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The Memory Function of REM Sleep

A Dissertation submitted in partial satisfaction
of the requirements for the degree of

Doctor of Philosophy

in

Psychology

by

Elizabeth Ann McDevitt

September 2017

Dissertation Committee:
Dr. Sara C. Mednick, Chairperson
Dr. Aaron Seitz
Dr. Michael Silver

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The Dissertation of Elizabeth A. McDevitt is approved:

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Sex Differences in Sleep-Dependent Perceptual Learning

Elizabeth A. McDevitt*, Ariel Rokem*, Michael A. Silver, Sara C. Mednick

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DEDICATION

"*A well-spent day brings happy sleep*" – Leonardo da Vinci

Thank you to all the people who have contributed to so many of my well-spent days. I am indeed a very happy (napper) sleeper.

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ABSTRACT OF THE DISSERTATION

The Memory Function of REM Sleep

by

Elizabeth Ann McDevitt

Doctor of Philosophy, Graduate Program in Psychology
University of California, Riverside, September 2017
Dr. Sara C. Mednick, Chairperson

How does the human brain adapt to changes in the environment and store information to form memories? Decades of research has explored how information input from the environment triggers plastic changes in the brain, leading to new memory traces that have the potential to become long-term memories. My thesis asks what the optimal brain states (i.e., level of engagement with the external environment and the internal neural dynamics) are for these memory consolidation processes to occur. Sleep promotes memory consolidation (Rasch & Born, 2013), with the majority of prior studies focusing on the role of non-rapid eye movement (NREM) sleep for reducing forgetting in explicit memory contexts. Less is known about the role of rapid eye movement (REM) sleep, however, studies have shown REM may be critical for implicit or procedural learning (Cai, Mednick, Harrison, Kanady, & Mednick, 2009; Mednick, Nakayama, & Stickgold, 2003; Plihal & Born, 1997). The current thesis examines the effect of different brain states on memory consolidation, with a specific focus on visual perceptual learning. In the first two studies, I manipulated levels of

sensory input from the external environment by using different wake conditions (active and quiet wake) compared with sleep, and manipulated internal neural dynamics by using different sleep conditions (naps with NREM sleep alone or NREM plus REM sleep). I tested perceptual learning of both motion direction (Study 1) and texture (Study 2) discrimination. My results show that REM sleep promotes training-induced improvements in performance (i.e., plasticity) on visual skills tasks. I hypothesize that REM sleep is the optimal brain state for this consolidation due to its unique combination of low external input coupled with neural dynamics that promote plasticity. As a secondary aim of this thesis, I explored the utility of napping beyond its use as an experimental tool by examining individual differences in nap-dependent learning. In other words, should everyone nap to boost daytime performance? I found that learning profiles after a nap are different in men and women (Study 1), and that people who regularly nap show greater magnitude of nap-dependent learning compared to people who nap infrequently (Study 3). These findings should be taken into consideration when recommending napping in operational settings.

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General Introduction

Overview of memory processing

Memory can be broken down into three broad stages of processing – encoding, consolidation and retrieval. *Encoding* refers to the acquisition of new information, or at the neuronal level, external input activating neurons that bind together to form a new memory trace. *Consolidation* encompasses processes that lead to the strengthening or stabilization of memory traces, which prevents interference from new encoding, and the transfer of recent memories to long-term stores where they can become integrated with preexisting knowledge (McGaugh, 2000). During *retrieval*, memories are accessed and recalled. This thesis will be primarily focused on the consolidation stage, although it should be noted that encoding dynamics have a strong influence on subsequent consolidation (Cahill, Gorski, & Le, 2003; Diekelmann, Wilhelm, & Born, 2009), and it is difficult to disentangle consolidation and retrieval effects when behavior is the only memory outcome that is measured. Myriad studies have demonstrated memory improvements following a period of sleep compared to an equivalent time awake (Diekelmann & Born, 2010; Rasch & Born, 2013), suggesting that sleep promotes the consolidation stage. Before discussing this further, I will give a brief introduction to sleep stages and terminology.

Overview of sleep stages

Sleep is typically separated into four stages characterized by stereotypic electrical activity (Carskadon & Dement, 2011). The four stages progress in structured cycles from light Stages 1 and 2 through deep slow wave sleep (SWS, formerly Stages 3 and 4) and into REM sleep. Together, Stages 1, 2 and SWS are often referred to as non-REM (NREM) sleep. Stage 1 is briefly observed at sleep onset and can be identified by the presence of slow rolling eye movements and a disappearance of alpha (8-12 Hz) activity over occipital regions. Stage 2 sleep is more synchronized than Stage 1 and is characterized by sigma activity (12-15 Hz, i.e., spindles) and high-amplitude K-complex signals (characterized by a brief negative high-voltage peak followed by a slower positive complex). SWS is named for the high amplitude, slow wave activity [slow oscillations (.5-1 Hz) and delta (1-4 Hz)] that predominates. REM sleep is characterized by fast, low-amplitude EEG similar to waking, as well as increased heart rate, increased cortical blood flow, muscle paralysis and its eponymous rapid eye movements.

Sleep and memory consolidation

There are different memory systems in the brain, and one way to broadly divide these systems is based on hippocampal involvement (Squire, 1992). Declarative memories are hippocampal-dependent and include conscious or explicit recall of episodic and semantic memories. Non-declarative memories do

not depend on the hippocampus and include implicit memories such as procedural skills, perceptual learning and priming.

Studies of sleep effects on consolidation generally find a different pattern of behavioral performance for declarative and non-declarative memories (Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011). Compared to baseline memory tested immediately after encoding, declarative memories generally show some amount of forgetting that is decreased following a period of sleep, specifically NREM sleep, compared to wake (hence, a sleep-dependent memory benefit). Further, declarative memory retention is often associated with NREM sleep features. This includes minutes of Stage 2 and/or SWS as well as the number and density of sleep spindles, the signature electrophysiological feature (discrete 12-15Hz oscillatory events) of NREM sleep (Clemens, Fabó, & Halász, 2005; Schabus et al., 2004; Schmidt et al., 2006).

However, for non-declarative memories, performance is typically enhanced above and beyond the level of performance achieved at encoding. This behavioral improvement often depends on REM sleep (Cai et al., 2009; Mednick et al., 2003). This behavioral dichotomy suggests an interesting possibility that different consolidation mechanisms are at work during NREM and REM sleep, and that each sleep stage may be optimized for a different memory system. For example, declarative memories may require a protective consolidation state favoring low plasticity in order for synaptic connections to be stabilized to reduce

forgetting; non-declarative memories may require a state of high plasticity so that synaptic connections can be strengthened, thereby improving memory.

REM sleep: The new frontier

To date, the majority of studies have focused on NREM sleep and its role in memory consolidation, possibly via neural "replay" (Ji & Wilson, 2007; Wilson & McNaughton, 1994) or synaptic downscaling (Tononi & Cirelli, 2006, 2014) (see General Discussion for a more in-depth description of these models). These studies have been incredibly important for advancing the field and our understanding of the function of NREM sleep. However, a large question regarding the role of REM sleep for memory consolidation has not been addressed in these models.

In this thesis, I aim to test the hypothesis that REM sleep is the optimal brain state for consolidation of learning characterized by performance improvement over time (as opposed to forgetting). To do this, I conducted two studies, each testing non-declarative, perceptual learning in the visual domain. In each study, I experimentally manipulated consolidation brain states between a training session and memory test. These consolidation brain states included two wake conditions that varied the amount of information input. In the active wake (AW) condition, participants left the lab and carried out their normal daily activities. Participants in the quiet wake (QW) condition rested quietly, without sleeping, with limited amounts of information input. I also tested two different

sleep conditions – a NREM-only nap, and a nap with both NREM and REM. In these studies, I used a nap paradigm because it eliminates circadian confounds, does not require harsh sleep deprivation conditions, and allows for exquisite control of sleep stages (Mednick et al., 2002, 2003). For these reasons, the nap paradigm is a very useful experimental tool for investigating the specific roles of NREM and REM sleep. However, there remains a question as to the translational application of napping to real-world settings. If napping improves learning and memory, should everyone nap to boost daytime performance? As a secondary aim, I tested the hypothesis that there are individual differences in nap-dependent learning. In two separate studies examining nap effects on visual perceptual learning, I examined differences in learning profiles between men and women and between habitual and non-habitual nappers.

In Study 1, I examined improvement in the ability to discriminate motion direction as well as the generalizability of this learning to novel stimulus conditions (McDevitt, Rokem, Silver, & Mednick, 2013). Further analyses examined differences in the magnitude and specificity of learning between men and women. In Study 2, I introduced additional interference to the system at encoding, and examined if any consolidation brain state(s) was able to overcome this interference to show normal amounts of learning on a texture discrimination task (McDevitt, Duggan, & Mednick, 2015). In Study 3, I investigated if both habitual and non-habitual nappers show perceptual learning gains after a nap,

and if “practicing” or “restricting” napping for four weeks impacts the magnitude of nap-dependent learning in these two types of individuals.

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CHAPTER 1

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Sex Differences in Sleep-Dependent Perceptual Learning

Elizabeth A. McDevitt, Ariel Rokem, Michael A. Silver, Sara C. Mednick

Vision Research (2013), *99*, 172–179

Abstract

Sex differences in learning and memory suggest differences between men and women in mechanisms of neural plasticity. Such differences have been reported in a variety of explicit memory tasks, but implicit memory has not been studied in this context. We investigated differences between men and women in offline consolidation of perceptual learning (PL) of motion direction discrimination. Initially, discrimination thresholds were measured for two opposite directions of motion, followed by approximately forty minutes of training on one of the directions. During a post-training consolidation period, subjects either took a nap or remained awake. Thresholds were then reassessed for both directions of motion. We found that rapid eye movement (REM) sleep facilitates consolidation of PL but that the pattern of specificity in the REM condition differed between men and women. PL for men whose naps contained REM sleep was highly specific to the trained direction of motion, whereas REM sleep in women resulted in generalized learning to the untrained direction as well as to a novel direction that was not previously tested. Moreover, for subjects in the REM condition, men

exhibited greater PL than women for the trained direction. Our findings provide the first evidence of sex differences in the magnitude and specificity of PL and in the role of REM sleep in implicit learning. Our results have important implications for optimization of educational and training strategies designed for males and females.

Introduction

Cognitive performance is influenced by a variety of psychological and biological factors, including sex. In the domain of episodic memory, there are systematic differences between men and women in performance of hippocampal-dependent tasks (reviewed in Herlitz, Airaksinen, & Nordström, 1999). In particular, women outperform men on episodic memory tasks, including word recall, word recognition, story recall, name recognition, face recognition, and concrete picture recall and recognition (Lewin, Wolgers, & Herlitz, 2001). Women also have better memory for emotional stimuli than men (Canli, Desmond, Zhao, & Gabrieli, 2002). In contrast, men excel on visuospatial episodic memory tasks (Herlitz et al., 1999; Lewin et al., 2001). Although complete mechanistic explanations of sex differences in cognition are still lacking, there are many biological dimorphisms that could account for these differences, such as dimorphisms in brain structure, sex hormones and neurotransmitters, and differing responses to stress hormones (reviewed in Cahill, 2006). In particular, no studies have determined whether sex differences exist for implicit learning and whether such differences interact with the documented effects of sleep on

implicit learning. In the present study, we directly measure sex differences in sleep-dependent implicit learning of a visual perceptual skill.

Perceptual learning (PL) is the long-term improvement of performance on a sensory task. One of the hallmarks of PL is that it is specific to the physical features of the trained stimulus. That is, the performance improvement does not fully generalize to stimuli that are not used during training. In the visual system, specificity of PL has been demonstrated for spatial location (Ball & Sekuler, 1987; Nishina et al., 2009), orientation (Ahissar & Hochstein, 1997), spatial frequency (Fiorentini & Berardi, 1980), and ocularity, when training is monocular (Fahle, Edelman, & Poggio, 1995; Karni & Sagi, 1991), suggesting that the mechanism of training effects is a change in encoding in early stages of visual processing and/or decoding of activity in these early stages by higher-order areas involved in perceptual decisions. In particular, visual PL of motion direction discrimination is specific to the direction of motion and visual field location used for training (Ball & Sekuler, 1987; Rokem & Silver, 2010). In the present study, we assessed sex differences in the magnitude and specificity of PL of motion direction discrimination following sleep-dependent consolidation.

Offline consolidation during sleep has substantial effects on the magnitude and specificity of PL (Mednick et al., 2002; Mednick, Nakayama, & Stickgold, 2003). For example, post-training improvement of texture discrimination is dependent on both slow wave sleep and rapid eye movement (REM) sleep (Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; Stickgold, Whidbee,

Schirmer, Patel, & Hobson, 2000). A recent study reported sex differences in motor and verbal learning following a nap and found that sleep-dependent learning effects in women were mediated by the phase of the menstrual cycle (Genzel et al., 2012). However, PL was not examined in this study.

In the current study, we examined the effects of sleep during the consolidation period on the magnitude and specificity of PL of motion direction discrimination. We also assessed sex differences in these sleep effects. We utilized a nap paradigm that controls for circadian confounds and daytime interference. Our nap paradigm also allows for exquisite control of sleep stages (i.e., naps with and without REM sleep) and can produce the same magnitude of PL as a full night of sleep (Mednick et al., 2002, 2003). The experimental design includes a group of subjects that rested quietly during the consolidation period but were electroencephalographically monitored to insure they did not fall asleep (quiet wake) and a group that conducted their normal daily activities (without sleep or rest) during consolidation (active wake). Our results reveal a novel interaction between sex and sleep that affects both the magnitude and specificity of PL. This interaction demonstrates differences in the mechanisms of offline consolidation of PL between men and women.

Method

2.1 Subjects

150 healthy non-smoking adults between the ages of 18 and 35 gave informed consent to participate in the study. All experimental procedures were

approved by the University of California, San Diego Human Research Protections Program. Exclusion criteria included: a) irregular sleep-wake schedule; b) sleep disorder; c) significant psychopathology in immediate family; d) current use of any psychotropic medications; e) history of head injury and/or seizures; f) history of substance dependence; g) any other major medical condition. These exclusion criteria were evaluated based on subject self-report.

Subjects were asked to maintain their usual sleep-wake schedule during the week prior to the experiment and to refrain from consumption of caffeine, alcohol, and all stimulants for 24 hours prior to the beginning of the experiment as well as throughout the study day. Heavy caffeine users were not enrolled to exclude the possibility of significant withdrawal symptoms during the experiment. Subjects completed sleep diaries during the entire week prior to the experiment and wore actigraph wristwatches (Actiwatch-64, Respironics) the night before the experiment to provide subjective and objective measures of sleep-wake activity, respectively. We also assessed trait daytime sleepiness with the Epworth Sleepiness Scale (Johns, 1991) and evaluated circadian phase preference for morningness or eveningness with the Horne-Ostberg Morningness-Eveningness Questionnaire (Horne & Ostberg, 1976).

2.2 Stimulus and task

Visual stimuli for the motion direction discrimination (MDD) task have been previously described (Rokem & Silver, 2010) and were created using the

Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). Random dot kinetograms were presented within an annulus subtending 1.5-3.1 degrees of visual angle and centered at the fixation point (Figure 1A). The radius of each dot was 0.03 deg, and the dot density was 17 dots/deg^2. The dots were moving at a speed of 8 deg/sec, and each dot moved continuously for two monitor frames (approximately 27 msec at the 75 Hz refresh rate used) before being reassigned to another random location within the annulus. The dots were displayed at full luminance (158.9 cd/m^2). Two quadrants of the annulus, located on opposite sides of the fixation point, contained 100% coherent dot motion, and the remaining quadrants contained 0% coherent motion (Figure 1A).

In each trial, subjects reported whether the dots in two sequentially-presented stimuli were moving in the same or in different directions within the two quadrants containing coherent dot motion (Figure 1B) (Ball & Sekuler, 1987; Rokem & Silver, 2010, 2013, 2009). Presentation of task-relevant information in locations on opposing sides of the fixation point encouraged subjects to maintain central fixation throughout the trial, and subjects were also explicitly instructed to maintain fixation. The angular difference between the sequentially-presented stimuli was adjusted according to a Quest psychophysical staircase, converging on 70% correct performance, and each threshold was estimated from all trials in the staircase (Watson & Pelli, 1983). In addition, the Quest algorithm was used to calculate a 95% confidence interval for each threshold measurement. The

stimulus presentation software can be downloaded from: http://github.com/arokem/motion_th.

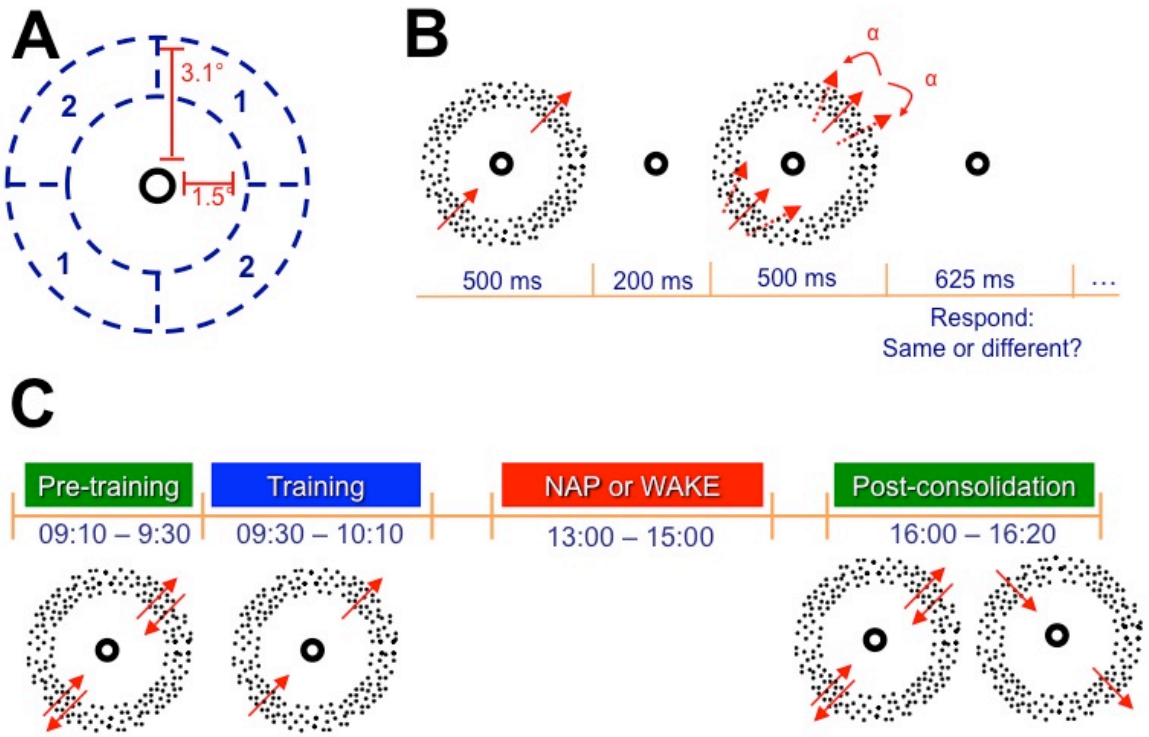

Figure 1.1. Experimental procedures (Study 1). **A)** Stimulus configuration. Coherent motion was presented in one of two pairs of spatial locations (1 or 2), and the other pair of spatial locations contained dots with 0% motion coherence. **B)** Motion direction discrimination task. In each trial, two fields of dots with 100% coherent motion were sequentially presented. The two stimuli contained either the same or slightly different directions of motion. Direction of motion is indicated by the arrows, and angular difference in motion direction is denoted here by **α**. **C)** Experimental timeline. At 9:10, pre-training thresholds were obtained for two oblique directions of motion (in this example, 45° and 225° in location 1). One of these directions (here, 45° in location 1) was then randomly chosen to be the trained direction, and subjects performed the task with this direction/location combination for 1000 trials. Subjects then either napped or remained awake from 13:00 to 15:00. At 16:00, post-consolidation thresholds were obtained for the two directions of motion used in the pre-training measurements as well as a novel direction/location combination (in this example, 135° in location 2).

2.3 Protocol

The full experimental timeline is displayed in Figure 1C. At 09:00, subjects practiced MDD for several minutes until they could reliably perform the task (95% confidence interval of discrimination threshold less than 30 degrees). Next, pre-training thresholds were measured for each of two opposite oblique directions and one of the two possible visual field locations within the stimulus annulus, randomly chosen for each subject (Rokem & Silver, 2010, 2013). Each pre-training threshold was the average of thresholds from two assessments of 50 trials each. At 09:30, one of the pre-training directions was randomly chosen to be the trained direction (the opposite direction was the untrained direction), and subjects performed 1000 trials of the MDD task for this direction/location combination.

At 11:00, subjects were randomly assigned to one of three groups. Subjects took a nap recorded with polysomnography (PSG), sat in a recliner listening to classical music with PSG monitoring (quiet wake (QW), n=23), or carried out their normal daily activities but were instructed to abstain from caffeine, alcohol, and napping (active wake (AW), n=30). Within the nap group, sleep stage scoring was used to assign subjects to either the REM (n=41, naps contained one or more minutes of REM sleep) or non-REM (NREM, n=36) groups after completion of the experiment. Subjects in the nap group were randomly assigned to either a 60-minute or 90-minute nap condition. Given that shorter naps tend to have less REM sleep than longer naps, the use of these two

durations increased the likelihood of having a significant number of subjects in both the REM and NREM groups. Wakefulness in the AW group was monitored using actigraph wristwatches.

At 16:00, MDD thresholds were again obtained for both the trained and untrained directions of motion. For each direction of motion, the threshold was based on an average of four 50-trial assessments. A subset of subjects (n= 81) was also tested on a completely novel direction of motion in a novel location. Over the course of the experimental day, we assessed momentary state levels of subjective sleepiness/alertness with the Karolinska Sleepiness Scale (KSS; Åkerstedt & Gillberg, 1990) at 09:00, 11:00, 16:00, and 18:00.

2.4 Polysomnography

PSG data were collected using Astro-Med Grass Heritage Model 15 amplifiers and Grass Gamma software. Scalp electroencephalogram and electrooculogram electrodes were referenced to unlinked contralateral mastoids (C3/A2, C4/A1, O1/A2, LOC/A2 and ROC/A1), and muscle tone electromyogram electrodes were attached under the chin. PSG data were digitized at 256 Hz and visually scored in 30-second epochs according to the sleep staging criteria of Rechtschaffen and Kales (1968). A given subject's data were excluded if he or she had less than fifteen minutes of total sleep time in the nap group (3 subjects), if sleep efficiency (defined as the ratio of total sleep time to time spent in bed)

was less than 30% (2 subjects), or if the PSG data indicated that he or she had slept despite being assigned to the QW group (5 subjects).

