Sleep-Induced Changes in Associative Memory

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Abstract

■ The notion that dreaming might alter the strength of associative links in memory was first proposed almost 200 years ago. But no strong evidence of such altered associative links has been obtained. Semantic priming can be used to quantify the strength of associative links between pairs of words; it is thought to measure the automatic spread of activation from a "node" representing one word to nodes representing semantically related words. Semantic priming could thus be used to test for global alterations in the strengths of associative links across the wake-sleep cycle.

Awakenings from REM and nonREM (NREM) sleep produce a period of state carry-over during which performance is altered as a result of the brain's slow transition to full wakefulness, and cognitive testing in this period can provide information about the functioning of the brain during the prior sleep period. When subjects were tested across the night—before and after a night's sleep as well as immediately following forced awakenings from REM and NREM sleep—weak priming (e.g., thief-wrong) was found to be state dependent ($p = 0.016$), whereas strong priming (e.g., hot-cold) was not ($p = 0.89$). Weak primes were most effective in the presleep and REM sleep conditions and least effective in NREM and postsleep conditions.

Most striking are analyses comparing weak and strong priming within each wake-sleep state. Contrary to the normal pattern of priming, subjects awakened from REM sleep showed greater priming by weak primes than by strong primes ($p = 0.01$). This result was seen in each of three protocols. In contrast, strong priming exceeded weak priming in NREM sleep.

The shift in weak priming seen after REM sleep awakenings suggests that cognition during REM sleep is qualitatively different from that of waking and NREM sleep and may reflect a shift in associative memory systems, a shift that we hypothesize underlies the bizarre and hyperassociative character of REM-sleep dreaming. Known changes in brainstem activity that control the transition into and maintenance of REM sleep provide a possible explanation of this shift. ■

INTRODUCTION

Sleep, especially REM sleep, provides an exceptional opportunity to study the brain basis of cognitive processes. As one proceeds from waking into nonREM (NREM) and then REM sleep, a series of dramatic and well-defined changes occur in the neurophysiology and neurochemistry of the brain. In parallel with these shifts, the experiences of the mind change in equally dramatic and well-defined ways, culminating in the visually complex, hyperassociative dreams of REM sleep. Presumably, these changes in cognition can be explained in terms of the underlying neurophysiological and neurochemical changes occurring in the nervous system. For example, it should be possible to provide a neurobiological explanation of the bizarre and hyperassociative aspects of REM-sleep dreams (Hartley, 1801). Although Hartley first suggested that dreaming might alter the strengths of associative links in memory, direct evidence for such alterations remains scant. We present below results from a study of semantic priming (Farah, 1989; Meyer & Schvaneveldt, 1971; Neely, 1977) that bear on this question.

Following the discovery of the robust correlation between dreaming and REM sleep (Aserinsky & Kleitman, 1953), numerous attempts have been made to determine how REM sleep physiology produces the changes in mental activity that lead to dreaming, and why sleep appears beneficial to mental functioning in general (e.g., Aserinsky & Kleitman, 1953; Crick & Mitchison, 1983; Dement & Kleitman, 1957; Hobson & McCarley, 1977; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; Llinas & Ribary, 1993; Pavlides & Winson, 1989; Smith, Young, &

Young, 1980; Wilson & McNaughton, 1994). But despite continued scientific efforts, the cognitive functions of sleep remain in large part unknown (Hobson, 1990; Rechtschaffen & Gilliland, 1989).

The search for links between the objective neurobiological and subjective experiential levels of description has been greatly facilitated by the advent of the cognitive neurosciences, although the application of its techniques to sleep research has been relatively slow. Brain imaging studies (Braun et al., 1997; Braun et al., 1998; Maquet et al., 1997; Maquet et al., 1996; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997) have identified changes in regional brain activation during REM sleep, including increased activation of the pons, hippocampus, amygdala, anterior cingulate, and extrastriate cortex, along with decreased activation of the dorsolateral prefrontal cortex. These findings support and extend results from depth electrode recordings in the cat, which showed pontine (Hobson, McCarley, Pivik, & Freeman, 1974; Jouvet, 1959) and amygdaloid (Calvo & Fernandez-Guardiola, 1984) activation in REM sleep.

Sleep still presents a particular challenge to studies of cognition. Although some analyses, such as auditory event-related potentials (ERP) or conditioned response studies, can be carried out during sleep, cognitive performance can only be tested during waking. To approximate sleep-state testing, researchers have tested subjects immediately upon awakening from various sleep stages. Subjective reports (Dinges, 1990) and behavioral measures (Lavie, Matanya, & Yehuda, 1984; Stones, 1977) point to the existence of a period of "sleep inertia" (Lubin, Hord, Tracy, & Johnson, 1976) following awakening when the brain and mind still display properties of the previous sleep condition (see Dinges, 1990, for review).

Awakenings from deeper, slow wave sleep (SWS; stages 3 and 4) produce impaired performance on "virtually every type of performance, especially all cognitive performances based on memory and attention" (Dinges, 1990, p. 170). Dinges proposed that this component of sleep inertia reflects decreased brain activity caused by the globally decreased core body temperature carrying over into the wake state, with performance most dramatically impaired following SWS awakenings and least impaired following REM sleep awakenings.

When depths of sleep are similar, postsleep performance may be under more subtle control. Thus, for awakenings from stage 2 NREM sleep and REM sleep carried out at similar times of the night, differences in performance may reflect sleep-state-specific differences in regional brain metabolism and biochemistry that only slowly recover after awakening. In such cases, postawakening performance might well reflect the activity of the neurochemically regulated brain during the sleep state preceding the awakening. This could lead to qualitative rather than simply quantitative differences in performance following REM and NREM awakenings. Such results have been obtained by Lavie and his colleagues (1984), who reported that performance on "right brain" (spatial) tasks was enhanced relative to "left brain" (verbal memory) tasks following REM awakenings, whereas the opposite pattern was observed after NREM awakenings. Cognitive tests run during this period of state carryover thus provide a window into the behavior of cognitive systems during different sleep stages. Using this state carryover paradigm, with awakenings from REM and stage 2 NREM sleep at similar times of the night, we have used a semantic priming task to probe the hyperassociative thought processes observed in REM sleep dreams.

