Sleep and Emotional Memory Processing

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The ability of the human brain to generate, regulate, and be guided by emotions represents a fundamental process governing not only our personal lives but also our mental health and societal structure. The recent emergence of cognitive neuroscience has ushered in a new era of research connecting affective behavior with human brain function and has provided a systems-level view of emotional information processing, translationally bridging animal models of affective regulation and relevant clinical disorders.^{1,2}

Independent of this research area, a recent resurgence has also taken place within the basic sciences, focusing on the functional effect of sleep on neurocognitive processes.³ However, surprisingly less research attention has been given to the interaction between sleep and affective brain function, considering the remarkable overlap between the known physiology of sleep, especially rapid eye movement (REM) sleep, and the associated neurochemistry and network anatomy that modulate emotions, as well as the prominent co-occurrence of abnormal sleep (including REM sleep) in almost all affective psychiatric and mood disorders.

Despite the relative historical paucity of research, recent work has begun to describe a consistent and clarifying role of sleep in the selective modulation of emotional memory and affective regulation. This review provides a synthesis of these findings, describing an intimate relationship between sleep, emotional brain function, and clinical mood disorders and offers a tentative first theoretical framework that may account for these observed interactions.

SLEEP

The sleep of mammalian species has been broadly classified into 2 distinct types; non-REM (NREM) sleep and REM sleep, with NREM sleep being further divided in primates and cats into 4 substages (1-4) corresponding, in that order, to increasing depth of sleep.⁴ In humans, NREM and REM sleep alternate or "cycle" across the night in an ultradian pattern every 90 minutes (Fig. 1). Although this NREM-REM cycle length remains largely stable across the night, the ratio of NREM to REM within each 90-minute cycle changes, so that early in the night, stages 3 and 4 of NREM dominate, whereas stage-2 NREM and REM sleep prevail in the latter half of the night. The functional reasons for this organizing principal (deep NREM early in the night, stage-2 NREM and REM late in the night) remain unknown.⁵

As NREM sleep progresses, electroencephalographic (EEG) activity begins to slow in frequency. Throughout stage-2 NREM, there is the presence of phasic electrical events, including K-complexes (large electrical sharp waves in the EEG) and sleep spindles (short synchronized bursts of EEG electrical activity in the 11–15 Hz range).⁶ The deepest stages of NREM, stages 3 and 4, are often grouped together under the term slow wave sleep (SWS), reflecting the occurrence of low frequency waves (0.5–4 Hz), representing an expression of underlying mass cortical synchrony.^{7,8} During REM sleep, however, EEG wave forms once again change in their composition, associated with oscillatory activity in the theta band range (4–7 Hz),

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Fig. 1. The human sleep cycle. Across the night, NREM and REM sleep cycle every 90 minutes in an ultradian manner, while the ratio of NREM to REM sleep shifts. During the first half of the night, NREM stages 3 and 4 NREM (SWS) dominate, while stage-2 NREM and REM sleep prevail in the latter half of the night. EEG patterns also differ significantly between sleep stages, with electrical oscillations, such as slow delta waves developing in SWS, K-complexes and sleep spindles occurring during stage-2 NREM, and theta waves seen during REM.

together with higher frequency synchronous activity in the 30 to 80 Hz (gamma) range.^{9,10} Periodic bursts of rapid eye movement also take place, a defining characteristic of REM sleep, associated with the occurrence of phasic endogenous waveforms. These waveforms are expressed in, among other regions, the pons (P), lateral geniculate nuclei of the thalamus (G), and the occipital cortex (O), and as such, have been termed PGO waves.¹¹

As the brain passes through these sleep stages, it also undergoes dramatic alterations in neurochemistry.¹² In NREM sleep, subcortical cholinergic systems in the brainstem and forebrain become markedly less active ^{13,14} while firing rates of serotonergic Raphé neurons and noradrenergic locus coeruleus neurons are also reduced relative to waking levels.^{15,16} During REM sleep, both these aminergic populations are strongly inhibited, while the cholinergic systems become as or more active compared with wake,^{17,18} resulting in a brain state largely devoid of aminergic modulation and dominated by acetylcholine (ACh).

At a whole-brain systems level, neuroimaging techniques have revealed complex and dramatically different patterns of functional anatomy associated with NREM and REM sleep (for review, see¹⁹). During NREM SWS, brainstem, thalamic, basal ganglia, prefrontal, and temporal lobe regions all appear to undergo reduced activity. However, during REM sleep, significant elevations in levels of activity have been reported in the pontine tegmentum, thalamic nuclei, occipital cortex, mediobasal prefrontal lobes together with affect-related regions including the amygdala, hippocampus, and anterior cingulate cortex (Fig. 2). In contrast, the dorsolateral prefrontal cortex, posterior cingulate, and parietal cortex appear least active in REM sleep.

Although this summary only begins to describe the range of neural processes that are affected by the brain's daily transit through sleep states, it clearly demonstrates that sleep itself cannot be treated as a homogeneous entity, offering a range of distinct neurobiological mechanisms that can support numerous brain functions. The following sections examine the role of sleep, and specific stages of sleep, in the modulation of emotional memories and the regulation of affective reactivity, which culminate in a heuristic model of sleepdependent emotional brain processing.

Sleep and Emotional Memory Processing

The effect of sleep has principally been characterized at 2 different stages of memory: (1) before learning, in the initial formation (encoding) of new information; and (2) after learning, in the long-term solidification (consolidation) of new memories.^{3,20,21} Each of these stages are considered now, and focus is on reports involving affective learning.

