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Sleep Selectively Enhances Hippocampus-Dependent Memory in Mice

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Sleep has been implicated as playing a critical role in memory consolidation. Emerging evidence suggests that reactivation of memories during sleep may facilitate the transfer of declarative memories from the hippocampus to the neocortex. Previous rodent studies have utilized sleep-deprivation to examine the role of sleep in memory consolidation. The present study uses a novel, naturalistic paradigm to study the effect of a sleep phase on rodent Pavlovian fear conditioning, a task with both hippocampus-dependent and -independent components (contextual vs. cued memories). Mice were trained 1 hour before their sleep/rest phase or awake/active phase and then tested for contextual and cued fear 12 or 24 hr later. The authors found that hippocampus-dependent contextual memory was enhanced if tested after a sleep phase within 24 hr of training. This enhancement was specific to context, not cued, memory. These findings provide direct evidence of a role for sleep in enhancing hippocampus-dependent memory consolidation in rodents and detail a novel paradigm for examining sleep-induced memory effects.

Keywords: context, fear conditioning, Pavlovian, circadian, medial temporal lobe

A growing body of evidence suggests that sleep enhances consolidation of human memory. Several studies have found that sleep facilitates retention of declarative memory (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006; Ellenbogen, Payne, & Stickgold, 2006; Plihal & Born, 1999), and recently formed episodic memories can reportedly even be cued by an odor present during training to increase memory reactivation during slow-wave sleep (SWS) and improve subsequent memory retention (Rasch, Buchel, Gais, & Born, 2007) In one view, sleep-related memory reactivation may be the consolidation mechanism by which declarative memory is transformed from a hippocampus-dependent state to an independent state (Pavlides & Winson, 1989; Poe, Nitz, McNaughton, & Barnes, 2000; Squire & Alvarez, 1995). Here, we demonstrate, for the first time, sleep-related improvements specific to hippocampus-dependent memory for a rodent learning task with a well-defined neurobiology—Pavlovian fear conditioning (Anagnostaras, Gale, & Fanselow, 2001; Anagnostaras, Maren, & Fanselow, 1999; Gale et al., 2004).

In Pavlovian fear conditioning, a tone is paired with a shock in a novel environmental context. After training, rodents will exhibit fear when presented with the training tone or when returned to the training environment. This latter phenomenon, known as *contextual fear conditioning,* has garnered considerable interest in recent years because it is hippocampus dependent and has become a prominent rodent model of declarative memory (Anagnostaras et al., 2001). As with human declarative memory, over time contextual fear becomes independent of the hippocampus, as this memory becomes consolidated to neocortical structures (Anagnostaras et al., 1999; Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Maren, Aharonov, & Fanselow, 1997; Quinn, Ma, Tinsley, Koch, & Fanselow, 2008). This consolidation process is thought to reflect coordinated activity whereby fast-changing connections in the hippocampus initially subserve the memory and, over time, entrain slow-changing connections in the neocortex, at which time the hippocampus is no longer necessary to maintain the memory (Squire & Alvarez, 1995). The memory may also change in content during this period so that small bits of episodic memory become integrated into cohesive and permanent semantic knowledge (McClelland, McNaughton, & O'Reilly, 1995). In contrast, tone (cued) fear is independent of the hippocampus (Anagnostaras et al., 2001; Anagnostaras et al., 1999). Both contextual fear memory and cued fear memory depend on the amygdala for the lifetime of the rat (Gale et al., 2004).

Considerable indirect evidence suggests a role for sleep in hippocampus-dependent memory in rodents. In 1989, Pavlides and Winson (Pavlides & Winson, 1989) showed what appeared to be a neurophysiological correlate of memory processing during sleep. Hippocampal "place cells" that were active during maze running were more likely to be activated during subsequent REM and non-REM sleep, a phenomenon known as *neuronal replay*. Since then, similar results of replay during sleep have been observed (Qin, McNaughton, Skaggs, & Barnes, 1997; Wilson & McNaughton, 1994), and the temporal sequence of paired neuronal firing during wakefulness, arguably a neuronal trace of spatial memory, has also been found to be preserved in subsequent non-REM sleep (Skaggs & McNaughton, 1996). In addition to hippocampal neuronal replay, it has been asserted that the hippocampus and neocortex communicate during sleep by means of hippocampal-generated high frequency burst patterns (sharp waves or ripples;