The semantic priming task is a robust measure of associative memory processes (Farah, 1989; Meyer & Schvaneveldt, 1971; Neely, 1977). Subjects are shown a "prime" word followed by a "target" word or nonword and must indicate whether or not the target is a word. Prime-target pairs can have varying semantic relationships, including similarity (e.g., car-truck) or learned association (pilot-airplane). In addition, the relationship can have varying strengths: no semantic relationship (e.g., car-apple), a weak relationship (crime-gun), or a strong relationship (hot-cold). Reaction times depend on the strength of the prime-target relationship; a target word preceded by a semantically related prime is recognized more rapidly than one preceded by an unrelated word (Meyer & Schvaneveldt, 1971; for review see Neely, 1991), a phenomenon known as "semantic priming," and reaction times for strongly related words are generally faster than for weakly related words, the "strength of priming" effect (Fischler & Goodman, 1978; de Groot, Thomassen, & Hudson, 1982; Neely, 1977). Semantic priming is operationally defined as the difference between reaction times for target words preceded by primes with no semantic relationship ($RT_{unrelated}$) and reaction times to target words preceded by semantically related primes ($RT_{related}$).

Three lines of reasoning led us to predict that semantic priming would be greater following awakenings from REM sleep than after awakenings from NREM sleep. First, in terms of their content, their flow of events, and their apparent relationship to waking experiences, REM dreams are classically considered hyperassociative (Hartley, 1801). As an example, Rittenhouse, Stickgold, and Hobson (1994) have shown that when objects in dreams are suddenly and unexpectedly transformed into other objects, the two objects are normally related to each other by unpredictable and weak associations. NREM mentation, on the other hand, appears more thought-like and perseverative in nature, with less of the bizarreness that characterizes REM dreams (Foulkes, 1962; Rechtschaffen, Verdone, & Wheaton, 1963). Our second line of reasoning was that semantic priming had already shown state- and trait-dependence in other areas: priming is weakened by sleep deprivation (Babkoff, Genser, Sing, Thorne, & Hegge, 1985; Babkoff et al., 1985) and enhanced in thought-disordered schizophrenics (Maher,

Manschreck, Hoover, & Weisstein, 1987; Manschreck et al., 1988; Spitzer, Braun, Hermle, & Maier, 1993; Spitzer et al., 1994). Thus the brain mechanisms which mediate semantic priming are clearly modulated by other brain systems, including those involved in the wake-sleep cycle. Finally, weak and strong priming appear to be under lateralized control, with presentation of targets to the left hemisphere inhibiting recognition of weakly primed targets (Nakagawa, 1991; Beeman et al., 1994). Thus, changing patterns of regional brain activation across wake-sleep states could lead to qualitative differences in semantic priming following REM and NREM awakenings.

Our prediction of enhanced REM sleep priming is supported by pilot studies in normal subjects (Spitzer et al., 1991; Stickgold, Rittenhouse, & Hobson, 1995). We further predicted that weak primes in particular would be strengthened during REM sleep. This prediction was based in part on the large number of unexpected and bizarre associations found in REM dream reports (Hobson, Hoffman, Helfand, & Kostner, 1987) and in part on theoretical (Mamelak & Hobson, 1989a) and neural network (Sutton, Mamelak, & Hobson, 1992) studies that indicated that the physiological properties of REM sleep, including tonic aminergic demodulation and phasic cholinergic or cholinoceptive activation, predict an increase in unexpected associative sequences. Thus we expected an increase in weak priming following awakenings from REM sleep.

To probe for state-dependent shifts in associative memory processes, we have compared performance on the semantic priming task at various times during the day with performance after awakenings from REM and NREM sleep and report here that following awakenings from REM sleep the amount of priming produced by weakly and strongly related words is reversed, with "weak" primes now producing more priming than "strong" primes.

RESULTS

To compare semantic priming across wake-sleep states, subjects were tested four times on each of two nights—before going to sleep (PRE) and again 5 minutes after awakening in the morning (POST), as well as after two forced awakenings during the night. Most subjects were awakened each night once from REM and once from NREM sleep; subjects run in a modified protocol were awakened twice from REM sleep each night (Figure 1). An additional group of control subjects took the test only in the afternoon (PM).

Differences among the three wake states and between wake states and sleep states could not be controlled for circadian effects. But awakenings from REM and NREM sleep were balanced, and the mean times of awakening for the two sleep states differed by only 7 min.

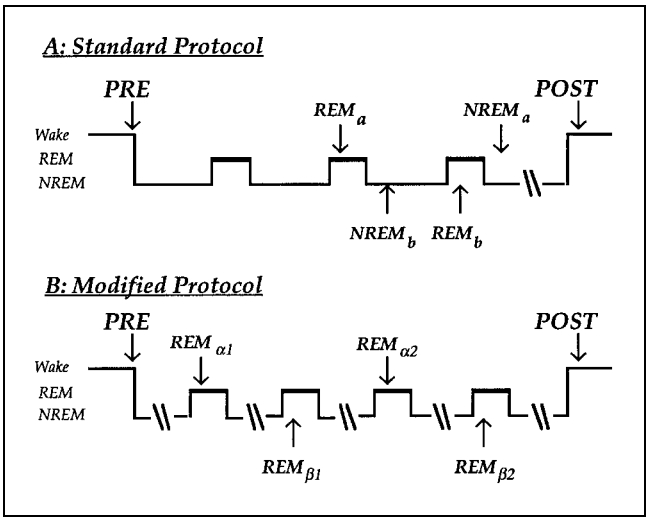

Figure 1. Test protocols. On all nights, subjects were tested immediately before retiring for the night (PRE) and 5 min after awakening in the morning (POST). (A) Standard protocols. On each night, subjects were awakened from one REM period and one NREM period. Order of nights (*a* and *b*) balanced across subjects. (B) Modified protocol. On each night, subjects were awakened from two different REM periods. Order of nights (α and β) balanced across subjects. Arrows indicate times at which awakenings would be performed. Actual awakenings are not shown on hypnograms.

