

# Overnight Therapy? The Role of Sleep in Emotional Brain Processing

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Cognitive neuroscience continues to build meaningful connections between affective behavior and human brain function. Within the biological sciences, a similar renaissance has taken place, focusing on the role of sleep in various neurocognitive processes and, most recently, on the interaction between sleep and emotional regulation. This review surveys an array of diverse findings across basic and clinical research domains, resulting in a convergent view of sleep-dependent emotional brain processing. On the basis of the unique neurobiology of sleep, the authors outline a model describing the overnight modulation of affective neural systems and the (re)processing of recent emotional experiences, both of which appear to redress the appropriate next-day reactivity of limbic and associated autonomic networks. Furthermore, a rapid eye movement (REM) sleep hypothesis of emotional-memory processing is proposed, the implications of which may provide brain-based insights into the association between sleep abnormalities and the initiation and maintenance of mood disturbances.

*Keywords:* REM sleep, emotion, affect, memory, depression

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 as well as our 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 (Labar & Cabeza, 2006; Phelps, 2006).

Independent of this research area, a recent resurgence has taken place within the basic sciences, focusing on the functional impact of sleep on neurocognitive processes (Chee & Chuah, 2008; M. P. Walker, 2009; M. P. Walker & Stickgold, 2006). However, surprisingly less research attention has been given to the interaction between sleep and affective brain function. We say “surprising” in consideration of 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 for sleep in the selective modulation of emotional information and affective regulation. In the following review, we provide a synthesis of these

findings, describing an intimate relationship between sleep, emotional brain function, and clinical mood disorders. We proceed to offer a tentative initial theoretical framework that may account for these observed interactions.

## Sleep

The sleep of mammalian species has been broadly classified into two distinct types: non-rapid eye movement (NREM) sleep and REM sleep, with NREM sleep being further divided, in primates and cats, into four substages (1–4), corresponding, in that order, to increasing depth of sleep (Rechtschaffen & Kales, 1968). In humans, NREM and REM sleep alternate, or cycle, across the night in an ultradian pattern every 90 min (Figure 1). Although this NREM–REM cycle length remains largely stable across the night, the ratio of NREM to REM sleep within each 90-min cycle changes, so that early in the night, Stages 3 and 4 of NREM sleep dominate, whereas Stage 2 NREM and REM sleep prevail in the latter half of the night. Interestingly, the functional reasons for this organizing principal (deep NREM sleep early in the night, Stage 2 NREM and REM sleep late in the night) remain unknown (M. P. Walker, 2009).

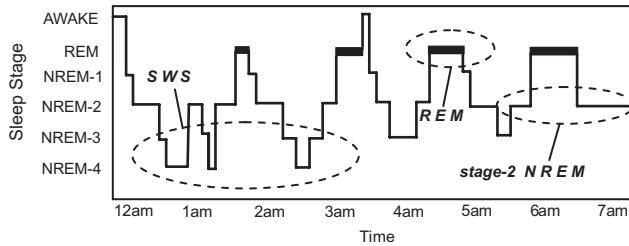
As NREM sleep progresses, electroencephalographic (EEG) activity begins to slow in frequency. Throughout Stage 2 NREM sleep, phasic electrical events are present, including K-complexes (large electrical sharp waves in the EEG) and sleep spindles (short synchronized bursts of EEG electrical activity in the 11- to 15-Hz range; Steriade & Amzica, 1998). The deepest stages of NREM sleep, Stages 3 and 4, are often grouped together under the term *slow wave sleep* (SWS), which reflects the occurrence of low-frequency waves (0.5–4 Hz) representing an expression of underlying mass cortical synchrony (Amzica & Steriade, 1995). During REM sleep, however, EEG waveforms once again change in composition, which is associated with oscillatory activity in the theta band range (4–7 Hz), together with higher frequency synchronous activity in the 30- to 80-Hz (gamma) band range (Llinas

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This work was supported in part by grants from the National Institutes of Health (MH069935) and the American Academy of Sleep Medicine. We wish to thank Ninad Gujar, Allison Harvey, and Edwin Robertson for thoughtful insights.

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**Figure 1.** The human sleep cycle. Across the night, non-rapid eye movement (NREM) and rapid eye movement (REM) sleep cycle every 90 min 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 (slow-wave sleep [SWS]) dominate, while Stage 2 NREM and REM sleep prevail in the latter half of the night. Electroencephalographic (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 presenting during REM.

