Sleep and rest facilitate implicit memory in a visual search task

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ABSTRACT

Several forms of learning have been demonstrated to show improvements with sleep. Based on rodent models, it has been suggested that replay of waking events in the hippocampus during sleep may underlie memory consolidation in humans. However, behavioral data for the role of sleep in human hippocampal-related memory have been inconsistent. To further investigate the role of sleep in hippocampal-mediated learning, we tested subjects in two sessions of a contextual cueing paradigm, a form of hippocampus-dependent implicit learning, separated by intervals of sleep, active wake, or carefully controlled quiet rest. Participants completed a visual search task, and unbeknownst to them, some search displays were occasionally repeated in the experiment. Contextual cueing was revealed by faster search speed on repeated trials (Old) than unrepeated ones (New), even though subjects were unaware of the trial repetition. Notably, performance in a second testing session was equivalent for participants who underwent quiet resting, daytime sleep, or nocturnal sleep between the two sessions. These four groups showed equivalent transfer of learning from Session 1. Notably, learning of New configurations in Session 2 was absent in the active wake group, but was equally strong among the other three groups. These results indicate that this form of hippocampal learning is independent of sleep, and vulnerable to proactive interference during active wake. They prompt a reevaluation of the hippocampal replay hypothesis as a general model of sleep-dependent learning.

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1. Introduction

Over the past 20 years, a substantial number of studies have shown a relationship between sleep and improvement on memory tasks (for review see Gais & Born, 2004; Hennevin, Huetz, & Edeline, 2007; Walker, 2008). Studies report performance increases after a bout of sleep compared with the same period of waking, implicating a slow, offline process during sleep that strengthens and enhances the memory trace (Stickgold, 1998). The majority of these studies have examined cognitive tasks that utilize non-declarative, procedural memory (e.g., knowing "how", learning actions, habits, perceptual and motor skills, and implicit learning) (Smith, 2001; Squire, 1992). Neural models of procedural memories suggest that learning occurs through a selective reweighting of neuronal synapses (Petrov, Dosher, & Lu, 2005; Saarinen & Levi, 1995) or through optimization of tuning functions (Raiguel, Vogels, Mysore, & Orban, 2006; Schoups, Vogels, Qian, & Orban, 2001) in neural networks within primary sensory areas, cerebellum, and basal ganglia (Molinari et al., 1997). Importantly, non-declarative memory has been anatomically dissociated from declarative memory by the fact that procedural learning does not rely on the medial

temporal lobe structures for consolidation (Squire, Knowlton, & Musen, 1993).

Some of the clearest evidence of sleep benefits for memory comes from perceptual learning in a texture discrimination task (Karni & Sagi, 1991). Karni and Sagi reported post-training improvement that is only evident several hours after training (Karni & Sagi, 1993), and the greatest amount of learning is shown after inter-session nocturnal sleep, specifically rapid eye movement (REM) sleep (Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994). Extending these findings, researchers demonstrated that: (1) improvement in performance on the texture discrimination task requires nocturnal sleep that lasts for at least 6 h (Stickgold, James, & Hobson, 2000; Stickgold, Whidbee, Schirmer, Patel, & Hobson 2000); (2) 60–90 min of daytime sleep also produces retinotopically-specific learning (Mednick, Nakayama, & Stickgold, 2003); (3) primary visual areas show increased fMRI BOLD signals after sleep, which correlate with performance improvement (Schwartz, Maquet, & Frith, 2002; Yotsumoto, Watanabe, & Sasaki, 2008). Other procedural learning paradigms that have shown performance improvement with sleep include visuo-motor learning (Gais et al., 2008; Maquet, 2004), perceptual learning (Mednick, Cai, Kanady, & Drummond, 2008; Mednick, Drummond, Boynton, Awh, & Serences, 2008; Plihal & Born, 1997, 1999), motor skills (Laureys, Peigneux, Perrin, & Maquet 2002; Mednick, Cai, et al., 2008;

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Mednick, Drummond, et al., 2008; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002), and implicit memory (Plihal & Born, 1997, 1999).

Until recently, the relationship between sleep and declarative memory had not been well examined. Declarative memories are the consciously accessible memories of fact-based information (i.e. knowing "what", in terms of events, places, and general knowledge) (Tulving, 1983). Neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe (Eichenbaum, 2000). In contrast with "enhancement" models of procedural memory, traditional declarative memory consolidation models involve stabilization and protection of memories from interference. Memories are formed and maintained by long-term potentiation in the hippocampus, but are also vulnerable to being overwritten by subsequent induction of LTP in the formation of newer memories (Wixted, 2004). Thus, memory traces are not enhanced by processes occurring during sleep, per se, but rather sleep is a period of reduced interference.