2.5 Statistical Analyses

A given subject's data were excluded if he or she had a 95% confidence interval of larger than 30 degrees for all pre-training, training, or post-training MDD thresholds (2 subjects) or if the absolute value of the difference between pre-training thresholds for the two directions of motion was more than three standard deviations from the mean of these thresholds, indicating unreliable pre-training measurements (4 subjects). Individual subject data were also excluded due to experimenter error (4 subjects). Data from a total of 130 remaining subjects are presented here.

Sleep variables were examined using one-way analysis of variance (ANOVA), with sex as a between-subject factor. The relationship between specific sleep variables and behavioral performance was examined by computing bivariate Pearson correlations. Because there is substantial between-subject variability in MDD thresholds, we computed a measure of learning (percent improvement) that is normalized to each subject's individual pre-training performance. This measure was calculated by comparing thresholds in the pre-training and post-consolidation sessions:

$$\%\ improvement = 100(1 - \frac{threshold(post)}{threshold(pre)})$$

Specificity of learning was calculated for each subject by subtracting percent improvement for the untrained direction of motion from percent improvement for the trained direction. For each participant, percent improvement for the novel condition was calculated relative to the average of pre-training thresholds from the trained and untrained directions of motion. To assess effects on PL magnitude, a three-way ANOVA was performed, with direction (trained/untrained) as a within-subject factor and sex and nap condition (AW/QW/NREM/REM) as between-subject factors. Similarly, specificity of PL was examined with a two-way ANOVA, with sex and condition as between-subject factors. All correlations and post-hoc pairwise comparisons were family-wise corrected for multiple comparisons. For all statistical tests, we report effect size in the form of R^2 for *t*-tests and partial eta squared (η_p^2) for ANOVA.

Results

3.1 Experimental nap parameters and other sleep variables

Consistent with previous studies of nocturnal sleep architecture in young adults (Dijk, Beersma, & Bloem, 1989; Voderholzer, Al-Shajlawi, Weske, Feige, & Riemann, 2003), we found no significant sex differences in sleep architecture for either NREM or REM experimental naps. In particular, there were no significant differences between men and women in total sleep time, sleep latency, wake after sleep onset, and sleep efficiency. There were also no detectable sex differences in minutes or percent of Stage 1, Stage 2, SWS, or REM sleep. Table 1 contains a summary of values of experimental nap sleep variables.

There were also no significant differences between men and women on any of the other sleep variables examined in this study: 1) prior nocturnal sleep; 2) trait or state subjective sleepiness; 3) morningness versus eveningness preference; or 4) nap habits (as assessed by the sleep diary).

Table 1.1

Experimental nap sleep variables as measured with polysomnography

	Non-REM Naps		**REM Naps**	
	Men *n = 17*	***Women*** *n = 19*	***Men*** *n = 15*	***Women*** *n = 26*
Total Sleep Time (min)	56.0 (4.3)	52.2 (4.3)	76.9 (5.3)	80.6 (2.8)
Sleep Latency (min)	10.4 (3.4)	10.4 (1.1)	7.1 (1.6)	7.3 (0.7)
WASO (min)	15.5 (4.0)	19.2 (4.1)	12.7 (3.8)	7.8 (1.6)
Sleep Efficiency (%)	70.8 (4.7)	62.4 (4.1)	80.2 (3.6)	84.3 (1.5)
Stage 1 (min)	5.5 (1.4)	6.9 (1.3)	6.7 (1.5)	4.2 (0.5)
Stage 2 (min)	35.4 (3.1)	36.8 (4.4)	47.4 (4.3)	45.5 (2.7)
SWS (min)	15.0 (3.4)	8.5 (2.3)	10.6 (2.7)	15.7 (2.8)
REM (min)	0	0	12.2 (2.2)	15.1 (1.7)

Note: Mean (SEM). WASO, wake after sleep onset; SWS, slow wave sleep; REM, rapid eye movement.

3.2 Pre-training thresholds

There were no significant sex differences in pre-training thresholds ($t_{(128)} = 1.58$, $p > .05$, $R^2 = .02$), and all subsequent analyses employ a percent improvement measure that is normalized to each subject's pre-training performance (see section 2.5). All pre-training and post-training thresholds are reported in Table 2.

Table 1.2

Motion direction discrimination pre- and post-training thresholds

Direction of Motion	Men				Women			
	AW	**QW**	**NREM**	**REM**	**AW**	**QW**	**NREM**	**REM**
Trained (pre)	19.2 (1.5)	19.1 (2.0)	16.0 (1.4)	18.8 (1.6)	19.7 (1.7)	17.6 (1.6)	19.6 (1.2)	18.2 (0.9)
Trained (post)	17.2 (1.9)	17.3 (1.5)	13.9 (1.6)	12.4 (1.3)	16.2 (1.1)	15.1 (0.8)	17.1 (1.3)	14.8 (0.8)
Untrained (pre)	16.8 (1.3)	20.8 (2.2)	16.5 (1.4)	15.2 (1.7)	17.4 (1.2)	18.6 (1.7)	20.8 (1.2)	19.7 (1.0)
Untrained (post)	17.7 (1.2)	15.5 (1.5)	14.2 (1.5)	13.7 (1.6)	15.9 (1.5)	15.2 (1.5)	17.3 (1.4)	14.0 (0.8)
Novel	20.7 (2.2)	20.3 (3.3)	15.2 (1.9)	16.7 (1.4)	16.9 (1.6)	15.9 (1.0)	14.9 (1.1)	14.0 (1.8)

Note: Mean (SEM) in degrees. AW, active wake; QW, quiet wake; NREM, non-rapid eye movement naps; REM, rapid eye movement naps.

3.3 Sleep affects motion PL

We assessed the effects of sex and sleep on magnitude of motion PL with a 2 x 2 x 4 ANOVA, with direction of motion (trained or untrained) as a within-subject factor and sex and nap condition (AW, QW, NREM, REM) as between-subject factors. There were no significant main effects of either motion direction or sex, but there was a significant main effect of nap condition ($F_{(3,122)} = 2.81$, $p < .05$, $\eta_p^2 = .07$), indicating a role of sleep in consolidation of motion PL. Post-hoc *t*-tests demonstrated significant learning in the QW ($t_{(22)} = 4.00$, $p = .001$, $R^2 = .42$), NREM ($t_{(35)} = 3.33$, $p < .01$, $R^2 = .24$), and REM ($t_{(40)} = 5.91$, $p < .001$, $R^2 = .46$) conditions. However, percent improvement was not significantly different from zero in the AW group ($t_{(29)} = 0.97$, $p > .05$, $R^2 = .03$). We directly compared percent improvement in the QW, REM and NREM groups to the AW control group and found that only the REM group had significantly more learning than the AW group ($t_{(69)} = 2.70$, $p < .01$, $R^2 = .10$) (Figure 2). These results reveal a substantial facilitation of motion PL consolidation by REM sleep.

There were no significant correlations between basic sleep variables and percent improvement (all p values >.05): time in Stage 1 (NREM naps: r = -.08, REM naps: r = -.36), time in Stage 2 (NREM naps: r = .02; REM naps: r = -.14), slow wave sleep time (NREM naps: r = .12; REM naps: r = -.10), REM sleep time (r = .01), and total sleep time (NREM naps: r = .08; REM naps: r = -.28).

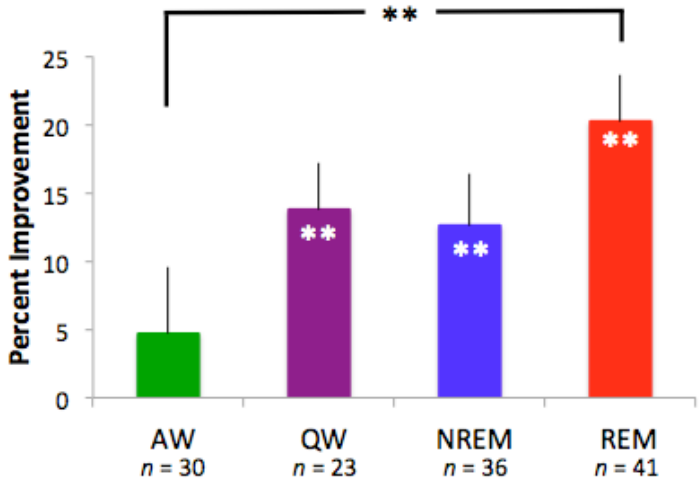

Figure 1.2. REM sleep after training increases motion perceptual learning. Quiet wake (QW), non-REM (NREM), and REM nap conditions all showed significantly enhanced motion direction discrimination, but only the REM group had significantly more percent improvement compared to active wake (AW). Error bars denote SEM. **indicates p < .01

3.4 The effects of naps on magnitude of PL are sex-specific

In addition to the main effect of nap condition on percent improvement, we found a significant three-way interaction among nap condition, trained versus untrained directions of motion, and sex ($F_{(3,122)} = 3.27$, $p < .05$, $\eta_p^2 = .07$) (Figure 3). We further explored this interaction with post-hoc *t*-tests. In the REM nap condition, both men and women exhibited significant learning for the trained direction of motion (men: $t_{(14)} = 6.97$, $p < .001$, $R^2 = .77$; women: $t_{(25)} = 3.36$, $p < .01$, $R^2 = .31$). Additionally, women in the REM nap condition had significant learning for the untrained direction ($t_{(25)} = 5.58$, $p < .001$, $R^2 = .56$), while men did not ($t_{(14)} = 0.25$, $p > .05$, $R^2 = .005$).

Within the REM nap group, men showed more learning than women for the trained direction of motion ($t_{(39)}$ = 2.34, p < .05, R^2 = .12), whereas women showed significantly more learning than men for the untrained direction ($t_{(39)}$ = 2.08, p < .05, R^2 = .10). These differential effects of sex on learning for the trained and untrained directions in the REM nap group suggest that there are differences between men and women in the specificity of PL following REM sleep, a possibility that we explicitly test below. Finally, there was learning for the untrained direction for men in QW ($t_{(11)}$ = 4.79, p = .001, R^2 = .67).

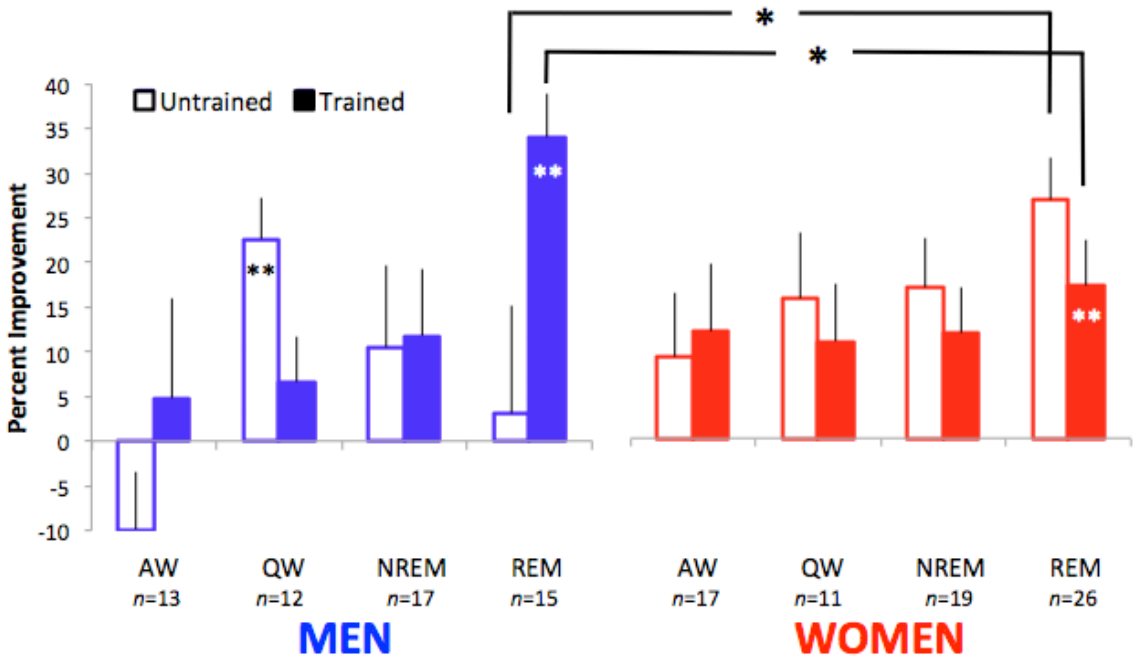

Figure 1.3. Specificity of motion perceptual learning differs in men and women. Following a nap with REM sleep, men showed significant improvement for the trained (filled bars) direction of motion, whereas women showed improvement for both trained and untrained (open bars) directions of motion. Error bars denote SEM. *indicates p < .05 and **indicates p < .01

3.5 REM sleep enhances specificity of PL in men but not women

To directly assess the effects of sex on specificity of PL, we calculated the difference in percent improvement for the trained and untrained directions of motion for each subject (Figure 4). There was a significant sex-by-nap condition interaction for this measure of direction specificity of PL ($F_{(3,122)} = 3.27$, $p < .05$, $\eta_p^2 = .07$). For men, there was a main effect of nap condition on specificity ($F_{(3,53)} = 3.62$, $p < .05$, $\eta_p^2 = .17$), with the greatest specificity occurring in the REM group (significantly greater specificity for REM than for QW: $t_{(25)} = 3.52$, $p < .01$, $R^2 = .33$). In contrast, there was no detectable effect of nap condition on specificity of PL for women ($F_{(3,69)} = .62$, $p = .61$, $\eta_p^2 = .03$), with women showing generalization of PL to the untrained direction in all nap conditions. Within the REM nap condition, men showed significantly more direction specificity of PL than women ($t_{(39)} = 3.33$, $p < .01$, $R^2 = .22$).

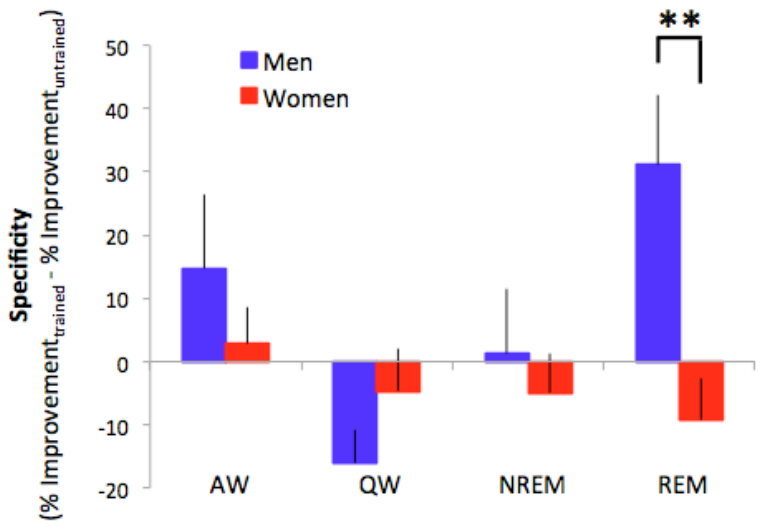

Figure 1.4. REM sleep enhances direction specificity of motion perceptual learning more for men than women. Following REM sleep, men showed greater specificity of PL than women. Error bars denote SEM. **indicates $p < .01$

3.6 Women generalize learning to a novel direction and location

It is possible that exposure to the untrained direction during pre-training measurements could have influenced percent improvement for the untrained direction (T. Zhang, Xiao, Klein, & Levi, 2010). Therefore, we also examined transfer of PL to a completely novel direction of motion and visual field location in a subset of subjects (n_{men} = 37, n_{women} = 44). Results from a three-way ANOVA, with motion direction (trained, untrained, or novel) as a within-subject factor and sex and nap condition as between-subject factors, revealed a significant interaction between motion direction and sex ($F_{(2,146)} = 4.22$, $p < .05$, $\eta_p^2 = .06$). There is insufficient power (due to small sample size in some groups) to fully

assess the effects of nap condition for the novel stimulus. Therefore, to increase power for this analysis, we combined nap groups (NREM + REM) and wake groups (AW + QW). In general, women showed greater percent improvement for the novel stimulus than men ($t_{(79)}$ = 2.79, $p < .05$, R^2 = .09), and this pattern of results was obtained following both wake and sleep (Figure 5). However, percent improvement was only significantly greater in women compared to men following a nap ($t_{(38)}$ = 2.63, $p < .05$, R^2 = .15), and the magnitude of improvement was only significantly different from zero in women following a nap ($t_{(19)}$ = 3.90, $p < .01$, R^2 = .44). These data demonstrate generalization of PL to a completely novel stimulus in women but not men and that this effect was enhanced following a nap, consistent with our finding of significant learning of the untrained direction in the REM nap group in women but not men.

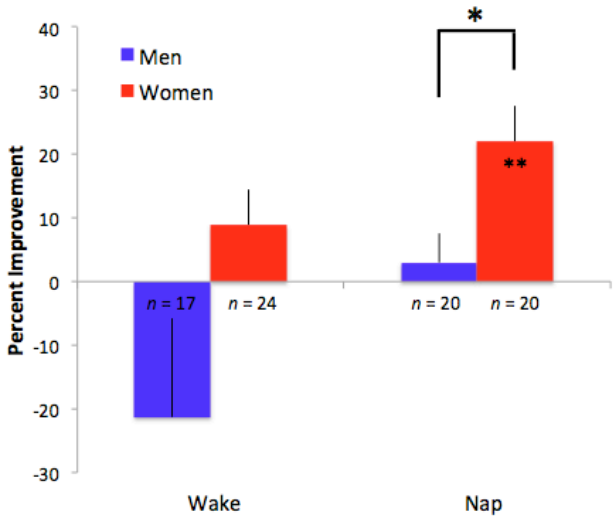

Figure 1.5. Women generalize learning to a novel motion direction and location, but men do not. Following a nap, women showed greater percent improvement for the novel stimulus compared to men. Error bars denote SEM. *indicates $p < .05$ and **indicates $p < .01$

Discussion

This is the first study of sleep-dependent PL to 1) measure the effects of sleep during offline consolidation of motion PL, and 2) demonstrate sex differences in consolidation of PL. We have found that the critical stage of sleep for these consolidation processes is REM sleep and that the magnitude and specificity of learning of the trained stimulus depends on sex.

4.1 REM sleep facilitates motion PL

We defined motion perceptual learning (PL) as the percent improvement in motion direction discrimination after an offline consolidation period during which subjects either took a nap (with or without REM sleep) or remained awake (quiet or active wake). We found that while quiet wake, NREM and REM groups all showed significant motion PL, only the REM group had greater learning than the active wake group. Importantly, total sleep time was not correlated with motion PL, consistent with other studies reporting that the quality of sleep is more important than the quantity (Mednick et al., 2003). Our finding of a unique role of REM sleep in consolidation of motion PL is consistent with prior studies showing that REM sleep, either from nighttime sleep (Stickgold et al., 2000) or a daytime nap (Mednick et al., 2003), is necessary for PL of texture discrimination. Motion PL has previously been examined across multiple days of training (Ball & Sekuler, 1987; Rokem & Silver, 2010, 2013), with nocturnal sleep occurring between training sessions. However, sleep was not monitored in those studies.

In the present study, we interpret the effects of sex and sleep on PL as effects on consolidation, as our design treated all subjects identically during encoding and retrieval, while the nap groups differed in the consolidation portion of the experiment. The sex differences we observed interacted with nap condition, providing further evidence that the effects we report are on the process of consolidation of PL. However, our methods, like those used in any behavioral study of PL, employ performance at retrieval to measure the consequences of

consolidation. It is therefore possible that the effects of different types of nap during consolidation actually manifest as differences in post-nap retrieval. Similarly, the sex differences we found could reflect retrieval processes (although these sex differences in retrieval would have to depend on the type of sleep in the prior consolidation period). Thus, while the most straightforward explanation of our findings involves effects of sleep and sex on consolidation of PL, we cannot exclude effects on retrieval of PL that are modulated by experience during the consolidation period. It is possible that consolidation and retrieval could be dissociated in future studies employing physiological measures of the effectiveness of consolidation and/or pharmacological manipulations that separately target the consolidation and retrieval phases of PL.

4.2 Sex differences in motion PL

Within the REM group, men showed greater learning of the trained direction and also more specificity of PL for the trained motion direction, whereas women showed generalized learning across motion directions and visual field locations. Across nap conditions, these sex differences in specificity of PL extended to a novel direction and location, with women showing greater learning than men for a stimulus configuration that they had never seen before. Our findings suggest that while REM sleep facilitates specific PL in men, generalization of learning to untrained and novel stimuli occurs for women, regardless of nap condition.

Using an experimental nap paradigm, we identified REM sleep as the sleep stage involved in sex-dependent specificity of PL. The sex differences reported here were not due to other sleep-related factors that we studied: there were no significant differences between men and women in any other measured sleep variable: nap architecture, prior nocturnal sleep, nap habits, trait or state daytime sleepiness, and morningness-eveningness preference. Thus, the sex differences in sleep-dependent learning we report here were not due to sex differences in any of these factors.

There were also no significant pre-training differences in task performance between men and women for displays with 100% motion coherence, generally consistent with the finding that young men and women do not differ in their sensitivity in detecting low coherence motion signals, although older women have lower sensitivity than older men (Atchley & Andersen, 1998). Thus, the sex differences we report are not due to overall differences in motion direction discrimination ability between the men and women studied here but instead are specific to consolidation of PL during REM sleep.

Sex differences have recently been reported for fast task-irrelevant PL (TIPL) in younger adults (Leclercq, Seitz, Sulitzeanu-Kenan, Xu, & Martinez, 2012). Specifically, fast TIPL depended on whether subjects were instructed to explicitly memorize or to simply attend to the information presented with the target. Men exhibited fast TIPL in both instruction conditions, whereas women showed fast TIPL only in the explicit memorization condition. However, fast TIPL is used to

study learning within a single training session, not across a post-training consolidation period, suggesting that the results of Leclercq and Seitz (2012) stem from a different underlying mechanism than the sex differences in REM sleep-dependent consolidation we report here.

One unexpected result from our study was the magnitude of learning of the untrained motion direction for men in the quiet wake condition. One previous study has shown similar profiles of learning in quiet wake and sleep conditions but found no learning in an active wake condition (Mednick, Makovski, Cai, & Jiang, 2009). This result should be examined in future studies on sex differences in PL in the context of active wake, quiet wake, and sleep.