Sleep and Affective Memory Encoding

The initial stage of memory formation can be strongly modulated by the elicitation of emotion at the time of learning.²² Emotionally arousing stimuli are consistently remembered better than neutral stimuli both in experimental laboratory studies and in real-life accounts (Heuer and Reisberg 1990²³; Bradley and colleagues 1992²⁴; Buchanan and Lovallo 2001²⁵; Christianson, 1992²⁶); studies of autobiographical memory have found that individuals are more likely to remember those events that have increased emotional and personal significance.²⁷ The adrenergic system appears to play a key role in orchestrating the enhancing effect of arousing emotion on memory at the initial moment of learning (and



Fig. 2. Regional brain activation during REM sleep (positron emission tomography scan). The areas include: (a) the pons; (b) amygdala; (c) thalamus; (d) right parietal operculum; and (e) anterior cingulate cortex. The z-value color scale indicates strength of activation. A z value of 3.09 corresponds to a P value of less than .001. (*Data from* Maquet P, Peters JM, Aerts J, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 1996;383:163.)

also during consolidation, discussed later). For example, Cahill and colleagues²⁸ have demonstrated that the administration of propanolol, a β adrenoceptor antagonist, to participants before learning of emotional and neutral narrative texts blocks the memory enhancing effects elicited by arousal. Similarly, propranolol administration before the encoding of affectively arousing word stimuli subverts the normal facilitation of emotional memory recall when tested shortly after.²⁹ However, this autonomic enhancing effect on memory is not observed in patients with amygdala lesions, suggesting a role not only for a specific neurochemical system in affective learning but also for a particular brain region.^{30,31} Indeed, functional neuroimaging studies have since confirmed the critical role of the amygdala in facilitating emotional memory formation at the time of experience.²⁸⁻³⁶

These beneficial enhancing effects of emotion on the initial process of learning pertain to conditions when the brain has obtained adequate prior sleep. There is now considerable evidence that sleep loss before encoding can significantly and selectively alter and impair the canonical profile of emotional memory enhancement. Although early studies investigating the role of sleepdependent memory in humans focused primarily on postlearning consolidation (see later sections), more recent data similarly support the need for adequate prelearning sleep in the formation of new human episodic memories. Some of the first studies of sleep deprivation and memory encoding focused on neutral forms of learning, indicating that the temporal memory (ie, the memory for events that occur) was significantly disrupted by a night of pretraining sleep deprivation^{37,38}; even when caffeine was administered to overcome nonspecific effects of lower arousal.

More recent investigations have examined the importance of pretraining sleep for the formation of emotional and neutral memories.3 Subjects were either sleep deprived for 36 hours or allowed to sleep normally before a learning session composed of emotionally negative, positive, and neutral words, with the efficiency of encoding subsequently tested after 2 recovery nights of sleep. Averaged across all memory categories, subjects who were sleep deprived demonstrated a 40% deficit in memory encoding, relative to subjects who had slept normally before learning (Fig. 3A). However, when these data were separated into the 3 emotional categories (negative, positive, or neutral), selective dissociations became apparent (see Fig. 3B). In subjects who had slept (control group), both positive and negative stimuli were associated with superior retention levels relative to the neutral condition,



Fig. 3. Sleep deprivation and encoding of emotional and nonemotional declarative memory. Effects of 38 hours of total sleep deprivation on encoding of human declarative memory. (*A*) When combined across all emotional and nonemotional categories. (*B*) When separated by emotional (positive and negative valence) and nonemotional (neutral valence) categories, demonstrating a significant group (sleep, sleep-deprivation) \times emotion category (positive, negative, neutral) interaction (*F*[1,18] 3.58, *P*<.05). Post hoc *t*-test comparisons: **P*<.08, ***P*<.05, ****P*<.01; NS, not significant; error bars represent standard error of the mean. d', d-prime (discrimination index). (*From* Walker MP, Stickgold R. Sleep, memory, and plasticity. Annu Rev Psychol 2006;57:139–66; Fig. 2, p. 144; with permission.)

consistent with the notion that emotion facilitates memory encoding.²² In the sleep-deprived group, a severe encoding impairment was evident for neutral and especially positive emotional memories, showing a significant 59% retention deficit, relative to the control condition. Most interesting was the relative resistance of negative emotional memory to sleep deprivation, showing a markedly smaller and nonsignificant impairment.

These data indicate that sleep loss impairs the ability to commit new experiences to memory and has recently been associated with dysfunction throughout the hippocampal complex.³⁹ The data also suggest that, although the effects of sleep deprivation are directionally consistent across emotional subcategories, the most profound effect is on the encoding of positive emotional stimuli, and to a lesser degree, on the emotionally neutral stimuli. In contrast, the encoding of negative memory seems to be more resistant to the effects of prior sleep loss. Moreover, such results may offer novel learning and memory insights into affective mood disorders that express co-occurring sleep abnormalities,⁴⁰ whereby sleep deprivation imposes a skewed distribution of learning, resulting in a dominance of negative memory representations.