Consistent with the *interference* model, studies have shown that non-REM (NREM) sleep, a period of suppressed LTP, facilitates declarative memory compared with wake and REM sleep (Barrett and Ekstrand, 1972; Fowler, Sullivan, & Ekstrand, 1973; Peigneux et al., 2004; Plihal & Born, 1997, 1999; Takashima et al., 2006), (for review, see Stickgold, 2005). The dampened brain state of NREM sleep may reduce the likelihood of retroactive interference of information learned prior to sleep. Thus, studies that compare periods of NREM to equivalent periods of wake or REM, both periods of high LTP-like activity in the brain, may find retroactive facilitation of prior experiences (Wixted, 2004). In other words, NREM sleep may produce improved performance compared to an active wake group or REM due to an absence of LTP-induced interference during the consolidation phase. Many nocturnal sleep studies, however, are confounded by fatigue effects of sleep deprivation, circadian effects on memory performance, and interference effects on the waking control group. More recent studies have attempted to address the first two mentioned confounds through the use of extensive control groups for time of day effects (Ellenbogen, Payne, & Stickgold, 2006; Gais, Lucas, & Born, 2006) or by enhancing slow wave sleep through electrical stimulation (Marshall, Molle, Hallschmid, & Born, 2004). These studies have also found support for a relationship between NREM sleep and increased medial temporal lobe memory processing. Until now, however, interference effects have not been well controlled.

Since the mechanisms underlying consolidation for declarative and non-declarative memories are still unknown, further clarification of the relationship between medial temporal lobe memory processing and sleep would be useful. We investigate the effect of sleep on learning in an implicit visual learning task that has been shown to rely on the hippocampus and surrounding medial temporal lobe area. In this task, observers search for a "T" among "L" distractors. Throughout an individual session and unbeknownst to the observer, some of the search displays are occasionally repeated. These trials provide an opportunity for participants to learn the association between the repeated display configuration and the target's location. Previous studies have shown that participants show faster response times to these repeated displays (*Old* condition) than to displays involving random configurations (*New* condition). The advantage in the *Old* condition is known as a contextual cueing effect (Brady & Chun, 2007; Brockmole, Castelhano, & Henderson, 2006; Brockmole & Henderson, 2006; Chun & Jiang, 1998; Kunar, Flusberg, Horowitz, & Wolfe, 2007), since the display configuration provides a context for locating the target. Interestingly, learning and memory in this task have been demonstrated to be implicit (Chun & Jiang, 1998, 2003) (but see Weinstein & Shanks, 2008). Participants are at chance in distinguishing Old from New configurations in an explicit recognition task, even though response times present clear differences between the conditions. Furthermore, brain-lesion studies and fMRI studies showed that this implicit learning requires the hippocampus and surrounding medial temporal lobe areas. Amnesics with medial temporal lobe lesions were able to show an overall improvement in the visual search task. However, these patients showed no difference between Old and New trials in their response time (Chun & Phelps, 1999). Although the exact brain area subserving the contextual cueing effect is unclear; both the hippocampus specifically (Greene, Gross, Elsinger, & Rao, 2007) and the medial temporal lobe generally (Manns & Squire, 2001) have been implicated.

The contextual cueing effect has been shown to be highly robust with its effect lasting for up to a week (Jiang, Song, & Rigas, 2005), however the effect of sleep on contextual cueing has never been examined. One may expect that sleep would enhance implicit contextual cueing compared to wake due to a number of different prior findings including implicit and declarative memory enhancement with sleep. To test this hypothesis, we compared performance on the contextual cueing task before and after a nap or an equal period of wake. Importantly and in contrast to past studies, we used two wake groups: (1) a quiet-rest group that relaxed in a comfortable chair for 90-min with EEG-monitoring, in order to reduce interference effects that naturally occur during normal waking, and (2) an active wake group that went about their day, as a "typical" control comparison group. According to the sleep-enhancement hypothesis, participants with intervening sleep should show increased implicit memory of the Old configurations during the second session compared with the no-nap groups. Specifically, learning acquired from the first session should show more robust transfer to the second session. However, according to the interference model, when interference effects are controlled, medial temporal lobe memory consolidation in the contextual cueing paradigm would not benefit more from a period of sleep than from quiet rest. However, the active wake group would not show the same magnitude of contextual cueing between Sessions 1 and 2 due to waking interference. Finally, in a follow-up experiment we added a nocturnal sleep control to corroborate the nap group results.

2. Methods

2.1. Participants

Seventy four volunteers from the University California, San Diego, and 38 volunteers from the University of Minnesota took part in the study in exchange for payment or course credits. All participants were between ages 18–39 with normal or correct to normal vision and no personal history of neurological, psychological or other chronic illnesses. Participants gave informed consent to participate in the experiment, which was approved by the institutional review boards of the University of California, San Diego and University of Minnesota.

2.2. Equipment

Participants were tested individually in a normally lit room and sat unrestricted at about 57 cm from a 17″ monitor. The experiment was programmed with the psychophysics toolbox (Brainard, 1997; Pelli, 1997) implemented in MATLAB (www.mathworks.com).

3. Study procedures

3.1. Experiment 1

Three groups of 28 participants each took part in the first experiment. Participants maintained a sleep schedule for 1 week prior to

the study. For seven nights prior to the study, participants were instructed to get an average of 7 h of sleep each night. Participants filled out sleep diaries and wore actigraphs as subjective and objective measures of sleep–wake activity. Participants were restricted from consuming caffeine and alcohol 24 h prior to and during the experimental day.

