturnal sleep < 5 hr/day, habitual napping regimen of more than twice per week, BMI > 30, and excessive alcohol (>10 drinks/week) or caffeine (>10 of 12-oz caffeinated drinks/week) consumption.

We administered the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) to survey habitual sleep quality and the Morningness–Eveningness Questionnaire (Horne & Ostberg, 1976) to assess chronotype. Participants also completed a sleep and wake diary, 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). Testing procedures were approved by the University of Massachusetts Amherst Institutional Review Board, and written informed consent was obtained before the experiment.

Word Pair Recall Task

The task was a word pair learning task reported in previous studies (Wilson et al., 2012; Donohue & Spencer, 2011) and programmed using E-Prime (Psychology Software Tools, Inc., Sharpsburg, PA). Stimuli consisted of single-syllable, high-frequency, concrete nouns that were paired to create two lists of 40 semantically unrelated cue–target word pairs (e.g., bath–grass, rail–bag).

The task had three phases: Encoding, Immediate Recall, and Delayed Recall. In the Encoding phase, each word pair was presented for 4 sec, in a random order, with an ISI of 250 msec. Participants were instructed to study each pair carefully for subsequent recall and try to remember them by forming associations between the words (see Wilson et al., 2012). After a 5-min break, participants continued the Encoding phase by practicing recall of the encoded words with feedback provided. Participants were presented a cue word and asked to verbally report the target word, which the experimenter typed into the computer. If their

response was incorrect, the correct target word was displayed for 750 msec. If the response was correct, the word “correct” appeared on the screen and the participant moved on to the next pair. Practice continued until accuracy was >65% or the list was repeated five times.

Immediate Recall started 20 min after the end of Encoding. Participants were presented with each cue word and were asked to recall the target word. Their responses were entered into the computer by the experimenter. At this time, no feedback was given. Delayed Recall started 5 hr after the Encoding phase and took place in the MRI scanner. Participants were presented with the cue word for 4 sec and were asked to make a yes/no response with a button press to indicate whether or not they recalled the target word. Each trial was followed by a 14-sec fixed ISI to reach optimal experimental design for event-related functional imaging (Dale, 1999). The memory task consisted of a single run of fMRI that lasted 14 min 20 sec. After the MRI session was completed, participants did the same memory task with procedures identical to Immediate Recall to determine the accuracy of yes/no responses made in the MRI scanner. Only the trials for which the participants indicated recalling the target word in the scanner and correctly recalled the target outside the scanner were identified as correct recall trials. The primary measure of memory was Intersession Change in Recall calculated as Delayed Recall accuracy (% correct) minus Immediate Recall accuracy.

Procedures

Participants were scheduled for an initial session 7 days before the start of the experiment during which they completed a neuropsychological battery of verbal memory (California Verbal Learning Test-II; (Delis, Kramer, Kaplan, & Ober, 2000) and executive function tests (sub-tests of the Delis Kaplan Executive Function System; Delis, Kaplan, & Kramer, 2001). To provide an objective measure of sleep/wake habits, participants were monitored with wrist actigraphy (Actiwatch Spectrum, Philips Respironics, Murrysville, PA) for the subsequent 7 days.

Participants completed two conditions separated by 7 days, a nap condition and a wake condition, the order of which was counterbalanced across participants. Testing for both conditions started at 11 a.m. (± 1 hr). In each condition, the Encoding and Immediate Recall phase of the word pair learning task was followed by a 5-hr interval in which participants either napped or stayed awake (Figure 1). In the nap condition, participants were given a 2-hr nap opportunity. Participants napped in their own bedrooms, and the naps were monitored by PSG. For the wake condition, participants were instructed to refrain from any strenuous mental or physical exercise. Delayed Recall was tested in the MRI scanner. Subsequent overnight sleep took place in the participant’s home and was also monitored by PSG. Each testing phase started at the same time for both conditions within a participant to avoid any possible circadian confound on brain activation.

fMRI Data Acquisition

All brain imaging data were acquired using a 3-T Philips Achieva scanner (Amsterdam, The Netherlands) with a standard 12-channel head coil housed at University of Massachusetts Medical School Advanced MRI Center. Anatomical scans were acquired as high-resolution

T1-weighted magnetization-prepared rapid acquisition with gradient-echo volumes (1 mm × 1 mm × 1 mm voxel size; flip angle = 3°, repetition time = 8.3 msec, echo time = 3.75 msec, slice thickness = 1 mm, 181 slices). EPI data were acquired (flip angle = 80°, echo time = 30 msec, repetition time = 2500 msec) as 43 interleaved axial T2-weighted slices yielding a voxel size of 3 × 3 × 3 mm and were preceded by two preparatory (i.e., dummy) scans.