Sleep and Affective Memory Consolidation

The role of sleep in declarative memory consolidation, rather than being absolute, may depend on more intricate aspects of the information being learned, such as the novelty, the meaning to extract, and also the affective salience of the material. A collection of findings has described a preferential offline consolidation benefit (reduction in forgetting) for emotional information compared with neutral information. Furthermore, this differential emotional advantage seems to persist and even improve over periods containing a night of sleep.^{36,41-44} Indeed, several reports have directly examined whether it is time, with sleep, that preferentially modulates these effects. Based on the coincident neurophysiology that REM sleep provides and the neurobiological requirements of emotional memory processing,^{45,46} work has now begun to test a selective REM sleep-dependent hypothesis of affective human memory consolidation.

For example, Hu and colleagues⁴⁷ have compared the consolidation of emotionally arousing and nonarousing picture stimuli after a 12-hour period across a day or after a night of sleep. A specific emotional memory benefit was observed only after sleep and not across an equivalent time awake. Atienza and Cantero¹⁵ have also demonstrated that total sleep deprivation the first night after learning significantly impairs later 1-week retention of emotional as well as neutral visual stimuli. This difference was greatest for neutral items relative to emotional items. Such a difference may indicate that emotional items are more resistant to the effect of first-night sleep

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deprivation (a finding with clinical treatment consequences), or that subsequent postdeprivation recovery sleep is more capable of salvaging consolidation of emotional relative to neutral memories. Wagner and colleagues⁴⁸ have also shown that sleep selectively favors the retention of previously learned emotional texts relative to neutral texts, and that this affective memory benefit is only present after late-night sleep (a period rich in REM sleep). This emotional memory benefit was found to persist in a follow-up study performed 4 years later.49 It has also been demonstrated that the speed of recognizing emotional face expressions presented before sleep is significantly improved the next day, a benefit that is positively correlated with the amount of intervening REM sleep.⁵⁰

Sleep has also been shown to target the consolidation of specific aspects of emotional experiences, as well as mediate the extinction of human fear memories. By experimentally varying the foreground and background elements of emotional picture stimuli, Payne and colleagues⁵¹ have demonstrated that sleep can target the strengthening of negative emotional objects in a scene but not in the peripheral background. In contrast, equivalent time awake did not afford any selective benefit to emotional object memory (or the background scene). This finding may suggest that sleep-dependent processing can selectively separate episodic experience into component parts, preferentially consolidating those of greatest affective salience. Using a conditioning paradigm in humans, Pace-Schott and colleagues⁵² recently investigated the effects of sleep and wake on fear extinction and generalization of fear extinction. Concurrent fear conditioning to 2 different stimuli was followed by targeted extinction of conditioned responding to only 1 of the stimuli. Participants were then tested after a 12-hour offline delay period across the day or after a night of sleep. On returning 12 hours later, generalization of extinction from the target stimuli to the nontargeted stimuli occurred after a night of sleep, yet not across an equivalent waking period. Therefore, sleep may not only modulate affective associations between stimuli but also additionally facilitate their generalization across related contexts.

Nishida and colleagues⁵³ have demonstrated that sleep, and specifically REM sleep neurophysiology, may underlie such consolidation benefits. Subjects performed 2 study sessions in which they learned emotionally arousing negative and neutral picture stimuli; 1 session was 4 hours prior and 1 was 15 minutes before a recognition memory test. In one group, participants slept (90-minute nap) after the first study session,

whereas in the other group, participants remained awake. Thus, items from the first (4-hour) study sessions transitioned through different brain states in each group before testing, containing sleep in the nap group and no sleep in the no-nap group, yet experienced identical brain-state conditions after the second study session, 15 minutes before testing. No change in memory for emotional (or neutral stimuli) occurred across the offline delay in the no-nap group. However, a significant and selective offline enhancement of emotional memory was observed in the nap group (Fig. 4A), the extent of which was correlated with the amount of REM sleep (see Fig. 4B), and the speed of entry into REM sleep (latency; not shown in figure). Most striking, spectral analysis of the EEG demonstrated that the magnitude of rightdominant prefrontal theta power during REM sleep (activity in the frequency range of 4.0-7.0 Hz) showed a significant and positive relationship with the amount of emotional memory improvement (see Fig. 4C, D).

These findings move beyond demonstrating that affective memories are preferentially enhanced across periods of sleep and indicate that the extent of emotional memory improvement is associated with specific REM sleep characteristics, both quantity and quality (and independent of nocturnal hormonal changes). Corroborating these correlations, it has previously been hypothesized that REM sleep represents a brain-state particularly amenable to emotional memory consolidation, based on its unique biology.47,54 Neurochemically, levels of limbic and forebrain ACh are markedly elevated during REM sleep,^{55,56} reportedly quadruple those seen during NREM and double those measured in quiet waking.¹⁸ Considering the known importance of ACh in the long-term consolidation of emotional learning,46 this procholinergic REM sleep state may promote the selective memory facilitation of affective memories, similar to that reported using experimental manipulations of ACh.⁵⁷ Neurophysiologically, theta oscillations have been proposed as a carrier frequency, allowing disparate brain regions that initially encode information to selectively interact offline, in a coupled relationship. By doing so, REM sleep theta may afford the ability to strengthen distributed aspects of specific memory representations across related but different anatomic networks.58,59

Sleep and Emotional Regulation

Relative to the interaction between sleep and affective memory, the effect of sleep loss on basic regulation and perception of emotions has



