69. T. R. Barrett, B. R. Ekstrand, *J. Exp. Psychol.* **96**, 321 (1972).
70. M. J. Fowler, M. J. Sullivan, B. R. Ekstrand, *Science* **179**, 302 (1973).
71. R. Yaroush, M. J. Sullivan, B. R. Ekstrand, *J. Exp. Psychol.* **88**, 361 (1971).
72. A. Giuditta, *et al.*, *Behav. Brain Res.* **69**, 157 (1995).
73. R. Stickgold, L. Scott, C. Rittenhouse, J. A. Hobson, *J. Cognit. Neurosci.* **11**, 182 (1999).
74. S. Gais, W. Plihal, U. Wagner, J. Born, *Nature Neurosci.* **3**, 1335 (2000).
75. L. De Gennaro *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **95**, 252 (1995).
76. J. H. Herman, H. P. Roffwarg, *Science* **220**, 1074 (1983).
77. L. De Gennaro, M. Ferrara, L. Urbani, M. Bertini, *Exp. Brain Res.* **130**, 105 (2000).
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REVIEW

Sleep, Learning, and Dreams: Off-line Memory Reprocessing

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Converging evidence and new research methodologies from across the neurosciences permit the neuroscientific study of the role of sleep in off-line memory reprocessing, as well as the nature and function of dreaming. Evidence supports a role for sleep in the consolidation of an array of learning and memory tasks. In addition, new methodologies allow the experimental manipulation of dream content at sleep onset, permitting an objective and scientific study of this dream formation and a renewed search for the possible functions of dreaming and the biological processes subserving it.

It is 200 years since David Hartley (*1*) first suggested that dreaming might alter the strength of associative memories, but the basic proposition that either sleep or dreaming plays a role in the off-line reprocessing of memories remains hotly debated (*2–4*). Recent developments in molecular genetics, neurophysiology, and the cognitive neurosciences have produced a striking body of research that provides converging evidence for an important role of sleep in learning and the reprocessing of memories (*5*).

On the basis of patterns of brain electrical activity measured in the electroencephalogram (EEG), eye movements, and muscle tone (*6*), sleep can be broadly divided into rapid eye movement sleep (REM) and non–rapid eye movement sleep (NREM), with the human REM-NREM cycle typically having a 90-min period. Recent evidence strengthens the hypothesis that sleep plays a role in learning and memory processing at several levels, including the REM-dependent developmental wiring of binocular cells in visual cortex (*7*, *8*), procedural learning of a visual discrimination task (*9–12*), and the development of problem-solving skills (*13*).

In contrast, since Freud proposed his theory of dream interpretation (*14*), there has been a frustrating dearth of scientific evidence concerning the mechanism of dream construction and its possible functions. One such function might be as part of a multilevel system of sleep-dependent learning and memory reprocessing, wherein dreams would be the conscious manifestation of these processes. New approaches described below offer a methodology for experimentally approaching these questions.

Behavioral Studies of Learning and Memory in Sleep

Behavioral studies of sleep and learning in humans and animals, neurochemical and neurophysiological studies of the brain basis of possible sleep-dependent memory processing, and neurocognitive studies of information processing during sleep provide evidence for an interdependence between sleep, learning, and memory. Still, considerable controversy surrounds the question (*2*, *4*, *15*). For additional discussions of these questions, see the accompanying reviews by Maquet (*5*) and Siegel (*16*).

Research into sleep and memory began in earnest after the discovery of REM in 1953 (*17*). Since then, a wide range of animal studies have supported the hypothesis that REM plays a critical role in learning (*18–21*). A meta-analysis concluded that REM sleep plays a critical role in the consolidation of procedural learning but not of declarative memory (*22*). In a synthesis of the animal literature, Smith proposed the existence of "REM windows" (*18*), periods of time after procedural training when rats show increased amounts of REM and during which REM deprivation leads to diminished retention. For many of the early REM deprivation studies, the apparent decrease in recall after deprivation may be the consequence of deprivation-induced stress (*2*, *4*). But other studies (*23*) have demonstrated performance decrements 20 hours after REM deprivation, but not 8 to 16 hours after deprivation (*24*, *25*). This is the opposite of what a stress model would predict. Other studies have shown effects as long as a week after REM deprivation (*26*).

These findings in no way suggest that REM is critical for all memory consolidation. Substantial memory consolidation occurs during normal waking, and many memory tasks are unaffected by subsequent REM deprivation (*2*, *4*, *15*). Nor is there clear evidence that REM sleep enhances subsequent encoding (*27*). Furthermore, memory consolidation is most likely not the only function of REM sleep, not explaining, for example, the decrease in REM during the first year of life (*2*).

In humans, posttraining REM deprivation impairs retention of procedural learning (*20*, *28*). Declarative memory tasks in general have not shown any sleep dependence [e.g., (*29*)], although some studies have suggested that deep, slow-wave sleep (SWS) early in the night may aid in their consolidation (*30*, *31*).

REM may also enhance the processing of emotional memories. There is enhanced recall for emotionally salient memories after periods of sleep rich in REM (*32*), and several older studies similarly support a role for REM in processing emotional memories (*27*, *33–36*). In addition, shortenings of REM latencies and increases in REM densities have been reported in major depression (*37*, *38*), the state of bereavement (*37*, *39*), war-related anxiety (*40*), and, more generally, posttraumatic stress disorder (*41*).

Some of the strongest evidence for human learning being sleep dependent comes from a

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visual texture discrimination task (*10*, *42*, *43*). On this task, improvement is not seen until after posttraining sleep (Fig. 1A) (*11*), and sleep deprivation on the night after training eliminates all benefits of training, even when measured after two full nights of recovery sleep (Fig. 1B) (*12*). Karni *et al.* (*10*) found no improvement after a night with selective REM deprivation, but did see improvement after selective SWS deprivation. Other studies suggest that both SWS and REM are required (Fig. 1, C and D) (*11*), a result in keeping with the two-step model proposed by Giuditta *et al.* (*44*) for the consolidation of learning in rats, but contrary to what would have been expected on the basis of the Karni *et al.* study (*10*).