fMRI Analysis

Functional data were preprocessed and analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 7.7 (The MathWorks, Natick, MA). Raw BOLD images were realigned and corrected offline for slice-timing acquisition. The images were normalized to the Montreal Neurological Institute (MNI) template. Spatial smoothing was completed with a 6-mm isotropic Gaussian kernel before modeling the data. All trial types were modeled as events convolved with the canonical hemodynamic response function and inserted in the general linear models. A high pass filter with a cutoff of 128 sec was applied to remove slow signal drifts from the general linear model. Analyses were limited to hits (i.e., “yes” responses during functional imaging that were confirmed by correct recall outside the MRI scanner) as misses and false alarms were too few in number to provide sufficient statistical power.

Our approach to second-level (group) analysis was twofold: exploratory whole-brain analyses and hippocampal ROI activation analysis. First, we ran exploratory whole-brain analyses to investigate whether recall-related brain activation patterns following napping and wakefulness are similar between young and older adults. For that purpose, we ran paired-samples *t* tests to explore regions that are more active following a nap (nap > wake) and regions that are more active following wakefulness (wake > nap). For these analyses, we used an FWE-corrected *p* value of less than .05 and a cluster size of at least 5 contiguous voxels.

Second, we conducted an ROI analysis for the right and left hippocampus ROIs given the structure’s critical role in learning and memory (e.g., Squire, Stark, & Clark, 2004) and previous findings that retrieval-related hippocampal activity decreases with consolidation (Takashima et al., 2009). Of primary interest for the ROI analysis was the relationship between SWS physiology and postnap hippocampal activation during correct recall. ROIs were extracted anatomically using the WFU Pickatlas toolbox ver. 2.5 (Maldjian, Laurienti, Kraft, & Burdette, 2003; Lancaster et al., 2000) with the automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002) implemented in the toolbox. Signal intensity in the ROIs was measured by calculating contrast values (defined as the effect size of the *t* test) using the Marsbar toolbox ver. 0.43 (Brett, Anton, Valabrege, & Poline, 2002). Correlations between SWS measures and hippocampal signal intensity were measured using Pearson’s *r*.

Functional Connectivity Analysis

Using SPM8, anatomical images were segmented into white matter, gray matter, and cerebrospinal fluid masks. Preprocessed BOLD images were coregistered with the anatomical images. Functional connectivity analysis was performed using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), which uses the anatomical CompCor

method (Behzadi, Restom, Liau, & Liu, 2007) to estimate and regress out physiological sources of noise. The segmented white matter and cerebrospinal fluid masks were used as noise ROIs, and their signals were extracted from the functional volumes. A temporal band-pass filter of 0.008–0.09 Hz was applied to the time series. Head motion parameters (rotation and translations in x , y , and z directions and artifactual time points (as flagged by ART, www.nitrc.org/projects/artifact_detect/) were regressed out in the model. A time point was defined as an artifact if head displacement was greater than 2 mm from the previous frame or if the global mean intensity of the image was greater than 3 standard deviations from the mean image intensity for the entire functional scan. First-level correlation maps for each participant were calculated for the right and left hippocampus seeds (i.e., Pearson's r between time course of the seed and the time course of all other voxels). For second-level analyses, correlation coefficients were transformed to normally distributed z scores (Fisher's transformation). In all group-level comparisons, reported clusters survived a height threshold of uncorrected $p < .001$ and an extent threshold of FDR-corrected $p < .05$ at the cluster level.

Polysomnography

An ambulatory PSG device (Grass AURA PSG, Natus Neurology Incorporated, Middleton, WI) with six EEG channels (F_1 , F_2 , C_3 , C_4 , O_1 , and O_2), two EMG channels (submental), and two EOG channels (ROC, LOC) was used to monitor sleep. Sleep was scored according to the American Academy of Sleep Medicine standards (Iber, Ancoli-Israel, Chesson, & Quan, 2007). To carry out spectral analysis, EEG data were imported to BrainVision Analyzer software (Version 2.4, Brain Products GmbH, München, Germany) along with sleep staging notations. Data were filtered between 0.3 and 35 Hz, segmented to the sleep stage of interest (i.e., SWS), 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 delta power focused on a relative spectral power between 0.5 and 4 Hz. All power analyses are reported in power density ($\mu V^2/Hz$).

RESULTS

Participant Characteristics

Table 1 shows that subjective (i.e., PSQI) and objective (i.e., actigraphy) measures of habitual sleep were similar between young and older adults. Consistent with previous literature (Weitzman et al., 1981), older adults scored higher on morningness on the MEQ. Notably, none of the participants classified as extreme morning (total score ≥ 70) or extreme evening chronotypes (total score ≤ 30). Older adults performed worse on neuropsychological tests of verbal memory and executive function.