Fig. 4. REM sleep enhancement of negative emotional memories. (*A*) Offline benefit (change in memory recall for 4-hour-old vs 15-minute-old memories) across the day (wake, *gray bar*) or after a 90-minute nap (sleep, *filled bar*). (*B*) Correlation between the amount of offline emotional memory improvement in the nap group (ie, the offline benefit expressed in filled bar of *panel A*), and the amount of REM sleep obtained within the nap. (*C*) Correlation strength (Pearson's *r*-value) between offline benefit for emotional memory in the sleep group (the benefit expressed in filled bar of Fig. A) and the relative right versus left prefrontal spectral-band power (F4–F3) within the delta, alpha, theta, and beta spectral bands, expressed in average 0.5 Hz bin increments. Correlation strength is represented by the color range, demonstrating significant correlations within the theta frequency band (hot colors), and (*D*) exhibiting a maximum significance at the 5.75 Hz bin. ^a*P*<.05; error bars indicate standard error of mean. (*Modified from* Nishida M, Pearsall J, Buckner RL, et al. REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex 2009;19:1158–66; with permission.)

received substantially less research attention. Nevertheless, several studies evaluating subjective as well as objective measures of mood and affect, offer an emerging experimental understanding for the crucial role sleep plays in regulating emotional brain function, complimenting a rich associated clinical literature.

SLEEP LOSS, MOOD STABILITY, AND EMOTIONAL BRAIN (RE)ACTIVITY

Together with impairments of attention and alertness, sleep deprivation is commonly associated with increased subjective reports of irritability and affective volatility.⁶⁰ Using a sleep restriction paradigm (5 hours/night), Dinges and colleagues⁶¹ have reported a progressive increase in emotional disturbance across a 1-week period based on questionnaire mood scales. In addition, subjective descriptions in the daily journals of the participants also indicated increasing complaints of emotional difficulties. Zohar and colleagues⁶² have investigated the effects of sleep disruption on emotional reactivity to daytime work events in medical residents. Sleep loss was shown to amplify negative emotional consequences of disruptive daytime experiences while blunting the positive benefit associated with rewarding or goal-enhancing activities.

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Although these findings help to characterize the behavioral irregularities imposed by sleep loss, evidence for the role of sleep in regulating psychophysiologic reactivity and emotional brain networks is starting to emerge only now. To date, only 2 studies have addressed this interaction. Using functional magnetic resonance imaging (fMRI), Yoo and colleagues⁶³ examined the effect of 1 night of sleep deprivation on emotional brain reactivity in healthy young adults. During scanning, participants performed an affective stimulusviewing task involving the presentation of picture slides ranging in a gradient from emotionally neutral to increasingly negative and aversive. Although both groups expressed significant amygdala activation in response to increasingly negative picture stimuli, those in the sleep-deprivation condition showed a remarkable 60% greater magnitude of amygdala reactivity, relative to the control group (Fig. 5A, B). In addition to this increased intensity of activation, there was also

a marked increase in the extent of amygdala volume recruited in response to the aversive stimuli in the sleep-deprivation group (see Fig. 5B). Relative to the sleep-control group, those who were sleep deprived showed a significant loss of functional connectivity identified between the amygdala and the medial prefrontal cortex, a region known to have strong inhibitory projections to the amygdala (see Fig. 5C, D).⁶⁴ In contrast, significantly greater connectivity was observed between the amygdala and the autonomic-activating centers of the locus coeruleus in the deprivation group. Therefore, without sleep, an amplified hyperlimbic reaction by the human amygdala was observed in response to negative emotional stimuli, associated with a loss of top-down connectivity with the prefrontal lobe. A similar pattern of anatomic dysfunction has been implicated in several psychiatric mood disorders, which express co-occurring sleep abnormalities⁶⁵⁻⁶⁷ and directly raises the issue of



Fig. 5. The effect of sleep deprivation on emotional brain reactivity and functional connectivity. (*A*) Amygdala response to increasingly negative emotional stimuli in the sleep deprivation and sleep-control groups. (*B*) Corresponding differences in intensity and volumetric extent of amygdala activation between the 2 groups (average \pm standard error of mean (SEM) of left and right amygdala). (*C*) Depiction of associated changes in functional connectivity between the medial prefrontal cortex (mPFC) and the amygdala. With sleep, the prefrontal lobe was strongly connected to the amygdala, regulating and exerting and inhibitory top-down control. (*D*) Without sleep, however, amygdala-mPFC connectivity was decreased, potentially negating top-down control and resulting in an overactive amygdala. ^a*P*<.01; error bars indicate SEM. (*Modified from* Yoo SS, Gujar N, Hu P, et al. The human emotional brain without sleep—a prefrontal amygdala disconnect. Curr Biol 2007;17:R877; with permission.)

whether sleep loss plays a causal role in the initiation or maintenance of clinical mood disorders.

Complementing these findings, Franzen and colleagues⁶⁸ have examined the effect of total sleep deprivation on pupil diameter responses (a measure of autonomic reactivity) during a passive affective picture viewing task containing positive, negative, and neutral stimuli.68 Relative to a sleep-control group, there was a significantly larger pupillary response to negative pictures compared with positive or neutral stimuli in the deprivation group. Most recently, Gujar and colleagues⁶⁹ have compared the change in reactivity to specific types of emotions (fear, anger, happiness, sadness) across a 6-hour daytime waking interval that either did or did not contain a 90-minute nap. Without sleep, reactivity and intensity ratings toward threat-relevant negative emotions (anger and fear) significantly increased with continued time awake. However, an intervening nap blocked (anger) and even reversed (fear) these increases toward aversive stimuli, while conversely enhancing sensitivity toward rewardrelevant happy facial expressions. Only those subjects in the nap group who obtained REM sleep displayed this resetting of affective reactivity.