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Buzsaki, 1989), which are temporally correlated with spindles in the medial prefrontal cortex during SWS (Siapas & Wilson, 1998). This is especially significant for the present study, as the hippocampus is the initial site of acquisition for contextual fear conditioning, whereas the medial prefrontal cortex is one site of permanent memory storage (Frankland et al., 2004; Quinn et al., 2008). Despite this evidence, to our knowledge, not a single study specifically demonstrates improved memory after sleep in rodents (Frank, 2006; Frank & Benington, 2006), although several studies demonstrate deficits in memory due to sleep deprivation or positive correlations between the intensity of sleep components and memory retention (Datta, 2000; C. Smith & Butler, 1982).

The most commonly used approach to examine behavioral effects of sleep on memory consolidation has been the sleep deprivation method. Earlier studies trained rodents on particular tasks and then deprived them of sleep by placing them on a rotating disk or on top of an inverted partially submerged flower pot over water (Bergmann et al., 1989; Fishbein, 1971; Murison, Ursin, Coover, Lien, & Ursin, 1982; Van Hulzen & Coenen, 1979). These methods of sleep deprivation have been criticized for their potentially stress-inducing effects (for reviews, see Horne & McGrath, 1984; Smith, 1985; Vertes & Eastman, 2000). Recent sleep deprivation studies have utilized an alternative, more benign approach, handling the subjects during the sleep phase; for example, Graves and colleagues (Graves, Heller, Pack, & Abel, 2003) found that mice that were handled for 5 hr during the sleep/rest phase exhibited some impairments in contextual fear conditioning. Although this may be suggestive that sleep is important for memory, there may be other explanations for the impairment. Indeed, even the more benign sleep deprivation method has been shown to induce health problems, such as stomach ulcerations (Murison et al., 1982) and increased serum levels of glucoccorticoids, which in turn have been shown to negatively affect cognition (Plihal, Krug, Pietrowsky, Fehm, & Born, 1996). It has been reported that long-term potentiation (LTP) is diminshed in hippocampal slice preparations from sleep-deprived rats and correlates with increased corticosterone levels (Campbell, Guinan, & Horowitz, 2002). Thus, although the rodent sleep deprivation literature is suggestive that sleep is important for memory consolidation, it is still unclear whether the crucial component is the lack of sleep or the deprivation methods itself that impairs consolidation.

The present study used a naturalistic method to examine whether Pavlovian fear conditioning is enhanced after a sleep/rest phase, as compared with an equivalent passage of awake/active time. In the fear conditioning literature, investigators often find lower levels of contextual memory 30 min after training, with an enhancement 24 hr after training that persists for long periods of time (Miller et al., 2002). We asked if sleep might play a role in this enhancement. We used 12- and 24-hr intervals to control for time passage and circadian effects, adapted from designs used to investigate human sleep and memory consolidation (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). It is critical to properly control for passage of time, as consolidation may simply be a time-dependent process. We also controlled for differences in circadian activity by selecting training and testing times within the transition intervals between rest and activity phases (Chaudhury & Colwell, 2002). Our findings suggest that sleep plays an important and selective role in contextual fear conditioning, whereby contextual memory was enhanced if tested after a sleep period. These findings provide compelling evidence of a role for sleep in hippocampus-dependent memory.

Method

Subjects and Materials

Sixty-seven hybrid C57BL/6Jx129T2SvEms/J (Crawley et al., 1997) male and female mice (approximately equivalent numbers of sexes, stock from the Jackson Laboratory, West Sacramento, CA) were balanced across groups. Mice were entrained to a 12-hr light:dark cycle 5 weeks before the experiment began and remained in those conditions for the duration of the experiment. Lights were automated to turn on at 9 a.m. and turn off at 9 p.m. They had unrestricted access to food and water. All experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of California, San Diego, Institutional Animal Care and Use Committee.