More generally, studies suggest that REM might modify neocortical networks in general, rather than simply those involved in procedural learning, with REM effects reported for learning of complex logic games (*13*), for foreign language acquisition (*45*), and after intensive studying (*19*). The fact that REM appears to play little or no role in memory consolidation on simple tests of declarative memory has led some researchers (*2*, *4*, *46*) to doubt that REM plays any role in memory, citing studies that conclude that long-term REM suppression in depressed and narcoleptic humans produces "no adverse effects on cognition/memory" (*4*, p. 874). Unfortunately, none of the studies cited in these reviews looked at performance on either procedural or complex learning tasks after a night of posttraining sleep. Instead, they used almost entirely simple declarative memory tasks retested within minutes after training, where we would not expect to find any effect of REM deprivation. A resolution of this question must await the testing of these patient populations with tasks such as the texture discrimination task, which otherwise appear to be REM dependent.

Sleep Architecture and Physiology

Probing the mechanisms underlying the possible roles of sleep in memory processing requires knowledge of the complex physiology of sleep. The electrophysiologically defined stages of sleep differ along several dimensions, some of which are shown in Table 1. Researchers have speculated that many of these phenomena might contribute to learning and memory processing in sleep.

Synchronous brain activity. Steriade (*47*, *48*) has hypothesized that high rates of ~10-Hz firing of neocortical neurons during the long-lasting depolarization phase of SWS oscillations might induce long-term potentiation (LTP) at cortical synapses (*49*–*51*), which could serve to reorganize or respecify connections within neural networks and functionally connect distant cortical regions. Similarly, sharp wave potentials seen in SWS (*52*) might facilitate information flow from the hippocampus to the neocortex (*53*).

In contrast, theta rhythms in REM may support information transfer from neocortex to hippocampus (*53*), where theta waves enhance LTP, considered critical for hippocampal memory formation (*49*). Neural network simulations (*54*) have suggested that such an alternating "hippocampo-neocortical dialog" (*53*) could enhance the encoding of hip-

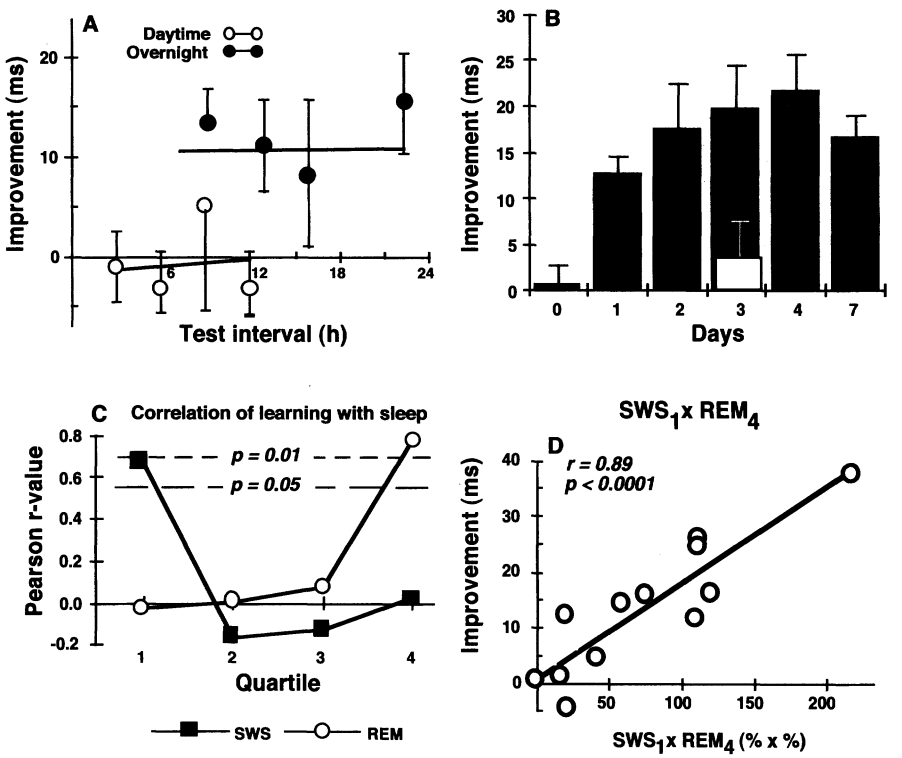

Fig. 1. Sleep-dependent learning of a texture discrimination task: Subjects were trained and then retested at a later time. Each subject was retested only once, and each point represents a separate group of subjects. (**A**) Improvement across a night's sleep. Subjects were trained and then retested either 3 to 12 hours later on the same day (open circles) or after 8 to 24 hours after a night's sleep (filled circles). All told, n = 57, with n = 7 to 9 for individual points. Error bars = SEM. (**B**) Improvement across a week. Solid bars: Subjects were retested the same day as training (day = 0) or after 1 to 7 days (n = 122). Open bar: Subjects were sleep deprived the night after training and retested after a total of 3 days (n = 11). Error bars = SEM. (**C**) Overnight improvement was correlated with both the amount of SWS (solid squares) and of REM (open circles) in each quarter of the night, and the Pearson correlation coefficient was plotted (n = 12). Significant correlations were seen for the percentages of time spent in SWS during the first quarter of the night (SWS_1) and in REM during the last quarter of the night (REM_4). (**D**) SWS_1 was multiplied by REM_4 for each subject and plotted against the individual's overnight improvement. From Stickgold *et al.* (*11*, *12*).

Table 1. Brain physiology shifts across sleep states. Human sleep is divided into REM and NREM, with NREM further subdivided into sleep onset (stage 1 sleep), light NREM (stage 2), and SWS (stages 3 and 4). The physiological parameters listed here are characterized by robust state-dependent changes that are thought to be linked to sleep-dependent learning and memory reprocessing. Arrow represents changes in activity relative to waking. See text for explanations.