A HEURISTIC MODEL OF SLEEP-DEPENDENT EMOTIONAL PROCESSING

Based on the emerging interaction between sleep and emotion, a synthesis of these findings is provided next, which converge on a functional role for sleep in affective brain modulation. A model of sleep-dependent emotional information processing is described, offering provisional brainbased explanatory insights on the effect of sleep abnormalities in the initiation and maintenance of certain mood disorders and leading to testable predictions for future experimental investigations.

The findings discussed earlier suggest a predisposition for the encoding of negative emotional memories and a hyperlimbic reactivity to negative emotional events under conditions of sleep loss, together with a strengthening of negative memories during subsequent REM sleep, all of which have potential relevance for the understanding of major depression. Thus, at both stages of early memory processing, that is, encoding and consolidation, the architectural sleep abnormalities expressed in major depression may facilitate an adverse prevalence and strengthening of prior negative episodic memories. Yet, there may be an additional consequence of sleep-dependent memory processing, beyond the strengthening of the experience itself, and one that has additional implications for mood disorders – that is, sleeping to forget.

EMOTIONAL MEMORY PROCESSING: A SLEEP TO FORGET AND SLEEP TO REMEMBER HYPOTHESIS

Founded on the emerging interaction between sleep and emotion, the authors outline a model of affective information processing that may offer brain-based explanatory insights regarding the effect of sleep abnormalities, particularly REM sleep, on the initiation or maintenance of mood disturbance.

Although there is abundant evidence to suggest that emotional experiences persist in our autobiographies over time, an equally remarkable but less noted change is a reduction in the affective tone associated with their recall. Affective experiences seem to be encoded and consolidated more robustly than neutral memories because of the autonomic neurochemical reactions elicited at the time of the experience,⁴⁶ creating what is commonly termed an emotional memory. However, the later recall of these memories tends not to be associated anywhere near the same magnitude of autonomic (re)activation as that elicited at the moment of experience, suggesting that, over time, the affective "blanket" previously enveloping the memory during learning has been removed, whereas the information contained within that experience (ie, the memory) remains.

For example, neuroimaging studies have shown that the initial exposure and learning of emotional stimuli is associated with substantially greater activation in the amygdala and hippocampus, relative to neutral stimuli.^{33,70,71} In 1 of these studies,³³ however, when participants were reexposed to these same stimuli during recognition testing many months later, a change in the profile of activation occurred.⁷⁰ Although the same magnitude of differential activity between emotional and neutral items was observed in the hippocampus, this was not true in the amygdala. Instead, the difference in amygdala (re)activity to emotional items compared with neutral items had dissipated over time. This finding may support the idea that the strength of the memory (hippocampus-associated activity) remains at later recollection, yet the associated emotional reactivity to these items (limbic network activity) is reduced over time.

This hypothesis predicts that such decoupling preferentially takes place overnight; such that we sleep to forget the emotional tone, yet sleep to remember the tagged memory of that episode (SFSR model; **Fig. 6**). The model further argues that if this process is not achieved, the magnitude



Fig. 6. The sleep to forget and sleep to remember model of emotional memory processing. (A) Neural dynamics. Waking formation of an episodic emotional memory involves the coordinated encoding of hippocampal-bound information within cortical modules, facilitated by the extended limbic system, including the amygdala, and modulated by high concentrations of aminergic neurochemistry. During subsequent REM sleep, these same neural structures are reactivated, the coordination of which is made possible by synchronous theta oscillations throughout these networks, supporting the ability to reprocess previously learned emotional experiences. However, this reactivation occurs in a neurochemical milieu devoid of aminergic modulation and dominated by cholinergic neurochemistry. As a consequence, emotional memory reprocessing can achieve, on one hand, a depotentiation of the affective tone initially associated with the events at encoding, while on the other, a simultaneous and progressive neocortical consolidation of the information. The latter process of developing stronger corticocortical connections additionally supports integration into previous acquired autobiographical experiences, further aiding the assimilation of the affective events in the context of past knowledge, the conscious expression of which may contribute to the experience of dreaming. Cross-connectivity between structures is represented by number and thickness of lines. Circles within cortical and hippocampal structures represent information nodes; shade reflects extent of connectivity: strong (filled), moderate (gray), and weak (clear). Fill of limbic system and arrow thickness represent the magnitude of co-activation with and influence on the hippocampus. (B) Conceptual outcome. Through multiple iterations of this REM mechanism across the night and/or across multiple nights, the long-term consequence of such sleep-dependent reprocessing would allow for the strengthening and retention of salient information previously tagged as emotional at the time of learning. However, recall no longer maintains an affective, aminergic charge, allowing for postsleep recollection with minimal autonomic reactivity (unlike encoding), thereby preventing a state of chronic anxiety.

of affective charge remaining within autobiographical memory networks would persist, resulting in the potential condition of chronic anxiety or posttraumatic stress disorder (PTSD).

