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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.

Keywords

interference; REM sleep; perceptual learning; plasticity; napping

1. 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

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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?

2. Materials and Methods

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.

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 (Rechtschaffen & 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.

3. 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.

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 × 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.

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 × 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 ($M = 2.5$ms, $p = .68$), nearly equivalent amounts of improvement in the QW and NREM nap groups ($M_{QW} = 15.1$ms and $M_{NREM} = 17.8$ms, both $p = .03$, but not significant after correcting for multiple comparisons), and REM naps displayed the greatest amount of learning ($M = 36.9$ms, $t(24) = 3.10$, $p = .005$). In the next sections, we examine the condition × group interaction.

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 × 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 × 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 × group interaction ($F(3,101) = 5.97$, $p = .001$). The REM group showed a large magnitude of perceptual learning ($M = 41.2$ms, $t(24) = 2.72$, $p = .01$), there was no learning in the QW ($M = -16.5$ms, p = .16) or NREM ($M = -13.2$ms, $p = .32$) groups, and there was significantly decreased performance in the AW group ($M = -26.6$ms, $p = .01$).

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 (SWS×REM 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 = $-.57B_{Stage1} + .66B_{Stage2} + 1.81B_{SWS} + 2.46B_{REM} + .03B_{SWS\times REM}$. 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.

4. 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 SWS×REM interaction in model 2, the parameters for SWS alone and SWS×REM 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.

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- When interference occurs after consolidation, AW supports perceptual learning (PL).
- Retroactive interference is more damaging to PL than proactive interference.
- For moderate proactive interference, NREM sleep is sufficient for PL.
- For high levels of retroactive interference, only naps with REM sleep rescue PL.

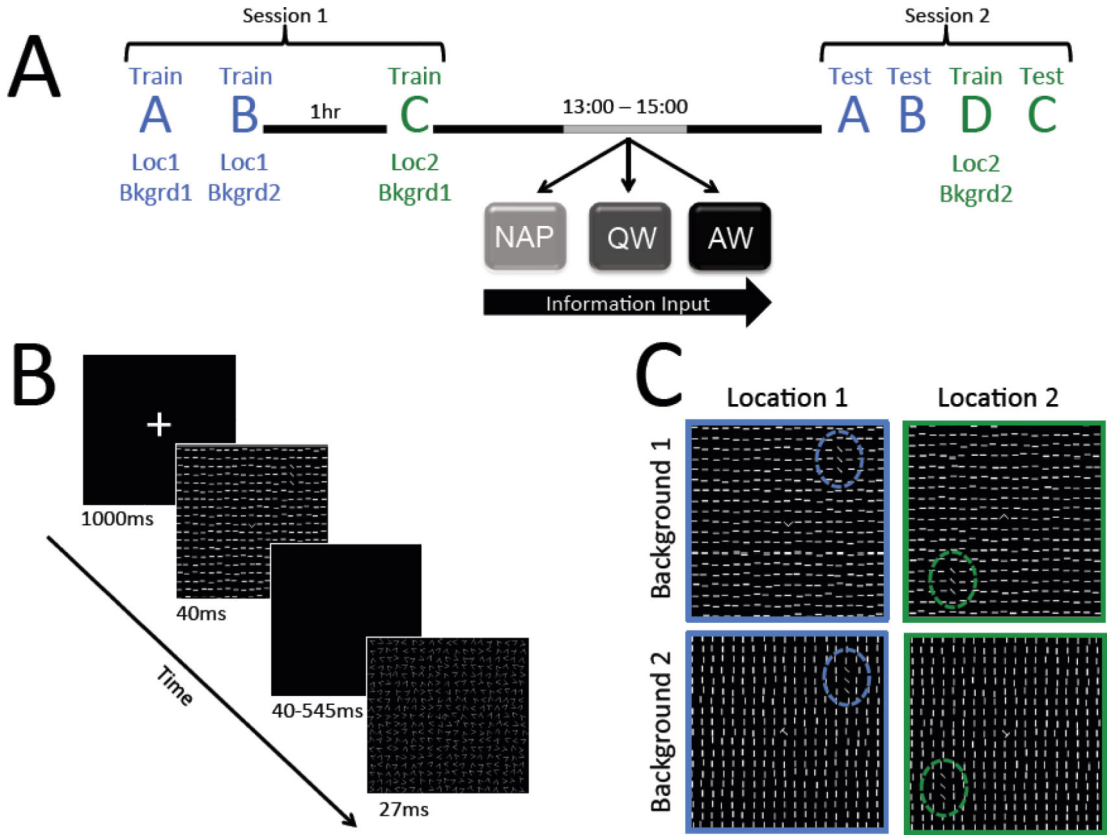

Figure 1.