4.3 Cognitive and biological factors contributing to PL specificity

Many factors modulate specificity of PL. During encoding of training stimuli, high-level mechanisms such as attention (Ahissar & Hochstein, 1993) and decision-making (Law & Gold, 2009) influence specificity of learning, as do training methods (Hussain, Bennett, & Sekuler, 2012; Liu, 1999; Wang, Zhang, Klein, & Levi, 2012), task difficulty (Ahissar & Hochstein, 1997), exposure to different stimulus features (e.g., Xiao et al., 2008), and sensory adaptation (Harris, Gliksberg, & Sagi, 2012).

The neurotransmitter acetylcholine (ACh) modulates both the magnitude and specificity of PL. Cholinergic enhancement with the cholinesterase inhibitor donepezil augments the magnitude and specificity of motion PL (Rokem & Silver,

2010, 2013), and administration of chewing tobacco containing nicotine, an agonist of nicotinic ACh receptors, during PL consolidation increased the magnitude and specificity of PL of texture discrimination (Beer, Vartak, & Greenlee, 2013). In general, high levels of cholinergic signaling have been proposed to set the appropriate neural dynamics for consolidation during REM sleep (Buzsáki, 1989; Hasselmo, 1999). Additionally, ACh is crucial for the induction and maintenance of long-term potentiation of synaptic transmission (Hasselmo & Bower, 1993; Matsukawa et al., 1997), a likely mechanism of synaptic plasticity in PL (Sale et al., 2011). Therefore, ACh modulation may be one candidate mechanism for understanding the differences between men and women in PL following REM sleep.

Indeed, animal studies have reported that male rats have more hippocampal ACh release than female rats (Dai Mitsushima, 2011; Dai Mitsushima, Masuda, & Kimura, 2003), particularly during the dark phase of the daily cycle (Masuda, Mitsushima, Funabashi, & Kimura, 2005). If similar sex differences are present in humans, they could contribute to the lower specificity of PL in women, compared with men, that we found following a nap with REM sleep. One way to further investigate this hypothesis is to examine different perceptual learning tasks. For example, the fact that cholinergic enhancement increases both the magnitude and specificity of PL of motion (Rokem & Silver, 2010) and texture (Beer et al., 2013) discrimination provides evidence for a general facilitatory role of ACh in PL as opposed to a task-specific mechanism. Therefore, if ACh mediates the sex-

dependent differences in motion PL we report here, these sex differences may also generalize to other forms of sleep-dependent PL. Further research is needed to determine the relationships among ACh, sex, and PL.

Another possible source of sex differences in the magnitude and specificity of PL are menstrual cycle effects mediated by sex hormones. Mitsushima et al. (2009) found that sex steroids – testosterone in males and estradiol (estrogen) in females – increase ACh release in the hippocampus of rats. Indeed, in humans, fluctuations in estradiol levels across the menstrual cycle are associated with changes in learning and memory (Genzel et al., 2012; Maki, Rich, & Shayna Rosenbaum, 2002), and a recent study reported sex differences in verbal and motor learning following a nap (Genzel et al., 2012). Specifically, women in their luteal phase (when estrogen levels are higher) and men showed significant improvement on both tasks following a nap, compared to a wake group, but women in the follicular phase (the first week of the menstrual cycle) did not. Our study included a relatively large sample of women participants (n=26 in the REM group alone), so it is unlikely that there was a significant bias towards a particular phase of the menstrual cycle in our sample. Nevertheless, we did not determine menstrual phase of the female subjects in our study and could therefore not assess possible effects of menstrual cycle on sleep-dependent PL.

Recent work suggests that effects on the magnitude and specificity of PL may be dissociated. Changing the state of local adaptation during texture discrimination PL did not affect the magnitude of learning but did increase

generalization (Harris et al., 2012). Moreover, specificity and magnitude of learning are reflected in different components of visual event-related potentials, suggesting that they are based on different neural mechanisms (G. Zhang, Cong, Song, & Yu, 2013). Thus, the two main sex-dependent results we report, that men learn more in the trained condition, and that women generalize more to other conditions, may arise from separate underlying biological causes.

4.4 Implications of our results for design of training procedures

Our finding that sex is an important factor in the sleep-dependent consolidation of PL has several significant practical implications. First, consolidation differences between men and women should be taken into account when designing courses of training, especially those having an element of PL, such as training in the detection of the occurrence of rare visual signals (satellite and radar imagery; video from security cameras). This could lead to refined learning strategies and even differential assignment of individuals to tasks that place high demands on visual processing. In most real-life learning situations, generalization of learning to novel and untrained stimuli is desirable. We have shown that REM sleep facilitates the consolidation of motion PL in both men and women but that generalization to untrained and novel stimuli is only apparent in women, suggesting that women may be better suited for tasks requiring generalization of perceptual skill learning. Finally, PL studies have typically used small sample sizes and have therefore been underpowered to detect sex

differences (e.g., for motion PL: Ball & Sekuler, 1987; Liu, 1999; Rokem & Silver, 2010). Our findings indicate that future studies would benefit from having sample sizes large enough to adequately test for individual differences such as sex, as this may help inform our understanding of underlying biological mechanisms and determine the generalizability of results.

4.5 Clinical implications

PL is used as a treatment for a variety of visual disorders, including amblyopia (Dennis M Levi & Li, 2009). Importantly, in patients with amblyopia, learning on a variety of PL tasks transfers to improvements in Snellen acuity (Levi & Polat, 1996; Zhou et al., 2006), stereoacuity (Roger W. Li, Provost, & Levi, 2007), and visual counting (Li et al., 2004). PL-driven improvements in these fundamental aspects of vision in patients with amblyopia should therefore enhance natural scene processing and quality of life. However, the efficacy of these treatments may be increased by individualized training procedures. Our findings suggest that sex and sleep should be taken into account when designing therapeutic interventions involving PL.

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CHAPTER 2

This chapter has previously been published as

REM Sleep Rescues Learning from Interference

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Abstract

Classical human memory studies investigating the acquisition of temporally-linked events have found that the memories for two events will interfere with each other and cause forgetting (i.e., *interference*; Wixted, 2004). Importantly, sleep helps consolidate memories and protect them from subsequent interference (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). We asked whether sleep can also repair memories that have already been damaged by interference. Using a perceptual learning paradigm, we induced interference either before or after a consolidation period. We varied brain states during consolidation by comparing active wake, quiet wake, and naps with either non-rapid eye movement sleep (NREM), or both NREM and REM sleep. When interference occurred after consolidation, sleep and wake both produced learning. However, interference prior to consolidation impaired memory, with retroactive interference showing more disruption than proactive interference. Sleep rescued learning damaged by interference. Critically, only naps that contained REM sleep were able to rescue learning that was highly

disrupted by retroactive interference. Furthermore, the magnitude of rescued learning was correlated with the amount of REM sleep. We demonstrate the first evidence of a process by which the brain can rescue and consolidate memories damaged by interference, and that this process requires REM sleep. We explain these results within a theoretical model that considers how interference during encoding interacts with consolidation processes to predict which memories are retained or lost.

Introduction

"A brain is a lot like a computer. It will only take so many facts, and then it will go on overload and blow up." – Erma Bombeck

Daily living involves copious information processing that has the potential to "overload" the brain and result in memory loss. For example, after too many hours gazing at paintings in a museum or studying for a chemistry exam in the library, people are liable to forget or confuse the details of this newly learned information. A century of psychological research has investigated this type of information overload, termed *interference,* by examining how the acquisition or encoding of new information can block recollection or retrieval of recent memories (Wixted, 2004). Memories can be protected from future interference by sleep. For example, Ellenbogen and colleagues (2006) trained subjects on two word-pair lists separated by a period of sleep or wake and found better retention of the first word-pair list when sleep occurred between encoding and retrieval (although see Deliens, Leproult et al., 2013 and Deliens, Schmitz, et al., 2013, for

data suggesting that sleep reinstates sensitivity to retroactive interference). However, in a single day we experience many events prior to going to sleep at night that may interfere with one another, yet can still be recalled days, weeks or years later. Since we do not need to stabilize each waking experience with sleep (e.g., a nap) before moving on to the next, there must be a mechanism that allows the brain to rescue memories damaged by interference prior to sleep. One possibility is that along with protecting new memories, sleep may also repair damaged memories, such as those degraded by interference (Norman, Newman, & Perotte, 2005). Here, we investigate whether memories damaged by interference may be rescued by different brain states of sleep or wake.

Traditionally, studies have experimentally manipulated interference and examined how prior learning of task A may disrupt subsequent learning of task B (proactive interference), or how learning task B may disrupt prior learning of task A (retroactive interference). In addition to this task-specific interference, the period between encoding and retrieval may influence how memories are consolidated as well (Wixted, 2004). Early studies by Jenkins and Dallenbach (1924) demonstrated that a period of wake between encoding and retrieval of nonsense syllables resulted in more forgetting than an equivalent period of sleep. The authors interpreted their results to mean that normal mental exertion during an active wake (AW) period, compared with sleep, disrupted consolidation of recent memories and caused “obliteration of the old by the new” (pg. 612). However, most studies compare sleep (low information input) with AW (high

information input; e.g., Fenn, Nusbaum, & Margoliash, 2003), but do not include quiet wake (QW, characterized as a medium level of information input when the brain is awake but not cognitively engaged). Only a handful of studies have systematically examined how brain states that vary in amount of information input affect consolidation and subsequent retrieval. Amongst these studies, some have found equivalent memory improvements following periods of sleep and QW, compared to decreased memory following AW on some tasks [e.g., auditory tone sequence learning task (Gottselig et al., 2004), a visual search task (Mednick, Makovski, Cai, & Jiang, 2009), and a pursuit motor task (Rieth, Cai, McDevitt, & Mednick, 2010)]. On the other hand, some have found a benefit of sleep compared to QW. For example, one study tested implicit priming in a creativity task and found significantly better performance only after a sleep period that included rapid eye movement (REM) sleep (Cai, Mednick, Harrison, Kanady, & Mednick, 2009). In fact, memory improvements are frequently associated with distinct sleep stages and features (Mednick, Nakayama, & Stickgold, 2003; Schabus et al., 2004; Tucker et al., 2006). These findings suggest that plasticity-related neural mechanisms during specific sleep stages may provide memory benefits above and beyond those of QW and AW (Diekelmann & Born, 2010; Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011). Yet, no study has examined how different brain states — AW, QW, non-REM (NREM), and REM sleep — influence our ability to rescue memories damaged by interference.

Using a perceptual learning interference paradigm, we examined how competing information is consolidated across brain states that vary in information input. Perceptual learning is the long-term improvement of performance on a sensory task that is specific to the physical features of the trained stimulus. Perceptual learning is vulnerable to interference when competing tasks share stimulus features (e.g., spatial location) and when two tasks are trained in short temporal succession (Seitz et al., 2005; Yotsumoto, Chang, Watanabe, & Sasaki, 2009). Additionally, perceptual learning deteriorates with repeated, within-day training, but is restored to baseline following a period of NREM sleep (Censor, Karni, & Sagi, 2006; Mednick et al., 2002; Mednick, Arman, & Boynton, 2005; Mednick et al., 2003), and is enhanced above baseline following a period of REM sleep (Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; McDevitt, Rokem, Silver, & Mednick, 2013; Mednick et al., 2003; Stickgold, James, & Hobson, 2000; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). Using a nap paradigm that controls for circadian confounds, allows for exquisite control of sleep stages, and produces the same magnitude of learning as a full night of sleep (Mednick et al., 2003), we examined how learning disrupted by retroactive and proactive interference on a texture discrimination task was consolidated across four different brain states: AW, QW, naps with NREM sleep only, and naps with both NREM and REM sleep. Specifically, we asked: (i) Does high information input during consolidation (AW) disrupt learning and make memories vulnerable to interference compared with medium input (QW) and low input

(sleep)?; and (ii), Following retroactive or proactive interference, which brain states rescue learning?

Method

2.1 Subjects

152 healthy, non-smoking adults between the ages of 18 and 35 with no personal history of neurological, psychological, or other chronic illness gave informed consent to participate in the study. All experimental procedures were approved by the Institutional Review Boards of the University of California at San Diego and University of California at Riverside. Subjects were asked to maintain their usual sleep-wake schedule during the week prior to the experiment and to refrain from consuming caffeine, alcohol, and all stimulants for 24 hours prior to and including the study day. Heavy caffeine users (> 240mg per day) were not enrolled to exclude the possibility of significant withdrawal symptoms during the experiment. Subjects completed sleep diaries during the entire week prior to the experiment and wore actigraph wrist monitors (Actiwatch-64, Respironics) the night before the experiment to provide subjective and objective measures of sleep-wake activity, respectively.

2.2 Stimulus and task

Subjects performed a texture discrimination task (TDT) similar to that developed by Karni & Sagi (1991). We used several different stimulus conditions

in the interference paradigm. Here we describe the methods common to all versions of the task. The interference paradigm is described in section 2.3.

Visual stimuli for the TDT were created using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). Each stimulus contained two targets: a central letter ('T' or 'L'), and a peripheral line array (vertical or horizontal orientation) in either the lower left or upper right quadrant at 2.5°-5.9° eccentricity from the center of the screen. The peripheral array consisted of three diagonal bars that were either positioned in a horizontal or vertical array against a background of horizontally or vertically oriented background distracters, which created a texture difference between the target and the background.

An experimental *trial* consisted of the following sequence of four screens: central fixation cross for 1000ms, target screen for 40ms, blank screen for a duration between 40 and 545ms (the inter-stimulus-interval, or ISI), mask for 27ms, followed by the response time interval and feedback (red fixation cross with auditory beep for incorrect trials and green fixation cross for correct trials) before the next trial (Figure 1B). Subjects discriminated two targets per trial by reporting both the letter at central fixation ('T' or 'L') and the orientation of the peripheral, three-element array (horizontal or vertical) by making two key presses. The central task controlled for eye movements.

Each *block* consisted of 15 trials, each with the same ISI. A threshold was determined from the performance across 8 blocks, with a progressively shorter ISI, starting with 545ms and ending with 40ms. The specific sequence of ISIs

across an entire session was [545, 440, 306, 200, 146, 106, 80, 40]. We used a short version of the task (120 trials per condition) to avoid perceptual deterioration effects (Censor & Sagi, 2008; Mednick et al., 2005). A psychometric function of percent correct for each block was fit with a Weibull function to determine the ISI at which performance yielded 80% accuracy.

Subjects controlled the onset of each block and were instructed to take as many breaks as they needed between blocks. Once a block began, a new trial was initiated every 2s, regardless of whether or not the subject made a response. Subjects practiced the task before each new stimulus condition. This practice ensured that subjects understood the task and were discriminating the peripheral target between 90% and 100% correct on the easiest version of the task.

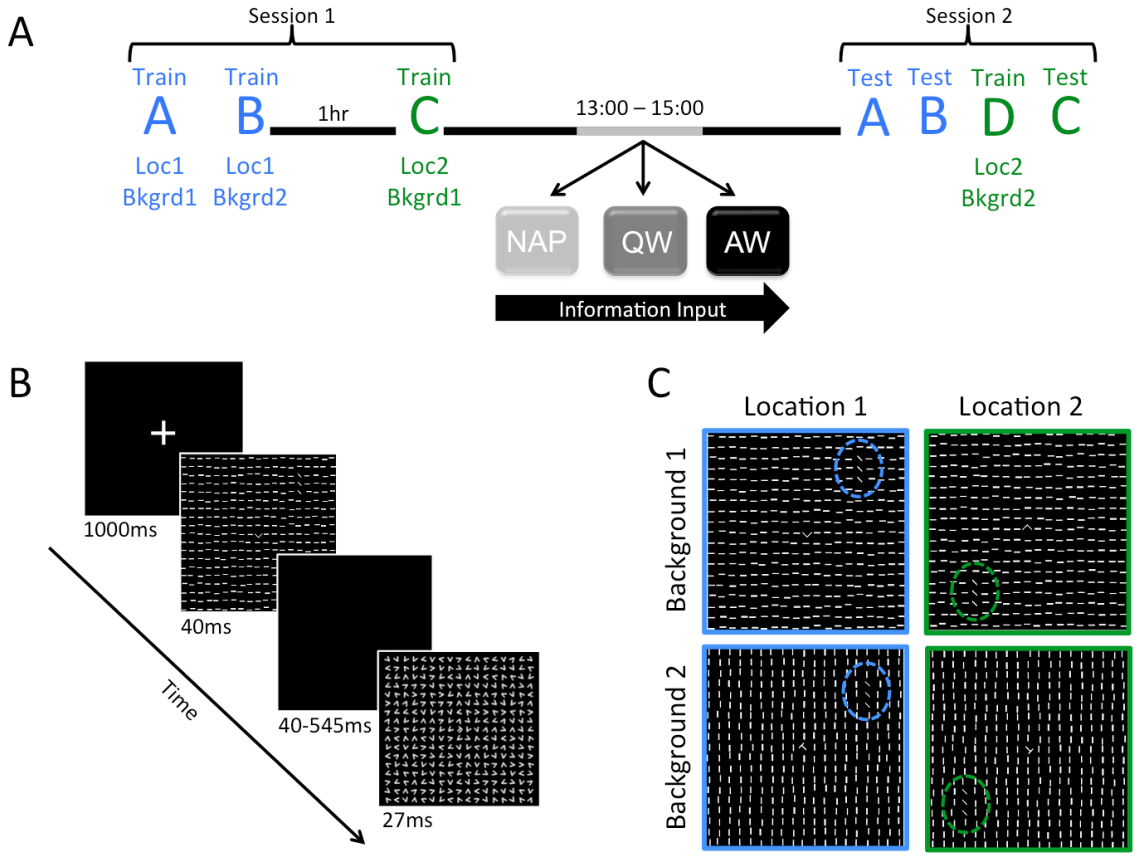

Figure 2.1. Experimental methods (Study 2). **(A)** Subjects were trained on all four TDT conditions (A, B, C, D). Based on prior work, conditions A & B and conditions C & D were designed to interfere with each other (same target location, different background orientation). That is, A-B: loc1/bkgrd1 – loc1/bkgrd2 with no delay between conditions; and C-D: loc2/bkgrd1 – loc2/bkgrd2 with a 7-hr delay between conditions. Baseline thresholds were obtained for conditions A, B and C during Session 1. During the retention interval, subjects took a nap, rested quietly (quiet wake, QW), or carried out their usual daily activities outside of the lab (active wake, AW). During Session 2, performance was retested for conditions A and B, followed by training condition D, and then re-testing condition C. **(B)** The texture discrimination task (TDT) entails 1000ms of fixation, followed by a target display for 40ms. Each display contained a central target ("L" or "T") and a peripheral target (three diagonal lines either stacked in a horizontal or vertical orientation). The next screen was blank, followed by a mask. The duration of the blank screen, the inter-stimulus interval (ISI), decreased from block to block. Subjects were asked to identify the central letter and report the orientation of the three diagonal lines. Subjects completed 8 blocks with 15 trials per block for each condition at training and testing (120 trials per condition). **(C)** Examples of target stimuli used across conditions. Peripheral texture targets were either presented in the upper right or lower left quadrant of the display (texture targets circled with dotted line for demonstration purposes only). Background orientation was either horizontal or vertical. Each subject was tested on a combination of four conditions in each spatial location with each background orientation.

2.3 Interference paradigm

Interference in perceptual learning is specific to the retinotopic location of the stimulus (Seitz et al., 2005). That is, training stimuli in the same visual quadrant causes interference, but when stimuli are trained in different visual quadrants there is no disruption. Additionally, in TDT learning, interference is specific to background orientation (Yotsumoto et al., 2009), such that no perceptual learning occurred when two different background orientations were trained in the same location. Taken together, these findings established that stimuli in the same location, different background cause interference, whereas stimuli in a different location, same background do not cause interference.

In the present study, we induced interference by training two sets of TDT conditions (A-B) and (C-D). Within a set, texture targets (three diagonal lines) appeared in the same spatial location, but the background elements were different orientations (either vertical or horizontal). Texture targets for set C-D were placed in the contralateral spatial location relative to set A-B (A-B: loc1/bkgrd1 and loc1/bkgrd2; C-D: loc2/bkgrd1 and loc2/bkgrd2), as seen in Figure 1C. The texture target was either presented in the upper right or lower left visual field, counterbalanced across subjects. By switching the background orientation within sets and the location of texture targets between sets, interference should occur within a set, but not between sets (Seitz et al., 2005; Yotsumoto et al., 2009).

Interference was induced in the A-B set by training B immediately after A, such that A experienced retroactive interference and B experienced proactive interference. Low interference was induced in the C-D set by separating conditions C and D by a 7-hr delay. Importantly, Seitz and colleagues (2005) demonstrated that a 1-hr temporal delay between training two similar tasks could stabilize visual learning and prevent interference. In the current study, although the stimulus conditions were such that C and D should interfere with one another if they had been trained back-to-back, the 7-hr delay between training C and D should provide enough time for C to be stabilized before training on D, resulting in low or negligible effects of interference for the C-D set.

2.4 Protocol (Figure 1A)

At 09:00, thresholds were measured for A and B. Approximately one hour later, condition C threshold was obtained.

At 11:00, subjects were randomly assigned to one of four groups. The AW group (n = 29) carried out their normal daily activities but were instructed to abstain from exercise and napping. Wakefulness in the AW group was monitored using actigraph wrist monitors. Subjects in the QW group (n = 26) rested for 75-min while seated in a recliner listening to classical music with their eyes closed and with polysomnograpic (PSG) monitoring to make sure they did not fall asleep. During QW sessions, experimenters woke subjects at the first sign of Stage 1 sleep. Subjects in the two nap groups were randomly assigned to take

either a 60-min or 90-min nap with PSG-recording between 13:00 and 15:00. Given that shorter naps tend to have less REM sleep than longer naps, the use of these two durations increased the likelihood of having naps with and without REM sleep. Post-hoc sleep stage scoring was used to place subjects into either the REM (*n* = 25, naps contained more than one minute of REM sleep) or NREM (*n* = 25) group after completion of the experiment.

At 16:30 (Session 2), TDT thresholds were again obtained for A and B, followed by training condition D, and then re-testing condition C. We did not retest condition D and therefore do not have a measure of learning for D.

2.5 Polysomnography

PSG data were collected using Astro-Med Grass Heritage Model 15 amplifiers and Grass Gamma software. Scalp electroencephalogram and electrooculogram electrodes were referenced to unlinked contralateral mastoids (C3/A2, C4/A1, O1/A2, LOC/A2 and ROC/A1), and electromyogram electrodes were attached under the chin to measure muscle tone. PSG data were digitized at 256 Hz and visually scored in 30-second epochs according to the sleep staging criteria of Rechtschaffen and Kales (1968). Data were excluded if there was less than fifteen minutes of total sleep time in the nap group (3 subjects), or if the data indicated that a subject reached Stage 2 sleep despite being assigned to the QW group (10 subjects). Of the remaining 26 subjects in the QW group, 3

subjects reached Stage 1 sleep (Range: 0.5 – 3.0 minutes), but were not removed from the sample.