Based on the unique neurobiology of REM, a REM sleep hypothesis of emotional brain processing (see Fig. 6A) is proposed. It is suggested that the state of REM provides an optimal biologic theater, within which can be achieved a form of affective "therapy." First, increased activity within limbic and paralimbic structures during REM sleep may first offer the ability for reactivation of previously acquired affective experiences. Second, the neurophysiologic signature of REM sleep involving dominant theta oscillations within subcortical as well as cortical nodes may offer large-scale network cooperation at night, allowing the integration and, as a consequence, greater understanding of recently experienced emotional events in the context of pre-existing neocortically stored semantic memory. Third, these interactions during REM sleep (and perhaps through the conscious process of dreaming) critically and perhaps most importantly take place within a brain that is devoid of aminergic neurochemical concentration,⁵² particularly noradrenergic input from the locus coeruleus; the influence of which has been linked to states of high stress and anxiety disorders.⁷² Therefore, the neuroanatomical, neurophysiologic, and neurochemical conditions of REM sleep may offer a unique biologic milieu in which to achieve, on one hand, a balanced neural facilitation of the informational core of emotional experiences (the memory), yet may also depotentiate and ultimately ameliorate the autonomic arousing charge originally acquired at the time of learning (the emotion), negating a long-term state of anxiety (see Fig. 6).

Specific predictions emerge from this model. First, if this process of seperating emotion from memory was not achieved across the first night after such an experience, the model would predict that a repeat attempt of affective demodulation would occur on the second night, because the strength of the emotional "tag" associated with the memory would remain high. If this process failed a second time, the same events would continue to repeat across ensuing nights. It is just such a cycle of REM-sleep dreaming (nightmares) that represents a diagnostic key feature of PTSD.73 It may not be coincidental, therefore, that these patients continue to display hyperarousal reactions to associated trauma cues,74,75 indicating that the process of separating the affective tone from the emotional experience has not been accomplished. The reason why such a REM mechanism may fail in PTSD remains unknown, although the exceptional magnitude of trauma-induced emotion at the time of learning may be so great that the system is incapable of initiating or completing one or both of these processes, leaving some patients unable to integrate and depotentiate the stored experience. Alternatively, it may be the hyperarousal status of the brain during REM sleep in these patients,74-76 potentially lacking sufficient aminergic demodulation, that prevents the processing and separation of emotion from memory. Indeed, this hypothesis has gained support from recent pharmacologic studies in patients with PTSD, demonstrating that nocturnal α-adrenergic blockade using prazosin (ie, reducing adrenergic activity during sleep) both decreases the trauma-dream symptoms and restores the characteristics of REM sleep.77-79 This model also makes specific experimental predictions on the fate of these 2 components, the memory and the emotion. As partially demonstrated, the first prediction would be that, over time, the veracity of the memory itself would be maintained or improved, and the extent to which these (negative) emotional experiences are strengthened would be proportional to the amount of postexperience REM sleep obtained, as well as how quickly it is achieved (REM latency).

Second, using physiology measures, these same predictions would hold in the inverse direction for the magnitude of emotional reactivity induced at the time of recall. Together with the neuroimaging studies of emotional memory recall over time and psychological studies investigating the role of REM sleep dreaming in mood regulation, a recent fMRI study offers perhaps the strongest preliminary support of this sleep-dependent model of emotional memory processing.⁸⁰ Relative to a control group that slept, participants who were deprived of sleep the first night after learning arousing emotion picture slides not only showed reduced recall of the information 72 hours later (the sleep to remember component of the hypothesis) but also showed a lack of reduction in amygdala reactivity when reexposed to these same negative emotional picture slides at recognition testing (Fig. 7; the sleep to forget component of the hypothesis). Thus, sleep after learning facilitated improved recollection of these prior emotional experiences, yet this later recollection was conversely associated with a reduction in amygdala reactivity after 3 nights. In contrast, participants who did not sleep the first night after the emotional learning session, despite obtaining 2 full recovery nights of sleep, showed no such depotentiation of subsequent amygdala reactivity.



Fig. 7. Effect of sleep deprivation on limbic brain activity during subsequent emotional memory retrieval. (*A*) Higher degree of amygdala reactivity during delayed (72 hours) recollection of previously learned negative emotion picture slides in participants who were sleep deprived the first night after learning, compared with a control group that slept the first night after learning. (*B*) The associated magnetic resonance signal from the amygdala in both groups of subjects, demonstrating a significant reduction in limbic reactivity in those who slept the first night after learning, together with the magnitude of response from the same region to neutral stimulus recollection. (*Modified from* Sterpenich V, Albouy G, Boly M, et al. Sleep-related hippocampo-cortical interplay during emotional memory recollection. PLoS Biol 2007;5:e282; with permission.)

SUMMARY

When viewed as a whole, findings at the cellular, systems, cognitive, and clinical level all point to a crucial role for sleep in the affective modulation of human brain function. Based on the remarkable neurobiology of sleep, and REM sleep in particular, a unique capacity for the overnight modulation of affective networks and previously encountered emotional experiences may be possible, redressing and maintaining the appropriate connectivity and hence the next-day reactivity throughout limbic and associated autonomic systems. However, if the canonical architecture and amount of sleep is disrupted, as commonly occurring in mood disorders, particularly major depression and PTSD, this symbiotic alliance of sleepdependent emotional brain processing may fail. The predicted consequences of this failure seem to support the development and/or maintenance of several clinical symptoms expressed in mood disorders, whereas the changes in sleep associated with common pharmacologic treatments of these cohorts support a relief of these aberrant overnight processes, all of which lead to experimentally testable hypotheses which can serve to guide future research. Ultimately, the timeless wisdom of mothers alike may never have been more relevant; that is, when troubled "get to bed, you'll feel better in the morning."