State-Dependent Shifts in Reaction Times

Reaction times varied significantly by test condition. Using the reaction times for target words with unrelated primes as a baseline measure, subjects reacted most slowly after REM awakenings (*RT* = 742 msec) and most rapidly in the PM conditions (*RT* = 607 msec) (Table 1). Thus, PM, NREM, PRE, and POST reaction times averaged 6 to 18% faster than in the REM condition. A repeated measures analysis of variance (ANOVA) of reaction times for the four nighttime conditions (PRE, REM, NREM, and POST) showed significant differences ($df = 3$, $F = 14.3$, $p < 0.0001$). Reaction times for pre- and postsleep tests were significantly faster than those following awakenings from REM and NREM sleep (Fisher's PLSD, $p = 0.0002$ for each comparison), and those for awakenings

Table 1. Reaction times across states. The median reaction times to target words primed with unrelated words was calculated for each subject for each wake/sleep condition, and the average and standard error calculated for each condition.

State	*RT, msec*	*Standard error of mean, msec*
PM	607	9.1
PRE	658	16.8
NREM	700	24.3
REM	742	15.6
POST	622	12.5

from NREM were significantly faster than those for awakenings from REM (Fisher's PLSD, $p = 0.003$).

The slower reaction times following nocturnal awakenings could result from slower linguistic/associative processing, slower motor responses, or both. To determine which of these contributed to the slowing, a separate group of 16 subjects was tested across the night for simple keypress reaction times. Subjects were shown words and nonwords without preceding primes and instructed to press a key whenever either appeared on the screen.

Simple reaction times showed the same state-dependency as did semantic priming (Figure 2, hatched bars). When reaction times on the semantic priming tests were adjusted for motor reaction time, the slowing of reaction times following REM and NREM awakenings was eliminated (Figure 2, black bars; repeated measures ANOVA, $df = 3, F = 1.02, p = 0.39$). $RT_{priming}$ averaged 13% lower in wake conditions (PM, PRE, POST) than in sleep conditions (REM, NREM), but when corrected reaction times were used ($RT_{priming} - RT_{simple\ RT}$), only a 3% difference was seen. Thus, it appears that motor reaction time, rather than the time required to identify words and nonwords, was responsible for the differences in reaction times seen across wake-sleep states.

Effect of Test Condition on Semantic Priming

Semantic priming is operationally defined as the decrease in reaction time to a target word when it is preceded by a semantically related "prime" word as opposed to an unrelated prime ($RT_{unrelated} - RT_{related}$). "Weak priming" is measured using primes that are only weakly associated with the target words, whereas "strong priming" is measured with strongly associated primes.

When priming is measured between groups or between states for which the base reaction times (to unrelated primes) differ, "relative" priming effects can correct for this discrepancy. Relative priming is calculated as $(RT_{unrelated} - RT_{related}) / RT_{unrelated}$ and is presented as the percentage of decrease in reaction time for related primes, whereas "absolute" priming remains defined as ($RT_{unrelated} - RT_{related}$) and is presented as a millisecond decrease in reaction time. Both reflect the increased speed with which words can be identified if they are preceded by semantically related primes.

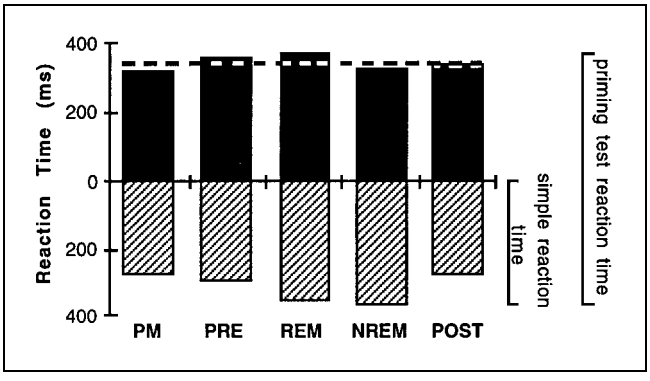

Figure 2. Relative contribution of motor response and priming to reaction times. Hatched bars represent simple reaction times to visual stimuli (RT_{simple}). Hatched + black bars ($RT_{priming}$) represent semantic priming reaction times for unrelated primes. The difference ($RT_{priming} - RT_{simple}$; black bars) is an estimate of the time required to make a cognitive decision on the priming task. Dashed line = $RT_{priming} - RT_{simple}$ averaged across conditions.

If the bizarre and hyperassociative nature of REM sleep dreams is caused by qualitative shifts in the functional strengths of associative memory links, one would expect to see this reflected in a state-dependent shift in semantic priming. Indeed, semantic priming did vary significantly across wake-sleep states and under some conditions appeared to be eliminated (Figure 3A). In the afternoon (PM) condition, strong priming was significant (Student's t test, $p < 0.005$) and weak priming showed a trend in this direction ($p = 0.08$); both were significant in the presleep (PRE) condition ($p < 0.01$ for each), but neither weak nor strong priming reached significance in the NREM ($p > 0.25$) or POST ($p > 0.30$) conditions. Most interestingly, only weak priming reached significance in the REM condition ($p < 0.005$; but $p > 0.80$ for strong priming).