The study timeline was as follows: At 09:30 AM, participants were administered the contextual cueing task. Task duration was approximately 50 min. Afterwards they were free to go about their business between test and nap sessions. The Active Wake Group was asked to return for the afternoon testing session and to avoid sleep and caffeine during that time. At 1 PM, participants in the nap and quiet rest conditions returned and were randomly assigned to a nap or a no-nap group. All participants were fitted with standard monitors for polysomography and were in bed by 1 PM. Sleep stages and nap or non-nap duration was visually monitored and scored in real time by trained sleep technicians. Non-nappers sat in a comfortable chair with EEG monitoring and listened to instrumental, classical music. Sleep technicians were alerted if their brainwaves indicated that they were falling asleep. Participants got out of the bed or chair after 90-min of sleep or 2-h in bed, whichever came first. Sleep during the nap in minutes (average and standard error): Total Sleep Time: 72 (3.50); Sleep Latency: 8 (.91); Stage 1: 5 (1.09); Stage 2: 29 (2.33); Slow Wave Sleep: 25 (2.96); Rapid Eye Movement: 13 (2.7). At 5 PM, participants were retested on the contextual cueing task.

3.2. Experiment 2

Experiment 2 was a nocturnal sleep control that was conducted to corroborate the nap results. Session 1 was given on Day 1, 28 new participants slept for at least 6.5 h and then Session 2 was performed 24 h later. All other aspects of the studies were identical.

3.2.1. Visual search task

Each search display contained 12 items (each subtended $1.5° \times 1.5°$): one target and 11 distractors. The items were randomly positioned and slightly jittered in an invisible 8×6 matrix that subtended $24° \times 18°$ (the position of each item was slightly jittered within to minimize co-linearity). Each quadrant contained three items. The target was a T stimulus rotated 90° to the right or to the left. Participants pressed one of the two keyboard keys corresponding to whether the bottom of the T was pointing to the right or to the left. The distractor stimuli were L shapes presented randomly in one of four orientations (0°, 90°, 180°, or 270°). The target was equally and randomly chosen on each trial, so that the identity of the target (right or left T) and its corresponding response (right or left key press) did not correlate with target location or the spatial configurations. Each trial started with a small white fixation dot (0.36° × 0.36°) appearing at the center of the screen for 500 ms, followed by the search array. Participants searched for the target and pressed a corresponding key as soon as possible upon detection. They pressed the N key if the target was pointing left, and the M key if it was pointing right. The response cleared the display with a blank screen, and a feedback was given in the form of a green plus (500 ms) or a red minus sign (2000 ms). Participants pressed the space bar to initiate each block of 24 trials in Session 1 and 36 trials in Session 2, which constituted an experimental block.

Each session began with instructions followed by a practice block of 24 trials to familiarize participants with the task and procedure. The spatial configurations used in practice were not used in the actual experiment. Participants were not informed that the spatial configurations of the stimuli in some trials would be repeated, nor were they told to attend to or encode the global array. They were also not warned about the recognition test at the end of

Session 2. They were simply given instructions on the visual search task procedure and shown sample displays of how the targets and non-targets looked. It was stressed that they should respond as quickly and as accurately as possible.

3.2.2. Session 1

Session 1 consisted of two conditions (Old and New, Fig. 1 left) randomly intermixed in each of 20 blocks. The Old set of stimuli consisted of 12 randomly generated unique configurations that were repeated across blocks, each appearing once per block. A target, a randomly chosen left or right rotated T, always appeared in the same location within a given configuration, so the configuration was predictive of the target location (but not target identity or motor response). The New set consisted of 12 different configurations that were newly generated for each block to serve as a control baseline. To control for the repetition of target location, the locations of the target in the New set were also repeated from block to block. That is, the target appeared equally often in 24 possible locations throughout the experiment: 12 target locations were used in the Old configurations, and the other 12 were used in the New configurations. In addition, each condition contained an equal number (3) of target locations in each of the four quadrants. The distractor locations in each configuration were randomly sampled from all possible locations including target locations used in other configurations.

3.2.3. Session 2

Session 2 was identical to Session 1 except for the addition of a new learning condition (Fig. 1 right). That is, the 12 Old displays used in Session 1 were also repeated for Session 2. Likewise, a fresh crop of 12 New displays were randomly generated for each block. To examine the effect of new learning, we generated a novel set of new displays prior to Session 2 and repeated these across the 20 blocks in Session 2. These will be referred to as repeated-New displays. By comparing repeated-New with Old displays repeated from Session 1, we can factor out any effects of learning that occurred within the second session. If a difference exists between the repeated-New and Old displays, this must be due to prior exposure to the Old displays in the first session.

3.3. Explicit recognition test

Participants' explicit memory was tested at the end of Session 2 in a recognition test. Participants were presented with 36 search configurations one at a time and were asked to report whether they have seen the display in the main experiment or this is a new display. The explicit recognition test consisted of three types of displays: 12 Old displays, which were repeated throughout
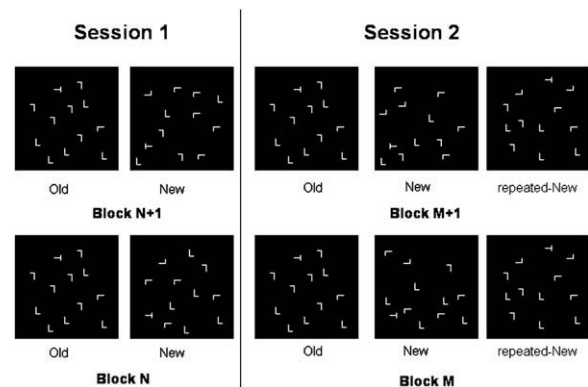

Fig. 1. Schematic illustration of trial conditions (not to scale). Trial conditions were intermixed within a block. Note that the Old configurations were identical across Session 1 (left) and Session 2 (right).