2.6 Statistical Analyses

Subjects' data were also excluded if any of their three baseline thresholds were greater than or equal to 2.5 standard deviations from the mean (8 subjects). Data from a total of 141 remaining subjects are presented here.

TDT thresholds were compared between Sessions 1 and 2 using repeated-measures analysis of variance (ANOVA) with group (AW/QW/NREM/REM) as a between-subject factor. To examine the magnitude of perceptual learning, we computed the difference score between Session 1 and Session 2 thresholds for each condition; positive values indicated decreased threshold in Session 2 (i.e., task improvement). We tested differences in magnitude of learning with a two-way ANOVA with condition ($A_{diff}/B_{diff}/C_{diff}$) as a within-subject factor and group (AW/QW/NREM/REM) as a between-subject factor. All post-hoc tests were family-wise corrected for multiple comparisons. Between group effects were tested with independent samples *t*-tests with the corrected significance level set at $p = .008$. The magnitude of learning was compared to zero (i.e., no change from baseline) using one-sample *t*-tests with the corrected significance level set at $p = .0125$.

Sleep variables were compared between NREM and REM groups using independent samples *t*-tests. Linear regressions were also used to examine the

relationship between each sleep stage and performance for all nappers combined. This is advantageous because the fit of the overall model (i.e., the time spent in all of the sleep stages for each subject) can be simultaneously examined. Furthermore, the significance of specific sleep stages controlling for time spent in other sleep stages can be tested. After reviewing descriptive statistics, variables were centered to aid in interpretation of the parameter estimates. Minutes of Stage 1 sleep were centered on 7, minutes of Stage 2 on 31, minutes of Slow Wave Sleep (SWS) on 14, and minutes of REM sleep on 0. Effects of total sleep time (TST) were not estimated because TST is the linear combination of the minutes spent in each sleep stage, thus the model simultaneously estimates the effects of all the sleep stages controlling for TST. Fit statistics (F, p) and variance explained (adjusted R^2) are provided for the overall model, and statistically significant parameters are noted in the text. In the regression equations, unstandardized regression coefficients (Bs) are interpreted as change in performance for every 1-minute increase on the parameter from its centered value, controlling for the effect of time spent in every other sleep stage. Note, however, that regressions were only used to determine the effects of sleep stages within the nap groups and comparisons between wake and nap conditions were not made.

Results

3.1 Prior sleep and experimental nap

Actigraphy data confirmed no differences between groups in prior sleep the night before the experiment, as reported in Table 1. A summary of nap PSG data can be found in Table 2. By design, the REM group had greater TST ($t(48) = 5.96$, $p < .001$) and minutes of Stage 2 ($t(48) = 2.16$, $p = .04$) than the NREM group. There was no difference between groups in minutes of Stage 1 ($t(48) = 0.05$, $p = .96$) or SWS ($t(48) = 0.82$, $p = .42$). However, due to decreased TST, nappers in the NREM group had significantly greater percentage of Stage 1 ($t(48) = 2.36$, $p = .02$) and Stage 2 ($t(48) = 2.70$, $p = .01$) sleep compared to the REM group. There was no difference in percentage of SWS ($t(48) = 0.20$, $p = .84$) between groups. REM nappers had greater sleep efficiency ($t(48) = 4.81$, $p < .001$) than NREM nappers, indicating they spent less time awake during the nap period.

Table 2.1

Prior sleep the night before the experiment (from actigraphy)

	AW	**QW**	**NREM**	**REM**	***p***
Bedtime	12:09 (0:55) AM	12:17 (1:14) AM	11:49 (1:15) PM	12:32 (0:48) AM	.16
Wake time	7:19 (0:52) AM	7:31 (0:51) AM	7:33 (0:49) AM	7:38 (0:36) AM	.63
Total Sleep Time (min)	386 (59.3)	384 (61.7)	411 (53.3)	372 (55.2)	.14
Sleep Latency (min)	11.4 (17.9)	12.5 (9.8)	12.7 (12.6)	16.5 (11.6)	.62
WASO (min)	44.8 (22.3)	50.6 (21.0)	52.7 (20.1)	54.1 (27.5)	.58
Snooze Time (min)	15.4 (20.7)	13.1 (11.6)	10.9 (9.9)	14.2 (14.7)	.77
Sleep Efficiency (%)	84.2 (8.3)	83.3 (6.6)	84.2 (5.3)	81.3 (7.6)	.46

Note: Values are *M* (*SD*). Wake after sleep onset, WASO. One-way ANOVA found no differences between groups for any prior sleep variable.

Table 2.2

Sleep architecture descriptives

	NREM Naps	**REM Naps**
Total Sleep Time (min)**	49.8 (16.7)	76.7 (15.2)
Sleep Efficiency (%)**	62.1 (21.4)	85.0 (10.3)
Minutes		
Stage 1	7.89 (5.5)	8.0 (6.2)
Stage 2*	28.1 (11.4)	35.6 (13.0)
SWS	13.7 (12.9)	16.7 (13.0)
REM	0.08 (0.28)	16.4 (11.1)
Percent (% TST)		
Stage 1*	18.7 (15.7)	10.6 (7.3)
Stage 2*	56.7 (13.4)	46.3 (13.9)
SWS	24.5 (21.3)	23.3 (19.1)
REM	0.12 (0.42)	19.9 (12.0)

Note: Values are *M* (*SD*). Total sleep time, TST; Slow wave sleep, SWS; Rapid eye movement, REM. Statistics tested differences between groups. *indicates $p < .05$, **indicates $p < .01$

3.2 Baseline performance (Figure 2)

An ANOVA with baseline thresholds for each condition (A/B/C) as a within-subjects factor and group (AW/QW/NREM/REM) as a between-subjects factor revealed a main effect of condition ($F(2,202) = 10.65$, $p < .001$), no effect of group ($p = .59$), and no condition x group interaction ($p = .11$). Baseline thresholds were improved for condition B compared to condition A ($t(104) = 4.66$, $p < .001$), but thresholds returned to initial performance on condition C [condition C no different than condition A, $t(104) = 0.72$, $p = .47$ and condition C thresholds higher than condition B, $t(104) = 3.58$, $p = .001$] (Figure 2A).

We suspected that the observed improvement from A to B was due to fast, within-session learning that is typical of perceptual learning tasks (Karni & Sagi, 1993), and that this fast learning was specific to spatial location (as it did not transfer to the new spatial location in condition C). Thus, we tested how much within-session learning occurred when subjects completed two sequential runs of the task with the same stimulus conditions (A-A) in a separate control experiment ($n = 22$, condition *AAonly*, Figure 2B). We calculated a threshold difference score between the first and second runs of the task in the control experiment, and compared this value with the threshold difference between tasks A and B in the main experiment. No differences were found (A-A: mean difference = 32.23ms, A-B: mean difference = 33.53ms; $t(125) = .08$, $p = .94$). These results suggested that the original condition A threshold was not an accurate baseline by which to compare changes in condition A performance because it did not take into

account the within-session improvement that occurred after two runs in the same spatial location. Therefore, we used each subject's condition B threshold as the baseline to which we compared post-consolidation condition A and B performance. We did not apply this correction for condition C because within-session learning did not transfer to a new spatial location.

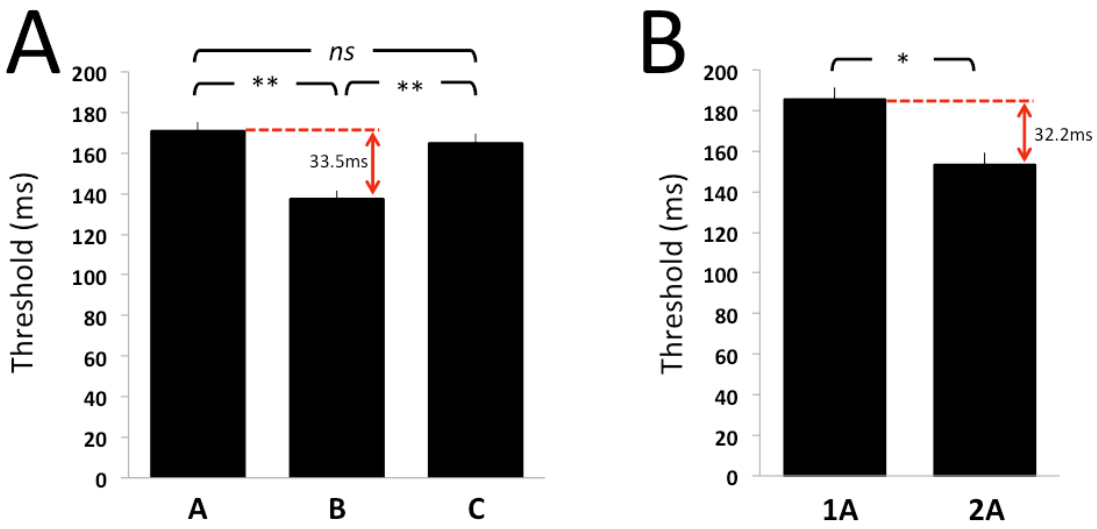

Figure 2.2. Baseline thresholds. **(A)** Session 1 thresholds for conditions A, B and C in the main experiment. The threshold is defined as the ISI at which subjects performed the task at 80% correct. Thresholds improved within a session for texture targets in the same spatial location (A-B, magnitude indicated by the red arrow), and this learning did not transfer to the new spatial location in condition C. **(B)** Thresholds for the *AAonly* control group. Subjects completed two back-to-back runs of condition A. Within-session improvement (indicated by the red arrow) was equivalent between the *AAonly* control group and all subjects in the main experiment. **indicates $p < .01$ and *indicates $p < .05$

3.3 Interference disrupts learning

We tested whether the interference paradigm produced performance impairments in conditions A and B (retroactive and proactive interference, respectively) compared to condition C (low interference). We computed the difference in threshold from Session 1 to Session 2 for each condition. An ANOVA with condition ($A_{diff}/B_{diff}/C_{diff}$) as a within factor and group as a between factor found a main effect of condition ($F(2,202) = 13.27$, $p < .001$), a main effect of group ($F(3,101) = 2.95$, $p = .04$), and a condition x group interaction ($F(6,202) = 2.91$, $p = .01$).

As shown in Figure 3A, condition C showed the greatest amount of learning ($M = 35.5$ms, $t(104) = 5.34$, $p < .001$), followed by condition B ($M = 21.4$ms, $t(104) = 3.95$, $p < .001$), and no learning occurred in condition A ($M = -4.8$ms, $p = .47$). The magnitude of learning in condition C was similar to prior nap studies using this task with no interference manipulation (~40ms; Mednick, Cai, Kanady, & Drummond, 2008). In order to quantify the magnitude of interference induced by our task manipulation, we compared performance in conditions A and B to condition C. Although only trending towards significance, there was a numerical decrease in condition B performance compared to C ($t(104) = -1.78$, $p = .08$), suggesting a moderate amount of learning disruption in the proactive interference condition. Performance in condition A was significantly decreased compared with condition C ($t(104) = -4.27$, $p < .001$), indicating a high level of learning impairment in the retroactive interference condition.

Examining the main effect of group, we found that the AW group showed no learning (M = 2.5ms, p = .68), nearly equivalent amounts of improvement in the QW and NREM nap groups (M_{QW} = 15.1ms and M_{NREM} = 17.8ms, both p = .03, but not significant after correcting for multiple comparisons), and REM naps displayed the greatest amount of learning (M = 36.9ms, $t(24)$ = 3.10, p = .005). In the next sections, we examine the condition x group interaction.

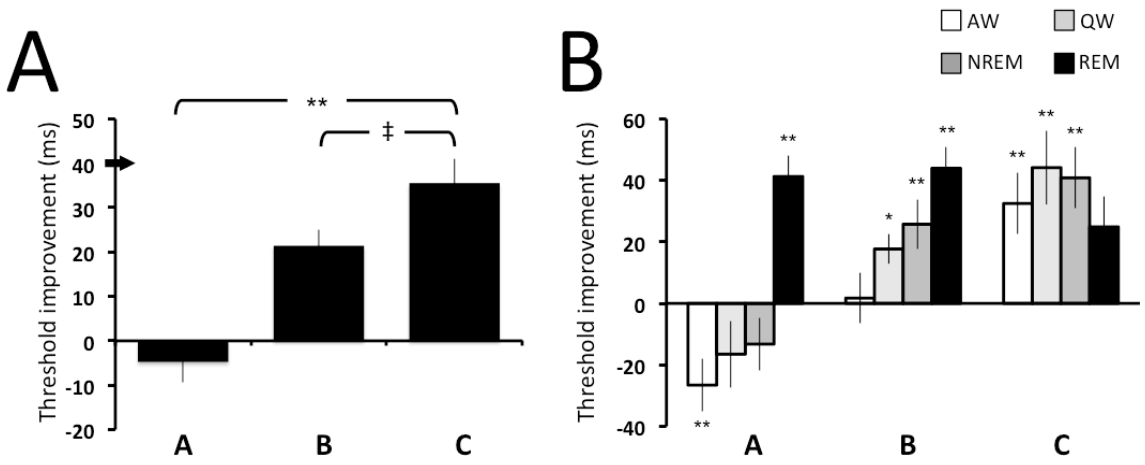

Figure 2.3. Behavioral effects of interference during encoding and varying levels of information input during consolidation. **(A)** Difference scores indicate threshold improvement (ms) for each interference condition (A: retroactive interference; B: proactive interference; C: low interference). The black arrow represents the magnitude of learning on the same task in a prior napping study (~40ms, Mednick et al., 2008), and **indicates p < .01 and ‡ indicates p = .08. **(B)** Difference scores indicate threshold improvement (ms) for each experimental group in the retroactive(A), proactive (B) and low interference (C) conditions. Statistics test for learning significantly different from zero, and *indicates p = .05 and **indicates $p \leq .0125$ (Note: Bonferroni correction for multiple comparisons sets the significance level at p < .0125).

3.4 Low interference: Active wake shows learning (Figure 3B, condition C)

We asked whether high information input (AW) disrupts consolidation, thereby decreasing learning and increasing vulnerability to interference compared with medium input (QW) and low input (sleep). We examined this question by comparing group differences in the low interference condition (C), which was paired with interference condition (D) after the retention interval containing either sleep or wake. A repeated-measures ANOVA with session as the within factor and group as the between factor yielded a main effect of session ($F(1,101) = 28.03$, $p < .001$). There was no main effect of group ($p = .14$), and no session x group interaction ($p = .75$). Although learning was not different between groups, we further tested whether specific groups showed learning significantly different from zero. We found significant learning in the AW ($t(28) = 3.10$, $p = .004$), QW ($t(25) = 3.01$, $p = .006$), and NREM ($t(24) = 3.19$, $p = .004$), but not the REM group ($t(24) = 1.57$, $p = .129$). Furthermore, a linear regression with all the sleep stages entered as predictors was non-significant ($R^2 = .03$, $p = .26$), and no stage in particular significantly contributed to explaining variance in condition C learning in the nap groups.

One possibility is that training condition D in Session 2 facilitated condition C performance, similar to the within-session learning observed between conditions A and B in Session 1. We ran a control experiment ($n = 14$, condition *ABC-noD*) in which thresholds were obtained for conditions A, B and C during Session 1 (just as in the main experiment), and again for conditions A, B and C

(without training D) after a 7-hour, AW retention interval. The magnitude of learning for condition C in the control experiment was not different from the AW group in the main experiment ($t(41) = .05$, $p = .96$), suggesting that condition C performance during Session 2 was not boosted by training condition D, likely due to the fact that consolidation of condition C occurred prior to training condition D (Seitz et al., 2005).

Thus, we found no evidence that high information input during AW is a source of memory loss in this perceptual learning task. Rather, under specific conditions of low interference and short training/test sessions (15 trials/block, 120 trials per condition), we found that AW produced the same magnitude of learning as QW or sleep, indicating that AW (and QW) were just as effective as sleep at protecting condition C from subsequent interference from condition D.

3.5 Proactive interference: NREM sleep rescues learning from moderate interference (Figure 3B, condition B)

Next, we investigated which brain state rescued perceptual learning from proactive interference (condition B). A repeated-measures ANOVA found a main effect of session ($F(1,101) = 17.64$, $p < .001$), no main effect of group ($p = .68$), and a session x group interaction ($F(3,101) = 2.81$, $p = .04$). The interaction was driven by the large magnitude of learning in the NREM ($t(24) = 2.72$, $p = .01$) and REM ($t(24) = 3.82$, $p = .001$) groups, less improvement in the QW group ($t(25) = 2.06$, $p = .05$, non-significant following correction for multiple comparisons), and

no learning in the AW group (p = .89). For subjects who napped, linear regression showed that sleep stages did not explain significant variance in condition B learning (p = .31, R^2 = .02), and the benefits elicited by sleep in this condition were not specific to any sleep stage. Taken together, our results showed that a period of NREM sleep was sufficient to rescue perceptual learning from moderate, proactive interference, whereas AW was not.

3.6 Retroactive interference: REM sleep rescues learning from high interference (Figure 3B, condition A)

We also examined which brain state could rescue perceptual learning from retroactive interference (condition A). A repeated-measures ANOVA found no main effect of session (p = .54) and no main effect of group (p = .91), but there was a session x group interaction (F(3,101) = 5.97, p = .001). The REM group showed a large magnitude of perceptual learning (M = 41.2ms, t(24) = 2.72, p = .01), there was no learning in the QW (M = -16.5ms, p = .16) or NREM (M = -13.2ms, p = .32) groups, and there was significantly decreased performance in the AW group (M = -26.6ms, p = .01).

To quantify the contribution of each sleep stage independent of the other stages to the learning observed in condition A, we used linear regression. The overall model was statistically significant (F(4, 45) = 4.47, p = .004), and explained 22% of the variance in performance. Results for minutes of each sleep stage showed that SWS was a significant predictor of improved performance (p =

.04), but that REM sleep was even more critical (p = .009): Condition A = -.67B_{Stage1} + .64B_{Stage2} + 2.00B_{SWS} + 2.42B_{REM}. Stage 1 and Stage 2 were non-significant. Because previous studies have examined the contribution of SWS and REM together by correlating the cross-product (SWSxREM minutes) with performance outcomes (Mednick et al., 2003; Stickgold, Whidbee, et al., 2000), we ran a subsequent regression model with an interaction term between SWS and REM. The addition of the interaction term lowered the overall significance (F(5, 44) = 3.54, p = .009) and the variance explained (20.56%) of the model. The parameter for REM sleep remained significant (p = .009), but SWS became non-significant (p = .10). Further, the interaction between SWS and REM was non-significant (p = .70), suggesting that the benefit of REM sleep is not moderated by time spent in SWS: Condition A = -.57B_{Stage1} + .66B_{Stage2} + 1.81B_{SWS} + 2.46B_{REM} + .03$B_{SWSxREM}$. Overall, these results show that REM is the critical sleep stage for recovery of disrupted learning.

We quantified the magnitude of damage due to retroactive interference by calculating the difference in learning between the retroactive and low interference conditions (A_{diff} – C_{diff}), such that negative values indicate damage and positive values indicate rescue [Figure 4A, magnitude of proactive interference (B_{diff} – C_{diff}) also shown with no significant differences]. The magnitude of difference between conditions A and C was significantly different from zero, and in the negative direction, for the AW (t(28) = -3.56, p = .001), QW (t(25) = -2.71, p = .01), and NREM (t(24) = -3.21, p = .004) groups, indicating that performance for

condition A was significantly impaired compared to condition C in these groups. However, this was not the case for the REM group (p = .31), indicating no difference in performance between condition A and condition C. Additionally, a one-way ANOVA demonstrated group differences in the magnitude of retroactive interference (F(3, 101) = 4.12, p = .008). The AW, QW, and NREM groups all showed the same magnitude of damage incurred by retroactive interference (all comparisons were $p \geq .82$), and all groups had significantly more damage than the REM group (AW: t(52) = -3.27, p = .002, QW: t(49) = -2.80, p = .007, NREM: t(48) = -3.06, p = .004). Linear regression revealed that sleep stages explained 20.1% of the variance in the magnitude of learning rescued from retroactive interference (F(4,45) = 4.08, p = .007): Retroactive rescue = $-2.73B_{Stage1} + 1.14B_{Stage2} + .19B_{SWS} + 3.30B_{REM}$. Above and beyond all other stages, REM sleep was critical for rescue (p = .003). No other sleep stages were significant, and the model was not significant for proactive interference. Additionally, within the REM group, the amount of learning rescued from retroactive interference was positively correlated with minutes (r = .41, p = .04, Figure 4B) and percent (r = .40, p = .05) of REM sleep. These results indicate that the benefit of REM sleep is dose-dependent, such that more time spent in REM means more learning rescued from retroactive interference.

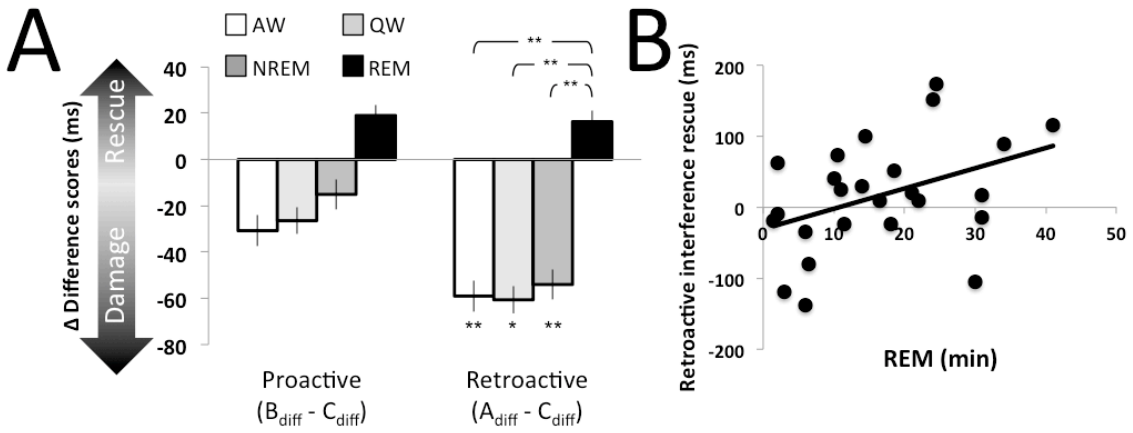

Figure 2.4. Retroactive and proactive interference effects. **(A)** Bars represent difference scores between B learning and C learning (proactive), and A learning and C learning (retroactive). Statistics test for learning significantly different from zero (asterisks located below bars) and group differences, and *indicates $p \leq .0125$ and **indicates $p < .008$. **(B)** In the REM group, minutes of REM sleep was positively correlated with the magnitude of rescue from retroactive interference ($r = .41$, $p = .04$).