Physiological correlates of sleep stages	REM	Stage 2 NREM	SWS
Synchronous brain electrical activity	4 to 6 Hz	12 to 14 Hz	0.5 to 4 Hz
Eye movements	⇈	⇊	⇊
Muscle tone	⇊	↓	↓
External inputs	⇊	↓	↓
Hippocampal-neocortical dialog (HC-NC)	NC→HC	?	HC→NC
Cholinergic modulation (ACh)	⇈	↓	↓
Aminergic modulation (NE and 5-HT)	⇊	↓	↓
Glucocorticoids (GC)	(↓)	–	(↑)
Frontal activation (DLPFC)	⇊	?	↓
Limbic activation (e.g., anterior cingulate cortex)	↑	?	↓
Sensory cortices	↑	?	↓

pocampally dependent memories in the neocortex (*3*).

Phasic ponto-geniculo-occipital (PGO) waves, which activate visual and motor cortices as well as the amygdala and hippocampus (*55*), are seen during the transition from NREM to REM and throughout REM. These waves may play an important role in memory consolidation in the rat (*56*) and have been proposed to reactivate memory traces during REM dreaming (*57*).

It has been hypothesized that gamma waves (~40 Hz) mediate the binding of sensory features in both waking consciousness (*58*) and REM dreaming (*59*), although there are no data linking them to learning or memory consolidation in sleep.

Neuronal replay. Stronger evidence of the possible role of these processes in learning and memory comes from analyses of neuronal activity in the rat hippocampus. During sleep, replay of recent waking patterns of neuronal activity is seen within the CA1 layer of the hippocampus. This reactivation is seen during SWS for about half an hour after learning (*60*, *61*) and in REM after 24 hours (*62*, *63*). Although this replay in SWS may simply reflect continued activity unrelated to sleep (*64*), the presence of replay in REM only after 24 hours demonstrates that these patterns of neuronal activation are specifically reactivated during REM. Neuronal replay during REM can be synchronized with theta wave activity, shifting from in-phase (i.e., coincident with peaks of theta waves) to out-of-phase (coincident with theta troughs) over 4 to 7 days (*65*), a time course similar to that over which initially hippocampally dependent memories become independent of the hippocampus (*66*, *67*). Such a shift might produce a switch from LTP and memory consolidation to long-term depression (LTD) (*50*, *68*) and memory erasure (*69*) after effective transfer of the memory to the neocortex. A similar replay during sleep has been found for neurons mediating vocal learning in song birds (*70*), and this may mediate the consolidation of this learning.

Neuromodulators. The REM-NREM cycle also displays marked shifts in levels of neuromodulators in the brain. Brainstem systems that control the REM-NREM cycle include the noradrenergic (NE) locus coeruleus, the serotonergic (5-HT) dorsal Raphe nucleus, and the cholinergic (ACh) nuclei of the dorsolateral pons (*71*). Whereas NREM is characterized by decreases in all three neuromodulators compared with waking, ACh levels in REM are equal to or higher (*72*) than during wake (Fig. 2), and levels of NE and 5-HT drop to near zero (*73*).

Regional brain activation. Finally, positron emission tomography (PET) studies have demonstrated unique patterns of regional brain activation across wake-sleep states (*74*). Almost all brain regions become less active in SWS compared with waking. But although many regions remain relatively inactive in REM (*75*), dorsolateral prefrontal cortex (DLPFC), which is involved in decision making and memory, becomes further inactivated in this state (*75*). At the same time, several midline limbic structures, including both the anterior cingulate and medial orbitofrontal cortices and the amygdala, (*76*) become reactivated to levels at or above waking levels (*77*).

Taken together, these studies of sleep physiology provide considerable circumstantial evidence for both REM and NREM playing important roles in memory consolidation. Direct evidence for such roles comes from studies that link physiological processes with behavioral outcomes.

Sleep Physiology, Memory Processing, and Behavior

Hennevin *et al.* investigated the ability of the brain to encode and consolidate memories during REM through direct brain stimulation (*24*). Their results indicate that both the consolidation of learning and the formation of new associations can be mediated by pontine reticular formation (PRF) activation during sleep (*78*). In addition, a correlation between an increased density of PRF-generated PGO waves during posttraining REM and subsequent improved task performance has been reported (*56*), suggesting that PGO waves facilitate learning in the rat.

Biochemical aspects of memory consolidation have recently been reviewed (*79*, *80*). Both protein synthesis and phosphokinase A (PKA) are required for hippocampally mediated learning, and their inhibition during REM windows produces effects similar to those produced by REM deprivation (*81*, *82*). In addition, exposure to an enriched learning environment induces the immediate early gene *zif-268* during subsequent REM (*83*). *Zif-268* expression normally coincides with synaptic modification and, during REM, presumably reflects the consolidation of learning. These and related findings led to the suggestion that the PKA signaling pathway mediates sleep-dependent learning and memory processes (*79*).

A qualitatively different form of sleep-dependent synaptic plasticity has been demonstrated during early postnatal development of the cat visual system (*8*, *84*). Studies combining monocular visual deprivation with sleep deprivation (*7*) suggest that sleep contributes as much to developmental changes in synaptic connectivity as does visual experience, presumably by consolidating or enhancing the changes that occurred during the prior period of monocular deprivation.

Similarly, molecular changes accompany the reorganization of the receptive fields of barrel cortex neurons after trimming of mystacial whiskers in the rat. These fluctuations, in nerve growth factor (*85*) as well as levels of mRNA for the GABA-synthetic enzyme glutamate decarboxylase (*86*), are modulated by sleep deprivation. Stimulation of whiskers also affects subsequent sleep EEG patterns (*87*).

Cognitive Processing in REM and NREM

Studies of dreaming often investigate aspects of this conscious experience that are potentially relevant to our understanding of learning and memory. One approach, which seeks to identify isomorphisms between the basic neurophysiological features of REM and the formal properties of REM dreams (*57*), led to the first physiologically based model of dream construction (*57*, *88*) and has yielded rich and novel data. We have recently reviewed this literature in detail (*89*).

An alternate approach is to actually measure cognitive processes within minutes of awakenings from REM and NREM. During this period of "sleep inertia" (*90*), the brain is thought to remain in a state similar to that of the prior sleep period (*91*).