Memory Performance

Figure 2A shows recall performance. A repeated-measures ANOVA on recall accuracy (percent correct) with Condition (nap vs. wake) and Session (Immediate vs. Delayed Recall) as the within-subject factors and Age group (young vs. old) as the between-subject factor revealed a significant main effect of Session (i.e., decrement in recall performance after a delay, $F(1, 24) = 6.48$, $p = .018$), a significant main effect of Condition (i.e., less forgetting

following a nap, $F(1, 24) = 20.83, p < .001$), and a significant main effect of Age group (i.e., worse performance in older adults, $F(1, 24) = 20.19, p < .001$). We observed a significant interaction of Session $\times$ Age group (i.e., less decrement in recall after a delay in young adults, $F(1, 24) = 5.01, p = .035$) and a near-significant interaction of Condition $\times$ Age group (i.e., less decrement in recall following a nap in young adults, $F(1, 24) = 3.95, p = .059$) but no significant three-way interaction ($F(1, 24) = .69, p = .416$). Post hoc comparisons with our primary measure of memory (Delayed minus Immediate Recall) that controls for baseline differences in performance revealed a significant main effect of Age group for the nap condition ($t(24) = 2.28, p = .032$), but not for the wake condition ($t(24) = 1.33, p = .196$). Although the overnap change in performance did not significantly differ from that seen overwake in either age group (young: $t(12) = 1.17, p = .265$; older: $t(12) = -0.21, p = .835$), presumably due to the small sample size compared with prior studies (Wilson et al., 2012), young adults forgot less over the nap interval compared with older adults (Figure 2B).

Relationship between Sleep and Memory

Nap characteristics were similar between young and older adult groups (Table 2) with the exception of REM sleep where seven young adults and one older adult reached REM. In young adults, overnap change in memory was positively correlated with %SWS, such that a larger proportion of the nap spent in SWS was associated with less forgetting ($r = .59, p = .034$). This relationship was not significant for older adults ($r = .01, p = .97$; Figure 2C; if participants with 0% SWS are excluded: $r = .44, p = .33$). Notably, for Figure 2C the comparison of the regression slopes did not reveal a significant group difference (age group by %SWS interaction, $\beta = -.26, p = .46$). Exploratory analyses of the relationship between change in recall and other sleep architecture and duration measures did not reveal any significant relationships in either age group (all $ps > .2$).

fMRI

Exploratory whole-brain analyses comparing recall-related brain activation patterns following napping versus wakefulness in either group did not yield any clusters that surpass FWE correction. On the basis of a priori hypotheses, we conducted an ROI analysis focused on the hippocampus. Bilateral hippocampal activation during recall predicted recall success (% delayed recall) for both the nap condition ($r = .39, p = .05$) and the wake condition ($r = .56, p = .006$) across participants. Next, we examined the relationship between postnap hippocampal activation and measures of SWS. For young adults, hippocampal activation for correct recall was negatively correlated with %SWS (left hippocampus: $r = -.67, p = .012$; right hippocampus, trend: $r = -.51, p = .073$) and delta power of SWS (left hippocampus, trend: $r = -.51, p = .079$; right hippocampus: $r = -.73, p = .004$). That is, greater nap SWS was associated with decreased reliance on the hippocampus during successful recall in young adults. This relationship was not significant for older adults either for SWS duration (left hippocampus: $r = -.45, p = .145$; right hippocampus: $r = -.05, p = .869$; if participants with 0% SWS are excluded, left hippocampus: $r = -.37, p = .42$; right hippocampus: $r = -.15, p = .76$) or for delta power (left hippocampus: $r = .28, p = .54$; right hippocampus: $r = -.38, p = .40$; Figure 3A, B). Comparison of regression slopes did not reveal a significant group difference for either Figure 3A (age group by %SWS interaction, $\beta = .17, p = .62$) of Figure 3B (age group by frontal delta power interaction, $\beta = .59, p = .20$).