Fear Conditioning

Mice were trained 1 hr before their primary awake period (i.e., dark phase) for the Awake First conditions or were trained 1 hr before their main sleep period (i.e., light phase) for the Sleep First conditions. For the Awake First groups, the dark phase immediately followed training for a duration of 12 hr, in which then began the light phase, also for a duration of 12 hr. For the Sleep First group, the reverse occurred. The light phase began immediately after training for 12 hr, followed by 12 hr of darkness. In both groups, mice were tested 12 or 24 hr later for contextual and tone fear memories (see Figure 1). During training, mice were placed in a fear conditioning chamber (see *Conditioning Context*) and, after a 2-min baseline, were given three tone–footshock (tone: 2.8-kHz, 30-s, 85-dB; footshock: 2-s, 1.0-mA) pairings, each 1 min apart. After an additional 5 min, which served as an extended postshock freezing test, they were returned to their home cages. To test contextual memory, we placed the mice back in the original chamber (12 or 24 hr posttraining) for 2 min (Anagnostaras, Maren, Sage, Goodrich, & Fanselow, 1999). Mice were also tested for cued memory 1 hr later; they were placed in an alternate context (discussed later) for a 2-min baseline period, followed by presentation of the same three successive 30-s tones played during training, each separated by 30 s, now without shock. Freezing and gross movement were assessed for the entire training and testing periods using an automated algorithm (discussed later).

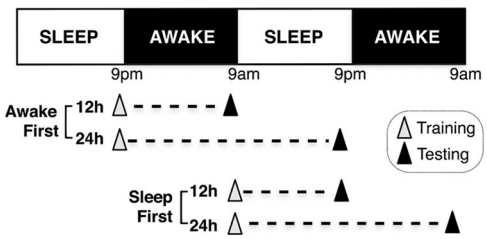

Figure 1. Study timeline. Mice were trained 1 hr before their awake/active phase (Awake First) or rest/sleep phase (Sleep First) and then tested for contextual and cued fear 12 or 24 hr later.

Conditioning Context

Four mice were tested concurrently in individual conditioning chambers housed in a windowless room. Each chamber (32 cm wide, 25 cm high, 25 cm deep) was located within a sound-attenuating chamber (63.5 cm wide, 35.5 cm high, 76 cm deep; Med-Associates Inc., Georgia, VT) and equipped with a speaker in the side wall, a stainless steel grid floor (36 rods, with each rod 2 mm in diameter and 8 mm center to center; Med-Associates Inc., Georgia, VT), and stainless steel drop pan. During each trial, chambers were scented with 7% isopropyl alcohol to provide a background odor, and background noise (65-dB) was provided by internal fans. Each sound-attenuating chamber was equipped with an overhead LED light source providing white and near-infrared light and an IEEE 1394 progressive scan video camera with a visible light filter (VID-CAM-MONO-2A; Med-Associates Inc., Georgia, VT) connected to a computer and video equipment in an adjacent room. Each chamber was connected to a solid-state scrambler providing AC constant current shock, and an audio stimulus generator controlled through an interface connected to a Windows computer running Video Freeze (Med-Associates Inc., Georgia, VT), a novel program designed for the automated assessment of freezing and motor activity. In results that will be published more fully elsewhere, computer- and human-scored data had a correlation of .971 and a linear fit of computer $= -0.007 + 0.974 \times$ human (for additional details, see, for e.g., (Anagnostaras, Josselyn, Frankland, & Silva, 2000; Shuman, Wood, & Anagnostaras, in press; Wood & Anagnostaras, 2008). Motor activity scores correspond roughly to the number of video pixels changing per second at 30 Hz; for this reason, they are presented as arbitrary units (au).

Alternate Context

For testing cued (tone) fear, the conditioning context was modified along several dimensions. White acrylic sheets were placed over the grid floor to provide a different sensory experience, and a black plastic, triangular tent translucent only to near-infrared light was placed inside each box, with each side of the triangle measuring 23 cm. Only near-infrared light was used, creating a completely dark environment visible only to the video camera. Between tests, the chambers were cleaned and scented with a 5% white vinegar solution.

Statistics

Data were entered into a general multivariate analysis of variance (MANOVA). After an omnibus comparison, we made group comparisons using the Wald test. The level of significance was set at $p < .05$.