Much of the bizarreness of dreams results from the unexpected juxtaposition of characters, objects, and situations, as if items normally only weakly associated with one another were being combined in the dream scenario. If this were so, one might specifically expect to find weak priming enhanced during REM sleep. Indeed, the amount of weak priming varied dramatically with wake-sleep state [ANOVA (subject × condition), $df = 3$, $F = 2.7, p = 0.044$]. Weak priming was more than twice as high in PRE and REM conditions (21 and 24 msec, respectively) as in the PM condition (10 msec) and not significantly different from zero in NREM and POST conditions (−2 and −7 msec, respectively). PRE and REM weak priming were significantly greater than in the POST condition and showed a trend toward exceeding weak priming in the NREM condition. These results are shown in Figure 3A, with priming levels for the PM condition shown for comparison. Relative priming showed even greater significance (ANOVA, $df = 3$, $F = 3.5, p = 0.016$), with the PRE and REM conditions each showing significantly more weak priming than the NREM and POST conditions (Figure 3B).

In contrast, strong priming showed no significant differences across wake-sleep states (ANOVA, $df = 3$, $F = 0.85, p = 0.47$; relative priming ANOVA, $df = 3, F = 0.63$, $p = 0.60$). Although the differences failed to reach statistical significance, large differences were seen across wake-sleep states, and the question of how strong priming is affected by wake-sleep state remains unanswered.

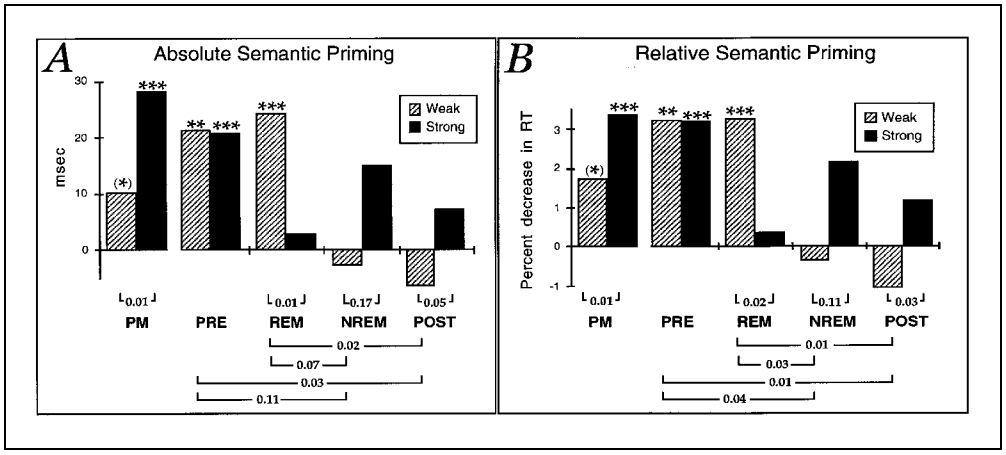

Figure 3. Semantic priming across wake-sleep states. Individual priming effects were tested for significance: (*)$p <$ 0.10, **$p < 0.01$, ***$p < 0.005$, compared to zero. Weak priming in nocturnal test conditions was compared by ANOVA. (A) Absolute priming (msec) = $RT_{unrelated} - RT_{related}$. (B) Relative priming (%) = $(RT_{unrelated} - RT_{related})/RT_{unrelated}$. Statistical comparisons are shown below the graph. Within-state comparison p values are shown in bars above graph labels. Between-state comparison p values are shown in bars below graph labels.

Relative Strengths of Weak and Strong Primes

State-dependent variability in semantic priming could reflect a simple increase or decrease in the efficacy of all associative links, or it could reflect a more subtle shift in the relative efficacy of different types of associative links. In the latter case, one might expect to see weak and strong semantic priming affected differentially across wake-sleep states. Indeed, when the strengths of "strongly" and "weakly" related primes for each test condition were compared, significant differences were seen (Figure 3A, statistics shown between graph and labels). In the PM and POST conditions, strong priming was significantly greater than weak priming, as would be expected (two-tailed paired t tests—PM: $df = 79, t = 2.53$, $p = 0.01$; POST: $df = 81, t = 1.99, p = 0.05$), and a trend in this direction was seen in the NREM condition ($df = 47$, $t = 1.39$, $p = 0.17$). In contrast, weak and strong primes produced equivalent amounts of priming in the PRE condition, and weak primes produced significantly *greater* priming than strong primes after REM awakenings ($df = 103$, $t = 2.58$, $p = 0.01$). Similar results were seen with relative priming (Figure 3B).

Further evidence of this reversal of weak and strong priming in the REM condition is seen by analyzing the data from each of the three protocols separately (Figure 4, see Methods for description of protocol differences). For each of the protocols, the weak priming in REM was as least five-fold higher than the strong priming, and in each case the difference showed a trend toward significantly greater weak priming ($p = 0.10 - 0.15$; Figure 4A). Similar results were seen with relative priming ($p = 0.14 - 0.16$; Figure 4B).