Slow wave activity present in NREM sleep that does not fulfill duration criteria to be scored as SWS may nevertheless play a critical role in declarative memory consolidation. For that purpose, we calculated spectral power in the delta band for NREM Stages 2 and 3 combined. Hippocampal activation for correct recall was negatively correlated with NREM delta power (left hippocampus, trend: $r = -.48$, $p = .09$; right hippocampus: $r = -.68$, $p = .01$) in young adults. However, this relationship was not significant for older adults (left hippocampus: $r = -.24$, $p = .46$; right hippocampus: $r = -.29$, $p = .36$). Next, we investigated whether these relationships are driven by power in the slow oscillation range. For that purpose, we divided NREM spectral power into two frequency bins: slow (0.5–1.5 Hz) and faster (1.5–4 Hz) delta. Compared with young adults, we observed reduced power in older adults both for the 0.5–1.5 Hz bin ($F(1, 23) = 5.76$, $p = .025$) and the 1.5–4 Hz bin ($F(1, 23) = 10.29$, $p = .004$). We observed that the negative relationship between right hippocampal activation and delta power remains for both frequency bins in young adults (0.5–1.5 Hz: $r = -.66$, $p = .01$; 1.5–4 Hz: $r = -.52$, $p = .06$) but does not exist for either frequency band in older adults (0.5–1.5 Hz: $r = -.26$, $p = .56$; 1.5–4 Hz: $r = -.39$, $p = .38$).

Functional Connectivity

We investigated the effects of aging on functional connectivity of the hippocampus during memory recall following a nap and wakefulness. We found that, following a nap, relative to the young adults, older adults had increased functional connectivity between the left hippocampus seed and two lateral prefrontal clusters (left PFC, MNI coordinates: $-44, 40, -8$, $CWP_{FDR} = .001$; right PFC, MNI coordinates: $34, 62, -2$, $CWP_{FDR} = .007$; Figure 4). There were no differences between young and older adults in functional connectivity of the hippocampus during post-wakefulness memory retrieval.

DISCUSSION

This study provides evidence that sleep is a unique period during which memory consolidation and systems-level reorganization takes place and that aging alters this reorganization. In a sample of healthy young adults, we found that SWS during a nap predicted better memory performance and was negatively associated with hippocampal activation during recall. 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. There was no SWS-dependent decrease in hippocampal activation.

The finding of an SWS (percent and delta activity)-related decrease in hippocampal involvement in memory recall in young adults provides evidence that systems-level neural reorganization of declarative memories takes place even over a brief nap following learning. This is consistent with the systems-level consolidation model (Buzsáki, 1998). New memories and their contextual properties are coded in the hippocampal system. During subsequent sleep, slow waves in the neocortex initiate a cortico-hippocampal dialogue. Hippocampal 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 (Nádasdy, Hirase, Czurkó, Csicsvari, & Buzsáki, 1999; Wilson & McNaughton, 1994). Simultaneous co-occurrence of slow waves 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; McClelland, McNaughton, & O'Reilly, 1995). Therefore, our finding of SWS-dependent decrease in hippocampal activation during recall in young adults provides evidence for the role of SWS in hippocampo-cortical transfer of memory traces.

Importantly, our data suggest that the sleep-dependent reorganization of declarative memories in older adults is distinct from that seen in young adults. Although SWS during a nap triggers a cascade of memory reorganization resulting in decreased hippocampal involvement during recall in young adults (as evident by the correlation between SWS and hippocampus activation; Figure 3), postsleep memory recall in older adults relies largely on hippocampoprefrontal connectivity (Figure 4). Importantly, SWS physiology is not associated with memory performance or hippocampal activation during recall in older adults. The present finding that aging interferes with neural reorganization is consistent with previous animal research. In young rats, neuronal firing patterns in the CA1 subfield of the hippocampus were found to significantly correlate between learning of the spatial navigation task and subsequent SWS (Lee & Wilson, 2002), providing evidence for sleep-dependent replay of episodic learning. However, it has been shown that aging interferes with hippocampal replay. Specifically, 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.

Recently, Mander and colleagues (2013) 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 that study had decreased delta activity, decreased gray matter volume in the medial PFC, and decreased overnight memory retention compared with young adults. Furthermore, the authors found that the effect of age on delta activity was mediated by medial PFC atrophy. Their conclusion, that age-related changes in the structural integrity of the cortex may be responsible for disrupted slow wave propagation, supports the present finding that the mechanism of sleep-dependent memory consolidation is unique in older adults. Disrupted slow wave propagation may alter sleep-dependent neural reorganization and thus, compared with young adults, postsleep retrieval in older adults requires strong functional connectivity between the hippocampus and the PFC, perhaps as a compensatory mechanism. Notably, this prefrontal compensatory pattern of activation and connectivity during memory retrieval, as also reported by other studies (e.g., Lighthall, Huettel, & Cabeza, 2014; McDonough, Wong, & Gallo, 2013; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008), may alternatively reflect a distinct mechanism (e.g., inefficient processing) independent from an age-related change in the transformation of memories.