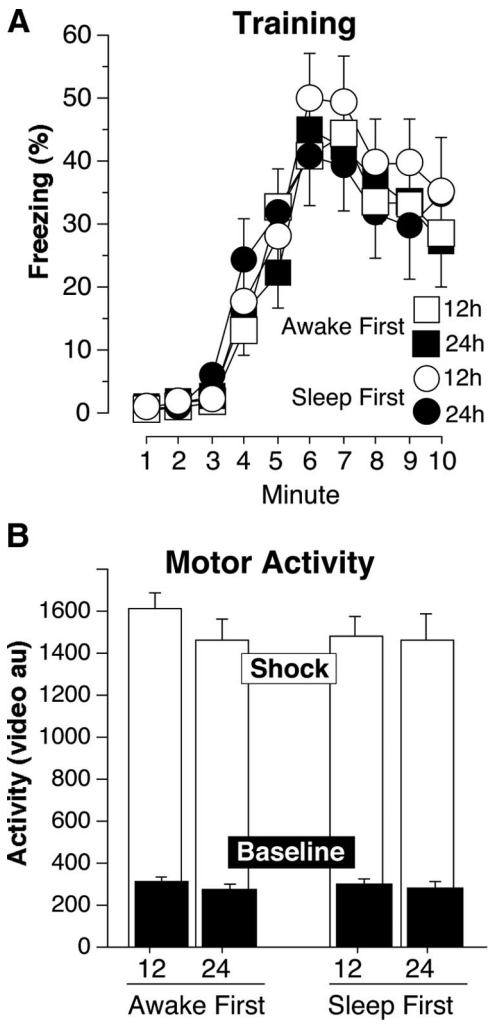

Figure 2. (A) Training. Mice were given fear conditioning either right before their sleep (Sleep First) or awake (Awake First) phase of the cycle. After a 2-min habituation period (Min 1–2), mice were given three tone–shock pairings (Min 2–5) and left in the chambers for an additional 5 min as an extended postshock freezing test. Freezing (mean percent time plus or minus standard error of the mean) is depicted for each minute of the training session. All groups exhibited good learning, and there were no group differences. (B) Motor activity. To assess any baseline differences in locomotor activity or shock reactivity due to time of day, we examined movement during the 2-min baseline before any shock and during the first 2-s shock on the training day. Computer-scored movement (mean arbitrary units plus or minus standard error of the mean) is depicted. All groups exhibited robust shock reactivity, and there were no group differences in terms of baseline (closed bars) or shock-elicited (open bars) activity.

Results

Mice were given fear conditioning either right before their awake/active (Awake First) phase or right before their sleep/rest phase (Sleep First) of the cycle. Although mice sleep in both the light and dark phases, they spend much more time sleeping in the light phase (65%) than in the dark phase (35%; Welsh, Richardson, & Dement, 1988). Data from the training session are shown in Figure 2. After a 2-min habituation period, mice were given 3 tone–shock pairings one min apart and left in the chambers for an additional 5 min, as an extended postshock freezing period. All groups exhibited good acquisition, and there were no differences among the groups (Figure 2A, Fs < 1, *ns*). To assess any baseline differences in locomotor activity or shock reactivity due to time of day, we examined computer-scored movement at 30 Hz during the 2-min baseline before any shock and during the first 2-s shock on the training day (Figure 2B; Anagnostaras et al., 2000; DeLorey et al., 1998). All groups exhibited robust shock reactivity compared

with the baseline (Fs > 9, ps $< .0001$), and there were no group differences in terms of baseline or shock-elicited activity (Fs < 2.1, *ns*). Thus, differences in fear conditioning could not be attributed to differences in locomotor activity or in shock reactivity.