Experimental methods. **(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.

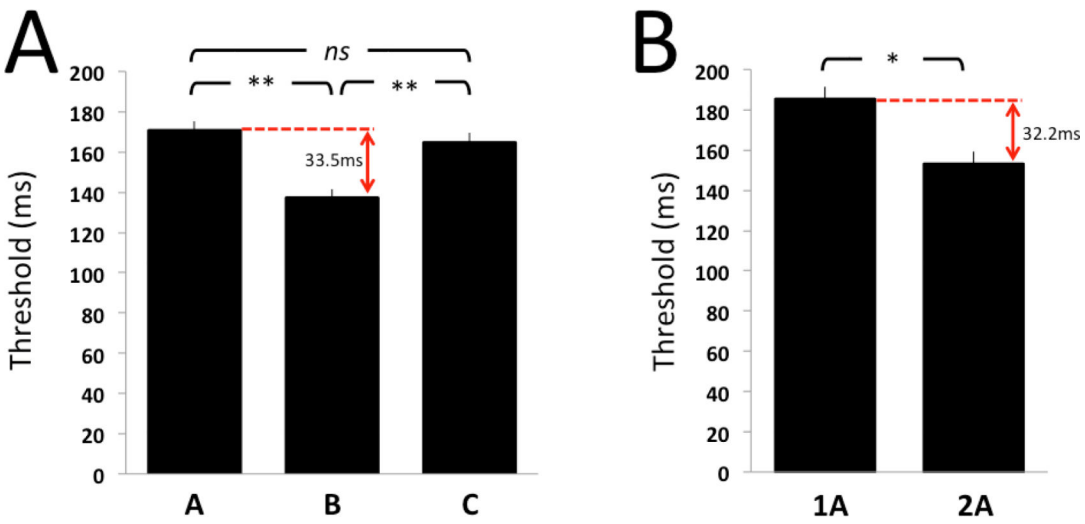

Figure 2.

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 $p < .05$

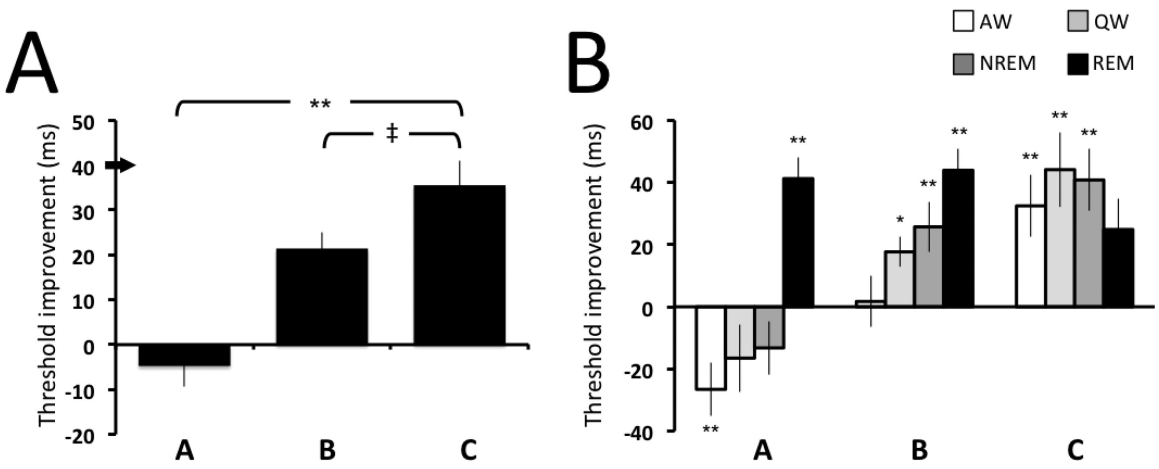

Figure 3.

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 $p < .0125$).