Surprisingly, we did not observe a significant sleep benefit on memory performance perhaps due to the small sample size, a limitation shared by several neuroimaging studies. Despite this, we confirmed our a priori hypothesis that SWS is associated with better memory and decreased retrieval-related hippocampal activation in young adults. Nevertheless, larger samples would be necessary to confirm that SWS-dependent memory consolidation

mechanisms are altered in aging. By virtue of using a recall paradigm, we were not able to use a more memory-specific measure of fMRI (e.g., a contrast of hits vs. misses). Furthermore, our design allowed us to compare fMRI measurement of brain activity postnap and postwakefulness within participants but did not include measures from prenap and wakefulness. As such, a limitation of this study is that differences in encoding related brain activation across age groups cannot be considered.

Although both groups were trained to criterion during encoding practice, performance during immediate recall was significantly worse in older adults. Thus, it can be speculated that sleep-dependent reorganization of memories are at a different stage in older adults, likely because the memory was weaker to begin with. Future work should address whether age-related differences in brain activation during encoding may underlie differences in sleep-dependent consolidation. Furthermore, for the relationship between measures of SWS and memory retrieval, we did not observe significant group differences in regression coefficients. At any rate, our findings reveal a more heterogeneous relationship between sleep physiology and declarative memory consolidation in aging. This may reflect that sleep-dependent processes critical for consolidation are impaired in some older adults but not others. Further investigation of protective factors associated with reduced memory consolidation in aging is warranted.

In summary, this study shows that the efficiency with which systems level consolidation takes place in the first sleep opportunity following learning is altered in healthy older adults. This may suggest that the timescale of the SWS-dependent memory evolution is disrupted in aging, leaving memory traces at a more labile state of storage that still rely on hippocampal activation and hippocampoprefrontal coactivation.

Acknowledgments

This work was supported by National Institutes of Health (R01 AG040133 to R. M. C. S.) and also by the University of Massachusetts Amherst Graduate School Dissertation Research Award to B. B. We thank Jacquie Kurland, Rebecca Ready, Jeffrey Starns, and Matt Davidson for their feedback in design and analysis, Kristen Warren for help in participant recruitment and data collection, and Phil Desrochers for help in actigraphy analysis.

REFERENCES

- Alvarez P, & Squire LR (1994). Memory consolidation and the medial temporal lobe: A simple network model. *Proceedings of the National Academy of Sciences, U.S.A.*, 91, 7041–7045.
- Aly M, & Moscovitch M (2010). The effects of sleep on episodic memory in older and younger adults. *Memory*, 18, 327–334. [PubMed: 20182945]
- Anagnostaras SG, Maren S, & Fanselow MS (1999). Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: Within-subjects examination. *Journal of Neuroscience*, 19, 1106–1114. [PubMed: 9920672]
- Behzadi Y, Restom K, Liao J, & Liu TT (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage*, 37, 90–101. [PubMed: 17560126]
- Bendor D, & Wilson MA (2012). Biasing the content of hippocampal replay during sleep. *Nature Neuroscience*, 15, 1439–1444. [PubMed: 22941111]
- Brett M, Anton JL, Valabrege R, & Poline JB (2002). Region of interest analysis using an SPM toolbox. Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan Available on CD-ROM in *Neuroimage*, 16(2). 10.1016/j.neuroimage.2012.01.133.