Although weak priming exceeded strong priming after REM awakenings, the opposite was true following NREM awakenings. Thus, when priming in the REM and NREM conditions were compared (ANOVA, Prime Type × Test condition), no main effect was seen for Test condition ($df = 1, F = 0.42, p = 0.51$) or Prime Type ($df = 1, F = 0.03, p = 0.86$), but there was a trend toward an interaction effect, Prime Type × Test condition ($df = 1, F = 3.00$, $p = 0.08$; Figure 5A). This interaction effect was margin-

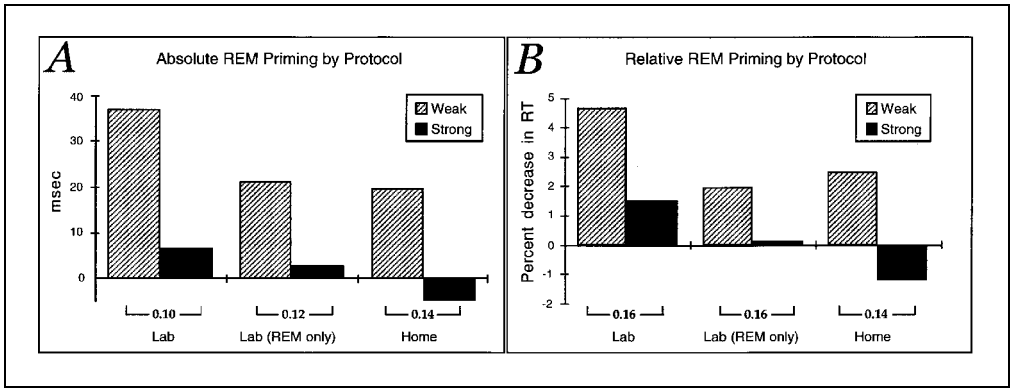

Figure 4. REM priming by protocol. The difference between weak and strong priming was analyzed for each of the three experimental protocols that collected data from REM sleep (see Methods). Similar values were seen in all three protocols, and there was a trend in each case toward weak priming exceeding strong priming on a Student's t test. (A) Absolute priming (msec). (B) Relative priming (%). Lab: One REM and one NREM awakening each night in sleep laboratory; Lab (REM only): Two REM awakenings each night in sleep laboratory; Home: One REM and one NREM awakening each night in the home. See Methods for details.

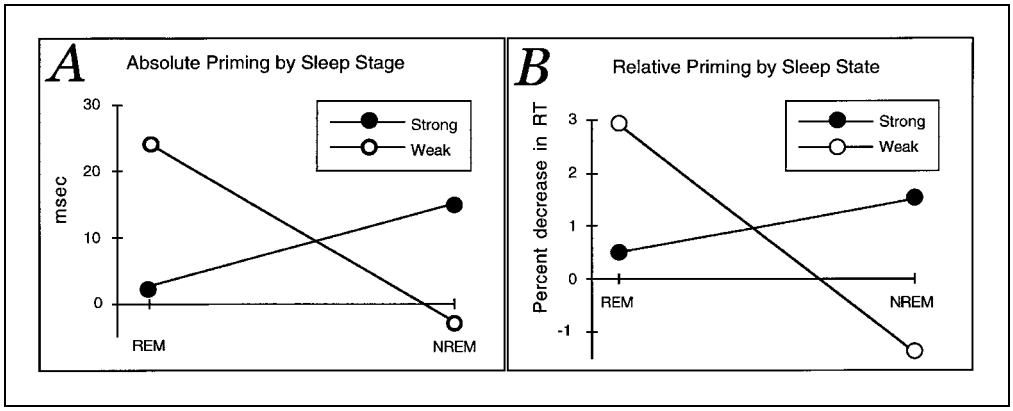

Figure 5. Sleep stage and priming strength. The interaction between relative power of weak and strong primes and sleep condition is displayed. (A) Absolute priming (msec). (B) Relative priming (%).

ally better for relative priming ($df = 1, F = 3.37, p = 0.07$; Figure 5B).

Time Courses of REM and NREM priming

As the night progresses, REM periods become longer and the size and frequency of rapid eye movements increase dramatically. In parallel with these physiological changes, REM dreams become more vivid and complex. Thus, one might expect that the state-dependent changes in semantic priming observed in the REM and NREM conditions might vary across the night. Just such an effect was seen. Although weak priming averaged 24.4 msec in REM and strong priming averaged only 2.7 msec (Figure 3A), this difference varied dramatically across the night. As time in bed increased, weak priming (Figure 6A, circles and solid line) decreased significantly (Pearson correlation, $r = -0.29$, $df = 102$, $p = 0.003$) from a best-fit value of 70 msec at the approximate time of the first REM period of the night to zero after 6.75 hr. In contrast, strong priming (Figure 6A, dashed line) showed no significant variation across the night ($r = 0.08$, $df = 102$, $p = 0.42$). By the end of the night, neither weak nor strong priming in REM differed significantly from zero. Analysis of relative priming (not shown) gave similar results ($r = -0.27$, $p = 0.006$ for weak priming; $r = 0.10$, $p = 0.32$ for strong priming).

In the NREM condition, where strong priming dominated, a similar pattern was observed (Figure 6B). Overall, strong priming in the NREM condition averaged 15.1 msec, whereas weak priming averaged -2.7 msec. Across the night, the amount of strong priming decreased significantly (Pearson correlation, $r = -0.32$, $df = 46$, $p = 0.025$) from 72 msec after 2 hr (the earliest time point) to zero after 5.3 hr of sleep. In contrast, weak priming remained minimal and essentially unchanged across the night ($r = 0.03$, $df = 46$, $p = 0.83$; Figure 6B, dashed line). Analysis of relative priming (not shown) gave similar results ($r = -0.33$, $p = 0.02$ for strong priming, $r = -0.04$, $p = 0.81$ for weak priming).

Wake-State Priming

In this study, semantic priming was measured in waking subjects in the afternoon, immediately before retiring for the night and 5 min after awakening in the morning.