Twelve or 24 hr after training, mice were given a 2-min contextual fear test followed immediately by a 5-min cued fear test (12 hr posttraining: Awake First, $n = 16$; Sleep First, $n = 20$; 24 hr posttraining: Awake First, $n = 16$; Sleep First, $n = 15$; see Figure 3A). An overall multivariate analysis of variance (MANOVA; four levels of group, with context and tone tests) revealed a Group × Test Type interaction, $F(6, 378) = 2.26$, $p < .05$; so planned comparisons were made. For the contextual fear test, mice in the Awake First group failed to exhibit robust memory when tested 12 hr later, compared with those in the Sleep First group, who were also tested 12 hr later but had robust memory, $F(1, 34) = 4.28$, $p < .05$; or when compared with those in the Awake First group who still had the opportunity to sleep by being tested 24 hr later, $F(1, 30) = 6.83$, $p = .01$. That is, a sleep phase enhanced contextual memory, and this effect was not due simply to passage of time. The Awake First and Sleep First groups tested 24 hr later did not differ from each other or from the Sleep First group tested 12 hr later (Fs < 1, *ns*). One hour after the context test, mice were brought to a novel context for a 5-min cued fear test. After a 2-min baseline period, the training tone was presented three times across 3 min. All groups exhibited robust tone-elicited freezing, and there were no group differences during the baseline or presentation of the three tones (for the baseline, or average of the three tones, or baseline subtracted from tone, all comparisons, Fs < 1, *ns*). Cued fear is depicted in Figure 3B as freezing during baseline subtracted from the average of freezing to the three tones. Overall, the design revealed a remarkably selective effect of the passage of a sleep period; contextual fear was impaired if tested before a sleep period and enhanced after a sleep period, but cued fear was unaffected by sleep.

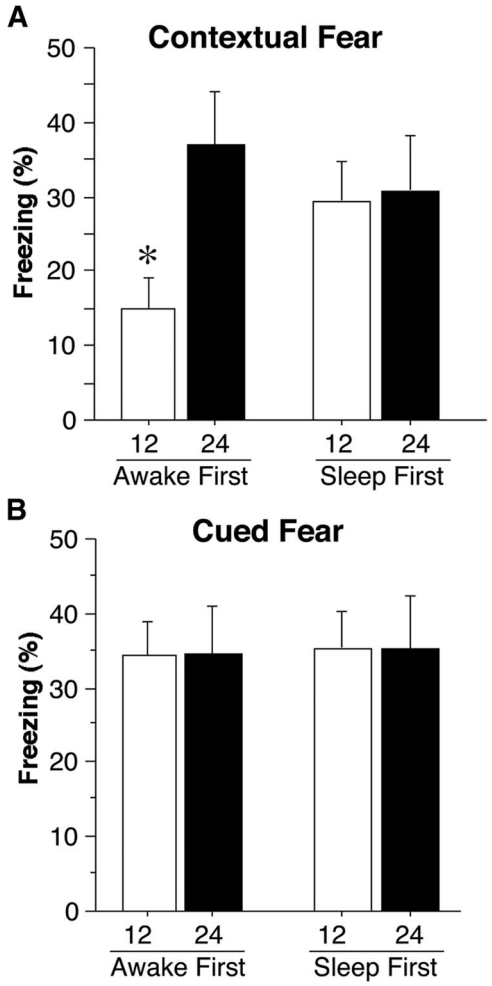

Figure 3. (A) Contextual fear. Twelve or 24 hr after training, mice were given a 2-min contextual fear test. Freezing (mean percent time plus or minus standard error of the mean) for the 2-min test is depicted. Mice in the Awake First group failed to exhibit robust memory when tested 12 hr later, compared with those in the Sleep First group who were also tested 12 hr later but had robust memory, or when compared with those in the Awake First group who still had the opportunity to sleep by being tested 24 hr later That is, a sleep phase enhanced memory, and this effect was not due simply to passage of time. (B) Cued fear. One hour after the context test, mice were brought to a novel context for a 5-min cued fear test. After a 2-min baseline period, the training tone was presented three times across 3 min. Cued fear is depicted as freezing (mean percent time plus or minus standard error of the mean) during the baseline subtracted from the average of freezing to the three tones. There were no group differences in baseline or cue-elicited fear.