- Buckley TM, & Schatzberg AF (2005). Aging and the role of the HPA axis and rhythm in sleep and memory-consolidation. *American Journal of Geriatric Psychiatry*, 13, 344–352. [PubMed: 15879582]
- Buyse DJ, Browman KE, Monk TH, Reynolds CF, III, Fasiczka AL, & Kupfer DJ (1992). Napping and 24-hour sleep/wake patterns in healthy elderly and young adults. *Journal of the American Geriatrics Society*, 40, 779–786. [PubMed: 1634721]
- Buyse DJ, Reynolds CF, III, Monk TH, Berman SR, & Kupfer DJ (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, 28, 193–213. [PubMed: 2748771]
- Buzsáki G (1998). Memory consolidation during sleep: A neurophysiological perspective. *Journal of Sleep Research*, 7(Suppl. 1), 17–23. [PubMed: 9682189]
- Cooke JR, & Ancoli-Israel S (2011). Normal and abnormal sleep in the elderly. *Handbook of Clinical Neurology*, 98, 653–665. [PubMed: 21056216]
- Dale AM (1999). Optimal experimental design for event-related fMRI. *Human Brain Mapping*, 8, 109–114. [PubMed: 10524601]
- Davis SW, Dennis NA, Daselaar SM, Fleck MS, & Cabeza R (2008). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex*, 18, 1201–1209. [PubMed: 17925295]
- Delis DC, Kaplan E, & Kramer JH (2001). *Delis-Kaplan Executive Function System: Examiner's manual*. San Antonio, TX: The Psychological Corporation.
- Delis DC, Kramer JH, Kaplan E, & Ober BA (2000). *California Verbal Learning Test—Second edition Adult version*. Manual San Antonio, TX: Psychological Corporation.
- Donohue KC, & Spencer RMC (2011). Continuous re-exposure to environmental sound cues during sleep does not improve memory for semantically unrelated word pairs. *Journal of Cognitive Education and Psychology*, 10, 167–177. [PubMed: 26435767]
- Gais S, & Born J (2004). Declarative memory consolidation: Mechanisms acting during human sleep. *Learning & Memory (Cold Spring Harbor, N.Y.)*, 11, 679–685.
- Gerrard JL, Burke SN, McNaughton BL, & Barnes CA (2008). Sequence reactivation in the hippocampus is impaired in aged rats. *Journal of Neuroscience*, 28, 7883–7890. [PubMed: 18667620]
- Gorfine T, & Zisapel N (2009). Late evening brain activation patterns and their relation to the internal biological time, melatonin, and homeostatic sleep debt. *Human Brain Mapping*, 30, 541–552. [PubMed: 18095278]
- Gutchess AH, Welsh RC, Hedden T, Bangert A, Minear M, Liu LL, et al. (2005). Aging and the neural correlates of successful picture encoding: Frontal activations compensate for decreased medial-temporal activity. *Journal of Cognitive Neuroscience*, 17, 84–96. [PubMed: 15701241]
- Horne JA, & Ostberg O (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, 4, 97–110. [PubMed: 1027738]
- Hornung OP, Danker-Hopfe H, & Heuser I (2005). Age-related changes in sleep and memory: Commonalities and interrelationships. *Experimental Gerontology*, 40, 279–285. [PubMed: 15820608]
- Iber C, Ancoli-Israel S, Chesson A, & Quan SF (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology, and technical specification (1st ed.)*. Westchester, IL: American Academy of Sleep Medicine Retrieved from www.aasmnet.org/library/default.aspx.
- Inostroza M, & Born J (2013). Sleep for preserving and transforming episodic memory. *Annual Review of Neuroscience*, 36, 79–102.
- King DR, de Chastelaine M, Elward RL, Wang TH, & Rugg MD (2015). Recollection-related increases in functional connectivity predict individual differences in memory accuracy. *Journal of Neuroscience*, 35, 1763–1772. [PubMed: 25632149]
- Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping*, 10, 120–131. [PubMed: 10912591]
- Lau H, Tucker MA, & Fishbein W (2010). Daytime napping: Effects on human direct associative and relational memory. *Neurobiology of Learning and Memory*, 93, 554–560. [PubMed: 20176120]

- Lee AK, & Wilson MA (2002). Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron*, 36, 1183–1194. [PubMed: 12495631]
- Lighthall NR, Huettel SA, & Cabeza R (2014). Functional compensation in the ventromedial prefrontal cortex improves memory-dependent decisions in older adults. *Journal of Neuroscience*, 34, 15648–15657. [PubMed: 25411493]
- Lombardo P, Formicola G, Gori S, Gneri C, Massetani R, Murri L, et al. (1998). Slow wave sleep (SWS) distribution across night sleep episode in the elderly. *Aging*, 10, 445–448. [PubMed: 10078313]
- Maldjian JA, Laurienti PJ, Kraft RA, & Burdette JH (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*, 19, 1233–1239. [PubMed: 12880848]
- Mander BA, Rao V, Lu B, Saletin JM, Lindquist JR, Ancoli-Israel S, et al. (2013). Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nature Neuroscience*, 16, 357–364. [PubMed: 23354332]
- McClelland JL, McNaughton BL, & O'Reilly RC (1995). Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, 102, 419–457. [PubMed: 7624455]
- McDonough IM, Wong JT, & Gallo DA (2013). Age-related differences in prefrontal cortex activity during retrieval monitoring: Testing the compensation and dysfunction accounts. *Cerebral Cortex*, 23, 1049–1060. [PubMed: 22510532]
- Nádasy Z, Hirase H, Czurkó A, Csicsvari J, & Buzsáki G (1999). Replay and time compression of recurring spike sequences in the hippocampus. *Journal of Neuroscience*, 19, 9497–9507. [PubMed: 10531452]
- Ohayon MM, Carskadon MA, Guilleminault C, & Vitiello MV (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*, 27, 1255–1273. [PubMed: 15586779]
- Rasch B, Büchel C, Gais S, & Born J (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*, 315, 1426–1429. [PubMed: 17347444]
- Scoville WB, & Milner B (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, 20, 11–21.
- Scullin MK (2013). Sleep, memory, and aging: The link between slow-wave sleep and episodic memory changes from younger to older adults. *Psychology and Aging*, 28, 105–114. [PubMed: 22708533]
- Siapas AG, & Wilson MA (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron*, 21, 1123–1128. [PubMed: 9856467]
- Sonni A, & Spencer RMC (2015). Sleep protects memories from interference in older adults. *Neurobiology of Aging*, 36, 2272–2281. [PubMed: 25890819]
- Squire LR, Slater PC, & Chace PM (1975). Retrograde amnesia: Temporal gradient in very long term memory following electroconvulsive therapy. *Science*, 187, 77–79. [PubMed: 1109228]
- Squire LR, & Spanis CW (1984). Long gradient of retrograde amnesia in mice: Continuity with the findings in humans. *Behavioral Neuroscience*, 98, 345–348. [PubMed: 6539119]
- Squire LR, Stark CEL, & Clark RE (2004). The medial temporal lobe. *Annual Review of Neuroscience*, 27, 279–306.
- Stickgold R (2005). Sleep-dependent memory consolidation. *Nature*, 437, 1272–1278. [PubMed: 16251952]
- Takashima A, Nieuwenhuis ILC, Jensen O, Talamini LM, Rijpkema M, & Fernández G (2009). Shift from hippocampal to neocortical centered retrieval network with consolidation. *Journal of Neuroscience*, 29, 10087–10093. [PubMed: 19675242]
- Takashima A, Petersson KM, Rutter F, Tendolkar I, Jensen O, Zwarts MJ, et al. (2006). Declarative memory consolidation in humans: A prospective functional magnetic resonance imaging study. *Proceedings of the National Academy of Sciences, U.S.A.*, 103, 756–761.