& Ribary, 1993; Steriade, Amzica, & Contreras, 1996). 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), the lateral geniculate nuclei of the thalamus (G), and the occipital cortex (O) and, as such, have been termed *PGO waves* (Callaway, Lydic, Baghdoyan, & Hobson, 1987).

As the brain passes through these sleep stages, it also undergoes dramatic alterations in neurochemistry (Saper, Chou, & Scammell, 2001). In NREM sleep, subcortical cholinergic systems in the brain stem and forebrain become markedly less active (Hobson, McCarley, & Wyzinski, 1975; Lydic & Baghdoyan, 1988) while firing rates of serotonergic Raphé neurons; noradrenergic locus coeruleus neurons are also reduced relative to waking levels (Aston-Jones & Bloom, 1981; Shima, Nakahama, & Yamamoto, 1986). During REM sleep, both of these aminergic populations are strongly inhibited while cholinergic systems become as, or more, active compared with wake periods (Kametani & Kawamura, 1990; Marrosu et al., 1995), resulting in a brain state largely devoid of aminergic modulation and dominated by acetylcholine.

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 a review, see Nofzinger, 2005). During NREM SWS, brain stem, thalamic, basal ganglia, prefrontal, and temporal lobe regions all appear to undergo reduced activity. However, during REM sleep, significant elevations in activity have been reported in the pontine tegmentum, the thalamic nuclei, the occipital cortex, and the mediobasal prefrontal lobes, together with affect-related regions, including the amygdala, the hippocampus, and the anterior cingulate cortex (Figure 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, this review of the literature 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. In the following sections, we

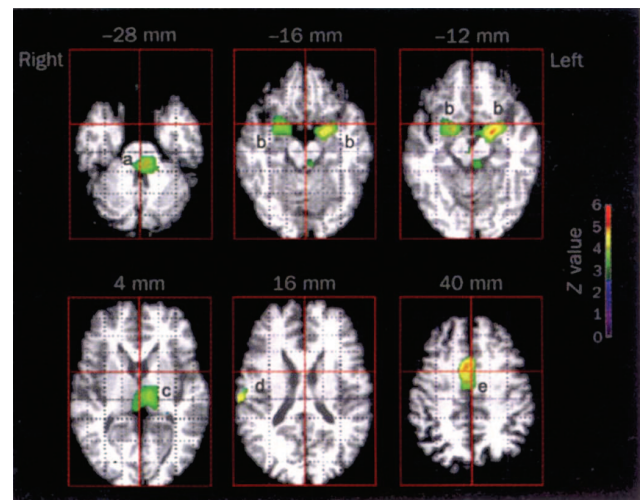
examine the role of sleep, and specific stages of sleep, in the modulation of emotional memories and the regulation of affective reactivity, which culminates in a heuristic model of sleep-dependent emotional brain processing.

## Sleep and Emotional Memory Processing

The impact of sleep has principally been characterized at two different stages of memory: (a) before learning, in the initial formation (encoding) of new information and (b) after learning, in the long-term solidification (consolidation) of new memories (Marshall & Born, 2007; M. P. Walker, 2009; M. P. Walker & Stickgold, 2004, 2006). In the following passages, we consider each of these stages, focusing on reports involving affective learning.

### Sleep and Affective Memory Encoding

**Emotional memory encoding.** The initial stage of memory formation can be strongly modulated by the elicitation of emotion at the time of learning (Phelps, 2004). Emotionally arousing stimuli are consistently remembered better than neutral stimuli both in experimental laboratory studies and in real life accounts (Bradley, Greenwald, Petry, & Lang, 1992; Buchanan & Lovallo, 2001; Christianson, 1992; Heuer & Reisberg, 1990). Studies of autobiographical memory have found that individuals are more likely to remember events that have greater emotional and personal significance (Conway et al., 1994). However, emotions are not necessarily unidimensional, and they have commonly been categorized along two dimensions: arousal (ranging from *calm* to *excitement*)



**Figure 2.** Regional brain activation during rapid eye movement (REM) sleep (positron emission tomography [PET] scan). The areas include the following: (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 From "Functional Neuroanatomy of Human Rapid-Eye-Movement Sleep and Dreaming," by P. Maquet, C. Degueldre, G. Delfiore, J. Aerts, J. M. Peters, A. Luxen, et al., 1996, *Nature*, 383(6596), p. 164. Copyright 1996 by Nature Publishing Group/Macmillan. Reprinted with permission.

and valence (ranging from *positive* to *negative*, with *neutral* often considered an intermediate value; Labar & Cabeza, 2006; Lang, Greenwald, Bradley, & Hamm, 1993). Moreover, evidence suggests that these two dimensions of emotion influence memory encoding in different ways.