Discussion

These results, for the first time, demonstrate a process by which the brain can rescue and consolidate memories damaged by interference, and that this process is mediated by specific brain states during consolidation (i.e., active wake (AW), quiet wake (QW), NREM, and REM sleep). We found: (i) When interference occurs after consolidation, AW supported learning and protected against future interference; (ii) Retroactive interference was more damaging to memory performance than proactive interference; (iii) For moderate proactive interference, NREM sleep was sufficient for performance improvement; and (iv) For high levels of retroactive interference, REM sleep was critical for rescuing performance. In contrast with many sleep and memory studies, these results show that under conditions of low interference, sleep is not necessary to stabilize

and enhance learning. But as interference during encoding increases, waking states are unable to rescue damaged learning and a period of sleep becomes necessary, with the benefits of NREM and REM sleep depending on the extent of damage incurred during encoding.

Prior studies investigating the role of sleep in perceptual learning have consistently shown improvements following sleep but not wake (Karni et al., 1994; Mednick et al., 2002, 2003; Stickgold, James, et al., 2000; Stickgold, Whidbee, et al., 2000). However, we found that the AW and QW groups showed equivalent learning to the sleep groups in the low interference condition. These results suggest that the enhancement of a visual skill is not sleep-dependent *per se*. TDT performance is sensitive to over-training on the stimuli, possibly caused by neural fatigue or sensory adaptation. Mednick et al. (2002, 2005) showed that repeated, within-day testing on the TDT results in performance deterioration. Censor and colleagues (2006, 2008) reported that long training sessions (50 trials/blocks, ~1600 trials per session) increased discrimination thresholds and decreased between-session learning, whereas short training sessions (12 trials/block, ~450 trials per sessions) eliminated adaptation-related performance decrements. It is possible that prior learning results may have been contaminated by interference from over-training, and that under specific conditions of short training and low interference, consolidation processes previously thought to occur only during sleep can also occur during waking brain states. Furthermore, because our task parameters did not produce deterioration due to neural fatigue

or sensory adaptation, it is likely that performance decrements observed in the retroactive and proactive conditions were specifically due to the task interference manipulation.

4.1 Does high information input during consolidation disrupt learning and make memories vulnerable to interference?

The low interference condition results showed that a period of high information input (AW) does not negatively impact perceptual learning, suggesting that mental exertion does not play an important role in this perceptual learning task. These results are contradictory to the classic Jenkins and Dallenbach (1924) findings, as well as theories of forgetting that suggest that recently formed memories may be impaired by the subsequent encoding of unrelated information that may compete for the same consolidation-related resources (Wixted 2004).

Additionally, AW appeared to be just as beneficial as QW or sleep for protecting the condition C memory trace from subsequent interference from condition D. Although we did not have a true no interference condition in this study, we infer that learning for the AW group in condition C was robust and unhindered by interference based on two main observations: 1) the magnitude of perceptual learning (*M* = 35.5 ms) was comparable to a prior napping study using the TDT with no interference (*M* ~ 40ms; Mednick et al., 2008); and 2) in the *ABC-noD* control condition, in which we did not train condition D prior to testing

condition C, the magnitude of condition C learning was equivalent to the main experiment (p = .96). These findings are in contrast to Ellenbogen et al. (2006) who found that sleep was required to protect declarative memories from subsequent interference, but are in agreement with other results from the perceptual learning domain showing that a one-hour passage of time is sufficient to stabilize learning (Seitz et al., 2005).

4.2 Interference: Encoding similar information disrupts learning

Although we found that learning on this task was not sensitive to the damaging effects of nonspecific, high information input, it was affected by proactive and retroactive interference from training on highly similar tasks. What might be the mechanism of this task-specific interference? Seitz and colleagues (2005) were the first to report task-specific disruption of perceptual learning. They proposed that the mechanism of perceptual learning is activation of a cluster of neurons that form a template optimized to process the target features. When multiple tasks present different target features in the same retinotopic location, the neural clusters overlap. Interference may occur when one template "overwrites" or blocks the formation of the other template representation. Within this framework, the current results and others (Seitz et al., 2005; Yotsumoto et al., 2009) suggest that conditions A and B would form overlapping templates and activate overlapping neural clusters (Figure 5, blue and red cells), whereas retinotopically-distinct condition C would form an independent template and

activate a distal neural cluster (Figure 5, green cells). Thus, after encoding these three memories, the A and B representations are weakened, while the C representation remains strong.

At what stage of memory processing does interference take effect – encoding, consolidation or retrieval? Walker and colleagues (2003) demonstrated that interference does not immediately reverse initial learning at encoding, but rather disrupts the subsequent consolidation process. Indeed, an assumption of the current study is that the interference manipulation occurs during encoding by learning two similar pieces of information back-to-back, but the effect of this intervention does not manifest until the memory has undergone a period of consolidation that is either disrupted or not, which is why brain states during consolidation are a critical consideration. However, another possibility is that interference occurs during retrieval. For example, reconsolidation theory hypothesizes that when memories are recalled, the underlying memory trace is reactivated, making it labile and once again vulnerable to interference (Dudai, 2004). An assumption of reconsolidation theory is that in order to be reactivated, a memory must initially be consolidated. In the context of the current study, it is possible that during Session 2, re-testing condition A may have reactivated memory A as well as similar memory B. In this view, re-testing A would labilize B, thereby subjecting memory B to another form of interference. However, the groups in which B was impaired, namely AW (and QW), were also the groups in which memory A consolidation was impaired. On the other hand, the group

where A was not impaired (REM), also showed robust learning for B. Nonetheless, it is possible that the impairment we are attributing to proactive interference during encoding may be due to reconsolidation interference during retrieval. To eliminate this potential bias, future studies utilizing a between-subjects design in which only A or only B is re-tested in Session 2 would be informative.

It has also been suggested that sleep may render memories more sensitive to interference by promoting the consolidation of an initial memory trace, thus making it more susceptible to reactivation and destabilization by a similar, interfering memory trace (Deliens, Leproult, Neu, & Peigneux, 2013; Deliens, Schmitz, et al., 2013). Using an AB-AC interference paradigm where subjects either slept or were sleep deprived between declarative learning of AB and AC word pairings, Deliens, Schmitz et al. (2013) found more retroactive interference following sleep. They hypothesized that the initial memory (AB) was better consolidated during sleep than wake, making it more susceptible to reactivation upon partial presentation (i.e., the word A) when exposed to an interfering word pair (AC). However, our data from the non-declarative memory domain are not in line with this finding. In our study, the C-D set is comparable to the AB-AC paradigm, where stimulus C (loc2/bkgrd1) was first learned, then consolidated, and then exposed to an interfering stimulus D (loc2/bkgrd2). Just as AB-AC share an overlapping representation of word A, so do set C-D share an overlapping representation for spatial location. Importantly, we found that

performance for condition C was the same regardless of whether or not D was exposed prior to re-testing C. Thus, not only does D not overwrite template C as previously shown, it also does not appear to promote reconsolidation during retrieval.

4.3 Following retroactive or proactive interference, which brain states rescue learning?

Proactive interference moderately disrupted learning, and NREM sleep was sufficient to recover this learning. We also found numerical improvement in the QW group, and learning reached traditional statistical significance levels (although this result did not survive correction). Interestingly, regression did not find a significant contribution of any particular sleep stage to learning in this condition, controlling for time spent in the other stages. One possibility is that the improvements observed in the NREM and REM groups were not due to any active sleep consolidation processes in a specific stage, but rather a passive reduction in information input, similar to that experienced during QW. Other studies have found similar learning profiles between QW and NREM sleep (McDevitt, Rowe, Brady, Duggan, & Mednick, 2014). QW and NREM sleep share some neurophysiological characteristics that may make both brain states conducive to consolidation. For example, the default mode, a quiet wake state when subjects are not engaged in a particular task (Andrews-Hanna, 2012; Buckner, Andrews-Hanna, & Schacter, 2008), activates a network of brain areas

similar to those activated during NREM sleep (Larson-Prior et al., 2009). Using simultaneous high-density EEG and functional magnetic resonance imaging, Larson-Prior and colleagues (2009) demonstrated no measureable change in functional connectivity as subjects moved from QW to early stages of NREM sleep. Future research on the similarities between NREM and QW should be addressed in order to identify distinctions in mechanisms of consolidation.

REM sleep was the only brain state able to rescue learning hindered by highly damaging retroactive interference. In fact, the REM group showed equivalent learning across all three interference conditions. Further, the magnitude of rescued learning was correlated with percentage and minutes of REM during the nap, suggesting a dose-dependent effect where more REM sleep is associated with greater rescue. Drosopoulos and colleagues (2007) investigated recovered declarative memory after retroactive interference and found that weakly encoded memories, produced by either retroactive interference or training to a learning criterion of 60% versus 90%, were consolidated better after sleep than after an equivalent period of wake. Although the effect of specific sleep stages was not reported, it is likely that these subjects experienced REM sleep during the night. Sleep was also shown to recover learning following retroactive and proactive interference on an auditory classification-learning task in starlings (Brawn, Nusbaum, & Margoliash, 2013). Taken together, consolidation processes occurring during REM sleep appear to be a general mechanism for consolidating

weaker, disrupted memories (Baran, Wilson, & Spencer, 2010), and likely not specific to perceptual learning.

In the retroactive interference condition, we found that both SWS and REM predicted performance, but they did not interact. These regressions are a strong statistical test of the independent contributions of SWS and REM, as well as their interaction, as they simultaneously control for the effects of time spent in each sleep stage. Previously, the independent contribution of each sleep stage has been tested using the night-half paradigm, in which consolidation across the first half of the night (rich in SWS) is compared with the second half of the night (rich in REM sleep) and the whole night (Gais, Plihal, Wagner, & Born, 2000). The authors showed that a whole night of sleep containing both SWS and REM sleep produced the greatest improvement on TDT, compared to moderate learning following early SWS-rich sleep only, and no improvement following late REM-rich sleep. This is further supported by the current data, which show that both SWS and REM predict performance independent of each other, with maximum memory benefits when both sleep stages co-occur. In other words, NREM and REM sleep play distinct, but additive roles, for consolidation of this type of visual skill. This is consistent with prior work demonstrating that NREM sleep restores perceptual learning that has deteriorated due to over-exposure to the stimulus (Censor et al., 2006; Mednick et al., 2002, 2003) and protects against further decline, whereas REM sleep enhances learning above and beyond baseline levels (McDevitt et al., 2013; Mednick et al., 2003). Whether REM necessarily

needs to follow SWS in order for learning to occur is an important and unanswered question. Additionally, we found that SWS is making a contribution to the rescue effect, and REM is not necessarily playing an exclusive role. However, the statistical results suggest that REM plays a more critical role than SWS for rescuing learning. This is evidenced by two main results: 1) the magnitude of the parameter estimate was larger for REM (B = 2.42) than SWS (B = 2.00) in model 1, and 2) after adding the SWSxREM interaction in model 2, the parameters for SWS alone and SWSxREM were non-significant, whereas the parameter for REM remained stable (B = 2.46) and significant (p = .009). REM sleep was also critical at the group level, as learning was only enhanced and made comparable to low (or no) interference levels of learning when the nap contained both SWS and REM sleep, but not SWS alone. Ideally, future studies should examine rescue effects with REM sleep alone, although this is methodologically challenging.

We chose to include the SWSxREM interaction term in model 2, as there is precedent for correlating the cross-product of SWS and REM with TDT learning and interpreting the result as the combined contribution of SWS and REM on learning, such that high levels of *both* sleep stages are needed to produce maximum performance benefits (Stickgold, Whidbee et al., 2000; Mednick et al., 2003). By interaction (also called moderation), we are referring to situations in which the effect of one independent variable (e.g., SWS) on the dependent variable (e.g., performance) depends on the level of another variable (e.g., REM;

Baron & Kenny, 1986). The cross-product correlation is problematic because it does not test whether high levels of both sleep stages are needed to produce maximum benefits. Rather, it tests whether high levels of *at least one* of the stages (given at least 1 minute of each sleep stage) are needed, and confounds this with the effects of each stage on its own. To test interactions using two continuous variables (such as the minutes spent in each sleep stage), it is appropriate to use multiple linear regression (Baron & Kenny, 1986). Additionally, linear regression has the added benefit of partialling out the effect of each sleep stage when estimating the interaction parameter, thereby controlling for the effects of each sleep stage as well as TST.

4.4 Possible sleep-dependent mechanisms of rescued learning

Although we did not directly test any one particular model, several current sleep-dependent consolidation models are considered to explain the neural dynamics during NREM and REM sleep that may rescue damaged memories. The synaptic homeostasis hypothesis (SHY) proposes that an important function of NREM sleep – specifically the slow wave activity (<1 Hz) that predominates during NREM sleep – is to downscale synapses that were potentiated in the course of encoding information during prior waking (Tononi & Cirelli, 2006). According to this hypothesis, highly potentiated, strong synapses (signals) are preferentially protected and receive less downscaling than weaker synapses (noise), which are downscaled below a threshold and nullified (Tononi & Cirelli,

2014). This increased signal to noise ratio is posited to result in improved memories for important, to-be-remembered information, while weaker memories are forgotten. This model can be used to explain some of our results. For example, learning for condition C was enhanced across a period of AW. Since the potentiation initiated at training was not disrupted by interference, potentiation of the synapses involved in learning memory C was maintained across a day of waking leading to enhanced performance. However, proactive interference weakened memory B, which may have then required other weaker information to receive relatively more downscaling during NREM sleep in order for B to be enhanced (Tononi & Cirelli, 2014).

On the other hand, the active systems consolidation hypothesis posits that newly encoded memories are reactivated during NREM sleep, facilitating the transfer of representations from temporary to long-term stores where they become integrated with pre-existing long-term memories and resistant to interference (see Diekelmann & Born, 2010 for review). It is equally plausible that either downscaling or reactivation could have salvaged condition B performance. Furthermore, the opportunistic consolidation hypothesis posits that the initiation of consolidation is contingent upon states of low information input, such as QW or NREM, when reactivation of freshly encoded memories can commence (Mednick et al., 2011). This hypothesis could explain why we found similar learning profiles in QW and NREM sleep groups for all three interference conditions (A, B, and C). More basic research is needed that directly compares

and contrasts these models with critical experimental tests to determine the neural mechanisms that give rise to consolidation.

For the case of highly damaged memory A, in which the memory trace was obliterated by AW, QW and NREM, but rescued by REM sleep, none of the current models present a plausible mechanism. First, the SHY and opportunistic consolidation models do not directly address REM-dependent memory consolidation. However, the current state of the SHY model, which suggests that downscaling competitively saves strong memories while weaker memories are abolished (Tononi & Cirelli, 2014), is not consistent with our finding that weak memories are preferentially enhanced during REM sleep. The active systems consolidation hypothesis posits that following systems consolidation during NREM sleep, memories are further enhanced by synaptic consolidation that takes place during subsequent REM sleep (Rasch & Born, 2013). Although the active systems consolidation hypothesis provides a useful framework for understanding how memories might be strengthened during sleep, it does not directly address the case of weak memories that would be lost during NREM sleep and rescued during REM. Thus, our data do not differentiate any of the aforementioned models, and any one or more of the mechanisms are possible (e.g., Genzel, Kroes, Dresler, & Battaglia, 2014).

A computational model by Norman and colleagues (2005) hypothesizes that weak memories are enhanced during sleep, and proposed a mechanism for a functional role of REM sleep in repairing damaged memories. Building upon

McClelland et al.'s (1995) Complementary Learning Systems framework, their model includes an offline learning process during REM sleep that rehearses and strengthens existing knowledge structures. In the model, the network can recall the intact version of a memory, even if the synapses underlying the memory have been disrupted (although too much damage will make recall impossible). Repair and subsequent enhancement is caused by a rehearsal mechanism during REM, guided by inhibitory oscillations (possibly strong theta activity). During high inhibitory states, weak parts of a disrupted memory show decreased activity, which triggers learning processes that strengthen those parts of the memory. Conversely, when inhibition is lowered, other memories that are similar to the damaged memory become active. This in turn triggers learning processes that shift the representations of these similar memories away from the damaged memories, allowing new memories to be integrated into the network without destroying or overwriting older memories. Consistent with this hypothesis, our results show that memories highly damaged by retroactive interference specifically benefitted from REM sleep. In addition, the REM group showed non-significant learning for the strongest memory C (although no differences were found between groups for condition C, nor was performance different from conditions A and B within the REM group). Although our data does not directly address this finding, it is possible that REM sleep preferentially processes weak memories, leading to smaller improvement for stronger memories. This intriguing hypothesis may be related to the process of pushing similar memories away from

damaged memories as proposed by Norman and colleagues (2005), and should be experimentally tested in future research.

4.5 A model of neural dynamics that predicts which memories are retained or lost

We hypothesize that the extent to which these brain states (AW, QW, NREM and REM) encourage plasticity via fluctuations in plasticity-related neuromodulators (e.g., acetylcholine) may contribute to understanding which memories are retained or lost. Acetylcholine (ACh) shows significant fluctuations across AW, QW, NREM and REM sleep. Microdialysis studies report higher ACh concentrations during AW than QW. These concentrations decrease to one-third of waking levels during NREM sleep, and then rise to levels above AW during REM sleep (Hasselmo & McGaughy, 2004; Jasper & Tessier, 1971; Kametani & Kawamura, 1990; Marrosu et al., 1995). High levels of cholinergic transmission allow for induction and maintenance of long-term potentiation (LTP; Hasselmo & Bower, 1993; Matsukawa et al., 1997), a likely mechanism of synaptic plasticity in perceptual learning (Sale et al., 2011). Thus, low cholinergic tone during NREM sleep and QW (Hasselmo & Bower, 1993) may reduce or even block LTP induction (Jones Leonard, McNaughton, & Barnes, 1987) without disrupting LTP maintenance (Bramham & Srebro, 1989). This state of low plasticity combined with low information input has been hypothesized to optimize conditions for stabilizing, but not enhancing, recently learned experiences (Mednick et al., 2011). In contrast, high cholinergic tone during AW and REM sleep distinguishes

these states as having high synaptic plasticity, which increases likelihood of successful encoding during AW (Hasselmo & McGaughy, 2004) and strengthening of memory representations at the synaptic level during REM sleep (Diekelmann & Born, 2010). We further hypothesize that REM, a unique state of low information input and high synaptic plasticity, is critical for consolidating and enhancing the weakest memories.

In light of these fluctuations in plasticity, we present a theoretical model that considers how interference influences the strength of memory representations during encoding, which then interacts with consolidation states that vary in degree of information input and plasticity, to predict which memories are retained and which are lost (Figure 5). In short, under conditions of little to no interference (C) during encoding, a period of high information input and high plasticity (AW) during consolidation will lead to increased signal in a smaller number of neurons representing the target, leading to improved memory performance. When learning is moderately disrupted at encoding (B), reduced information input and low synaptic plasticity (NREM and QW) are sufficient to resolve signal from moderately damaged targets, which leads to improved memory. A unique state of low information input and high synaptic plasticity (REM) is required to rescue and separate target templates highly obstructed by interference (A). Future work that tests the predictions of this model in interference and learning are needed.

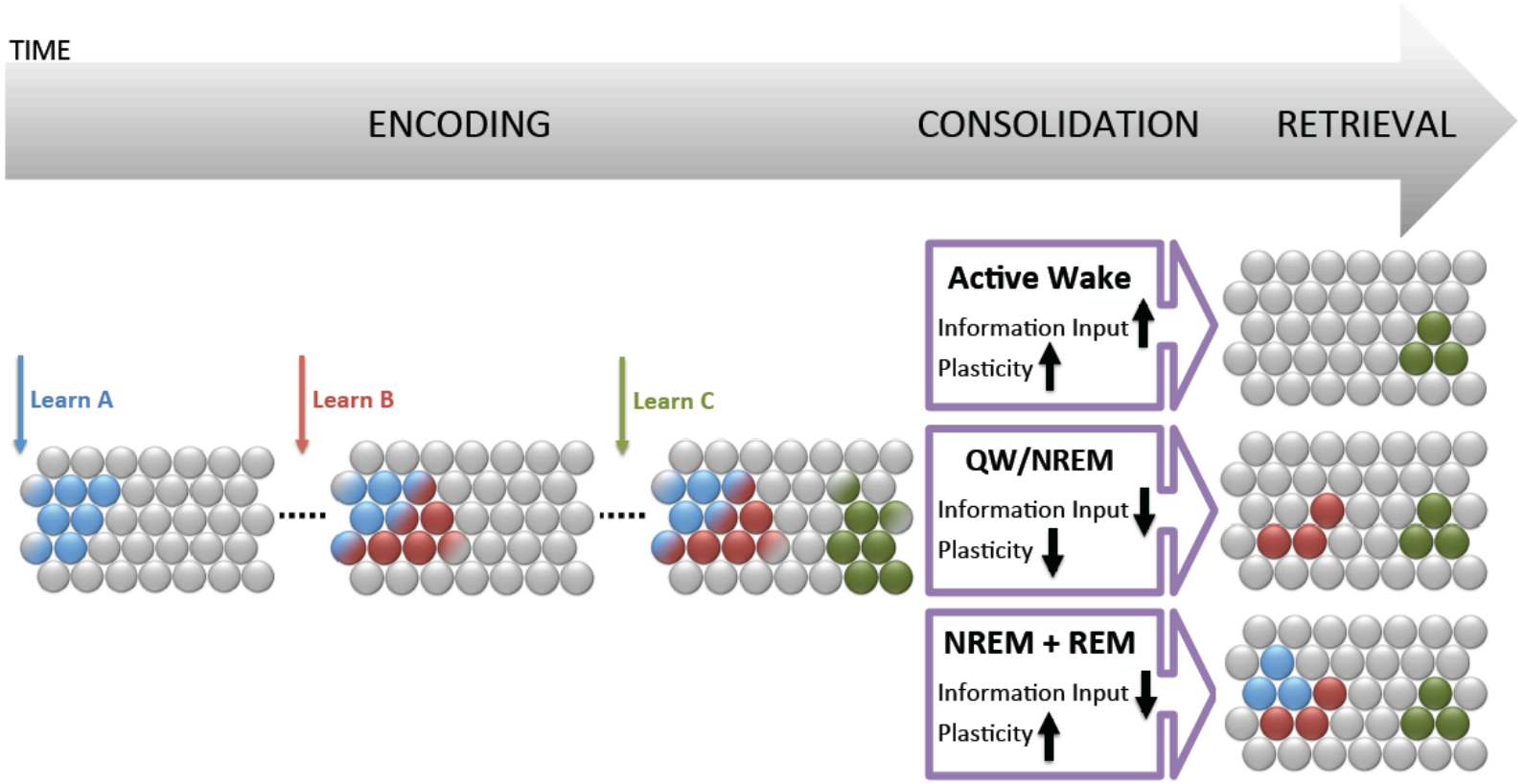
TIME
ENCODING
CONSOLIDATION
RETRIEVAL
Learn A
Learn B
Learn C
Active Wake
Information Input
Plasticity
QW/NREM
Information Input
Plasticity
NREM + REM
Information Input
Plasticity

Figure 2.5. Theoretical neural model predicting profiles of learning based on interference during encoding and information input during consolidation. During encoding, memory A activates 6 neurons (blue cells), and subsequent encoding of a similar memory B (red cells) also activates 6 neurons, three of which overlap with memory A. This overlap weakens the neural representation of memories A and B due to retroactive and proactive interference, respectively. Since retroactive interference is more damaging than proactive (see Results 3.3), memory A occupies less neural real estate compared to memory B. Retinotopically-distinct memory C (green cells) occupies 6 completely independent, non-overlapping neurons. Following a period of AW, memories A and B are not retained in the network due to disruption incurred during encoding and high information input during consolidation, while strong memory C is retained. Following QW and NREM sleep only, memory A is lost, whereas memories B and C are remembered. In contrast, following sleep that includes REM, which is a unique state of low information input and high plasticity, the network learns all three memories. Importantly, after consolidation each memory is represented by a more finely tuned group of neurons with no overlap between memories, which maximizes pattern separation and specificity.