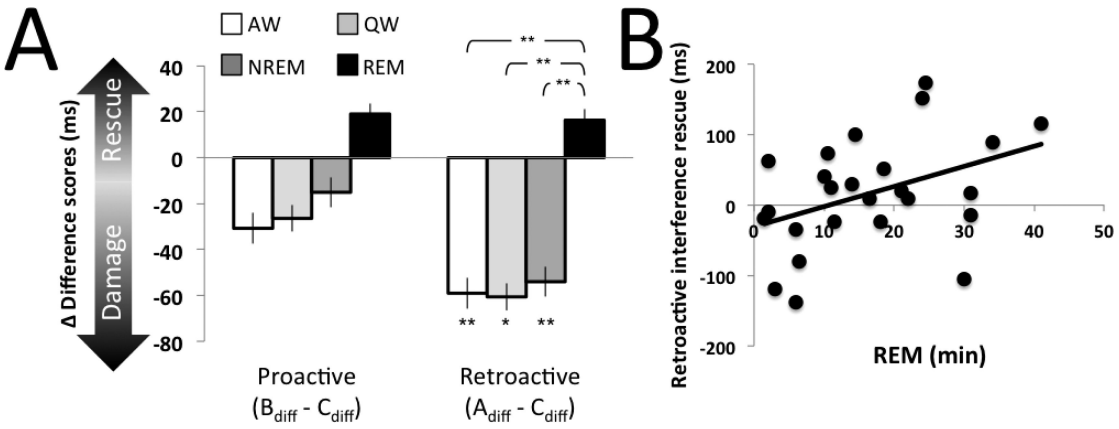

Figure 4.

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 ($r = .41$, $p = .04$).

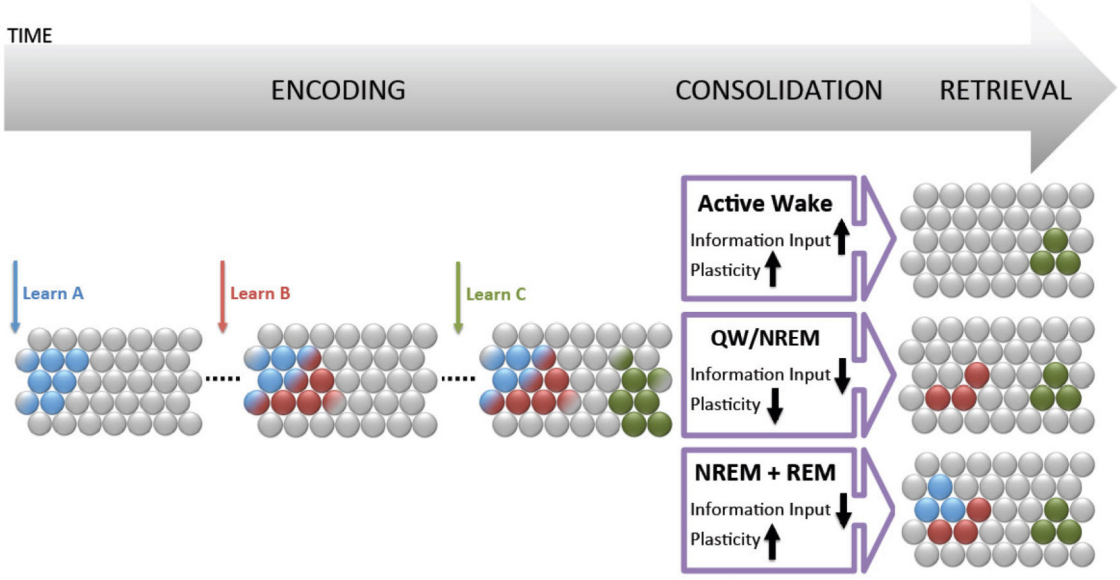

Figure 5.

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.

Table 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

Sleep architecture descriptives.

	NREM Naps	REM Naps
TST (min)**	49.8 (16.7)	76.7 (15.2)
SE (%)**	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 (.42)	19.9 (12.0)

Note: Values are *M* (*SD*). Total sleep time, TST; Sleep efficiency, SE; Slow wave sleep, SWS; Rapid eye movement, REM. Statistics tested differences between groups.

* indicates $p < .05$

** indicates $p < .01$