Sessions 1 and 2; 12 repeated-New displays, which were repeated throughout Session 2 only; and 12 New displays, which were completely novel except that the target location was the same as the New displays in the main experiment. Only accuracy was emphasized in this task.

4. Results Experiment 1

4.1. Accuracy

Visual search accuracy was over 98% in all conditions (Fig. 2). In Session 1, accuracy was unaffected by search *condition* (Old, New), *group* (nap, rest, active wake), or their interaction, all F's < 1. In Session 2, there was a main effect of group on accuracy, $F(2, 81) = 3.59$, $p < .05$, $\eta_p^2 = .08$, driven primarily by lower accuracy in the rest group compared with the nap group ($p < .05$) and the active wake group ($p < .08$). No other effects were significant (F's < 1). Because accuracy did not interact with any other factors, the accuracy effect across groups cannot account for differences in contextual cueing in RT reported below.

In the RT analysis, we excluded incorrect trials and trials whose RT exceeded three standard deviations above and below each participant's mean in each condition. The RT outlier trimming procedure eliminated less than 1.55% of trials. Because only 12 trials per condition were tested in each training block, there was a considerable amount of noise in the block data. We therefore binned data from four adjacent blocks to reduce statistical noise (Chun & Jiang, 1998). The 20 training blocks were binned into five epochs. Fig. 3 shows visual search RT as a function of epoch and experimental condition across Sessions 1 and 2, for the nap, quiet rest and active wake groups separately.

4.2. Session 1 RT: Old vs. New

A repeated-measures ANOVA on condition (Old, New) and Epochs (1–5) as within-subject factors and group (nap, quiet rest, active wake) as between-subject factor was conducted. Search was faster as the experiment progressed, leading to a significant main effect of epoch $F(4, 324) = 146.9$, $p < .01$, $\eta_p^2 = .65$, reflecting general, procedural learning. In addition, search was faster on Old displays than New displays, $F(1, 81) = 8.99$, $p < .01$, $\eta_p^2 = .1$. Importantly, the interaction between epoch and condition was also significant, $F(4, 324) = 9.22$, $p < .01$, $\eta_p^2 = .1$, revealing a contextual cueing effect. RT was faster in the Old condition than the New condition as the experiment progressed, suggesting that subjects had learned from the repeated presentation of Old displays. The three

Fig. 2. Mean accuracy of the rest, nap and active wake groups in the different sessions and experimental conditions. Error bars show standard error of the mean.

groups did not differ in their overall RT, $F < 1$, neither did group interact with condition, or with condition by epoch, both Fs < 1. Thus, the nap, quiet rest and active wake groups were comparable in Session 1; all of them showed a contextual cueing effect.

4.3. Session 2 RT: Old vs. New

After quiet rest, nap, or active wake periods of equal durations, the three groups were tested again in Session 2. In the second session, we tested participants in New displays, as well as repeated displays that were the same as Session 1's Old displays (the Old condition), and newly generated displays that repeated in Session 2 (the repeated-New condition). We first concentrate on the comparison between New and Old conditions. This difference reflected both the retention of learning from Session 1 and the additional learning in Session 2. A repeated-measures ANOVA on condition (Old, New) and Epochs (6–10) as within-subject factors and group as between-subject factor found significant main effects of epoch $F(4, 324) = 55.44$, $p < .01$, $\eta_p^2 = .41$, and condition, $F(1, 81) = 53.06$, $p < .01$, $\eta_p^2 = .40$. The interaction between epoch and condition was not significant, $F(4, 324) = 1.46$ $p > .21$. In other words, the additional five epochs of training did not seem to further increase the size of contextual cueing benefit obtained from Session 1. The Old condition was already faster than the New condition in the first epoch of the second session (Epoch 6 in Fig. 2), $F(1, 81) = 16.95$, $p < .01$, $\eta_p^2 = .17$, and this effect did not interact with the quiet rest, active wake and the nap groups, $F < 1$. In fact, the group factor did not significantly affect RT in the main effect or any interaction effects, all p's > .25. Thus learning of the Old displays acquired from Session 1 appeared to be retained in Session 2, and the retention was largely independent of the activity subjects underwent (quiet rest, nap, or active wake) between the two sessions.

A direct comparison across the two sessions revealed a significant interaction between session and condition, in that contextual cueing (Old vs. New) was numerically larger in Session 2 than Session 1, $F(1, 81) = 5.15$ $p < .05$, $\eta_p^2 = .06$. This difference, however, was driven primarily by the lack of contextual cueing at the beginning of Session 1. The magnitude of contextual cueing effects was comparable between the last two epochs of Session 1 and the first two epochs of Session 2, $F(1, 81) = 1.38$, $p > .24$.