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 also during consolidation; discussed later in this review). For example, Cahill, Prins, Weber, and McGaugh (1994) demonstrated that administration of propranolol, a  $\beta$ -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 will subvert the normal facilitation of emotional memory recall when recall is tested shortly after (Strange, Hurlmann, & Dolan, 2003). Interestingly, 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 (Adolphs, Cahill, Schul, & Babinsky, 1997; Cahill, Babinsky, Markowitsch, & McGaugh, 1995).

Functional neuroimaging studies further support the critical role of the amygdala in facilitating emotional memory encoding. Cahill et al. (1996) reported greater activity in the right amygdala while participants viewed emotional versus neutral films; across participants, the greater the activity, the larger was the recollection benefit. Subsequent work, consistent with animal literature, suggests that the amygdala facilitates the initial acquisition of emotional information by influencing key medial temporal lobe structures, including the hippocampal complex (McGaugh, 2004). For example, Dolcos, LaBar, and Cabeza (2004) demonstrated that the amygdala and the anterior hippocampus exhibit coupled activation during the successful encoding of emotional scenes, as indexed by later remembering. Furthermore, emotional arousal can enhance amygdala modulation not only of the ipsilateral parahippocampus but also of the ventrolateral prefrontal cortex, the latter of which is considered part of the extended limbic system (Kilpatrick & Cahill, 2003). Indeed, co-activation of the amygdala and the hippocampal complex during emotional memory encoding has been reported in a number of studies (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Dolcos et al., 2004; Hamann, Ely, Grafton, & Kilts, 1999; Kensinger & Corkin, 2004; Sharot & Phelps, 2004), with the extent of functional connectivity at the time of learning being especially predictive of robust (delayed) memory retention (Ritchev, Dolcos, & Cabeza, 2008). Emotionally valenced positive or negative stimuli of low arousal can also result in superior retention relative to neutral events, although this enhancement may occur independently of amygdala activation (Kensinger, 2004). Kensinger and Corkin (2003) described dissociable mechanisms for the encoding of emotional stimuli across these dimensions of valence and arousal. Relative to neutral words, high-arousing negative words generated greater memory encoding activation (difference between successful and unsuccessful encoding trials) in the hippocampus and the amygdala. In contrast, low-arousing negative words generated significantly greater memory encoding activation in the hippocampus and a posterior region of the lateral inferior prefrontal cortex. Therefore, distinct neural, and likely cognitive, effects underlie the formation of emotional memories,

depending on the contribution of arousal and valence strength and direction.

When viewed collectively, these pharmacological, behavioral, and neuroimaging findings indicate that the specific enhancing effects of emotional arousal on memory formation involve interactions between the amygdala and key medial temporal lobe structures, in addition to engagement of central and peripheral neurohormonal systems. Moreover, the facilitation of encoding by autonomically arousing stimuli appears to engage similar brain systems across positive and negative valence domains (Kensinger & Schacter, 2006; Labar & Cabeza, 2006). By contrast, the encoding benefit of emotional valence in the absence of high arousal may be governed, at least in part, by frontally mediated semantic and strategic processes that can modulate memory without key involvement of the amygdala (cf. Labar & Cabeza, 2006).

This account of the beneficial enhancing effects of emotion on the initial process of learning pertains to conditions in which the brain is sleep rested. There now exists considerable evidence, in both animals and humans, that sleep deprivation prior to encoding can significantly, but also selectively, alter and impair the canonical profile of emotional memory enhancement.

*Sleep and emotional memory formation.* At a behavioral level, pretraining sleep deprivation in rodents has been shown to impair encoding of numerous memory tasks, the evidence for which we only briefly summarize here. Critically, many, if not all, of these studies involve either appetitive or aversive learning paradigms, meaning that these tasks are of an emotional nature.

Sleep deprivation, and specifically REM sleep deprivation, imposes detrimental effects on the encoding of one-way and two-way avoidance learning, taste aversion, and passive avoidance learning (McGrath & Cohen, 1978; Smith, 1985). Even short (5-hr) bouts of pretraining REM sleep deprivation appear capable of disrupting the encoding of two-way avoidance learning in rats, effectively reducing the number of avoidances—impairments that cannot be overcome by continued practice during the training session (Gruart-Masso, Nadal-Aleman, Coll-Andreu, Portell-Cortes, & Marti-Nicolovius, 1995).