Discussion

We found that the passage of a sleep/rest phase enhanced contextual fear memory regardless of whether the sleep phase occurred immediately after training or 12 hr later. This enhancement was specific to context memory, as there were no differences between groups for cued memory. It is important to note that the group differences in freezing during the context test cannot be explained by circadian variability, as there were no group freezing differences for the cued test, which occurred at approximately the same time. This suggests that the contextual memory deficit in the 12-hr Awake First group was not due to the inability to express this memory. This group also controls for sleep, which may have occurred during the awake/active phase (Welsh et al., 1988). Despite 35% of sleep occurring during the dark (active/awake) phase, this sleep was not sufficient to enhance contextual memory, because the 12-hr Awake First group had very poor contextual memory. This suggests that whatever sleep that did occur in the dark phase was insufficient for consolidation. Although this could simply be due to the lower quantity of sleep during the dark phase, there may also have been a difference in the quality of sleep (Welsh et al., 1988). Taken together, our findings also suggest a more active role for sleep in consolidation. If consolidation relied only on the passage of time, then the 24-hr groups would outperform the 12-hr groups, regardless of sleep. As observed, this was not the case. The groups that had a sleep phase outperformed the group that had only an awake phase, regardless of the retention interval, suggesting that consolidation is not strictly time dependent.

One surprising finding was that contextual fear conditioning apparently decreased from training to 12 hr and then increased by 24 hr after training. One of our original motivations for the study was anecdotal evidence that studies examining short-term memory

(e.g., 30 min) often found fear levels lower than those found in studies of long-term memory (e.g., 24 hr; Miller et al., 2002). A review of the literature, however, suggests a longer history to this finding in aversive conditioning. In 1957, Leon Kamin published an influential paper in which he reported that weakly acquired avoidance fear conditioning dramatically decreased from training at 1 hr after training and then increased at 24 hr after training (and continued to increase when tested at 19 days; Kamin, 1957). This finding came to be known at the time as the *Kamin effect*, which is now readily confused with the better known blocking effect; this retention effect motivated considerable research (for a review, see Brush, 1971) but over time was largely forgotten. Here we suggest that this Kamin retention effect was at least partially due to sleep.

Until now, most rodent behavioral studies examining the role of sleep in memory have utilized potentially stress-inducing sleep deprivation techniques (Horne & McGrath, 1984; Rechtschaffen, Gilliland, Bergmann, & Winter, 1983; C. Smith, 1985; Smith, Conway, & Rose, 1998; Vertes & Eastman, 2000; Youngblood, Zhou, Smagin, Ryan, & Harris, 1997). Recent sleep deprivation studies have used gentle handling of the animals during the sleep/rest phase (Graves et al., 2003; Murison et al., 1982) and have shown that sleep deprivation after learning leads to poorer performance on retrieval tests. However, even this seemingly more benign deprivation technique has been shown to increase serum levels of glucocorticoids, which in turn have been shown to negatively affect cognition and the hippocampus (Plihal et al., 1996; Sapolsky, 2004). Therefore, sleep deprivation is a problematic approach to understanding the role of naturally occurring sleep in memory consolidation processes. Our approach is more naturalistic, allowing for the passage of awake/active and sleep/rest periods. Although considerable sleep does occur during the awake/active phase for mice (Welsh, Richardson, & Dement, 1988), this was clearly not sufficient for good contextual memory in our study, as the 12-hr Awake First group had very poor memory compared with all other groups, which had the passage of a sleep/rest period.

In any study of sleep-related memory enhancement, three very significant confounds exist that must have adequate controls. First, sleep necessarily involves the passage of time, and therefore studies must show that an equivalent passage of time without sleep is not sufficient for the consolidation effect. In our study, we compared mice with and without sleep 12 hr after training and found that a sleep/rest period was necessary to show good contextual memory. Moreover, if mice in the Awake First group were allowed a sleep/rest period, by testing them 24 hr after training, they showed robust memory. Second, one must control for time-of-day effects, both in terms of training and testing. Circadian effects could pose a significant problem for fear conditioning studies, because the form of the fear response, locomotor activity, pain sensitivity, and memory retrieval could be sensitive to time-of-day effects (Chaudhury & Colwell, 2002; Eckel-Mahan et al., 2008). We used several strategies to avoid circadian confounds. We tested mice at 12 or 24 hr after training, and with a 12-hr light:dark cycle, this meant that the 12-hr time point was at the same time of day as the 24-hr time point for some groups (see Figure 1). That is, time of day was not the cause of poor memory in the 12-hr Awake First group, as the 24-hr Sleep First group was tested at the same time of day but showed robust memory. Moreover, we minimized time-of-day differences by training and testing mice at times close to the light–dark transitions when behavioral differences are smallest (Chaudhury & Colwell, 2002). This is evidenced by the fact that Awake First and Sleep First groups did not differ in training in terms of postshock freezing, shock reactivity, or locomotor activity (see Figure 2). Third, one should control for fatigue—in our case, how long the mouse had been awake before testing (Mednick, Nakayama, & Stickgold, 2003; Rickard, Cai, Rieth, Jones, & Ard, 2008). Fatigue was not the cause of group differences described here, because the 12-hr Awake First group was awake no longer than the 24-hr Sleep First group, yet the latter had much better memory. Taken together, these findings do not seem to be attributable to simple passage of time, time-of-day effects, or fatigue. We believe that the present design may serve as a simple and efficient paradigm for avoiding these confounds in future sleep studies.