- Tucker MA, Hirota Y, Wamsley EJ, Lau H, Chaklader A, & Fishbein W (2006). A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. *Neurobiology of Learning and Memory*, 86, 241–247. [PubMed: 16647282]
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*, 15, 273–289. [PubMed: 11771995]
- Van Cauter E, Leproult R, & Plat L (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *Journal of the American Medical Association*, 284, 861–868. [PubMed: 10938176]
- Vandewalle G, Archer SN, Wuillaume C, Balet E, Degueldre C, Luxen A, et al. (2009). Functional magnetic resonance imaging-assessed brain responses during an executive task depend on interaction of sleep homeostasis, circadian phase, and PER3 genotype. *Journal of Neuroscience*, 29, 7948–7956. [PubMed: 19553435]
- Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement W, et al. (1981). Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. *Archives of General Psychiatry*, 38, 737–746. [PubMed: 7247637]
- Whitfield-Gabrieli S, & Nieto-Castanon A (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*, 2, 125–141. [PubMed: 22642651]
- Wierzynski CM, Lubenov EV, Gu M, & Siapas AG (2009). State-dependent spike-timing relationships between hippocampal and prefrontal circuits during sleep. *Neuron*, 61, 587–596. [PubMed: 19249278]
- Wilson JK, Baran B, Pace-Schott EF, Ivry RB, & Spencer RMC (2012). Sleep modulates word-pair learning but not motor sequence learning in healthy older adults. *Neurobiology of Aging*, 33, 991–1000. [PubMed: 22244090]
- Wilson MA, & McNaughton BL (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, 265, 676–679. [PubMed: 8036517]
- Winocur G, Sekeres MJ, Binns MA, & Moscovitch M (2013). Hippocampal lesions produce both nongraded and temporally graded retrograde amnesia in the same rat. *Hippocampus*, 23, 330–341. [PubMed: 23401223]

Figure 1.

(A) Study procedures. Prospective participants completed a phone screening and those determined eligible completed an initial session during which they completed a neuropsychological battery and were monitored with wrist actigraphy for 7 consecutive days until starting the first session. Participation included two conditions, a nap condition and a wake condition, separated by 1 week. In each condition, Encoding and Immediate Recall were followed by a 5-hr interval, in which participants either had a 2-hr nap opportunity or stayed awake, and Delayed Recall was tested in fMRI. Naps were monitored with PSG. (B) Word pair recall task. Following passive encoding, participants practiced word pairs with feedback until performance reached criterion (>65% accuracy or 5 rounds of practice). Immediate and Delayed Recall were tested 20 min and 5 hr after Encoding, respectively. Delayed Recall took place in an MRI scanner.

Figure 2.

Recall performance. (A) Recall accuracy was tested immediately following Encoding (“Immediate”) and after a 5-hr delay (“Delayed”) in young (blue) and older adults (orange) across two conditions: solid bars represent Nap and hatched bars represent Wake conditions. Error bars show *SEM*. (B) Inter-session change in recall measured as delayed minus immediate recall in young (blue) and older adults (orange) for the Nap (solid bars) and Wake conditions (hatched bars). Error bars represent *SEM*. (C) The relationship between percentage of time spent in SWS and inter-session change in recall over the nap period for young and older adults (young: $r = .59$, $p = .03$; older: $r = .01$, $p = .97$).