4.4. Learning in Session 2: New vs. repeated-New

In addition to the Old displays from Session 1, we also introduced New displays at the beginning of Session 2 and repeatedly presented these displays. Despite the potential of proactive interference from Session 1's learning, participants were overall able to learn to search faster on these newly repeated displays. In Session 2, a repeated-measures ANOVA of condition (New vs. repeated-New), Epochs (6–10), and group (nap, quiet rest, active wake) revealed a significant main effect of epoch, $F(4, 324) = 50.24$, $p < .01$, $\eta_p^2 = .38$, and interaction of condition by epoch, $F(4, 324) = 2.45$, $p < .05$, $\eta_p^2 = .03$. The main effect of condition was not significant, $F < 1$.

Notably, the group manipulation had a significant influence on the acquisition of new contextual cueing in Session 2, $F(2, 81) = 4.02$, $p < .05$, $\eta_p^2 = .09$. While both the *rest* and *nap* groups showed a contextual cueing effect (New slower than repeated-New), p's < .09, the *active wake* group revealed no contextual cueing. If anything, RT in the repeated-New condition was numerically slower than that in the New condition for the *active wake* group. A direct comparison between the last three epochs of Sessions 1 and 2 and Condition (Old (repeated-New) vs. New) revealed no significant interaction in the nap and rest groups (p's > .17) suggesting that contextual cueing (for newly repeated displays) was comparable across sessions in these two groups. In contrast, new learning
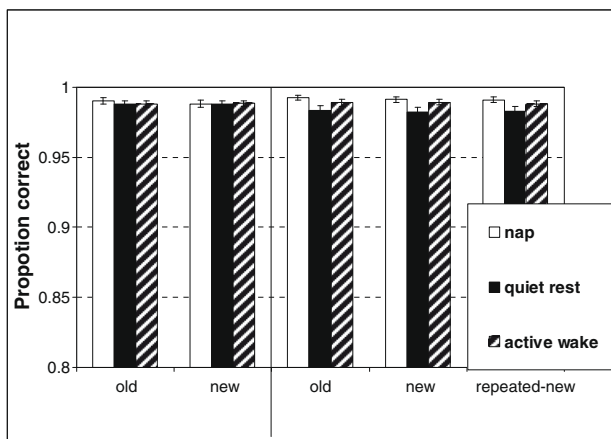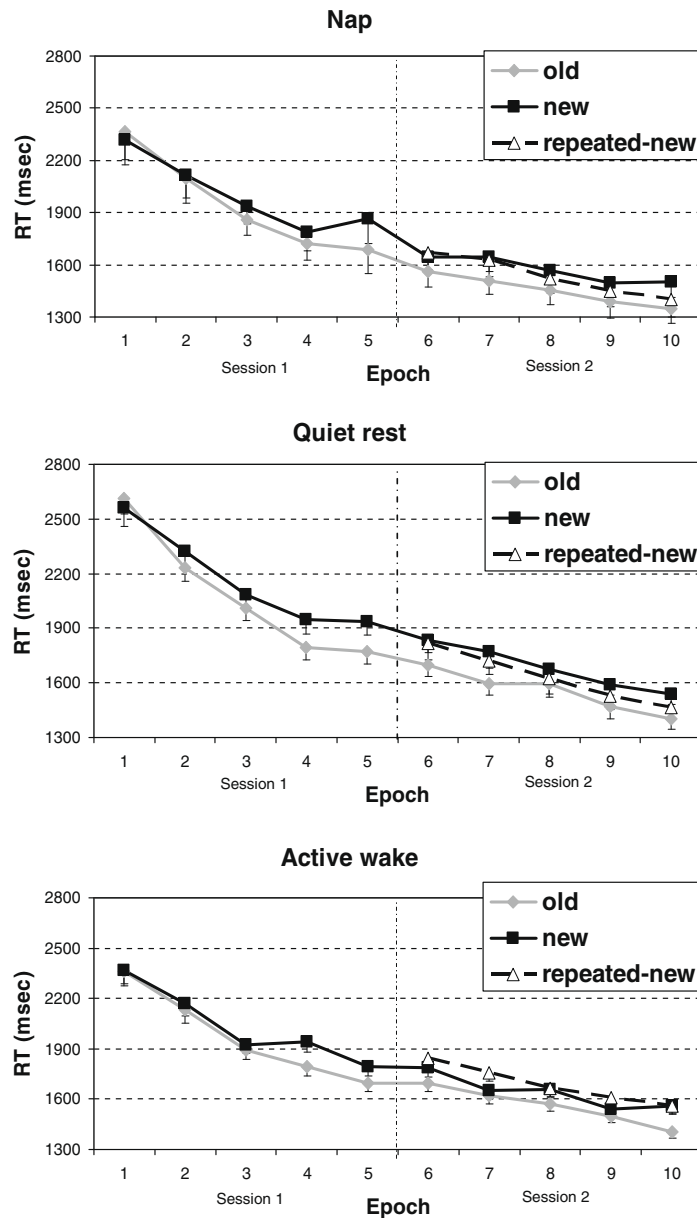
Fig. 3. Visual search RT as a function of epoch (Session 1: Epochs 1–5, Session 2: Epochs 6–10) and experimental condition for the nap, rest and active wake groups. Error bars show standard error of the mean.