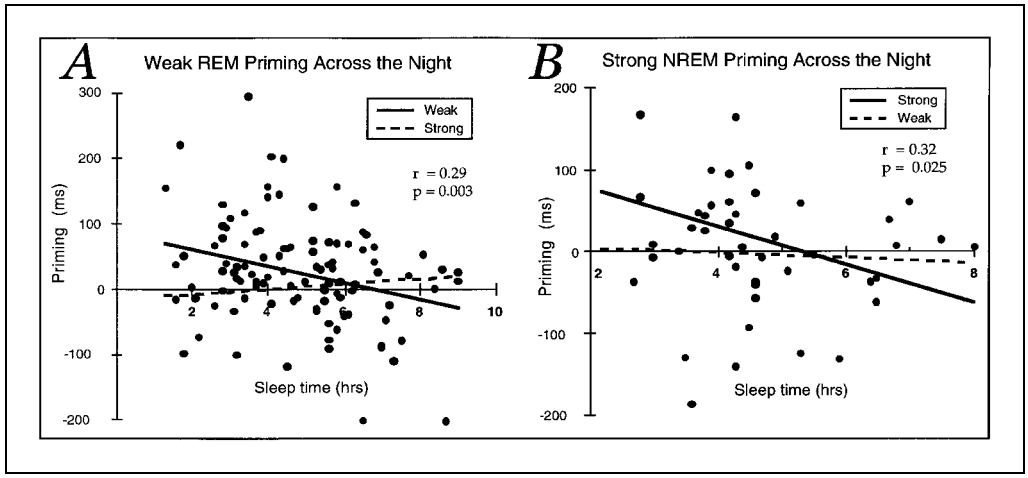

Figure 6. Time course of priming across the night. The amount of priming for each test block is shown as a function of how long the subject had been in bed. Solid line: regression analysis best fit line to points. (A) Weak priming in REM: Pearson coefficient of correlation, $r = 0.29$ ($p = 0.003$). For comparison, the regression fit for strong priming is shown (dashed line) without individual points. (B) Strong priming in NREM: Pearson coefficient of correlation, $r = 0.32$ ($p = 0.025$). For comparison, the regression fit for weak priming is shown (dashed line) without individual points.

When weak priming was measured in the morning, it was significantly lower than in the late evening and showed a strong trend toward being lower than in the afternoon as well (unpaired t test, $t = 1.92, df = 160, p = 0.06$; Figure 3). Because the pre- and postsleep tests were taken so close to the sleep period, it is unclear whether these results reflect circadian fluctuations in semantic priming or the cognitive changes known to arise in the hypnagogic and hypnopompic periods preceding and following sleep (Schacter, 1976; Rowley, Stickgold, & Hobson, 1998).

Although analysis of strong priming across the presleep, REM, NREM, and postsleep states did not show statistically significant variations, strong priming was significantly greater in the afternoon than either following awakenings from REM sleep (unpaired t test, $t = 2.16$, $df = 182, p = 0.03$) or in the morning ($t = 2.06, df = 160$, $p = 0.04$). The overall trend for strong priming is to decrease from the afternoon to the evening and then, after NREM awakenings, to decrease across the night, before showing a slight recovery in the morning (Figures 3 and 6). This trend follows the normal circadian cycle and is distinct from the time-independent decrease seen after REM awakenings. The latter supports the hypothesis that REM sleep allows for the strengthening of weakly linked associative memories by temporarily reducing strong associations to the advantage of weaker ones.

DISCUSSION

When cognitive tests are administered in the immediate postawakening period, performance is often different from that seen during normal waking. Dinges (1990) has suggested that the global impairment of cognition seen after awakenings from SWS, especially following prior sleep deprivation, reflects a global decrease in brain activation, a decrease that has subsequently been confirmed by PET studies (Maquet et al., 1997). Awakenings from lighter sleep, specifically REM and stage 2 NREM sleep, produce less global impairment and may reflect regional differences in brain activation between REM and stage 2 NREM sleep (e.g., Lavie et al., 1984). The results reported here would appear to fall into the latter class, where different effects were seen on response times for different classes of prime-target pairs. The findings of larger effects after REM awakenings than NREM awakenings provides further support for this interpretation (cf. Dinges, 1990).

When subjects carried out a semantic priming test after being awakened from REM sleep, the amount of priming produced by weak primes exceeded that produced by strong primes. This is the reverse of what was seen in waking and implies that the automatic spread of activation believed to underlie semantic priming is dramatically altered during REM sleep. We believe that this alteration in normal cognitive processing provides part of the explanation for the bizarre and hyperassociative nature of REM-sleep dreaming. Results from studies in neuropharmacology and brain imaging provide converging evidence for possible brain mechanisms underlying these phenomena.

REM sleep, from which the longest reports of vivid dreaming are consistently obtained, is a well-defined physiological and neurochemical state. Wake-sleep states are most clearly distinguished from one another based on three parameters—cortical activation, input thresholds, and neuromodulation (Hobson, 1992), as summarized in Table 2. For example, levels of ACh in the cortex and hippocampus have been shown to increase two- to four-fold between SWS and REM sleep (Marrosu et al., 1995).

Upon awakening from REM or stage 2 NREM sleep, cortical activation and input thresholds rebound to waking levels within seconds. But levels of cortical neuromodulators may shift to waking level more slowly, providing a possible basis for the state carryover effect exploited in this study.

Semantic Priming and Neuromodulation

Given that REM and NREM sleep differ dramatically in the levels of activation of noradrenergic, serotonergic, and cholinergic subsystems, it would be desirable to compare our REM/NREM data with pharmacological studies examining the effects of pharmacological alterations of these neuromodulatory systems on semantic priming. We are not aware of any such studies. The closest work we have found is that of Kischka et al.

Table 2. Physiological characteristics of wake-sleep states. High activation is defined both by high-frequency low-amplitude electroencephalographic signals and high cortical glucose utilization. High input thresholds are defined by diminished ERP responses and by raised sensory thresholds for awakening. Neuromodulation reflects cortical levels of released transmitter, measured by microdialysis or extrapolated from neuronal firing rates in the locus coeruleus, Raphe nucleus, and pontine reticular formation; ↑: high levels of neurotransmitter; ↓: low levels; ↗: moderately high levels; ↘: moderately low levels.