Figure 3.

The relationship between SWS and hippocampal activation recall. (A) Left hippocampal activation (contrast value, arbitrary units, a.u.) during successful retrieval and % time spent in SWS during a nap (young adults, blue: $r = -.67$, $p = .012$; older adults, orange: $r = -.45$, $p = .145$). (B) Left hippocampal activation (contrast value, arbitrary units, a.u.) during successful retrieval and mean delta power of SWS obtained from frontal (F_1 , F_2) electrodes during a mid-day nap (young adults, blue: $r = -.51$, $p = .079$; older adults, orange: $r = .28$, $p = .54$).

Figure 4. Functional connectivity analysis. (A) Group differences in functional connectivity of the left hippocampus seed during postnap memory retrieval. Regions showing stronger connectivity in older than young adults are displayed on the template brain. (B) Fisher's Z values for the significant clusters in young (blue) and older adults (orange). Error bars represent *SEM*.

Participant Characteristics

Table 1.

	Young Adults (n = 13)		Older Adults (n = 13)	Mean ± SD	Mean ± SD	^a p
<i>Demographic Measures</i>						
Age	23.2 ± 2.6		67 ± 3.4			<.001
Sex	5M/8F		3M/10F			.67 ^b
Education	16.5 ± 1.6		16.2 ± 1.6			.72
<i>Habitual Sleep Measures</i>						
Chronotype (MEQ)	52.3 ± 8.9		61.5 ± 10.1			.02
Sleep Quality (PSQI)	3.1 ± 1.4		4 ± 2.1			.21
Average Nocturnal TST (actigraphy)	425.8 ± 59.5		473.7 ± 63.7			.09
Sleep Onset Time Variability (actigraphy) ^b	56.1 ± 34.4		42.4 ± 16.7			.29
Wake Onset Time Variability (actigraphy) ^c	62.8 ± 36.8		45.1 ± 31.7			.26
Average Sleep Latency (actigraphy)	16.7 ± 11.1		12.7 ± 5.6			.34
<i>Neuropsychological Measures</i>						
CVLT: Long Delay Free Recall	14.1 ± 1.9		11.8 ± 2.7			.02
CVLT: Long Delay Cued Recall	14.4 ± 1.91		12.4 ± 2.5			.06
Phonemic Fluency	16.4 ± 3.1		16.03 ± 5.9			.85
Semantic Fluency	24.3 ± 2.4		20.75 ± 6.3			.08
Trail Making (switching–number/letter sequencing)	30.5 ± 24.7		47.3 ± 23.5			.12
Stroop (color naming—word reading)	24.9 ± 8.8		69.9 ± 63.7			.03

MEQ = Morningness–Eveningness Questionnaire total score; PSQI = Pittsburgh Sleep Quality Index global score; TST = Total Sleep Time; CVLT = California Verbal Learning Test-II.

^aUnless otherwise specified, *p* values correspond to one-way ANOVAs comparing young and older adults, *F*(1, 24).

^b*p* value is the result of a Fisher's exact test.

^cDerived by calculating the variance in bed times and rise times over the course of the week of actigraphy assessment.

Table 2.

Nap Characteristics for Young and Older Adults

	Young Adults Mean $\pm$ SD	Older Adults Mean $\pm$ SD	p^a
TST (min)	87.4 $\pm$ 20.5	71.8 $\pm$ 20.4	.07
Sleep latency (min)	6.8 $\pm$ 4.3	6.7 $\pm$ 5.8	.93
WASO (min)	5 $\pm$ 6.3	4.4 $\pm$ 3.9	.76
Sleep efficiency (%)	87.6 $\pm$ 9.9	86.8 $\pm$ 8.7	.83
NREM1 (%)	28.6 $\pm$ 24.3	48.1 $\pm$ 29.3	.08
NREM2 (%)	42.6 $\pm$ 17.2	38.9 $\pm$ 18.1	.59
SWS (%)	23 $\pm$ 12.3	12.6 $\pm$ 16.1	.08
REM (%)	5.7 $\pm$ 7.6	.5 $\pm$ 1.8	.03
REM latency (min)	53.9 $\pm$ 19.4	103.5	.05
Mean frontal delta power during SWS ($\mu V^2/Hz$)	213.2 $\pm$ 144.7	126.9 $\pm$ 65.5	.16
Mean central delta power during SWS ($\mu V^2/Hz$)	184.8 $\pm$ 146.7	84.9 $\pm$ 37.3	.09

TST = total sleep time; WASO = wake after sleep onset.

^a p values correspond to one-way ANOVAs comparing young and older adults, $F(1, 23)$.