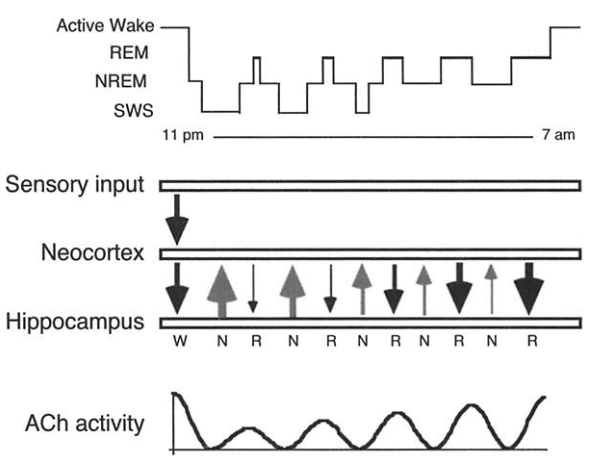

Fig. 2. The ultradian cycle and information processing. Changes in cholinergic neuromodulation and hippocampo-neocortical communication are superimposed on the 90-min human REM-NREM cycle across the night. The slow shift from SWS domination to REM domination across the night is seen in amounts of SWS and REM, as well as in the duration of REM periods and in both the amplitude and frequency of rapid eye movements within REM. The cholinergic neuromodulation is presumed to follow this pattern because rapid eye movements parallel the activity of brainstem cholinergic neurons. From Stickgold *et al.* (*3*).

Using this technique, we have shown (*92*) that semantic priming favors weaker associations after REM awakenings than after NREM awakenings (Fig. 3) and that solving anagrams is similarly enhanced after REM compared with NREM awakenings (*93*). Both of these findings support the contention that REM favors more "fluid thinking" than NREM, perhaps as a result of the decreased aminergic and increased cholinergic modulation found in this state (*94*).

More generally, the cognitive changes seen during REM may be the combined result of three physiological characteristics of REM: (i) the shift in neuromodulatory balance from aminergic to cholinergic, (ii) the decreased activity in DLPFC and increased activity in both the anterior cingulate cortex and amygdala (*75–77*), and (iii) the decreased outflow of information from hippocampus to neocortex (*53*). Taken together, these findings suggest that the brain in REM is tuned more for the processing of associative memories than for the simple consolidation of recent memory traces and may explain, in part, various features of REM dreams, including their bizarre, hyperassociative quality (*95*) and minimal incorporation of episodic memories (*96*, *97*).

Dreams and Memory

Sources of dream elements in waking and sleep. Dreams presumably reflect the activation and recombination of memories, and both these memories and associations to them may be altered in some ways in the process. But which memory systems are activated during dreaming remains uncertain.

Evidence of memory activation comes from verbal reports of dreaming. Such reports indicate, for example, that as the brain state progresses from quiet waking to sleep onset, NREM, and finally REM, hallucinations increase sharply in frequency, whereas directed thinking gradually decreases (Fig. 4) (*98–101*). Along with the increase in hallucinations, REM dreams show a parallel increase in bizarre, hyperassociative elements (*89*) and emotions (*102*, *103*).

Changes in sleep states appear to be accompanied by a shift in the sources of memories incorporated into the dreams as well. In a recent meta-analysis, it was found that when subjects were asked to identify the waking sources for dream elements, episodic memory sources were less frequently identified in REM than in NREM or at sleep onset, paralleling the decline in directed thinking across these stages (*104*) (Fig. 4).

Dream elements often appear to arise from memories of waking events. But the fact that an element can be traced to a specific waking event does not necessarily mean that an episodic memory was used for dream construction. Episodic memories are defined as a memory of an event, recalled as an integrated whole, with the actual waking event (or "episode") replayed in one's mind. Episodic memories are thought to consist of multiple hippocampally linked memory traces located within neocortical regions and dependent on the hippocampus for their integrated recall (*105*). In contrast, dream researchers normally ask if the source of a dream element is a waking event, independent of how memories of the event are stored in the brain. Thus, if a subject has a phone conversation with an old friend in the evening and subsequently dreams of mountain climbing with the friend, the dream element is judged to have an episodic memory source, even though the dream element shows almost no similarity to the event and clearly is not, itself, a replay of an episodic memory.

In fact, when subjects identify waking events as the sources of dream elements, the dreams themselves rarely replay episodic memories. When 364 dream elements from 299 dream reports with identified origins in prior waking were analyzed, only 1 to 2% were found to have these properties of epi-

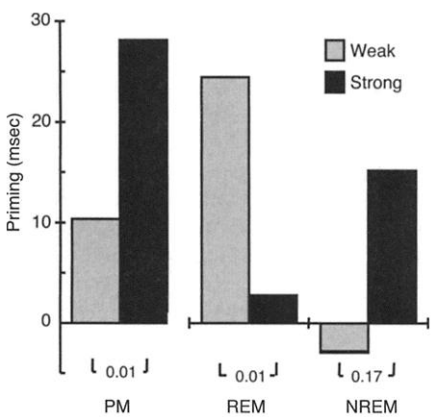

Fig. 3. Semantic priming across wake-sleep states. Priming is defined as the decrease in reaction times when identifying a target word that is preceded by a semantically related "prime" word compared with identifying a target preceded by an unrelated prime. Priming (ms) = $RT_{unrelated} - RT_{related}$. Within-state comparison p values are shown in bars below the graph. From Stickgold *et al.* (*92*). PM: wake subjects, tested in the afternoon, $n = 20$; REM and NREM: $n = 44$.