(acquired in Session 2) was significantly smaller than that found in Session 1 in the active wake group, $F(1, 27) = 5.79$, $p < .05$, $\eta_p^2 = .18$.

The similarity in learning between the nap and quiet-rest group suggests that sleep is not necessary for the retention of Old learning or for the acquisition of New learning. But difference in learning between the active wake group and the other two groups suggests that interference is a critical factor in blocking the acquisition of new learning. The implications of these results are presented in the discussion section.

4.5. Session 2 RT: Old vs. repeated-New

A direct comparison between the Old condition (trials repeated across both sessions) and the repeated-New condition (trials repeated across Session 2 only) revealed a significant main effect of condition, $F(1, 81) = 29.08$, $p < .01$, $\eta_p^2 = .26$ as search RT was faster on displays repeated across both sessions than on displays repeated only in the second session. This difference was not affected

by the group manipulation ($F < 1$) and appeared to diminish as Session 2 progressed, hinting at a "floor" (or asymptote) as learning progressed. The interaction between condition and epoch, however, was only marginally significant, $F(4, 324) = 2.29$, $p = .06$. The asymptote pattern is consistent with other kind of procedural learning in visual search (Logan, 1988).

4.5.1. Explicit recognition

Explicit recognition data were obtained from 16 participants in the *quiet-rest* group, 28 participants in the active wake group and 18 participants in the *nap* group. Fig. 4 shows the proportion of identifying displays as "Old", as a function of display type and group. A repeated-measures ANOVA with these factors showed that participants were no more likely to identify a repeated display (e.g., Old, or repeated-New) as "Old" than to identify a novel display (New) as "Old", $F(2, 118) = 1.8$, $p > .17$. The group (nap, rest, active wake) factor did not affect the pattern of results in the explicit recognition test, F's < 1. Thus, there appeared to be dissociation
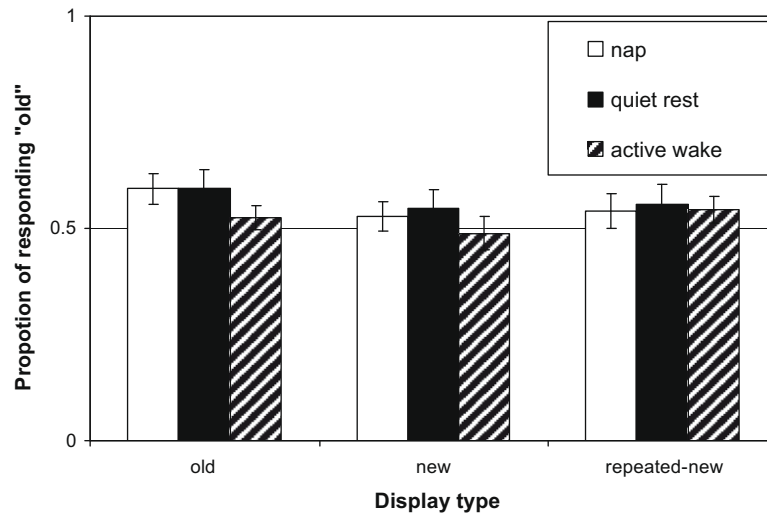
Fig. 4. Proportion of identifying displays as "Old" as a function of display type and group. Error bars show standard error of the mean.

between participants' visual search behavior (sensitive to display repetition) and their explicit recognition of the repetition.

4.5.2. Discussion

Experiment 1 showed once again that performance in a visual search task benefits from display repetition (Chun & Jiang, 1998). Although participants were unable to explicitly recognize the repeated trials (Chun & Jiang, 2003), search was faster in the Old than in the New conditions, and this benefit survived an intervention period (Chun & Jiang, 2003; Jiang et al., 2005). Importantly, we found no support for the suggestion that sleep enhances implicit memory traces for this medial temporal lobe-dependent task. That is, search latency and visual learning was unaffected by the type of the intervention.

Interestingly, only the nap and quiet rest conditions were able to learn new configurations in Session 2, whereas the active wake group failed to learn new, repeated configurations. The impaired New learning observed here is consistent with models of proactive interference (Wixted, 2004), such that prior information (i.e. waking experience) can interfere with learning of new information (i.e. new contextual cues). This finding is in accord with the idea that interference-reduction might underlie some of the sleep effects reported in the past (Wixted, 2004). When a sleep group was compared with a quiet-rest group that was carefully controlled to minimize possible interference, we found no evidence that sleep improves learning and memory.

Before accepting the conclusion that sleep does not enhance implicit memory of Old configuration, we need to rule out an alternative explanation. Specifically, one might argue that the lack of any sleep effect might be the result of a "weak" sleep manipulation. That is, the 90-min nap may be insufficient to reveal improvement in learning. Although past studies have shown that 90-min nap is enough to show robust learning effects (Mednick et al., 2003; Takashima et al., 2006), we tested additional 28 participants who had nocturnal sleep between sessions.