State	*Activation*	*Input threshold*	*Neuromodulation*
Wake	High	Low	NE ↑ 5HT ↑ ACh ↗
NREM	Low	Medium	NE ↘ 5HT ↘ ACh ↓
REM	High	High	NE ↓ 5HT ↓ ACh ↑

(1996), who reported that when dopamine levels are elevated with L-dopa and benserazide, a decrease in indirect priming is seen, with no effect on direct priming. They proposed that the increased levels of dopamine causes a parallel increase in the signal-to-noise ratio in semantic networks, which, in turn, produces a more focused activation and hence a decrease in the spread of semantic activation. The enhanced indirect priming seen in schizophrenics (Spitzer et al., 1993) would then follow from a decrease in cortical dopamine.

A similar mechanism may be at work in REM sleep. Norepinephrine is known to increase signal-to-noise ratios in cortical neurons (Foote, Bloom, & Ashton-Jones, 1983), a fact that suggests that the increased weak priming seen on awakening from REM sleep may result in part from the reduction in cortical norepinephrine observed during REM sleep. Simulations have shown that such a reduction can lead to an increased spread of activation (Mamelak & Hobson, 1989a; Sutton et al., 1992), which, in turn, could reasonably be expected to result in enhanced weak priming.

Semantic Priming, Brain Laterality, and Regional Brain Activation

Lateralization of strong and weak priming has been reported by several groups. Nakagawa (1991) reported that presentation of target words 750 msec after the prime to the left hemisphere (via the right visual field), but not to the right hemisphere, led to an inhibition of response for remote and unrelated primes. No such inhibition was seen when strong (antonym) primes were used. Because loading of the anterior attentional system with a shadowing task eliminated the inhibition, she proposed that this system inhibited responses to weakly associated words presented to the left hemisphere. Similar lateralized effects were obtained by Beeman et al. (1994). They reported that summation primes (three words each weakly related to the target, presented simultaneously) were more effective when presented to the right hemisphere (left visual field), whereas direct primes (one strong associate flanked by two unrelated words) were more effective when presented to the left hemisphere. In contrast to Nakagawa's attentional hypothesis (Nakagawa, 1991), they proposed that the lateralized effects resulted from the right hemisphere activating larger semantic fields (including distantly related concepts) than the left hemisphere (which tended to activate only closely related concepts). Similar lateralization effects have been reported by Chiarello (Chiarello, Burgess, Richards, & Pollock, 1990; Chiarello & Richards, 1992). In a related study, Abdullaev and Posner (1997) have shown increased right posterior activation during the generation of remote associations.

These results suggest that the enhanced weak priming that we have seen following awakenings from REM sleep might result from regional shifts in brain activation during REM sleep, perhaps in response to REM-associated changes in chemical neuromodulation. Because the regional distribution of neuromodulators such as norepinephrine from the locus coeruleus and acetylcholine from the basal ganglia and pontine brainstem differ, it is not unreasonable to hypothesize that shutting down the locus coeruleus and Raphe nucleus and activating the pontine brainstem, as occurs in REM sleep, could lead to changes in regional brain activation.

Indeed, differences in regional brain activation have been reported between REM and NREM sleep, with relatively higher activation during REM sleep or lower activity during NREM sleep observed in the pons, thalamus, hippocampus, and amygdala, as well as in the orbito-frontal, anterior cingulate, and extrastriate cortex (Braun et al., 1998; Hofle et al., 1997; Maquet et al., 1997; Maquet et al., 1996; Nofzinger et al., 1997). Most interesting in this context is the apparent hypoperfusion of the dorsolateral prefrontal cortex during REM sleep (Braun et al., 1998; Maquet et al., 1996; but see also Nofzinger et al., 1997) combined with the hyperperfusion of the anterior cingluate. This combination of decreased activation in one portion of the anterior attentional system accompanied by increased activation of another could lead to a qualitative shift in the functioning of this system. Such a perturbation of the normal, waking attentional mechanism could not only contribute to the inattention noted in dream studies (Hobson, Pace-Schott, Stickgold, & Kahn, 1998) but, in conjunction with the results of Nakagawa (1991), could suggest a mechanism for our findings of enhanced weak priming during REM sleep.

Circadian Influences on Semantic Priming

The most perplexing of our results are the data showing that the amount of weak priming seen on tests following awakenings from REM sleep decreases as the night progresses. Because the duration of REM periods, intensity and frequency of rapid eye movements during REM, and vividness and complexity of REM-associated dream reports all increase late in the night, we predicted that the weak REM priming effect would likewise be maximal late in the night. In contrast to this expectation, weak priming late in the night (after at least 7 hr of sleep) showed an average priming of −34 msec; reaction times to weakly related primes, on average, were actually slower than reaction times to unrelated primes. Although this inhibition of priming (relative to unrelated primes) was not statistically significant (t test, $df = 10$, $t = -1.61$, $p = 0.14$), the data are suggestive, and weak priming clearly decreased, rather than increased, across the night.

This may reflect a circadian influence on priming that exceeds the REM/NREM state-dependency. Such an influence would also explain why the amount of priming seen in the morning wake state (POST) was less than that in the evening. Such a model would have priming

lowest in the morning, rising across the day, and then decreasing across the night. Thus, after the weak REM and strong NREM priming effects decreased to zero across the night, the morning wake-state priming was not significantly different from zero for either weak or strong primes. Studies of circadian influences on semantic priming would add valuable information for understanding the state-dependent nature of these cognitive processes.