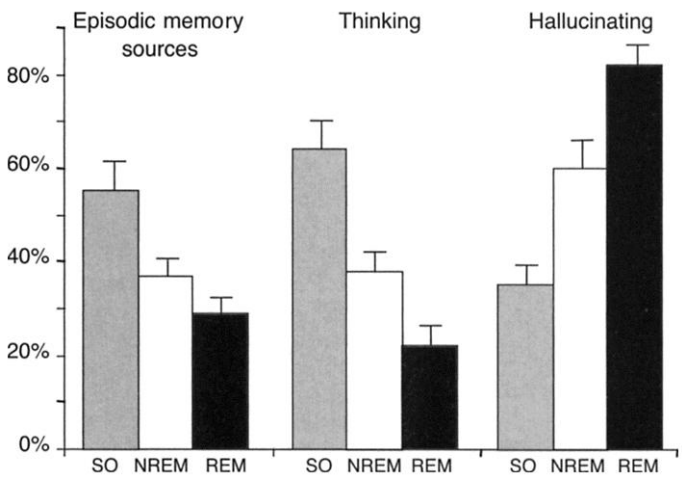

Fig. 4. Memory sources, thoughts, and hallucinations. Percentage of dream elements ("thematic units") with identified episodic memory sources and percentage of dreams containing directed thinking and hallucinating. Data for episodic memory sources are taken from Baylor and Cavallero (*104*) and for thinking and hallucinating from Fosse *et al.* (*101*). For episodic memory sources, sleep onset (SO): $n = 27$; REM and NREM: $n = 93$. For thinking and hallucinating, $n = 16$.

Table 2. Memory systems and dream elements. Subjects recorded 299 dream reports (criterion A) containing 364 dream elements (criterion B) indicated by the subjects to have identifiable sources in waking thoughts and events of the preceding 2 weeks. Although subjects ascribed the sources of 147 of these dream elements to prior events (criterion C), the remaining 217 elements were ascribed not to events, but to prior waking thoughts. Of the 147 dream elements that could conceivably represent replays of episodic memories, only 38 (10% of all elements) occurred in the same location in both the dream and waking event (criterion D), and only 12 (3% of all elements) conserved at least two other aspects of the waking event (e.g., characters and actions). When these 12 dream elements were compared by external judges with their ascribed waking sources, only five were rated as probable replays of episodic memories and only three additional elements were judged as possible replays, representing a total of five to eight instances (1 to 2%) of possible episodic replay. Data from Fosse *et al.* (*96*, *97*).

Criterion	Subjects	Reports	Elements
A All reports with content	29	299	–
B Elements with waking sources	27	194	364 (100%)
C Elements with episodic sources	22	104	147 (40%)
D +Conserved location	17	31	38 (10%)
E +Additional conserved features	9	11	12 (3%)
F +Judged episodic	4 to 6	5 to 8	5 to 8 (1 to 2%)

sodic memories. Instead, the dream elements normally reflect only one or two aspects of the waking experience (Table 2).

This suggests that the brain sources for dream elements are not hippocampally mediated episodic memories, but cortical traces of discrete components of the episodic memories, which then presumably are combined with associated semantic memories. With dorsolateral prefrontal cortex deactivated in both REM and NREM (*75*, *76*, *106*, *107*) and the hippocampal formation producing only minimal cortical output in REM (*53*), actual episodic memories may be inaccessible and hence irrelevant to the dream construction process. Such a conclusion would profoundly alter the standard conceptualization of dreaming and would strongly constrain any models of dream construction and function. Further evidence in support of this conclusion comes from studies of sleep onset dreaming, reviewed below.

Emotions and dreams. Emotions may play a central role in the functioning of the brain-mind during dreaming. In REM, the central nucleus of the amygdala plays a crucial role in the activation of medial prefrontal cortical structures associated with the highest order regulation of emotions (*76*, *108*, *109*). This adds to the deactivation of DLPFC, normally associated with higher cognitive functions (*110*), in REM. Thus, the brain appears to be biased toward emotional processing in this state.

As noted earlier, there is evidence for both emotion-enhanced REM and REM-facilitated retention of emotionally salient memories. Moreover, both depression (*111*) and the presleep viewing of unpleasant films (*112*) correlate with reports of negative emotion in early night REM dreaming. How specific aspects of emotional events affect dream construction remains obscure, as it has been difficult to reliably induce the incorporation of waking events or emotions into subsequent dreams.

Sleep onset dreaming. Many of the problems associated with identifying dream sources can be eliminated by studying hypnagogic dreams, which occur at sleep onset. These truncated dreams show robust incorporation of daytime experiences and are experimentally controllable. We have manipulated hypnagogic dream content by having subjects play the video game Tetris (*113*) or the arcade style downhill skiing simulator, Alpine Racer II (*114*, *115*). Reports were collected from subjects in their own homes, with their sleep monitored by the Nightcap sleep monitoring system, rather than standard polysomnography (*116*, *117*). Using these games, we obtained sleep onset reports of images of Tetris or downhill skiing in up to 89% of subjects and 42% of first-night reports (*114*, *115*), with no difference in frequency or content between normal and densely amnesic subjects (*113*). Nevertheless, the neocortical sources of these images were not simply stored sensory representations of recent stimuli, as Tetris players occasionally reported images from past versions of Tetris and Alpine Racers reported images from actual skiing (*115*).

These initial experimental studies have demonstrated that hypnagogic dreaming involves (i) a high rate of incorporation of memories of events from the day or (ii) from older related memories, with (iii) a preference for emotionally salient material but (iv) without high dream affect (*114*, *115*) and (v) without hippocampal or medial temporal lobe involvement. Although the sleep onset period differs from normal NREM and REM sleep both in its characteristic dream features (*117*, *118*) and polysomnographic features (*6*), these findings nevertheless further constrain the shape of any general theory explaining the nature and function of dreaming.

Modeling Dream Theory

A comprehensive theory of dreaming must address two questions: how dreams are constructed and what purpose that construction process might serve. To answer the first question, we need to show (i) how neurophysiology sets the stage for memory selection, (ii) how it favors associative processes that produce bizarre and unrecognizable representations of memories, and (iii) how these elements are combined with others into a narrative, often with high emotional content. To answer the second question, we need to know if, how, and why the dream construction process is behaviorally, psychologically, and psychosocially useful. Theories of dreaming continue to appear unabated (*46*, *57*, *89*, *119*–*121*), but each theory addresses only a subset of the questions necessary for a comprehensive theory, and all contain enormous explanatory gaps.

In the context of a multilevel system of sleep-dependent memory reprocessing, dreams represent the conscious awareness of complex brain systems involved in the reprocessing of emotions and memories during sleep. But in discussing the functions of sleep and dreaming, it is important to remember that neither is a uniform process. Sleep onset, NREM, and REM each are characterized by a unique physiology and normative dream structure. As such, there is a need to discuss each of them separately.