REFERENCES

1. Labar KS, Cabeza R. Cognitive neuroscience of emotional memory. Nat Rev Neurosci 2006;7:54.

- 2. Phelps EA. Emotion and cognition: insights from studies of the human amygdala. Annu Rev Psychol 2006;57:27.
- 3. Walker MP, Stickgold R. Sleep, memory and plasticity. Annu Rev Psychol 2006;10:139.
- Rechtschaffen A, Kales A. A manual standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda (MD): USA: U.S. Department of Health; 1968.
- 5. Walker MP. The role of sleep in cognition and emotion. Ann N Y Acad Sci 2009;1156:168–97.
- Steriade M, Amzica F. Coalescence of sleep rhythms and their chronology in corticothalamic networks. Sleep Res Online 1998;1:1.
- Armitage R. Sleep and circadian rhythms in mood disorders. Acta Psychiatr Scand Suppl 2007;104.
- Aston-Jones G, Bloom FE. Activity of norepinephrinecontaining locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1981;1:876.
- Llinas R, Ribary U. Coherent 40-Hz oscillation characterizes dream state in humans. Proc Natl Acad Sci U S A 1993;90:2078.
- Steriade M, Amzica F, Contreras D. Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation. J Neurosci 1996; 16:392.
- Canli T, Zhao Z, Brewer J, et al. Event-related activation in the human amygdala associates with later memory for individual emotional experience. J Neurosci 2000;20:RC99.
- 12. Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 2001;24:726.

- Hobson JA, McCarley RW, Wyzinski PW. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 1975;189:55.
- Lydic R, Baghdoyan HA. Handbook of behavioral state control: cellular and molecular mechanisms. Boca Raton (FL): CRC Press; 1988.
- Atienza M, Cantero JL. Modulatory effects of emotion and sleep on recollection and familiarity. J Sleep Res 2008;17:285.
- Shima K, Nakahama H, Yamamoto M. Firing properties of two types of nucleus raphe dorsalis neurons during the sleep-waking cycle and their responses to sensory stimuli. Brain Res 1986; 399:317.
- Kametani H, Kawamura H. Alterations in acetylcholine release in the rat hippocampus during sleepwakefulness detected by intracerebral dialysis. Life Sci 1990;47:421.
- Marrosu F, Portas C, Mascia MS, et al. Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. Brain Res 1995;671:329.
- 19. Nofzinger EA. Functional neuroimaging of sleep. Semin Neurol 2005;25:9.
- 20. Marshall L, Born J. The contribution of sleep to hippocampus-dependent memory consolidation. Trends Cogn Sci 2007;11:442.
- 21. Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. Neuron 2004;44:121.
- 22. Phelps EA. Human emotion and memory: interactions of the amygdala and hippocampal complex. Curr Opin Neurobiol 2004;14:198.
- 23. Heuer F, Reisberg D. Vivid memories of emotional events: the accuracy of remembered minutiae. Mem Cognit 1990;18:496–506.
- Bradley MM, Greenwald MK, Petry MC, et al. Remembering pictures: pleasure and arousal in memory. J Exp Psychol Learn Mem Cogn 1992;18: 379–90.
- Buchanan TW, Lovallo WR. Enhanced memory for emotional material following stress-level cortisol treatment in humans. Psychoneuroendocrinology 2001;26:307–17.
- Christianson SA. Emotional stress and eyewitness memory: a critical review. Psycho Bull 1992;112: 284–309.
- Adolphs R, Cahill L, Schul R, et al. Impaired declarative memory for emotional material following bilateral amygdala damage in humans. Learn Mem 1997;4:291.
- Cahill L, Prins B, Weber M, et al. Beta-adrenergic activation and memory for emotional events. Nature 1994;371:702.
- Strange BA, Hurlemann R, Dolan RJ. An emotioninduced retrograde amnesia in humans is amygdala- and beta-adrenergic-dependent. Proc Natl Acad Sci U S A 2003;100:13626.

- Amzica F, Steriade M. Short- and long-range neuronal synchronization of the slow (<1 Hz) cortical oscillation. J Neurophysiol 1995;73:20.
- Cahill L, Haier RJ, Fallon J, et al. Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci U S A 1996;93:8016.
- Conway MA, Anderson SJ, Larsen SF, et al. The formation of flashbulb memories. Mem Cognit 1994; 22:326.
- Dolcos F, LaBar KS, Cabeza R. Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. Neuron 2004;42:855.
- 34. Hamann SB, Ely TD, Grafton ST, et al. Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nat Neurosci 1999;2:289.
- 35. Kensinger EA, Corkin S. Two routes to emotional memory: distinct neural processes for valence and arousal. Proc Natl Acad Sci U S A 2004;101:3310.
- Sharot T, Phelps EA. How arousal modulates memory: disentangling the effects of attention and retention. Cogn Affect Behav Neurosci 2004; 4:294.
- 37. Harrison Y, Horne JA. Sleep loss and temporal memory. Q J Exp Psychol 2000;53:271.
- Morris GO, Williams HL, Lubin A. Misperception and disorientation during sleep. Arch Gen Psychiatry 1960;2:247.
- Yoo SS, Hu PT, Gujar N, et al. A deficit in the ability to form new human memories without sleep. Nat Neurosci 2007;10:385.
- 40. Buzsaki G. Theta oscillations in the hippocampus. Neuron 2002;33:325.
- Kleinsmith LJ, Kaplan S. Paired-associate learning as a function of arousal and interpolated interval. J Exp Psychol 1963;65:190.
- 42. LaBar KS, Phelps EA. Arousal-mediated memory consolidation: role of the medial temporal lobe in humans. Psychol Sci 1998;9:490.
- 43. Levonian E. Retention over time in relation to arousal during learning: an explanation of discrepant results. Acta Psychol (Amst) 1972;36:290.
- Walker EL, Tarte RD. Memory storage as a function of arousal and time with homogeneous and heterogeneous lists. J Verb Learn Verb Behav 1963;2:113.
- 45. Cahill L, Babinsky R, Markowitsch HJ, et al. The amygdala and emotional memory. Nature 1995; 377:295.
- 46. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 2004;27:1.
- Hu P, Stylos-Allen M, Walker MP. Sleep facilitates consolidation of emotionally arousing declarative memory. Psychol Sci 2006;17:891.
- 48. Wagner U, Gais S, Born J. Emotional memory formation is enhanced across sleep intervals with high