5. Results Experiment 2

5.1. Accuracy

Visual search accuracy was above 98.8% in the *Old* and *New* trials of Session 1 and above 99% in the *Old*, *New* and *repeated-New* trials of Session 2. The four groups – nap, quiet rest, active wake and nocturnal sleep – were comparable in their accuracy in Session

1. In Session 2, there was a main effect of group on accuracy, $F(3, 108) = 3.4$, $p < .05$, $\eta_p^2 = .09$. Accuracy in the nocturnal sleep condition was comparable to that in the *nap* and *active wake* groups (p's > .4), but was higher in the nocturnal sleep condition than the quiet-*rest* group ($p < .01$). Importantly however, condition (Old, New, repeated-New) did not affect any of the accuracy effects (all F's < 1). In the RT analysis we excluded incorrect trials as well as trials exceeding three standard deviations above and below each participant's mean of each condition (1.3%).

Fig. 5 shows the averaged RT for Sessions 1 and 2 as a function of epoch and display type in the nocturnal-sleep group. A repeated-measures ANOVA of Sessions (1 and 2), condition (Old, New) and Epochs (1–5) revealed significant main effects of all of these factors (p's < .01): participants were faster in Session 2 than Session 1, and faster searching through repeated displays than New displays, and were faster as learning progressed in each session. In addition, there was a significant interaction between epoch and session, $F(4, 108) = 21.87$, $p < .01$, $\eta_p^2 = .45$, as search speed gradually reached floor (Logan, 1988), and a borderline interaction between condition and epoch, $F(4, 108) = 2.37$, $p = .06$, $\eta_p^2 = .08$, as contextual cueing was gradually developed. No other significant effects were found, p's > .16.

What about the acquisition of New learning in Session 2's repeated-New condition? Note that because the nocturnal-sleep group did not take a nap or quiet rest after Session 1, interference should have occurred on Day 1. However, the nocturnal sleep was apparently sufficient to reset the system into full capacity to acquire New learning. Specifically, in Session 2, there was a significant contextual cueing effect, reflected by a significant interaction between condition (repeated-New vs. New) and epoch), $F(4, 108) = 3.54$, $p < .01$, $\eta_p^2 = .12$. The new learning in Session 2 was similar to a previous study involving nocturnal sleep showed new learning in each of five sessions tested on five separate days (Chun & Jiang, 2003).

Finally, the nocturnal-sleep group showed no evidence of explicit learning. The proportion of identifying displays as "Old" was if anything, higher for *New* displays compared to *Old* and *repeated-New* displays (51.28%, 58.59% and 52.58%, respectively, $F(2, 50) = 2.77$, $p > .07$).

5.2. Between experiments analysis

An overall analysis of Sessions (1 and 2), condition (Old, New), Epochs (1–5) and group (rest, nap, active wake, nocturnal-sleep) showed the same pattern of results as the main experiment. Search
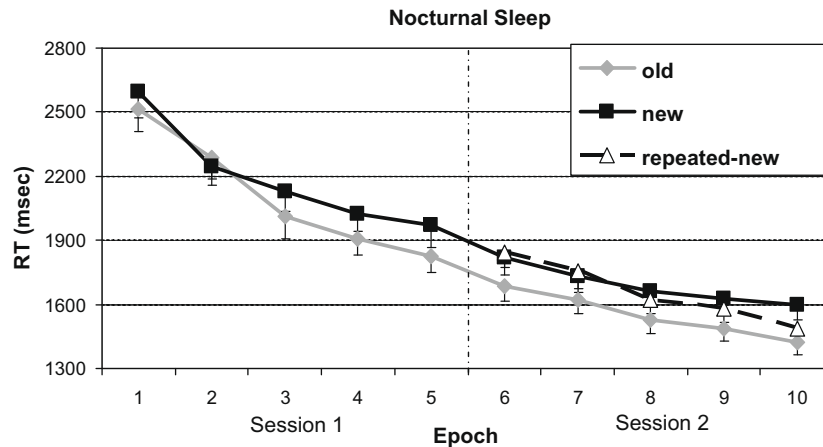
Fig. 5. RT data from the nocturnal-sleep group as a function of epoch (Session 1: Epochs 1–5, Session 2: Epochs 6–10) and experimental condition. Error bars show standard error of the mean.

was faster both between sessions ($p < .01$), and across epochs, ($p < .01$). The interaction between session and epoch was significant, ($p < .01$). Contextual cueing was observed as a main effect of condition, ($p < .01$) with Old displays responded to faster than New displays. There was no interaction between group and any of the contextual cueing effects, all p's > .19.

6. Conclusions

We investigated the benefit of sleep, both a nap and a night, on implicit, associative memory in a contextual cueing paradigm (Chun & Jiang, 1998; Chun & Phelps, 1999). Our results show that learning a target location and its associated configuration increases with training, but does not improve during an offline process. Compared with quiet rest and active wake groups, neither a short 90 min nap nor a 6.5 h night of sleep produced increased learning between training and test. This finding of no sleep effect makes an important contribution to our understanding of how we differentiate mechanisms of memory consolidation that rely on sleep and those that do not. These data are particularly informative for discussions of sleep and medial temporal lobe processing, a brain area responsible for contextual cueing effect and implicated in a hypothesized mechanism of sleep-dependent learning (Chun & Phelps, 1999). Although we did not investigate brain activity during testing, prior studies have pinpointed both the hippocampus and surrounding medial temporal lobe structures as necessary for contextual cueing effect (i.e. amnesic patients with hippocampal damage (Chun & Phelps, 1999), patients with medial temporal lobe damage (Manns & Squire, 2001), and functional magnetic resonance imaging in healthy individuals (Greene et al., 2007)).