Hypnagogic dreams normally lack the bizarreness, self-representation, emotions, and narrative complexities common to REM dreams. Although they are often tightly linked to prior waking activities, they can also display associated memories from the distant past. Here, as in REM, it appears that the hippocampal episodic memory system is inactive. And although emotions appear to play an important role in the selection of memories for incorporation into dreams, the dreams themselves often show little or no emotional content (*114*). They thus seem to access and integrate memories and emotions in a manner uniquely different from that seen, for example, in REM. The nature of NREM dreaming and how it does and does not differ from REM dreaming remains a confusing field (*46*, *89*) and is beyond the scope of this review.

Because REM dreams are normally the longest and the most visually intense, bizarre, and emotional, researchers have proposed that the unique physiology of REM must contribute to this more intense dream production. In 1977, Hobson and McCarley (*57*) proposed that REM dreams are initiated by chaotic brainstem activity that then activates cortical regions, where the "brain/mind" makes the best sense it can out of a noisy signal, bringing forth, rather than hiding, meaning. Almost 25 years later, our increased understanding of brain systems makes a more detailed picture possible.

During REM, limbic forebrain structures and the amygdala are activated while both DLPFC and the locus coeruleus become less active. This presumably inhibits the ability of DLPFC to allocate attentional resources (and the dreaming brain classically pays little attention to bizarre incongruities in dreams). At the same time, the inhibition of hippocampal outflow would prevent the reactivation of episodic memories (*53*). Dreams would thus be constructed largely from those primarily weak neocortical associations available during REM (*92*). Although the process of incorporation of these weak associates is unknown, we predict that associated emotions, mediated by both the amygdala and medial orbitofrontal cortex, play an important role. Thus, the resulting dreams would appear to be not only unpredictable and bizarre but highly emotional as well.

We hypothesize that these features reflect an attempt, on the part of the brain, to identify and evaluate novel cortical associations in the light of emotions mediated by limbic structures activated during REM. This would be in keeping with the proposed role in waking of these structures in the identification of mismatches between expected and actual behavioral outcomes (*122*–*125*) and would also explain the similarities seen between cholinergic and PGO activity in the amygdala during REM on the one hand and during alerting and orienting responses in awake animals on the other (*126*–*128*). Such evaluations could then lead to the strengthening or weakening of specific activated associations, providing the functional consequence of REM dreaming. Although this model is highly speculative, it is only through such integration of the

converging neuroscientific and psychological data that we can hope to construct a new cognitive neuroscience of dreaming.