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amounts of rapid eye movement sleep. Learn Mem 2001;8:112.

- 49. Wagner U, Hallschmid M, Rasch B, et al. Brief sleep after learning keeps emotional memories alive for years. Biol Psychiatry 2006;60:788.
- Wagner U, Kashyap N, Diekelmann S, et al. The impact of post-learning sleep vs. wakefulness on recognition memory for faces with different facial expressions. Neurobiol Learn Mem 2007;87:679.
- 51. Payne JD, Stickgold R, Swanberg K, et al. Sleep preferentially enhances memory for emotional components of scenes. Psychol Sci 2008;19:781.
- 52. Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Nat Rev Neurosci 2002;3:591.
- 53. Nishida M, Pearsall J, Buckner RL, et al. REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex 2009;19:1158.
- 54. Pare D, Collins DR, Pelletier JG. Amygdala oscillations and the consolidation of emotional memories. Trends Cogn Sci 2002;6:306.
- 55. Vazquez J, Baghdoyan HA. Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. Am J Physiol Regul Integr Comp Physiol 2001;280:R598.
- 56. Wagner U, Fischer S, Born J. Changes in emotional responses to aversive pictures across periods rich in slow-wave sleep versus rapid eye movement sleep. Psychosom Med 2002;64:627.
- 57. Power AE. Muscarinic cholinergic contribution to memory consolidation: with attention to involvement of the basolateral amygdala. Curr Med Chem 2004; 11:987.
- Cahill L. Neurobiological mechanisms of emotionally influenced, long-term memory. Prog Brain Res 2000; 126:29.
- 59. Jones MW, Wilson MA. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. PLoS Biol 2005;3:e402.
- 60. Horne JA. Sleep function, with particular reference to sleep deprivation. Ann Clin Res 1985;17:199.
- Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. Sleep 1997;20:267.
- Zohar D, Tzischinsky O, Epstein R, et al. The effects of sleep loss on medical residents' emotional reactions to work events: a cognitive-energy model. Sleep 2005;28:47.
- 63. Yoo SS, Gujar N, Hu P, et al. The human emotional brain without sleep—a prefrontal amygdala disconnect. Curr Biol 2007;17:R877.
- 64. Sotres-Bayon F, Bush DE, LeDoux JE. Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. Learn Mem 2004; 11:525.

- 65. Davidson RJ. Anxiety and affective style: role of prefrontal cortex and amygdala. Biol Psychiatry 2002;51:68.
- 66. Davidson RJ, Pizzagalli D, Nitschke JB, et al. Depression: perspectives from affective neuroscience. Annu Rev Psychol 2002;53:545.
- 67. New AS, Hazlett EA, Buchsbaum MS, et al. Amygdalaprefrontal disconnection in borderline personality disorder. Neuropsychopharmacology 2007;32:1629.
- Franzen PL, Buysse DJ, Dahl RE, et al. Sleep deprivation alters pupillary reactivity to emotional stimuli in healthy young adults. Biological Psychology 2009;80:300–5.
- 69. Gujar N, McDonald SA, Nishida M, et al. A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. Cereb Cortex 2011;21(1):115.
- Dolcos F, LaBar KS, Cabeza R. Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. Proc Natl Acad Sci U S A 2005;102:2626.
- Kilpatrick L, Cahill L. Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. Neuroimage 2003;20: 2091.
- 72. Sullivan GM, Coplan JD, Kent JM, et al. The noradrenergic system in pathological anxiety: a focus on panic with relevance to generalized anxiety and phobias. Biol Psychiatry 1999;46:1205.
- 73. Lavie P. Sleep disturbances in the wake of traumatic events. N Engl J Med 2001;345:1825.
- 74. Harvey AG, Jones C, Schmidt DA. Sleep and posttraumatic stress disorder: a review. Clin Psychol Rev 2003;23:377.
- 75. Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. Psychol Bull 2007;133:725.
- Strawn JR, Geracioti TD Jr. Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. Depress Anxiety 2008; 25:260.
- 77. Raskind MA, Peskind ER, Hoff DJ, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry 2007;61:928.
- 78. Taylor FB, Martin P, Thompson C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry 2008;63:629.
- 79. Tsuno N, Besset A, Ritchie K. Sleep and depression. J Clin Psychiatry 2005;66:1254.
- 80. Sterpenich V, Albouy G, Boly M, et al. Sleep-related hippocampo-cortical interplay during emotional memory recollection. PLoS Biol 2007;5:e282.