Summary

Semantic priming is thought to reflect the automatic spread of activation from neural ensembles representing a prime word to other ensembles representing the target word, a process that proceeds without intent or conscious awareness (Cañas, 1990; Collins, Chow, & Imhoff, 1995; Posner & Snyder, 1975). Under conditions in which such spreading activation is enhanced, associative mental processes might well be expected to be accelerated. Nowhere is such enhanced association more evident than during dreaming, an automatic process in which images showing only the weakest relationships with one another are strung together to produce bizarre and incongruous dream narratives. Because dreams are constructed without apparent conscious intent, we hypothesize that they result from sequential activation of associated memories. Thus, we predicted and found that the effects of weak semantic primes are enhanced upon awakening from REM sleep. These findings provide further evidence for the existence of state-dependent, qualitative changes in associative memory.

We believe that the dramatic increases in priming seen on awakening from REM sleep reflect the continued activity of changes in cognitive processing present *during* REM sleep. We further believe that these cognitive changes result from the changes in brain physiology and neurochemistry that are known to accompany the shift from NREM to REM sleep. These include changes in neuromodulatory systems and possibly concomitant changes in regional brain activation. We suggest that this shift in cognitive processing is responsible, in large part, for the bizarre nature of dreams and may serve to enhance the strength of associations between weakly associated memories (Stickgold, 1998).

METHODS

Test Protocols

Seventeen male and 27 female college undergraduates participated in a three-night protocol consisting of one adaptation night followed by two test nights. For 31 of these subjects, sleep stages were monitored on-line in the sleep laboratory using standard polysomnographic techniques (Rechtschaffen & Kales, 1968). A Macintosh computer placed adjacent to the bed was used for administration of the semantic priming task. For the remaining 13 subjects, sleep was monitored on-line in the home using the Nightcap sleep monitor (Mamelak & Hobson, 1989b; Stickgold, Pace-Schott, & Hobson, 1994), connected to a Macintosh computer (Rowley et al., 1998). On test nights, either the Macintosh computer (using prerecorded voice prompts) or the EEG technician awakened the subject at appropriate times and administered the semantic priming test. In the home setting, the sleep stage data from the Nightcap, the time of the prompted awakenings, and the length of time it took the subject first to respond to the awakening prompt and then to start the test were recorded along with actual test data.

To determine the effect of wake-sleep state on semantic priming, subjects performed four blocks of trials on each of the two test nights—once prior to bedtime (PRE), twice immediately upon being awakened from sleep, and a fourth time 5 min after awakening in the morning (POST).

Three different protocols were used. In the "Home" and "Lab" protocols (Standard Protocols, Figure 1A), one awakening was performed from NREM sleep and one from REM sleep. In the "Lab" protocol, all NREM awakening were confirmed to be from stage 2 NREM sleep. REM and NREM awakenings were order-matched between nights: 10 min into the second REM period (Figure 1A, REM_a) and 15 min into the fourth NREM period (Figure 1A, $NREM_a$) on one night and 15 min into the third NREM period (Figure 1A, $NREM_b$) and 10 min into the third REM period (Figure 1A, REM_b) on the other night. The order of awakenings was counterbalanced across subjects.

To investigate the effect of time of night in the REM condition, 18 subjects (8 males, 10 females) were tested in a third, "Lab (REM only)," protocol. In this protocol, both awakenings were from REM sleep (Modified Protocol, Figure 1B). Scheduled REM awakenings were balanced across subjects, with awakenings scheduled from REM periods 1 and 3 (Figure 1B, $REM_{\alpha 1}$ and $REM_{\alpha 2}$), 2 and 4 (Figure 1B, $REM_{\beta 1}$ and $REM_{\beta 2}$), or 3 and 5 (not shown). All awakenings were made 10 min into the

Table 3. Test times. The time of administration of the semantic priming task under each of the four test conditions was averaged across subjects and protocols. The number of tests in each condition is indicated as well.

Stage	*(n)*	*Mean time, a.m.*
PRE	83	12:02
NREM	49	4:44
REM	104	4:51
POST	82	7:56

appropriate REM period. The average times of awakenings for all protocols are shown in Table 3.

Semantic Priming Task

On the first (adaptation) night, subjects performed a brief practice test of the semantic priming task before going to bed. On each of the two test nights, four lists of 72 prime-target pairs provided by M. Posner were presented. List order was balanced across subjects. On the second night each list was presented in the opposite order of the first night, and lists presented following nocturnal awakenings on one night were used in pre- and postsleep tests on the other night. Each list contained 12 pairs each of unrelated (e.g., cream-right), weakly related (e.g., thief-wrong), and strongly related (e.g., long-short) words, as well as 36 word/nonword pairs (e.g., fall-lova) to ensure that processing was automatic. Strong primes consisted of antonym pairs, whereas weak primes were primarily object-characteristic pairs (e.g., thief-wrong, cowboy-rough, or dream-sweet). Stimuli were presented in lowercase letters in the center of the visual field. Each trial consisted of a 700-msec fixation point in the center of the computer screen and then the prime displayed for 200 msec, followed immediately by the target displayed until response. Subjects were instructed to read the first word (prime) and then respond to the second character string (target), identifying it as either a word or a nonword by pressing an appropriate key on the keyboard. Each block of 72 trials lasted 2 to 3 min. Five additional practice trials were presented at the start of each block and were omitted from analysis.

Statistical Analyses

Analyses of reaction times were carried out by repeated measures ANOVAs. For analyses of priming effects across wake-sleep states, both repeated measures and randomized block ANOVAs were carried out, as condition × subject, with night nested under subject. Random block analyses showed no effects of subject ($F < 1.1$ and $p > 0.35$ for each of eight analyses), and repeated measures and random block analyses showed similar results, with the random block analyses showing slightly better F values, as expected. For comparison of weak and strong priming within states and of the PM condition with other states, Student's t test was used. Correlations of priming with sleep time were performed using Pearson's correlation analysis. Analyses were performed using StatView and SuperANOVA software for the Macintosh.

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