References and Notes

1. D. Hartley, *Observations on Man, His Frame, His Duty and His Expectations* (Johnson, London, 1791).
2. J. A. Horne, *Neurosci. Biobehav. Rev.* **24**, 777 (2000).
3. R. Stickgold, *Trends Cognit. Sci.* **2**, 484 (1998).
4. R. P. Vertes, K. E. Eastman, *Behav. Brain Sci.* **23**, 867 (2000).
5. P. Maquet, *Science* **294**, 1048 (2001).
6. A. Rechtschaffen, A. Kales, *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects* (Brain Information Service, Univ. of California, Los Angeles, 1968).
7. M. G. Frank, N. P. Issa, M. P. Stryker, *Neuron* **30**, 275 (2001).
8. J. P. Shaffery, H. P. Roffwarg, S. G. Speciale, G. A. Marks, *Brain Res.* **114**, 109 (1999).
9. S. Gais, W. Plihal, U. Wagner, J. Born, *Nature Neurosci.* **3**, 1335 (2000).
10. A. Karni, D. Tanne, B. S. Rubenstein, J. J. M. Askenasy, D. Sagi, *Science* **265**, 679 (1994).
11. R. Stickgold, D. Whidbee, B. Schirmer, V. Patel, J. A. Hobson, *J. Cognit. Neurosci.* **12**, 246 (2000).
12. R. Stickgold, L. James, J. A. Hobson, *Nature Neurosci.* **2**, 1237 (2000).
13. C. Smith, in *The Functions of Dreaming*, M. K. A. Moffitt, R. Hoffman, Ed. (SUNY Press, New York, 1993), pp. 341–361.
14. S. Freud, *The Interpretation of Dreams*, J. Strachey, Ed. (Basic Books, New York, 1900).
15. J. A. Horne, M. J. McGrath, *Biol. Psychol.* **18**, 165 (1984).
16. J. Siegel, *Science* **294**, 1058 (2001).
17. E. Aserinsky, N. Kleitman, *Science* **118**, 361 (1953).
18. C. Smith, *Neurosci. Biobehav. Rev.* **9**, 157 (1985).
19. ———, L. Lapp, *Sleep Res.* **16**, 211 (1987).
20. C. Smith, *Behav. Brain Res.* **69**, 137 (1995).
21. ———, G. M. Rose, *Physiol. Behav.* **59**, 93 (1996).
22. C. Smith, *Behav. Brain Res.* **78**, 49 (1996).
23. ———, J. M. Conway, G. M. Rose, *Neurobiol. Learn. Mem.* **69**, 211 (1998).
24. E. Hennevin, B. Hars, C. Maho, V. Bloch, *Behav. Brain Res.* **69**, 125 (1995).
25. C. Smith, S. Butler, *Physiol. Behav.* **29**, 469 (1982).
26. C. Smith, C. MacNeill, *Psychobiology* **21**, 109 (1993).
27. M. H. McGrath, D. B. Cohen, *Psychiatr. Bull.* **85**, 24 (1978).
28. C. Smith, M. Whittaker, *Sleep Res.* **16**, 536 (1987).
29. V. Castaldo, V. Krynicki, J. Goldstein, *Percept. Mot. Skills* **39**, 1023 (1974).
30. W. Plihal, J. Born, *J. Cognit. Neurosci.* **9**, 534 (1997).
31. ———, J. Born, *Psychophysiology* **36**, 571 (1999).
32. U. Wagner, S. Gais, J. Born, *Learn. Mem.* **8**, 112 (2001).
33. C. Grieser, R. Greenberg, R. H. Harrison, *J. Abnorm. Psychol.* **80**, 280 (1972).
34. R. D. Cartwright *et al.*, *Psychophysiology* **12**, 561 (1975).
35. R. Greenberg, R. Pillard, C. Pearlman, *Psychosom. Med.* **34**, 257 (1972).
36. I. Lewin, D. Gombosh, in *Sleep: Physiology, Biochemistry, Psychology, Pharmacology, Clinical Implications*, W. P. Koella, P. Levin, Eds. (Karger, Basel, Switzerland, 1973), pp. 399–403.
37. R. Cartwright, *Arch. Gen. Psychiatry* **40**, 197 (1983).
38. D. J. Kupfer, F. G. Foster, *Lancet* **2**, 648 (1972).
39. C. I. Reynolds *et al.*, *Biol. Psychiatry* **34**, 791 (1993).
40. R. Greenberg, C. A. Pearlman, D. Gampel, *Br. J. Med. Psychol.* **45**, 27 (1972).
41. R. J. Ross, W. A. Ball, K. A. Sullivan, S. N. Caroff, *Am. J. Psychiatry* **146**, 697 (1989).
42. A. Karni, D. Sagi, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 4966 (1991).
43. ———, *Nature* **365**, 250 (1993).
44. A. Giuditta *et al.*, *Behav. Brain Res.* **69**, 157 (1995).
45. J. DeKoninck, D. Lorrain, G. Christ, G. Proulx, D. Coulombe, *Int. J. Psychophysiol.* **8**, 43 (1989).
46. M. Solms, *Behav. Brain Sci.* **23**, 843 (2000).
47. M. Steriade, *Neuroscience* **101**, 243 (2000).
48. ———, *Trends Neurosci.* **22**, 337 (1999).
49. T. Otto, H. Eichenbaum, S. Wiener, C. Wible, *Hippocampus* **1**, 181 (1991).
50. C. Pavlides, Y. J. Greenstein, M. Grudman, J. Winson, *Brain Res.* **439**, 383 (1988).
51. P. T. Huerta, J. E. Lisman, *Neuron* **15**, 1053 (1995).
52. J. J. Chrobak, G. Buzsáki, *J. Neurosci.* **14**, 1660 (1994).
53. G. Buzsáki, *Cerebr. Cortex* **6**, 81 (1996).
54. G. E. Hinton, P. Dayan, B. J. Frey, R. M. Neal, *Science* **268**, 1158 (1995).
55. J. M. Calvo, A. Fernandez-Guardiola, *Sleep* **7**, 202 (1984).
56. S. Datta, *J. Neurosci.* **20**, 8607 (2000).
57. J. A. Hobson, R. W. McCarley, *Am. J. Psychiatry* **134**, 1335 (1977).
58. A. K. Engel, P. Fries, P. Konig, M. Brecht, W. Singer, *Conscious. Cognit.* **8**, 128 (1999).
59. R. Llinas, U. Ribary, *Proc. Natl. Acad. Sci. U.S.A.* **90**, 2078 (1993).
60. C. Pavlides, J. Winson, *J. Neurosci.* **9**, 2907 (1989).
61. M. A. Wilson, B. L. McNaughton, *Science* **265**, 676 (1994).
62. K. Louie, M. A. Wilson, *Neuron* **29**, 145 (2001).
63. H. Hirase, X. Leinekugel, J. Csicsvari, A. Czurko, G. Buzsaki, *J. Neurosci.* **21**, RC145 (2001).
64. J. A. Hobson, R. A. Stickgold, *Curr. Biol.* **5**, 35 (1995).
65. G. R. Poe, D. A. Nitz, B. L. McNaughton, C. A. Barnes, *Brain Res.* **855**, 176 (2000).
66. J. J. Kim, M. S. Fanselow, *Science* **256**, 675 (1992).
67. G. Winocur, *Behav. Brain Res.* **38**, 154 (1990).
68. C. Holscher, R. Anwyl, M. J. Rowan, *J. Neurosci.* **17**, 6470 (1997).
69. F. Crick, G. Mitchison, *Nature* **304**, 111 (1983).
70. A. S. Dave, D. Magoliash, *Science* **290**, 812 (2000).
71. J. A. Hobson, R. W. McCarley, P. W. Wyzinski, *Science* **189**, 55 (1975).
72. H. Kametani, H. Kawamura, *Life Sci.* **47**, 421 (1990).
73. Changes in both ACh and 5-HT have been proposed as mediators of sleep-dependent memory consolidation (*79*, *129*). Cortisol levels also vary across the night and appear to affect memory consolidation during sleep (*130*).