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CHAPTER 3

Napping for Memory Enhancement Cannot Be Learned

Abstract

Napping benefits memory consolidation, making it a useful experimental tool in sleep science, as well as a practical, everyday tool to improve cognitive performance. Here, we found that compared to people who habitually nap, people who do not frequently nap (non-nappers): (a) did not receive the same memory benefits from a daytime nap; (b) had more post-nap cognitive impairment; and (c) showed different associations between sleep oscillations and memory consolidation. Additionally, four weeks of nap practice did not improve outcomes in non-nappers. These results suggest that an update is needed to current thinking about the benefits of napping and models of nap-dependent learning.

Introduction

Sleep plays an important role in stabilizing or enhancing memory for newly learned information (i.e., memory consolidation) (Diekelmann & Born, 2010). Daytime naps are often as effective as nocturnal sleep in facilitating these memory processes (Korman et al., 2007; Mednick, Nakayama, & Stickgold, 2003; Nishida & Walker, 2007). For example, a daytime nap containing both slow wave sleep (SWS) and rapid eye movement (REM) sleep resulted in the same magnitude of learning on a perceptual task as a full night of sleep (Mednick et al.,

2003). Similar performance enhancement from naps has been found across a wide range of cognitive abilities, including episodic memory (Cellini, Torre, Stegagno, & Sarlo, 2016; van der Helm, Gujar, Nishida, & Walker, 2011), emotion regulation (Goldschmied et al., 2015; Gujar, McDonald, Nishida, & Walker, 2011), procedural skills (Backhaus & Junghanns, 2006; Nishida & Walker, 2007), and attention (Cellini et al., 2015). Napping has also been reported to boost creativity (Cai, Mednick, Harrison, Kanady, & Mednick, 2009; Whitehurst, Cellini, McDevitt, Duggan, & Mednick, 2016) and productivity in the workplace (Baxter & Kroll-Smith, 2005), improve performance in athletes (Waterhouse, Atkinson, Edwards, & Reilly, 2007), and help people cope with fatigue related to shiftwork (Macchi, Boulos, Ranney, Simmons, & Campbell, 2002; Purnell, Feyer, & Herbison, 2002; Takahashi & Arito, 2000).

Despite the demonstrated benefits of napping, only 40-50% of adults nap regularly (National Sleep Foundation Sleep Health Index 2014 https://sleepfoundation.org/sleep-health-index), while others avoid it. Non-nappers often report that they eschew the practice because they wake up feeling groggy, unproductive, and do not receive any benefits from a nap (Duggan, McDevitt, Whitehurst, & Mednick, 2016). This post-waking cognitive impairment (i.e., sleep inertia) may be associated with the amount of SWS and waking from SWS (Dinges, Orne, & Orne, 1985). Indeed, we previously found that during a daytime nap, non-nappers spent more time in deep SWS and that habitual nappers spent more time in light, Stage 2 sleep (McDevitt, Alaynick, & Mednick,

2012). Thus, habitual napping may change the quality of daytime sleep, which may, in turn, decrease symptoms of sleep inertia and increase post-nap cognitive performance. A separate study found that nap habits moderated motor performance following a short nap – habitual nappers showed performance improvement whereas non-nappers showed performance deterioration, and post-nap performance correlated with Stage 2 sleep spindles only in habitual nappers (Milner, Fogel, & Cote, 2006). Given these results, we asked whether there is a benefit of napping for non-nappers and whether napping can be trained, such that with practice, a non-napper can acquire the skill of napping and all its advantages.

Here, we investigated the impact of four weeks of "nap practice" or "nap restriction" on perceptual learning in habitual nappers (HN) and non-nappers (NN). Participants in the nap practice group (Practice) were instructed to take at least three naps per week for a minimum of twenty minutes, whereas participants in the nap restriction group (Restriction) were instructed to not nap at all. Adherence to this experimental regimen and nighttime sleep variables were assessed with sleep diaries and activity monitors (i.e., actigraphs). We examined the effects of nap training on four outcomes: nap sleep architecture, behavioral performance, sleep inertia, and subjective sleepiness. To assess nap architecture across the four-week period, subjects took a polysomnographically-recorded (PSG) nap in the laboratory at three different time points during the intervention – baseline, midpoint and endpoint – each two weeks apart. Learning

associated with the nap intervention was tested using a texture discrimination task that has repeatedly demonstrated performance gains with a daytime nap (McDevitt, Duggan, & Mednick, 2015; Mednick et al., 2002, 2003). On each in-lab nap assessment day, we also measured immediate post-nap cognitive functioning (i.e., impairment due to sleep inertia) using a descending subtraction test (Mullington & Broughton, 1993, 1994), and collected ratings of subjective sleepiness throughout the day.

Our overarching hypotheses were that habitual nappers gain more benefits from naps than non-nappers but that napping is a trainable skill. Thus, we predicted that at initial baseline assessment, compared to HNs, NNs would show greater post-nap cognitive impairment and smaller post-nap gains in perceptual learning. These behavioral decreases would be explained by nap sleep architecture differences, with NNs having less Stage 1 and 2, and more SWS, than HNs. During the four weeks of nap practice, we also predicted that NNs would show increased benefits from napping, with performance profiles and sleep inertia levels similar to HNs at the end of the intervention. Additionally, we expected that these changes associated with nap practice would shift the architecture of the nap to lighter sleep for NNs.

Method

2.1 Subjects

83 (51 F) healthy, non-smoking adults between the ages of 18 and 35 with no personal history of sleep disorders, neurological, psychological, or other

chronic illness gave informed consent to participate in the study. Fifty-eight people participated in the experimental nap protocol explained below, and the 25 remaining participants were part of a one-day Wake control group. Our sample size was based on the Mednick et al. (2003) study. All subjects reported having a regular sleep-wake schedule, which was defined as regularly going to bed no later than 2AM, waking up no later than 10AM, and getting at least 7 hours of total sleep per night on average. The Epworth Sleepiness Scale (ESS; Johns, 1992) and the reduced Morningness-Eveningness Questionnaire (rMEQ; Adan & Almirall, 1991) were used to exclude potential subjects with excessive daytime sleepiness (ESS score >10) or extreme chronotypes (rMEQ < 8 or > 21). All experimental procedures were approved by the Human Research Review Board at the University of California at Riverside.

2.2 General procedure

This was a five-week protocol that included one week of at-home baseline monitoring and four experimental weeks. Subjects completed three in-lab study days, one each at the beginning (Visit 1), middle (Visit 2), and end (Visit 3) of the experimental period, spaced two weeks (14 +/- 2 days) apart. Subjects in the Wake group only completed Visit 1.

During the study, subjects agreed to adhere to a 2hr bedtime window (no later than 2AM) and a 2hr wake time window (no later than 10AM), which corresponded as closely as possible to their habitual sleep-wake schedule, and

to spend at least 7 hours time in bed per night. The subjects' sleep schedules were tracked with daily sleep diaries and actigraph wrist monitors (Actiwatch Spectrum, Respironics) for the duration of the study, including the baseline week. Subjects were asked to refrain from consuming caffeine, alcohol, and all stimulants for 24 hours prior to and including each study day. Heavy caffeine users (> 240mg per day) were not enrolled to exclude the possibility of significant withdrawal symptoms during the experiment. Nonetheless, one subject reported experiencing caffeine withdrawal symptoms and was therefore excluded from analyses.

2.3 Study Day Timeline

On each in-lab study day, subjects reported to the Sleep and Cognition Lab at the University of California, Riverside at 9AM. After the experimenters verified adherence to the sleep schedule by checking actigraphy data, subjects completed Session 1 of a texture discrimination task (TDT). At 12:30PM, electrodes were attached for standard polysomnographic (PSG) recording of sleep. All subjects were given a two-hour nap opportunity between 1:30PM and 3:30PM to obtain up to 90 min of total sleep time. If a subject spent more than 30 consecutive minutes awake during the nap window, he or she was removed from the bedroom, and the nap was ended. Upon awakening from the nap, sleep inertia was assessed using a descending subtraction test (DST; Mullington & Broughton, 1993, 1994) at three time points: 5 min, 20 min, and 35 min after

lights on. At 5PM (Session 2), subjects were re-tested on the TDT. Subjects also completed the Karolinska Sleepiness Scale (KSS) at three times during the study day – 1) at the end of Session 1 (~11AM), 2) 10 min post-nap (~3:40PM), and 3) at the beginning of Session 2 (~5PM). Between sessions, subjects left the lab and carried out their day as they normally would, but were instructed to not nap, exercise, or consume caffeine or alcohol. Subjects in the Wake group did not nap or complete the DST task or the 10 min post-nap KSS.

2.4 Nap Training

Following the first in-lab study day (Visit 1), subjects were categorized as either a habitual napper (HN) or non-napper (NN). HN were defined as people who regularly nap at least once per week, whereas NN nap less than once per week (i.e., never nap or only nap once or twice a month; McDevitt et al., 2012; Milner et al., 2006). We obtained information about nap habits in multiple ways. First, during either a telephone or online survey screening questionnaire prior to study enrollment, subjects were asked, “Do you take naps during the day? And if so, how many times per week? And how long do you nap?” Second, we counted the number of naps reported in subjects’ sleep diaries during the baseline week prior to starting the study, and then verified that these naps occurred by checking the actigraphy data. When these two sources of information did not match (e.g., a subject reported never napping on the screening survey but then took a nap during the week prior to the study), the subject was interviewed about their nap

habits by an experimenter who then made the final determination. For example, if the subject was labeled as a NN based on self-report, but he/she napped because of illness that week, the subject retained NN status, since illness was an unusual event.

Within each of these categories, HN and NN subjects were randomly assigned to either the nap Practice or nap Restriction condition. Subjects in the Practice group were instructed to nap at least three times per week for a minimum of 20 min for the remaining four weeks of the study, whereas those in the Restriction group were instructed to not nap unless asked to take one in the lab during a study visit. Compliance to these conditions was verified by checking sleep diaries and actigraphy. One HN in the Restriction group took one nap during Week 2 due to illness.

2.5 Polysomnography (PSG)

PSG data were collected using Astro-Med Grass Heritage Model 15 amplifiers and Grass Gamma software. Eight scalp electroencephalogram (EEG) and two electrooculogram (EOG) electrodes were referenced to unlinked contralateral mastoids (F3/A2, F4/A1, C3/A2, C4/A1, P3/A2, P4/A1, O1/A2, O2/A1, LOC/A2 and ROC/A1), and two electromyogram electrodes were attached under the chin to measure muscle tone. High-pass filters were set at 0.3 Hz and low-pass filters at 100Hz for all EEGs and EOGs. A 60 Hz notch filter was also used to eliminate potential background noise. PSG data were digitized at 256 Hz and visually scored in 30-s epochs according to the sleep staging criteria

of Rechtschaffen and Kales (1968). Sleep architecture variables included minutes and percentage of Stage 1, Stage 2, slow wave sleep (SWS) and rapid eye movement (REM), as well as total sleep time (TST), sleep latency (SL), and sleep efficiency (SE). Subjects were excluded if they did not fall asleep during their first nap (n=2), or if 2 out of 3 naps had TST less than 20 min and SE less than 35% (n=1).

EEG data were preprocessed and analyzed using BrainVision Analyzer 2.0 (BrainProducts, Munich Germany) and Matlab 2011b (MathWorks, Natick MA). EEG data were bandpass filtered between 0.3 and 35 Hz, and all epochs with artifacts and arousals were identified by visual inspection and rejected. Sleep spindles were automatically detected during Stage 2 and SWS using a wavelet-based algorithm developed by Wamsley et al. (2012). Following spindle detection, spindle densities were calculated by dividing the number of discrete spindle events by the number of minutes spent in each sleep stage at each scalp EEG electrode site. Data for an individual channel were excluded if the channel was determined to be unreliable.

Power spectral density (μV^2/Hz) was calculated by Fast Fourier Transform (FFT), applying a Hanning window to successive 3 sec epochs of sleep with 50% overlap. Spectral power was obtained for the following frequency bands: .5-1Hz (slow oscillations, SO), 1-4Hz (delta), 4-8Hz (theta), 8-12Hz (alpha), 12-15Hz (sigma), and beta (15-30Hz) during Stage 2, SWS, NREM (S2 + SWS combined), and REM.

2.6 Texture Discrimination Task (TDT)

Subjects performed a texture discrimination task (TDT) similar to that developed by Karni & Sagi (1991). Visual stimuli for the TDT were created using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). Each stimulus contained two targets: a central letter ('T' or 'L') and a peripheral line array (vertical or horizontal orientation) in one of four quadrants (lower left, lower right, upper left, or upper right), 2.5°-5.9° eccentricity from the center of the screen. The quadrant location was counterbalanced across subjects and visits. The peripheral array consisted of three diagonal bars that were either arranged in a horizontal or vertical array against a background of horizontally oriented background distracters, thereby creating a texture difference between the target and the background.

An experimental *trial* consisted of the following sequence of four screens: central fixation cross, target screen for 32 ms, blank screen for a duration between 0 and 600 ms (the inter-stimulus-interval, or ISI), mask for 16 ms, followed by the response time interval (2,000 ms) and feedback (250 ms, red fixation cross with auditory beep for incorrect trials and green fixation cross for correct trials) before the next trial. Subjects discriminated two targets per trial by reporting both the letter at central fixation ('T' or 'L') and the orientation of the peripheral array of three diagonal lines (horizontal or vertical) by making two key

presses. The central task encouraged subjects to maintain fixation throughout stimulus presentation.

Each *block* consisted of 25 trials, each with the same ISI. A threshold was determined from the performance (percent correct) across a series of 13 blocks, with a progressively shorter ISI, starting with 600 ms and ending with 0 ms. The specific sequence of ISIs across an entire session was [600, 500, 400, 300, 250, 200, 160, 140, 120, 100, 60, 30, 0]. A psychometric function of percent correct for each block was fit with a Weibull function to determine the ISI at which performance yielded 80% accuracy. TDT performance was calculated as the difference in threshold ISI between Session 1 and Session 2, such that a positive score indicates performance improvement (i.e., decreased threshold in Session 2), whereas a negative score indicates deterioration (Mednick et al., 2002, 2005).

Subjects were given task instructions and practiced the task during an initial session prior to starting the study. During this practice session, the peripheral target was located in a quadrant that was never used during the experimental sessions. This practice session ensured that subjects understood the task and was designed to reduce visit order effects due to the general task learning that typically occurs the first time a subject performs a task. Additionally, on each study day, subjects were allowed to practice an easy version of the task (ISI of 1,000-600 ms) to make sure that subjects were able to correctly discriminate the peripheral target between 90% and 100% of trials on the easiest version of the task.

2.7 Descending Subtraction Task (DST)

This task measures cognitive function over a brief (3 min) period of time by placing a considerable load on working memory while probing mental computation skills (Mullington & Broughton, 1993, 1994). To begin, the experimenter gave the subject a three-digit number, for example “865”, which the subject repeated out loud. Then the subject was instructed to mentally subtract the number 9 from 865 and to state the answer (856). This number became the new minuend from which the subtrahend was subtracted [the minuend is the number from which another number (the subtrahend) is to be subtracted]. The subtrahend progressively decreased by 1 until it reached a value of 2, after which it returned to 9. Thus, on the subsequent trial the subject should have subtracted the number 8 from 856. Subjects were given 3 minutes to complete as many trials as possible. Instructions prompted the subject to work as quickly and accurately as possible. The task was verbally administered, with the experimenter writing the subject’s responses on a piece of paper attached to a clipboard so that the written responses were not visible to the subject. Subjects were allowed to correct any response and were instructed to guess if they asked the experimenter for help. Total number of correct responses and number of correct responses as a proportion of total number of responses were calculated as indices of speed and accuracy, respectively. Difference scores (post-nap

minus pre-nap performance) were calculated and reported as Δaccuracy and Δspeed.

2.8 Data Reduction and Statistical Analyses

Subjects whose first TDT threshold (i.e., Visit 1, Session1) was more than 2.5 standard deviations from the mean (i.e., z-score) were flagged as outliers (*n*=2 for main experiment and *n*=2 for Wake; all were poor performers with negative z-scores). In the main experiment, the two outliers together with the two subjects removed for poor sleep and caffeine withdrawal were the worst-performing subjects in the sample. Therefore, we employed an equitable trim procedure: we removed the four best-performing subjects from Visit 1, Session 1 (who were all at ceiling). This left 48 subjects (26 HN, 22 NN) whose Visit 1 data were analyzed. We also applied equitable trim to the Wake group, removing the two worst-performing subjects as well as the top two performers, leaving 21 subjects in the Wake group.

Eight of the 48 subjects in the main experiment were dropped or withdrew before study completion, leaving 40 subjects who completed all three visits. Of these, 21 were assigned to the Practice group (11 HN, 10 NN) and 19 to the Restriction group (9 HN, 10 NN).

For spindle results, we focused on centro-parietal regions (Clemens, Fabó, & Halász, 2006) and averaged the number of spindles detected over central and parietal electrodes within each hemisphere (i.e., C3-$P3_{avg}$ and C4-

$P4_{avg}$). If no hemispheric differences were evident at the group level, we used the grand average (C3-C4-P3-$P4_{avg}$). For power spectral analysis, due to significant topographic differences in power between the frontal and central regions (but no hemispheric differences), we averaged frontal (F3-$F4_{avg}$) and central (C3-$C4_{avg}$) electrodes.

Differences between HN and NN at Visit 1 were tested using independent samples t-tests. Magnitude of performance change on the TDT at each visit was compared to zero (i.e., no change) using one-sample t-tests. Bivariate Pearson correlations were employed to examine associations between TDT performance and nap sleep features. In order to reduce the number of correlations tested, we made the a priori decision to focus on power spectra during NREM and REM sleep, and therefore chose specific frequency bands of interest for each sleep stage (NREM: SO, delta, alpha, sigma and REM: alpha, theta). In order to test for moderation, we separately calculated correlations for HN and NN and then tested for significant differences between correlation coefficients using the Fisher r-to-z transform and z-test (Cohen, Cohen, West, & Aiken, 2013). Changes across visits were tested using mixed-model ANOVAs, with Visit as a repeated measure and two between-subject factors: Nap Habit (HN/NN) and Group (Practice/Restriction). For analyzing spindles and power spectra across the three visits, we specifically only tested variables that showed significant differences and/or moderation during Visit 1.

Due to the longitudinal nature of this study, there are missing data for sessions and visits, including bad electrodes during nap recordings, KSS scores, or missing actigraphy data due to watch malfunction. Additionally, not all subjects had every stage of sleep in their nap (no SWS: Visit 1 *n*=3, Visit 2 *n*=4, Visit 3 *n*=4; no REM: Visit 1 *n*=10, Visit 2 *n*=4, Visit 3 *n*=5). As a result, degrees of freedom varied across analyses.

Results

3.1 Are there baseline differences between habitual nappers and non-nappers?

3.1.1 Daytime sleep architecture

During baseline assessment (prior to nap intervention assignment), we measured daytime sleep in each group (sample descriptives reported in Table 1). We found no significant differences in total sleep time or minutes or percent of any sleep stage between habitual nappers (HN, *n*=26, 16 F, age=21.0 ± 2.4 yrs) and non-nappers (NN, *n*=22, 13 F, age=22.4 ± 3.7 yrs) (Table 2). Differences were noted in several other sleep features, including the number and density (count/minute of sleep) of sleep spindles (Fig. 1d). HN had approximately 31% more sleep spindles during Stage 2 sleep (*p*=.04). Since HN numerically spent more time in Stage 2 sleep, we analyzed spindle density (number of spindles/minutes of sleep stage). A Hemisphere x Group ANOVA revealed a main effect of Hemisphere (left > right, $F(1,44)=4.27$, *p*=.045), a trending main

effect of Group (HN > NN, $F(1,44)=3.71$, $p=.06$), and a trending interaction ($F(1,44)=3.45$, $p=.07$). In the left hemisphere, HN showed greater spindle density ($p=.008$) than NN, and a similar, albeit non-significant ($p=.41$), pattern in the right hemisphere. HN also had numerically greater spindle densities during SWS in both hemispheres, but tests did not reach significance (all ps >.10).