One of the leading hypotheses proposed as a mechanism for sleep-dependent memory consolidation implicates the medial temporal lobe as an essential component of the process (Peigneux, Laureys, Delbeuck, & Maquet, 2001; Rauchs, Desgranges, Foret, & Eustache, 2005; Smith, 1995; Stickgold, 2005). This hypothesis comes from animal studies that show offline replay of neural activity in medial temporal lobe regions during post-training sleep (Dave & Magoliash, 2000; Hoffman & McNaughton, 2002; Wilson & McNaughton, 1994). Similarly, increased neuronal synchronization and metabolic activity in specific brain areas have been reported in humans following learning tasks (Huber, Ghilardi, Massimini, & Tononi, 2004; Maquet, 2001; Maquet et al., 2003; Peigneux et al., 2003, 2004). A couple of studies have shown small but significant correlations between hippocampal replay and thalamocortical spindles and delta waves during sleep (Benington & Frank, 2003; Frank,

Brown, & Stanley, 2006). Although the vast majority of studies investigating sleep and learning support the neuronal replay hypothesis, there are some reasons to be skeptical of the relationship between replay and sleep-dependent memory consolidation.

Frank and Benington (2006) outline four compelling reasons why advancement of the neuronal replay hypothesis should progress with caution (Frank et al., 2006). First, reactivation itself is not a robust finding. It is observed only after extensive training of rodents on familiar tasks, it rapidly dissipates, and it makes up a small proportion of total recorded activity in sleep. Second, replay has been found to occur during post-training, quiet wakefulness as well as sleep. Therefore, if replay is a mechanism for memory, its occurrence is not dependent on sleep (Axmacher, Haupt, Fernandez, Elger, & Fell, 2008; Kudrimoti, Barnes, & McNaughton, 1999; Peigneux et al., 2006). Third, most positive findings are based on correlational studies that may not reflect an actual transmission of information between the hippocampus and cortical areas (Pelletier, Apergis, & Pare, 2004). Fourth, with the exception of some correlational findings in humans (Huber et al., 2004; Peigneux et al., 2004), there is little evidence that reactivation of waking neural activity or spontaneous sleep rhythms promote functionally important changes in circuits. Additionally, numerous studies show that memory consolidation can occur without sleep (Axmacher et al., 2008; Foster & Wilson, 2006; Hussain, Sekuler, & Bennett, 2008; O'Neill et al., 2006; Peigneux et al., 2006; Rickard, Cai, Rieth, Jones, & Ard, 2008; Vertes, 2004). Taken together with the present findings reporting a lack of sleep-dependent memory consolidation in a medial temporal lobe-dependent learning, these studies suggest that sleep may play a more limited role with respect to medial temporal lobe memory consolidation.

A traditional model of medial temporal lobe memory consolidation suggests that an offline process is required to stabilize memories, but this process does not require sleep, per se (Wixted, 2004). Instead, sleep or quiet wake affords the brain a period of quietude without LTP that allows mechanisms of consolidation to occur without interference from new memory processing. Prior sleep and medial temporal lobe memory studies (e.g., Clemens, Fabo, & Halasz, 2005; Plihal & Born, 1997; Tucker et al., 2006) frequently overlooked the interference effects in the waking control group. The importance of utilizing a proper control for sleep cannot be underestimated, as, in some cases, quiet rest has shown the same learning benefits as sleep. A recent study found that a quiet wake interval provided similar benefits for auditory tone sequence learning as a sleep interval, and both were better than the active wake interval (Gottselig et al., 2004).

The present study controls for interference effects by comparing both nap and nocturnal sleep conditions with quiet rest and active wake comparison groups. These data are consistent with and further refine the interference model by demonstrating a limit to the amount of medial temporal lobe learning available during active wake. We find that quiet rest or sleep is necessary for increasing the amount of associations between configurations and target locations that can be learned within a day. Active wake showed no learning of repeated-New configurations in Session 2. Future studies may address whether these results are indicative of a limited-capacity storage of the hippocampal memory system, and to what extent blocking of New learning is due to the lack of repetition of the configurations in Session 1 and/or the presence of the Old configurations in Session 2. The present results are more consistent with prior declarative memory studies that show decreases in interference in sleep groups rather than increased fidelity of the memory trace (Barrett & Ekstrand, 1972; Plihal & Born, 1997, 1999). Furthermore, our finding introduces the possibility that other reports of sleep-dependent memory improvement may be in part due to lack of proper quiet rest comparison groups. Indeed, future research should carefully manipulate rest period activities to disassociate an interference-reduction account from sleep-enhancement account of memory improvement.

Taken together, the current results demonstrate the robustness of the contextual cueing effect as a form of implicit learning and memory, and go further to show that learning in this paradigm is dependent on training and does not require an offline process for improvement. The amount of new learning in contextual cueing, however, does appear to depend on a period of "quiet time" for stabilization and consolidation, as learning of a new group of associations between configurations and target locations in Session 2 were blocked in an active wake group. Investigating a range of memory processes and utilizing proper quiet rest control groups will further illustrate the underlying mechanisms of learning in the brain.

Acknowledgments

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