Sleep, therefore, plays an important role in the stabilization of contextual memory. For Pavlovian fear conditioning, this effect was specific to hippocampus-dependent memory, as cued memory was entirely unaffected by the presence or absence of an intervening sleep period. Thus, sleep may play an important role in consolidating memory as it moves from a hippocampus-dependent to neocortical state. Considerable indirect evidence suggests that replay of recent memories in the hippocampus may serve to entrain slow-changing connections in the neocortex during sleep (Poe, Nitz, McNaughton, & Barnes, 2000; Squire & Alvarez, 1995). One candidate theory for how this transfer occurs is through coordination of hippocampal sharp waves (ripples) and cortical spindles during SWS (Buzsaki, 1996; Ji & Wilson, 2007; Siapas & Wilson, 1998). These findings suggest that hippocampal-dependent memories may be strengthened and transferred (i.e., consolidated) to the neocortex during sleep. Alternatively, sleep may play a separate role in memory consolidation than what is meant by cellular or systems consolidation. Because the role of sleep has generally been identified in the range of days, it may be that sleep is involved in an intermediate form of consolidation between cellular and systems consolidation (McGaugh, 2000). Although interesting theoretically, it is too early to fully explain where sleep-related memory consolidation lies with respect to better studied forms of consolidation. Rather, we favor the interpretation that the first day of consolidation, as examined in the present study, represents the beginning of systems consolidation.

Why, then, does the brain need a sleep phase to consolidate memory? By one view, the hippocampus may need to switch from an acquisition or an "in-flow" mode to a consolidation or "outflow" mode to accomplish the transfer of memories to the neocortex. Acetylcholine has been suggested as one mechanism for switching the hippocampus from acquisition during wakefulness to consolidation during sleep (Anagnostaras, Maren, & Fanselow, 1995, 1999; Anagnostaras, Maren, Sage, Goodrich, & Fanselow, 1999; Anagnostaras et al., 2003; Buzsaki, 1989; Hasselmo, 1999). During active wakeful states, information coded by neocortical structures flows into the entorhinal cortex and then is encoded by rapidly changing synapses in the hippocampus. During deep sleep, information flows out of the hippocampus, and through repetitive activity, becomes entrained onto slow changing synapses in the neocortex (Marshall & Born, 2007). Thus, sleep may enable the hippocampus to shut off acquisition of new memories and turn on repetitive firing that can allow memories to be encoded permanently in the neocortex (Marshall & Born, 2007; Mehta, 2007).

In another view, sleep may possibly play a more passive role by protecting newly formed memories from retroactive interference (Wixted, 2004). Sleep (along with alcohol, benzodiazepines, and NMDA receptor antagonists) blocks new inputs to the hippocampus without compromising its ability to consolidate previously formed memories. Because new input is prevented, recently formed (and, therefore, incompletely consolidated) memories are protected from the retroactive interference that they would otherwise encounter. Thus, memories have an enhanced opportunity to consolidate during sleep, undisturbed from waking interference.

There also does not appear to be a brief critical time window for sleep to occur after training, as suggested by previous studies (Smith & Rose, 1996, 1997; Smith, Conway, & Rose, 1998). We found enhancements if sleep occurred during 24 hr posttraining on this task. However, the precise timing may be task specific, so that for contextual fear conditioning, there is a larger time window in which sleep benefits the consolidation process.

As the current novel paradigm controls for circadian variability, passage of time, and stress-induced amnesia, it may prove to be a valuable tool for further examination of the molecular, physiological, and neurobiological substrates of sleep-induced memory consolidation.

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