Table 3.1

Sample descriptives (Study 3)

	Visit 1 Baseline	**Nap Practice**	**Nap Restriction**
Habitual Nappers	N=26 (16 F)	N=11 (7 F)	N=9 (6 F)
Age (years)	21.0 ± 2.4	20.8 ± 2.3	20.9 ± 2.3
ESS	5.9 ± 1.9	6.2 ± 2.1	6.0 ± 2.3
rMEQ	14.7 ± 3.6	14.5 ± 3.6	15.2 ± 3.7
Non-Nappers	N=22 (13 F)	N=10 (7 F)	N=10 (5 F)
Age (years)	22.4 ± 3.7	22.9 ± 3.7	22.6 ± 3.8
ESS	6.1 ± 1.8	5.9 ± 2.2	6.3 ± 1.7
rMEQ	14.1 ± 3.6	14.1 ± 3.5	14.2 ± 3.6
Wake	N=21 (13 F)	--	--
Age (years)	19.1 ± 1.2	--	--
ESS	6.6 ± 2.5	--	--
rMEQ	12.7 ± 3.1	--	--

Note: ESS = Epworth Sleepiness Scale; rMEQ = reduced Morningness-Eveningness Questionnaire. Values (except *N*) are *M* ± *SD.* Visit 1 baseline data are for all subjects included in the Visit 1 baseline analyses; nap Practice and Restriction columns are the subjects who completed all three visits.

Table 3.2

Visit 1 nap polysomnography sleep variables

	Habitual nappers	**Non-nappers**	**Statistic**
TST (min)	82.9 (18.6)	82.3 (17.9)	t_{46}=-0.11, p=.91
Stage 1 (min)	8.0 (5.0)	7.2 (4.1)	t_{46}=-0.58, p=.57
Stage 2 (min)	41.1 (14.4)	37.5 (12.0)	t_{46}=-0.91, p=.37
SWS (min)	20.4 (10.9)	24.8 (3.7)	t_{46}=1.04, p=.31
REM (min)	13.5 (9.8)	12.8 (2.4)	t_{46}=-0.24, p=.82
SL (min)	7.4 (8.9)	5.3 (0.87)	t_{46}=-1.03, p=.31
WASO (min)	12.9 (15.3)	13.5 (3.9)	t_{46}=0.12, p=.91
SE (%)	80.2 (19.1)	81.7 (4.0)	t_{46}=0.28, p=.78

Note: TST = total sleep time; SWS = slow wave sleep; REM = rapid eye movement; SL = sleep latency; WASO = wake after sleep onset; SE = sleep efficiency. Values are *M* (*SD*).

Next, we examined spectral power in frequency bands 0.5-1Hz (slow oscillations, SO), 1-4Hz (delta), 4-8Hz (theta), 8-12Hz (alpha), 12-15Hz (sigma), and beta (15-30Hz) during Stage 2, SWS, NREM (S2 + SWS combined) and REM. There were no differences between HN and NN in any frequency band in any sleep stage.

Since daytime sleep may be directly related to nighttime sleep quality, we compared prior night's sleep between HN and NN and found no differences (Table 3). Actigraphy data showed that on average, HN subjects spent 7.34 hrs in bed and obtained 6.17 hrs of total sleep the night before the first in-lab visit; NN subjects spent 7.65 hrs in bed and obtained 6.50 hrs of total sleep. There were no differences between groups for any actigraphy variable, including time spent in bed and total sleep time (all *p*s>.19). Additionally, total sleep time the night before the experimental day did not correlate with nap sleep stages in either group (all *p*s>.17) or in the sample as a whole (all *p*s>.14).

Table 3.3

Visit 1 prior night's sleep actigraphy variables

	Habitual nappers	**Non-nappers**	**Statistic**
TST (min)	370.4 (50.6)	389.7 (47.2)	t_{41}=1.28, p=.21
SL (min)	13.1 (12.3)	8.1 (12.3)	t_{41}=-1.33, p=.19
WASO (min)	57.2 (30.2)	61.2 (30.9)	t_{41}=0.43, p=.67
SE (%)	84.1 (7.2)	85.0 (6.8)	t_{41}=0.43, p=.67

Note: TST = total sleep time; SL = sleep latency; WASO = wake after sleep onset; SE = sleep efficiency. Values are *M* (*SD*).

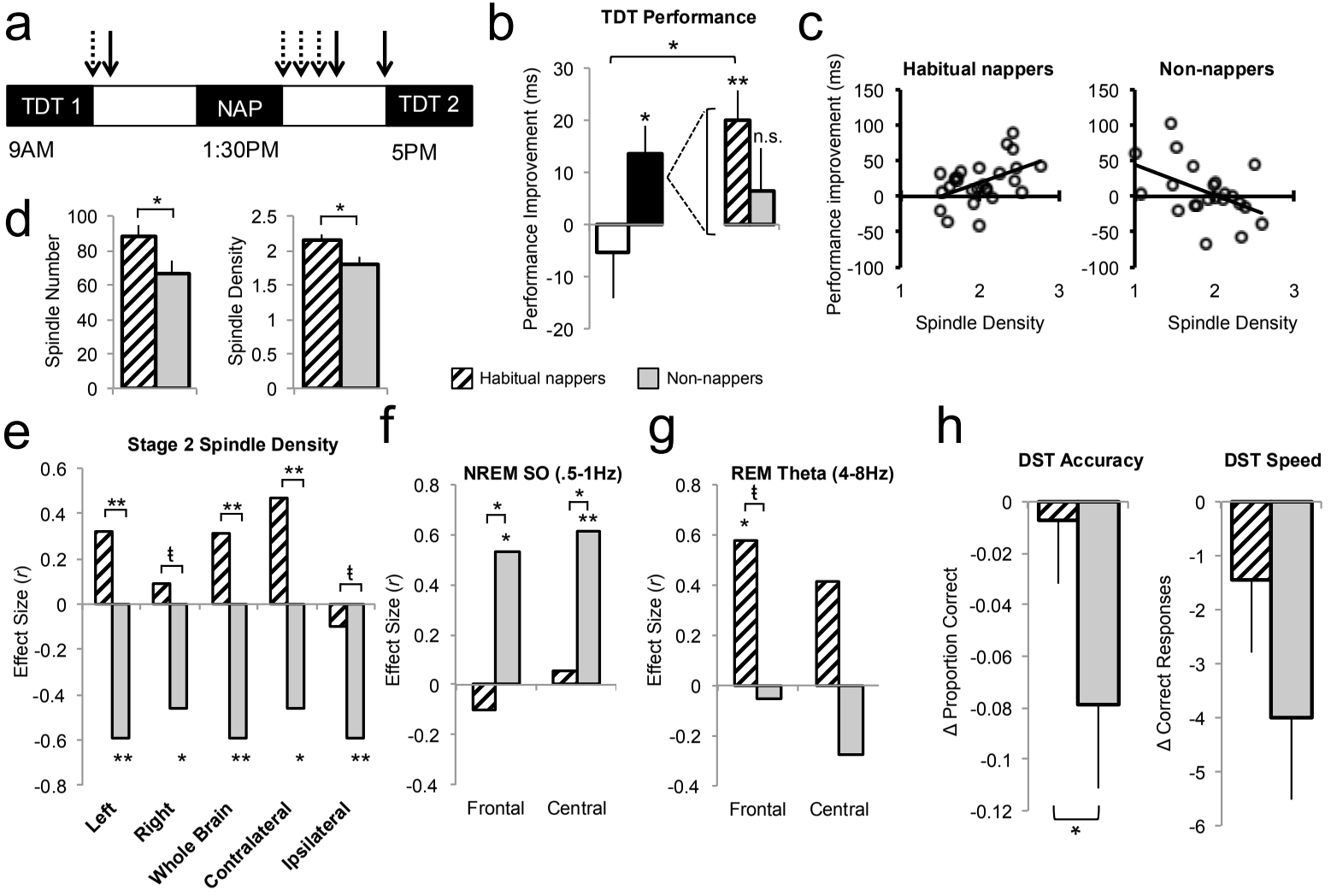
a
TDT 1
NAP
TDT 2
9AM
1:30PM
5PM
b
TDT Performance
Performance Improvement (ms)
n.s.
Habitual nappers
Non-nappers
c
Habitual nappers
Non-nappers
Performance improvement (ms)
Spindle Density
d
Spindle Number
Spindle Density
e
Stage 2 Spindle Density
Effect Size (r)
Left
Right
Whole Brain
Contralateral
Ipsilateral
f
NREM SO (.5-1Hz)
Frontal
Central
g
REM Theta (4-8Hz)
h
DST Accuracy
DST Speed
Δ Proportion Correct
Δ Correct Responses

Figure 3.1. Visit 1 baseline (Study 3). **(a)** In-lab test day procedure. Texture discrimination task (TDT) thresholds were obtained at 9AM and 5PM. All subjects napped between 1:30-3:30PM. Solid arrows indicate times of Karolinska Sleepiness Scale (KSS) administration; dashed arrows indicate times of the descending subtract test (DST) administration. **(b)** TDT threshold difference at baseline for the Wake (white bar) and Nap (black bar) groups indicate learning in the Nap group and no change in the Wake group. Within the Nap group, only HN (hatched bar) showed learning; NN (gray bar) did not show significant improvement. **(c)** Performance improvement was correlated with Stage 2 spindle density (grand average plotted), but in opposing directions for HN (positive, r=.31) and NN (negative, r=-.59). **(d)** HN had more spindles and greater spindle density during Stage 2 than NN (left hemisphere shown). **(e)** Effect sizes (Pearson r) for correlations between performance improvement and Stage 2 sleep spindle densities. There were also opposing patterns of associations between performance and **(f)** NREM slow oscillation (SO, .5-1 Hz) activity and **(g)** REM theta (4-8 Hz) power based on nap habits. NN performance was strongly associated with power in the SO band during NREM, while HN performance was strongly associated with power in the theta band during REM. Note that for panels E, F and G, an asterisk above or below the bar indicates a significant correlation; brackets indicate comparisons between r-values for HN and NN (i.e., test for moderation). **(h)** DST performance change 5 min after awakening from the nap (Test 1). NN had decreased accuracy following the nap, while HN remained at the same performance level as pre-nap. *HN = habitual nappers, NN = non-nappers. ŧ indicates $p \leq .07$, * indicates $p < .05$, ** indicates $p < .005$. Error bars are ±1 SEM.*

3.1.2 Behavioral Performance

Combining HN and NN groups, we replicated the classic finding that a nap enhances performance compared to wake [Session (AM, PM) x Condition (Nap, Wake) interaction, p=.05]. Discrimination thresholds significantly decreased (i.e., performance improved) in subjects who napped [13.7 ± 5.1 ms (mean, standard error), p=.01] and did not change in subjects who remained awake (-5.2 ± 8.9 ms, p=.57) (Fig. 1b).

Change in performance was negatively correlated with Stage 2% (r=-.33, p=.02) and positively correlated with SWS min (r=.36, p=.01) and SWS% (r=.32, p=.03), as well as the product of SWS and REM min (SWSxREM, r=.34, p=.02). These results are consistent with prior reports of a two-stage model of perceptual learning after both nighttime sleep (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000) and daytime naps (Mednick et al., 2003), where both SWS and REM contribute to improvement.

3.1.3 Only habitual nappers showed nap-dependent learning

As predicted, HN showed significant performance gains after a nap (20.0 ± 5.9 ms, p=.002) whereas NN did not (6.3 ± 8.5 ms, p=.47) (Fig. 1b), although the difference between the two groups did not reach statistical significance (p=.18). Compared with the Wake group (WK), only HN showed significant learning (HN vs. WK: p=.02; NN vs. WK: p=.36). These effects were not due to differences in AM IS thresholds between groups (p=.46).

3.1.4 Nap habits moderated the relation between sleep features and learning

We next examined associations between sleep features and performance separately for HN and NN. In order to test for a moderating effect of nap habit on these associations, we used the Fisher r-to-z transformation to test for significant differences in correlation coefficients between groups for all sleep/performance correlations. Nap habits did not moderate the association between sleep stages and performance change, with both HN and NN showing similar directions and magnitudes of effect sizes. However, there were substantial differences between the groups in how sleep spindles were associated with performance (Figs. 1c,1e). In NN, performance was consistently negatively correlated with the grand average spindle density during Stage 2 (r=-.59, p=.004), SWS (r=-.56, p=.015), and NREM stages combined (r=-.66, p=.001). This was not the case for HN, who did not show significant correlations in any stage (Stage 2: r=.31, SWS: r=-.17, NREM: r=.05; all ps>.12). The statistical difference between correlation coefficients for the two groups was significant for Stage 2 sleep spindles (p=.001), indicating that nap habits moderated the relation between spindles and performance change.

Given that learning on the TDT is retinotopically-specific (Karni & Sagi, 1991), we further examined Stage 2 spindles separately in the ipsilateral and contralateral hemispheres relative to the trained visual field location. HN showed a pattern of results predicted by a retinotopically-specific learning effect, with a

positive correlation between performance and contralateral spindles (r=.47, p=.02) and no significant relation between performance and ipsilateral spindles (r=-.10, p=.62). In NN, both contralateral (r=-.46, p=.03) and ipsilateral (r=-.60, p=.003) spindles were negatively correlated with performance. There was significant moderation for the contralateral effect (p=.001) and trending significance for the ipsilateral effect (p=.06).

We also investigated differences between groups in how performance was related to spectral power. Comparisons examined a priori frequency bands of interest over frontal and central electrode sites (collapsing across hemispheres), namely SO, delta, alpha, and sigma power in NREM sleep, and theta and alpha power in REM sleep. NREM SO and delta power strongly correlated with performance change in NN (SO frontal: r=.53, p=.013; SO central: r=.62, p=.003; delta frontal: r=.52, p=.015; delta central: r=.60, p=.005), whereas these associations were weaker and non-significant in HN (SO frontal: r=-.10, p=.63; SO central: r=.06, p=.79; delta frontal: r=.01, p=.95; delta central: r=.21, p=.30) (Fig. 1f). Correlation coefficients significantly differed between groups for SO power over frontal (p=.03) and central (p=.03) sites; group differences in delta power were marginally significant (frontal: p=.07, central: p=.10). NREM sigma power was negatively correlated with performance in NN (frontal: r=-.45, p=.03; central: r=-.38, p=.08), and there were no significant associations in HN (frontal: r=-.01, p=.96; central: r=.15, p=.46). Tests for moderation were trending in significance (frontal: p=.10; central: p=.08).

REM theta power was positively correlated with performance in HN (frontal: r=.58, p=.02; central: r=.41, p=.1), but there were no significant associations in NN (frontal: r=-.05, p=.84; central: r=-.28, p=.32) (Fig. 1g). Although the tests for moderation were trending (both p=.07); this analysis had decreased statistical power since not all subjects had REM sleep. Alpha power during NREM and REM was not significantly correlated with performance in either group (all ps>.3), and correlation coefficients did not differ between the groups (all ps>.4). Unlike the spindle result, we did not find retinotopically-specific differences in any of the frequency bands, which may be related to the more localized nature of spindles compared with the more global oscillations that occur during sleep (Genzel, Kroes, Dresler, & Battaglia, 2014). In summary, these results reveal differences in the underlying oscillatory circuitry driving consolidation mechanisms during naps for HN and NN.

3.1.5 Post-nap waking experience: Sleep inertia and subjective sleepiness

Since non-nappers often report not enjoying napping (Duggan et al., 2016) and anecdotally complain of feeling groggy and unproductive after a nap, we measured subjective sleepiness and cognitive functioning after the nap. Subjects rated their subjective sleepiness at three time points across the study day: 1) pre-nap, 2) 10 min post-nap, and 3) 90 min post-nap (see Fig. 1a). Overall, subjective sleepiness decreased across the day [$F(2,82)=16.46$, $p<.001$], with a reduction in sleepiness, or boost in alertness, evident 10 min post-nap (p=.06,

compared to pre-nap), and an even further reduction in sleepiness approximately 90 min after waking (p<.001, compared to 10 min post-nap). These changes in ratings did not differ between HN and NN (all ps>.3), indicating both HN and NN received similar benefits for alertness from the nap.

We indexed the degree of sleep inertia experienced by participants using a descending subtraction test (DST) (Mullington & Broughton, 1993, 1994) to measure cognitive functioning at 11AM and 5, 20 and 35 min after awakening from the nap (see Fig. 1a). Prior to the nap at 11AM, there were no differences in speed (total number of correct responses) or accuracy (correct responses/total responses) between groups (both ps>.5). However, as predicted, upon awakening from the nap, NN showed significant decrements in speed (-13%, p=.02) and accuracy (-10%, p=.03) (Fig. 1h). On the other hand, HN showed almost no post-nap impairment, with only a 1% change in speed (p=.30) and accuracy (p=.78) compared to their pre-nap performance. The difference between groups in Δaccuracy supported our a priori hypothesis that HN would show less cognitive impairment after a nap (p=.04, one-tailed), but the group difference in Δspeed did not reach significance (p= .22). By 20 min post-nap, DST speed had increased in both groups (NN: 31%, p=.003; HN: 27%, p<.001), and compared to pre-nap, HN were significantly faster (p=.01). On the other hand, NNs recovered, but did not improve, their speed after a nap (p=.30). NNs showed a trend toward enhanced speed by 35 min post-nap (p=.08). Accuracy did not show any significant differences at later time points.

3.2 Does Nap Practice change non-nappers' outcomes?

We also investigated the effect of four weeks of nap Practice or Restriction in HN and NN (Fig. 2a). Subjects in the Practice condition averaged 3.13 ± 0.90 naps per week prior to the study. We originally hypothesized that napping is a trainable skill and therefore predicted that across the four weeks of nap practice, NN would become more similar to HN in daytime sleep metrics and performance.

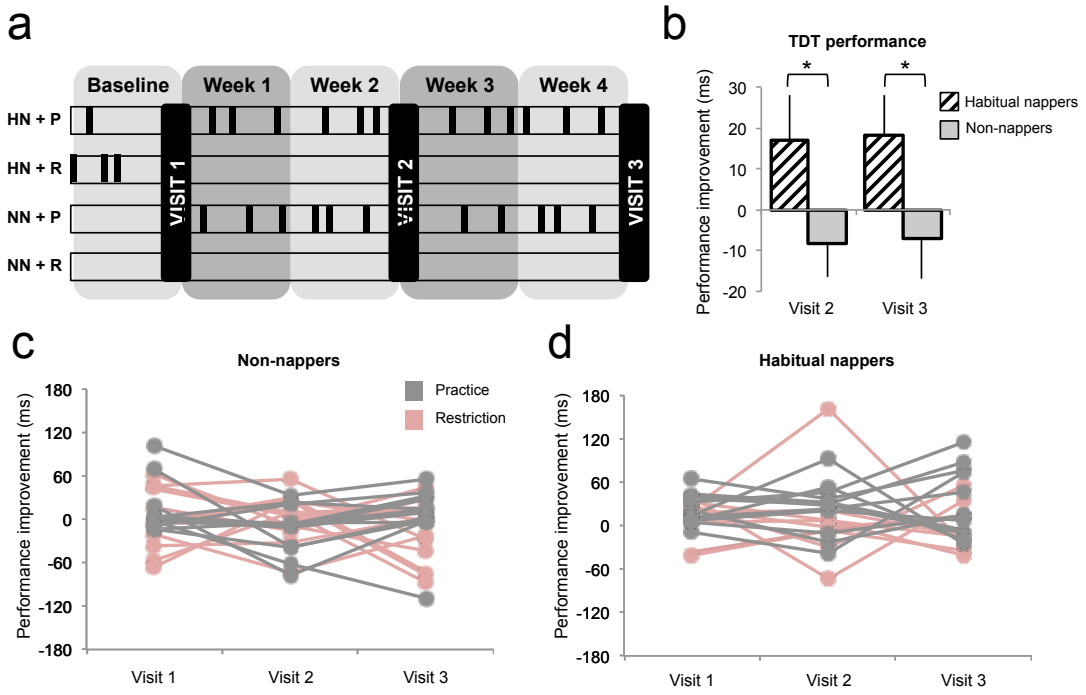

Figure 3.2. Nap practice/restriction intervention. **(A)** Example subjects in each experimental group. Black vertical lines indicate days when subjects napped. During the baseline week, habitual nappers (HN) napped and non-nappers (NN) did not. Following visit 1, subjects were assigned to one of two groups: nap practice (P; instructed to nap at least 3 times per week) or nap restriction (R; instructed not to nap). **(B)** TDT threshold difference at Visit 2 and Visit 3. Habitual nappers (hatched bar) always showed improvement and non-nappers (gray bar) did not. **(C-D)** The magnitude of nap-dependent memory improvement remains stable across the four-week nap Practice (gray lines) or nap Restriction (red lines) intervention in both habitual nappers (panel C) and non-nappers (panel D). ** indicates p=<0.1. Error bars are ±1 SEM.*

3.2.1 Daytime sleep

There were no significant differences in nap total sleep time (p=.88), Stage 1 (p=.49), Stage 2 (p=.89), SWS (p=.51), or REM (p=.69) minutes across the experiment (Visit x Group x Condition, Table 4). Likewise, there were no changes in spindle densities (p=.51) or power spectra (NREM SO: p=.64, NREM delta: p=.76, NREM sigma: p=.89, REM theta: p=.89) as a function of nap practice. These results indicate that asking NN to nap, and asking HN to abstain from napping, did not have a significant impact on the architecture of their daytime sleep.

Table 3.4

Nap polysomnography sleep variables across three visits

	Visit 1		Visit 2		Visit 3	
	Practice	**Restriction**	**Practice**	**Restriction**	**Practice**	**Restriction**
Habitual Nappers						
TST (min)	87.2 (16.9)	86.5 (9.1)	91.6 (11.7)	78.4 (26.6)	91.0 (16.0)	93.6 (4.9)
Stage 1 (min)	6.4 (4.0)	10.6 (5.5)	6.3 (4.2)	10.3 (7.7)	5.6 (4.2)	11.5 (6.2)
Stage 2 (min)	40.4 (12.2)	45.4 (9.1)	38.0 (14.3)	41.9 (14.0)	37.1 (17.8)	45.3 (17.2)
SWS (min)	23.3 (11.7)	16.6 (9.6)	26.0 (12.9)	11.7 (10.4)	28.7 (16.6)	21.8 (17.7)
REM (min)	17.1 (6.8)	13.9 (12.1)	21.2 (14.3)	14.6 (8.4)	19.5 (12.0)	15.0 (8.9)
SL (min)	4.4 (4.2)	7.3 (4.8)	5.3 (9.2)	2.6 (2.1)	1.4 (1.4)	3.2 (2.4)
WASO (min)	8.1 (17.2)	15.5 (13.1)	4.0 (4.9)	12.8 (14.5)	6.8 (11.0)	7.2 (5.4)
SE (%)	87.3 (18.0)	79.3 (12.3)	90.8 (11.0)	80.4 (25.7)	91.3 (13.4)	90.2 (5.6)
Non-napers						
TST (min)	83.0 (20.1)	80.4 (18.1)	92.6 (10.5)	82.7 (22.8)	83.4 (26.9)	84.2 (19.7)
Stage 1 (min)	6.8 (3.4)	7.9 (4.9)	6.8 (3.4)	4.9 (2.5)	7.0 (4.0)	7.6 (3.4)
Stage 2 (min)	36.8 (13.8)	37.4 (11.3)	41.6 (14.0)	44.8 (15.1)	42.8 (17.1)	44.2 (17.8)
SWS (min)	28.8 (17.5)	20.2 (17.9)	26.8 (19.7)	19.7 (18.6)	17.7 (13.3)	21.7 (18.4)
REM (min)	10.6 (9.3)	14.9 (13.7)	17.4 (9.6)	13.4 (12.5)	16.0 (9.9)	10.8 (9.0)
SL (min)	4.0 (3.0)	6.7 (5.0)	5.2 (4.7)	4.7 (2.3)	4.2 (7.2)	7.8 (9.2)
WASO (min)	12.0 (17.5)	16.3 (21.4)	5.6 (6.8)	10.8 (10.8)	11.3 (20.4)	10.5 (11.6)
SE (%)	83.6 (18.8)	78.5 (21.4)	89.7 (9.2)	82.6 (17.2)	84.4 (27.0)	81.9 (18.1)

Note: TST = total sleep time; SWS = slow wave sleep; REM = rapid eye movement; SL = sleep latency; WASO = wake after sleep onset; SE = sleep efficiency. Values are M (SD). Only data from subjects who completed all three visits are included in this table.