74. J. A. Hobson, E. F. Pace-Schott, R. Stickgold, D. Kahn, *Curr. Opin. Neurobiol.* **8**, 239 (1998).
75. A. R. Braun *et al.*, *Brain* **120**, 1173 (1997).
76. P. Maquet *et al.*, *Nature* **383**, 163 (1996).
77. J. A. Hobson, R. Stickgold, E. F. Pace-Schott, *Neuroreport* **9**, R1 (1998).
78. Her findings indicate that during REM, the rat brain can (i) respond at the neuronal level to associations learned during prior waking, (ii) form new associations after simultaneous stimulation of the central gray and the medial geniculate nucleus, and (iii) enhance the benefits of posttraining REM through direct stimulation of the mesencephalic reticular formation (MRF), presumably through augmentation of processes mediated by the pontine reticular formation. In addition, posttraining MRF stimulation decreases the normal posttraining REM increase as well as the deleterious effects of posttraining REM deprivation.
79. L. Graves, A. Pack, T. Abel, *Trends Neurosci.* **24**, 237 (2001).
80. G. Tononi, C. Cirelli, *Arch. Ital. Biol.* **139**, 221 (2001).
81. B. M. Gutwein, P. J. Shiromani, W. Fishbein, *Pharm. Biochem. Behav.* **12**, 377 (1980).
82. R. Bourtchouladze *et al.*, *Learn. Mem.* **5**, 365 (1998).
83. S. Ribeiro, V. Goyal, C. Mello, C. Pavlides, *Learn. Mem.* **6**, 500 (1999).
84. J. P. Shaffery *et al.*, *Dev. Brain Res.* **97**, 51 (1996).
85. J. A. Brandt *et al.*, *Brain Res.* **898**, 105 (2001).
86. L. Churchill *et al.*, *Sleep* **24**, 261 (2001).
87. V. Vyazovskiy, A. A. Borbely, I. Tobler, *Sleep Res.* **9**, 367 (2000).
88. J. A. Hobson, in *Sleep and Cognition*, R. Bootzin, J. Kihlstrom, D. Schacter, Eds. (American Psychological Association, Washington, DC, 1990), pp. 25–40.
89. J. A. Hobson, E. F. Pace-Schott, R. Stickgold, *Behav. Brain Sci.* **23**, 793 (2000).
90. A. Lubin, D. Hord, M. L. Tracy, L. C. Johnson, *Psychophysiology* **13**, 334 (1976).
91. D. F. Dinges, in *Sleep and Cognition*, R. Bootzin, J. Kihlstrom, D. Schacter, Eds. (American Psychological Association, Washington, DC, 1990), pp. 159–178.
92. R. Stickgold, L. Scott, C. Rittenhouse, J. A. Hobson, *J. Cognit. Neurosci.* **11**, 182 (1999).
93. M. P. Walker, C. Liston, J. A. Hobson, R. Stickgold, in preparation.
94. D. Q. Beversdorf, J. D. Hughes, B. A. Steinberg, L. D. Lewis, K. M. Heilman, *Neuroreport* **10**, 2763 (1999).
95. A. N. Mamelak, J. A. Hobson, *J. Cognit. Neurosci.* **1**, 201 (1989).
96. M. J. Fosse, R. Stickgold, R. Fosse, J. A. Hobson, *Sleep* **24**, A179 (2001).
97. M. J. Fosse, thesis, Harvard University, Cambridge, MA (2001).
98. D. Foulkes, *J. Abnorm. Social Psychol.* **65**, 14 (1962).
99. ———, P. S. Spear, J. D. Symonds, *J. Abnorm. Psychol.* **71**, 280 (1966).
100. A. Rechtschaffen, P. Verdone, J. Wheaton, *Can. J. Psychiatry* **8**, 409 (1963).
101. R. Fosse, R. Stickgold, J. A. Hobson, *Psychol. Sci.* **12**, 30 (2001).
102. I. Strauch, B. Meier, *In Search of Dreams: Results of Experimental Dream Research* (State University of New York Press, Albany, NY, 1996).
103. R. Fosse, R. Stickgold, J. A. Hobson, *Sleep*, in press.
104. G. W. Baylor, C. Cavallero, *Sleep* **24**, 165 (2001).
105. D. L. Schacter, E. Tulving, *Memory Systems 1994* (MIT Press, Cambridge, MA, 1994).
106. P. Maquet *et al.*, *J. Neurosci.* **17**, 2807 (1997).
107. E. A. Nofzinger, M. A. Mintun, M. B. Wiseman, D. J. Kupfer, R. Y. Moore, *Brain Res.* **770**, 192 (1997).
108. E. A. Nofzinger *et al.*, *Soc. Neurosci. Abstr.* **22**, 27 (1996).
109. A. R. Damasio *et al.*, *Nature Neurosci.* **3**, 1049 (2000).
110. P. S. Goldman-Rakic, *Philos. Trans. R. Soc. London Ser. B Biol. Sci.* **351**, 1445 (1996).
111. R. Cartwright, A. Luten, M. Young, P. Mercer, M. Bears, *Psychiatry Res.* **81**, 1 (1998).
112. C. Lauer, D. Riemann, R. Lund, M. Berger, *Psychophysiology* **24**, 263 (1987).
113. R. Stickgold *et al.*, *Science* **290**, 350 (2000).
114. K. M. Emberger, thesis, Harvard University, Cambridge, MA (2001).
115. R. Stickgold, J. A. Hobson, K. Emberger, *Soc. Neurosci. Abstr.*, in press.
116. J. A. Hobson, Stickgold, *Conscious. Cognit.* **3**, 1 (1994).
117. J. T. Rowley, R. Stickgold, J. A. Hobson, *Conscious. Cognit.* **7**, 67 (1998).
118. D. Foulkes, G. Vogel, *J. Abnorm. Psychol.* **70**, 231 (1965).
119. M. Jouvet, *The Paradox of Sleep: The Story of Dreaming* (MIT Press, Cambridge, MA, 1999).
120. A. Revonsuo, *Behav. Brain Sci.* **23**, 877 (2000).
121. M. Solms, *The Neuropsychology of Dreams: A Clinico-Anatomical Study* (Lawrence Erlbaum Associates, Mahwah, NJ, 1997).
122. W. J. Gehring, R. T. Knight, *Nature Neurosci.* **3**, 516 (2000).
123. W. J. Gehring, M. G. H. Coles, D. E. Meyer, E. A. Donchin, in *Perspectives of Event-Related Potentials Research*, G. Karmos *et al.*, Eds. (Elsevier, Amsterdam, 1995), pp. 261–272.
124. M. Falkenstein, J. Hohnsbein, J. Hoorman, in *Perspectives of Event-Related Potentials Research*, G. Karmos *et al.*, Eds. (Elsevier, Amsterdam, 1995), pp. 287–296.
125. C. S. Carter *et al.*, *Science* **280**, 747 (1998).
126. A. R. Morrison, L. D. Sanford, R. J. Ross, in *Rapid Eye Movement Sleep*, B. N. Mallick, S. Inoue, Eds. (Dekker, New York, 1999), pp. 51–68.
127. P. J. Whalen, *Curr. Dir. Psychol. Sci.* **7**, 177 (1998).
128. J. M. Calvo, K. Simon-Arceo, in *Handbook of Behavioral State Control: Molecular and Cellular Mechanisms*, R. Lydic, H. A. Baghdoyan, Eds. (CRC Press, Boca Raton, Fl, 1999), pp. 391–406.
129. M. E. Hasselmo, *Trends Cognit. Sci.* **3**, 351 (1999).
130. W. Plihal, R. Pietrowsky, J. Born, *Psychoneuroendocrinology* **24**, 313 (1999).

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