3.2.2 Perceptual learning of texture discrimination

In contrast with our prediction, there was no main effect of Visit or Group (Practice/Restriction) and no significant interactions, indicating that neither nap practice nor restriction altered texture discrimination performance across time. There was, however, a main effect of nap habits [$F(1,36)=5.61$, $p=.02$, partial $eta^2=.14$], which revealed that HN showed more performance gains with a nap than NN across all visits [Visit 2: 17.0 vs. -8.4 ms, $p=.07$; and Visit 3: 18.3 vs. -7.2 ms, $p=.08$) (Fig. 2b). In other words, the differential performance outcomes observed at Visit 1 (baseline) were maintained throughout the study. The lack of change in performance improvement over time is evident in spaghetti plots of performance across the three visits (Fig. 2c-2d), demonstrating that nap practice did not result in gain memory consolidation benefits from a nap in the NN group. On each visit, pre-nap thresholds were comparable between HN and NN (all ps>.2).

3.2.3 Post-nap waking experience: subjective sleepiness and sleep inertia

Across the four weeks of the study, there were no changes in subjective sleepiness after waking from the nap as a function of nap practice or restriction ($p=.56$). In addition, the degree of post-nap sleep inertia as measured by the DST remained stable across visits, with no changes due to nap practice or restriction (Δspeed: $p=.57$; Δaccuracy: $p=.19$).

Discussion

These data provide empirical evidence that previously reported cognitive benefits from napping may not be universal. We showed that in a young, healthy, and ethnically diverse sample, only habitual nappers (HN) demonstrated perceptual learning with a nap, whereas performance of non-nappers (NN) remained at baseline or worse throughout the day. These distinct performance profiles were associated with functional differences in oscillatory activity during sleep. Specifically, we found associations between spindles, EEG power spectra, and behavioral performance in opposing directions in these two groups. Furthermore, we demonstrated for the first time that napping might not be a trainable skill, as four weeks of nap practice did not improve nap-dependent learning in NN. These findings favor the view that nap preferences are not experience-dependent but instead are determined by an underlying biological drive for napping. Thus, individuals who are predisposed to napping may be the only people for whom a “nap is as good as a night” (Mednick et al., 2003).

Prior studies on differences in nap sleep architecture between nappers and non-nappers have consistently found that habitual naps are predominated by light sleep stages, whereas non-nappers experience deeper sleep (Dinges, 1992; Milner et al., 2006). For example, appetitive nappers – those who nap for pleasure – had more Stage 1 and sleep stage transitions that fluctuated through light sleep stages during a 40 min nap than non-nappers or people who use naps to replace lost nighttime sleep (Evans, Cook, Cohen, & Orne, 1977). We

previously found a dose-dependent effect of napping on nap sleep architecture – more napping during a one-week period was associated with greater amounts of Stage 1 and 2, and less SWS, but not with nocturnal sleep duration (McDevitt et al., 2012). Similarly, in the present study we found that habitual nappers had increased Stage 2 sleep spindles, a fast frequency sleep feature associated with plasticity in both verbal episodic memory (Schabus et al., 2004) and perceptual learning (Bang et al., 2014). Indeed, in our study, spindle density and REM theta were associated with better HN performance. In contrast, NN performance was correlated with power in slow frequency bands (i.e., <4Hz), whereas spindles and REM theta power did not correlate with improvement. Alpha power was not associated with performance in either group, arguing for specificity of sleep features known to play a role in memory consolidation processes (Diekelmann & Born, 2010). Thus, habitual nappers appear to depend on faster frequencies that are characteristic of light sleep for nap consolidation, whereas non-nappers may rely on the slower frequencies that are associated with deep sleep. These differential neural profiles of consolidation may dissociate pathways theat promote and impair efficient and successful learning.

Prior work has shown that REM sleep is critical for performance improvement on a texture discrimination task (Karni et al., 1994; Mednick et al., 2003). In the current study, only HN showed learning after the nap, even though the majority of both HN (*n*=20) and NN subjects (*n*=18) had equivalent amounts of REM sleep at the group level. REM theta activity indicated a qualitative

difference in REM sleep between the groups that may be informative. Specifically, REM theta power was was correlated with performance improvement only in HN. In humans, increased theta activity was reported following learning of word pairs (Fogel et al., 2007) and emotional pictures (Nishida et al., 2009). Animal studies have also demonstrated that hippocampal theta modulates the induction of long-term potentiation (LTP) – a mechanism underlying synaptic plasticity and memory formation – during wake (Huerta & Lisman, 1995) and that is continues to orchestrate synaptic changes during subsequent sleep (Poe et al., 2000) (however, it should be noted that hippocampal theta activity recorded in animal studies cannot be detected at the level of the scalp in humans). Perceptual learning involves neural plasticity, likely via LTP mechanisms (Sale et al., 2011). Taken together with the spindle results, our fast frequency findings in HNs are consistent with the hypothesis that HNs demonstrate learning because they have more efficient neural mechanisms to boost plasticity and strengthen synaptic connections during daytime sleep than NNs. Furthermore, these data suggest that consolidation processes during NREM sleep (e.g., spindles) and REM sleep (e.g., theta) both contribute to performance improvement on perceptual learning of texture discrimination and expand upon the two-process model proposed by Stickgold and colleagues (Stickgold et al., 2000), albeit with one large caveat – during a nap, this is only true for habitual nappers.

Typically, repeated training on the texture discrimination task without subsequent sleep leads to perceptual deterioration (Censor et al., 2006; Censor & Sagi, 2008, 2009; Mednick et al., 2002; Mednick et al., 2005). The observation that NN post-nap performance did not deteriorate between sessions suggests that some consolidation process did occur during daytime sleep in the NNs. This possibility is supported by two findings from the current study. First, NN performance was correlated with slow wave activity in NREM sleep (i.e., <4Hz). Prior studies have shown that NREM sleep alone alleviates deterioration (Mednick et al., 2003), and that perceptual learning is blocked when slow wave activity is suppressed (Aeschbach et al., 2008), arguing for a causal role of NREM slow wave activity for consolidation processes that are involved in recovery from perceptual deterioration. Second, we found that NN performance was negatively correlated with sleep spindles and theta power, suggesting that if there are consolidation processes that depend on these sleep features (e.g., synaptic plasticity and/or systems-level consolidation), these processes may be less efficient in NNs. The synaptic homeostasis hypothesis (SHY) posits that low frequency slow wave activity is a principal mechanism by which the brain downscales synaptic connections that have become potentiated during wake (Tononi & Cirelli, 2006, 2014). In terms of learning, SHY postulates that encoding during wake increases potentiation of synapses and that slow waves protect the synapses that are processing the encoded signals while preferentially downscaling weaker synapses that are processing noise. As a result, signal-to-

noise ratio is increased, and memory is improved. It is possible that slow waves may also be important for reducing perceptual deterioration through a similar downscaling mechanism and that this process is more effective in NNs.

Contrary to our hypothesis, our results indicate that nap habits may be more influenced by “nature” than “nurture.” The four-week, nap practice intervention produced no changes across any of the four outcomes of interest: nap sleep architecture, behavioral performance, sleep inertia, and subjective sleepiness. It is possible that our intervention was not long enough or did not require enough practice (minimum 20 minutes, 3 times per week for four weeks). Indeed, there is considerable variation in how long it takes people to form a habit (Lall et al.,, 2010), with one study showing an average of 66 days (range 18 to 254 days) to form an eating, drinking, or activity behavior, and the length of our intervention was significantly shorter than this. However, it should be noted that habit formation studies measure automaticity of a response given a cue in the environment, which may be different from measuring the cognitive benefits arising from frequent napping. In the current study, we did not collect self-reports that would have allowed us to examine automaticity of the behavior within a habit formation framework. However, in regards to the four outcomes, there was no hint of a trend towards a change in performance for the NNs assigned to the practice group, suggesting that they were not on a trajectory toward change that would have been more evident if the intervention had been extended.

What might be some possible explanations for these individual differences in nap preference? Genetics are likely to play role, and one candidate is the clock gene *PERIOD3*, which contains a variable number tandem repeat polymorphism. This polymorphism has been linked to morningness/eveningness preference, delayed sleep phase syndrome, slow wave activity, and changes in waking performance following sleep loss (Viola et al., 2007). Napping is also related to these factors, and we speculate that *PERIOD3* may be one marker of napping phenotype. Another possibility is that nap habits that arise early in development may affect adult habits (Mednick, 2013). A recent study reported that napping was important for learning in preschool children, such that no learning occurred in children restricted from napping (Kurdziel, et al.,,2013). Closer inspection of the data from this study revealed that the decreases in performance were only evident in habitual nappers that were restricted from napping, whereas no performance decrements were found in non-nappers. A working hypothesis that emerged from this study suggests that habitual nappers have an increased need for frequent consolidation and that this may be related to brain maturation during development. Although it is not yet known how preschool nap habits may be related to adult nap habits, there may be functional differences in learning strategies in adults that place differential demands on cognitive load and downstream sleep. Longitudinal studies that track nap patterns across the lifespan would be informative for understanding how nap habits develop and change (or do not change) over time. Further research is also needed to

determine how the present results may generalize to other populations, such as older adults and clinical samples, and how habitual napping might impact other outcomes related to health and well-being.

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General Discussion

The studies described in this dissertation tested the role of different brain states for offline consolidation of perceptual learning, as well as individual differences in consolidation profiles. Study 1 investigated how these brain states affect learning specificity and generalization. I trained participants to discriminate differences in motion direction and found that naps with REM sleep facilitated consolidation of perceptual learning for the trained direction (McDevitt et al., 2013). I also found that the pattern of specificity differed between men and women – learning was specific to the trained direction in men, whereas learning transferred to an untrained direction in women. Men also showed a greater magnitude of learning for the trained direction than women. Study 2 explored which brain state(s) could rescue learning that was damaged by interference. Using a texture discrimination task in an interference paradigm, I showed that wake was sufficient to consolidate perceptual learning in a no interference condition, but sleep was necessary to consolidate perceptual learning in the interference conditions (McDevitt et al., 2015). Critically, only naps that contained REM sleep were able to rescue performance that was otherwise obliterated by interference. Together, the results of these studies suggest that REM sleep is a special brain state that facilitates plasticity, enabling memories to grow stronger and leading to enhanced performance. These studies also suggest that napping is a tool that can be used to improve learning within the same day as training. In Study 3, I asked if all individuals receive these learning benefits from a nap.

Using a texture discrimination task, I found that only people who nap regularly (i.e., habitual nappers) showed significant perceptual learning after a nap and that there was no detectable nap-dependent learning in the non-habitual nappers. Additionally, I demonstrated for the first time that napping might not be a trainable skill, as four weeks of nap practice did not help non-habitual nappers to obtain any learning benefit from naps.

Existing models of memory consolidation

Are there existing models that can account for these results? The short answer is no, primarily because most models only consider consolidation mechanisms during non-rapid eye movement (NREM) sleep. In the standard model (Frankland & Bontempi, 2005), the hippocampus and neocortex are the hypothesized neural structures associated with temporary and long-term memory stores, respectively. New information is initially encoded concurrently in both stores. During subsequent periods of consolidation, successive reactivation, or "replay", of this network is presumed to allow new memories to become strengthened and integrated with pre-existing memories in the long-term store, as well as becoming less reliant on the fast-learning store (Diekelmann & Born, 2010; McClelland,et al., 1995). Neural replay has been observed in studies of rodent spatial memory, in which place cells that are activated in sequence together during spatial learning tend to fire in a similar sequence, and at a faster, time-compressed rate, during subsequent slow wave sleep (SWS) (Lee &

Wilson, 2002; Wilson & McNaughton, 1994). Specifically, studies have shown: 1) hippocampal replay during SWS in rats is coordinated with firing patterns in the visual cortex (Ji & Wilson, 2007); 2) the hippocampus and cortex appear to communicate during sleep by means of hippocampal sharp waves and ripples (Buzsáki, 1989), during which place cells are reactivated (Diba & Buzsáki, 2007); and 3) these hippocampal sharp wave-ripple events are temporally correlated with spindles in the medial prefrontal cortex during SWS (Siapas & Wilson, 1998).

Another model, the synaptic homeostasis hypothesis (SHY), proposes that low frequency slow wave activity during NREM sleep is the principal mechanism by which the brain downscales synaptic connections that were previously potentiated during waking (Tononi & Cirelli, 2006, 2014). In terms of memory, SHY postulates that encoding during wake increases potentiation of synapses in the network and that slow waves during sleep de-potentiate these synapses. However, stronger synapses with more potentiation (i.e., “signal") are downscaled relatively less compared to weaker synapses that are processing “noise.” This process is posited to increase signal-to-noise ratio in the brain and thereby improve memory.

A third model, the opportunistic consolidation hypothesis, posits that periods during which the brain is free from encoding new information are opportune times for consolidation (Mednick et al., 2011). I will refer to these brain states as having “low information input.”, including periods of time spent asleep,

when the brain is (mostly) disengaged from processing stimuli in the external environment, as well as periods of time under the influence of alcohol or benzodiazepines, both of which block encoding of new information (therby resulting in amnesia for events that occur when these substances are active in the body) (Coenen & van Luijtelaar, 1997; Fillmore et al., 2001; Mueller et al., 1983; Parker et al., 1980, 1981). Other experiments have shown that a period of quiet wake, when the subject is awake but not mentally engaged in a task, can also facilitate consolidation (Dewar et al.,,2012; Mednick et al., 2009).

Importantly, none of these hypothesized mechanisms are mutually exclusive with one another. A unified model would suggest that processes such as replay and synaptic downscaling might drive consolidation but that an equally critical factor is that the brain be in a state to allow consolidation to proceed without interference from external inputs. In the next section, I describe how the opportunistic model can be extended to include memory processing during REM to explain the results of the studies in this dissertation.

The opportunistic consolidation hypothesis: An update

In this thesis, I tested brain states ranging from high to low on an *axis of information input* – active wake (AW), quiet wake (QW), and sleep (see Figure 1). However, given that NREM and REM sleep are equated on this dimension (low information input), yet show different consolidation benefits in different memory

systems, it is likely they differ along at least one other (or likely many other) critical dimension, such as plasticity.

Different brain states may encourage plasticity via fluctuations in plasticity-related neuromodulators, and one neuromodulator that plays an important role in synaptic plasticity is acetylcholine (ACh). ACh shows significant fluctuations across AW, QW, NREM and REM sleep. Microdialysis studies report higher ACh concentrations during AW than QW. These concentrations decrease to one-third of waking levels during NREM sleep and then rise to levels above AW during REM sleep (Hasselmo & McGaughy, 2004; Jasper & Tessier, 1971; Kametani & Kawamura, 1990; Marrosu et al., 1995). Long-term potentiation (LTP) is the leading physiological model of synaptic plasticity (Bliss & Collingridge, 1993), and it has been shown that low cholinergic tone during NREM sleep and QW (Hasselmo & Bower, 1993) may reduce or even block LTP induction (Jones et al., 1987) without disrupting LTP maintenance (Bramham & Srebro, 1989). This state of low plasticity combined with low information input has been hypothesized to optimize conditions for stabilizing, but not enhancing, recently learned experiences (Mednick et al., 2011). In contrast, high cholinergic tone during AW and REM sleep contributes to increased synaptic plasticity in these states, which improves the likelihood of successful encoding during AW (Hasselmo & McGaughy, 2004) and strengthening of memory representations at the synaptic level during REM sleep (Diekelmann & Born, 2010), and perhaps in some cases during AW (McDevitt et al., 2015). Using ACh levels as an index of plasticity,

these brain states range from low to high on an *axis of plasticity* – NREM, QW, AW, and REM (see Figure 1).

Together, these four brain states – AW, QW, NREM and REM sleep – are distinguished by variations along both information input and plasticity dimensions (Figure 1). AW is a state of high information input and high plasticity; QW is intermediate information input and intermediate plasticity; NREM is low information input and low plasticity; and REM is low information input and high plasticity. I hypothesize that for memories that require protection from forgetting, brain states that are characterized by decreased information input and low plasticity (e.g., QW and NREM) are optimal for consolidation. For memories that need to grow stronger through consolidation, a brain state characterized by low information input and high plasticity is required, and REM sleep is the only brain state that is optimized along both these dimensions. In our studies, this was observed at the behavioral level, with REM sleep leading to improvement of a trained visual skill as well as rescue of memories damaged by interference.

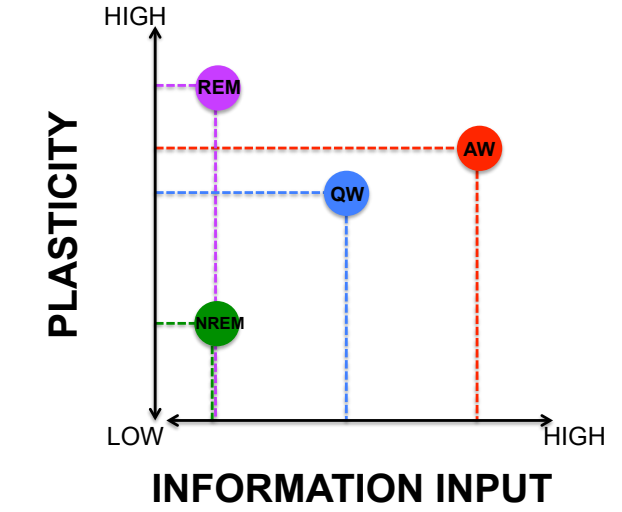

Figure 4.1. Brain-state consolidation model.

Is napping for everyone?

In 2003, *Nature Neuroscience* published a study that changed the face of sleep science by placing nap paradigms at the center of sleep and memory research (Mednick et al., 2003). This study showed that naps were as good as a night of sleep for memory consolidation and that naps were experimentally superior to nighttime sleep because they controlled for many confounds (e.g., mismatched circadian timing and sleep deprivation) that had plagued the field up to that point. Since then, nap paradigms have become ubiquitous in sleep and memory research. Naps have also become a highly popular topic in the media and corporate life (e.g., Arianna Huffington's book encouraging napping in the workplace and her new health start up that is centered on sleep). But is napping a useful tool for everyone? With all these incentives, why do some people *avoid*

napping? Can people who do not habitually nap be trained to benefit from this practice?

This thesis attempts to answer these questions by examining individual differences (sex and nap habits). In Study 1, we found that REM was the critical stage for consolidation of motion direction discrimination learning but that the magnitude and specificity of learning depends on sex. I speculate that sex differences in ACh modulation during REM sleep might be one factor underlying these differences in perceptual learning between men and women. For example, studies in rodents have reported higher ACh transmission in male versus female rats (Mitsushima, 2011; Mitsushima et al., 2003). If similar sex differences are present in humans, higher ACh transmission in men could lead to greater magnitude and specificity of learning (Rokem & Silver, 2010). However, future studies are needed to test the relationships among ACh, sex and perceptual learning and to investigate if these sex differences are specific to consolidation during naps or if similar sex effects are seen across a full night of sleep.

In Study 3, I replicated the Mednick et al. (2003) study and found significant perceptual learning after the nap but not after the period of wake. However, when I compared performance changes in people who regularly nap (habitual nappers, HN) with those who do not usually nap (non-nappers, NN), I found that all the improvement was concentrated in the HN group, and *no learning* was apparent in the NN group. These distinct performance profiles were associated with functional differences in oscillatory activity during sleep.

Specifically, we found relationships between performance and spindles, slow wave activity, and theta power that were opposed in these two groups. These findings suggest that some individuals may not show learning benefits from daytime sleep because of inefficient neural mechanisms that are engaged during a nap. Additionally, I demonstrated for the first time that napping may not be a trainable skill, as four weeks of nap practice did not help NN subjects obtain even a small amount of cognitive benefit from the nap. These findings favor the view that nap preferences are not primarily experience-dependent but rather may be determined by an underlying biological drive for napping. Thus, individuals who regularly nap (approximately 50% of the population; National Sleep Foundation Sleep Health Index 2014) may be the only people for whom a nap is as good as a night for consolidation of learning.

Taken together, although naps have proven to be a useful tool for exploring underlying mechanisms of memory consolidation during sleep, they may not have a direct translational application for everyone. The individual differences explored here are important factors to consider for a wide range of applications, including researchers drawing conclusions from nap studies, as well as administrators, policy makers, and clinicians who may recommend napping for military personnel, pilots, nurses and doctors, truck drivers, athletes, students, and office workers.

Outstanding questions

There are many outstanding questions regarding the role of REM sleep for memory consolidation. How do memory representations actually change during REM? Does REM drive memory representations apart to reduce interference in memory networks (Norman et al., 2005)? Or, in some instances, perhaps REM integrates memory representations to facilitate generalization? What are the mechanisms at the synaptic level? If new LTP can be induced during REM (Bramham et al., 1994), does this mean that if LTP is disrupted during waking then it can be restored during REM? Are there individual differences in ACh transmission during REM that could influence the magnitude of memory benefits? Does boosting ACh during sleep have an effect on consolidation (Gais & Born, 2004; Rokem & Silver, 2010)? Finally, is this REM model applicable in domains other than visual learning? Future studies should attempt to answer these questions to continue pursuing an understanding of the memory functions of REM sleep.

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