Building on these behavioral findings, a collection of studies has proceeded to explore the potential cellular mechanisms of sleep deprivation-induced encoding deficits, many of which have focused on aspects of the limbic system, specifically the hippocampus. At the cellular level, REM sleep deprivation (24–72 hr) not only reduces the basic excitability of hippocampal neurons but significantly impairs the formation of long-term potentiation (a foundational mechanism of memory formation) within these neurons (Davis, Harding, & Wright, 2003; McDermott et al., 2003). Furthermore, the small amount of long-term potentiation that does develop actually decays within 90 min, suggesting that even in the event of successful induction of long-term potentiation, hippocampal neurons are unable to maintain these plastic changes under conditions of REM sleep deprivation (Davis et al., 2003). Therefore, sleep prior to learning appears to be necessary in preparing and/or maintaining the cellular and subcellular ability of key subcortical networks to acquire new memory associations.

Whereas early studies investigating the role of sleep-dependent memory in humans focused primarily on postlearning consolidation (see later sections of this review), 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 human memory encoding focused on neutral forms of learning, indicating that *temporal memory* (memory for when events occur) was significantly disrupted by a night of pretraining sleep deprivation (Harrison & Horne, 2000; Morris, Williams, & Lubin, 1960), even when caffeine was administered to overcome nonspecific effects of lower arousal.

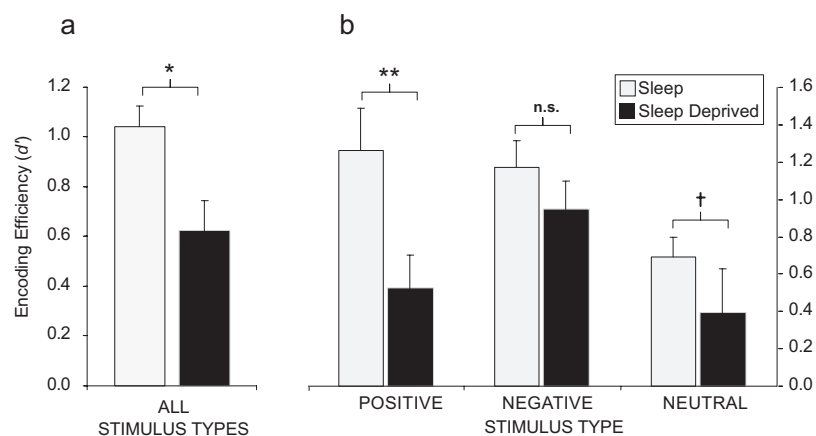
More recent investigations have examined the importance of pretraining sleep for the formation of emotional and neutral memories (M. P. Walker & Tharani, 2009). Participants were either sleep deprived for 36 hr or allowed to sleep normally prior to a learning session composed of emotionally negative, positive, and neutral words. Participants were then tested following two recovery nights of sleep so that in both groups, recollection was tested in a sleep-rested state. Thus, any differences observed in performance observed could not be accounted for by the effects of sleep deprivation on retrieval, as neither group was sleep deprived at later testing. Averaged across all memory categories, participants who were sleep deprived demonstrated a 40% deficit in memory encoding relative to participants who had slept normally prior to learning (Figure 3a). However, when these data were separated into the three emotional categories (negative, positive, neutral), selective dissociations became apparent (Figure 3b). In participants who had slept (control group), both positive and negative stimuli were associated with superior retention levels relative to the neutral condition, consistent with the notion that emotion facilitates memory encoding (Phelps, 2004). In the sleep-deprived group, a severe encoding impairment was evident for neutral and especially positive emotional memories, with sleep-deprived participants exhibiting a significant, 59% retention deficit relative to participants in the control condition. Most interesting was the relative resistance of negative emotional memory to sleep deprivation, for which a markedly smaller and nonsignificant impairment was evident.

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 (Yoo, Hu,

Gujar, Jolesz, & Walker, 2007). The data also suggest that although the effects of sleep deprivation are directionally consistent across emotional subcategories, the most profound impact is on the encoding of positive emotional stimuli and, to a lesser degree, emotionally neutral stimuli. In contrast, the encoding of negative memory appears 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 (Buysse, 2004). Indeed, if one compares the two profiles of memory encoding in Figure 3b, it becomes clear that the sleep control group completes the encoding session with a balanced mix of both positive and negative memories. However, those in the deprivation group have a skewed distribution, finishing the encoding session with an overriding dominance of negative memories and far fewer positive or neutral memories, an issue with clinical relevance that is discussed below.

The mechanistic cause of these differential encoding impairments requires greater elucidation. For example, at a whole-brain level, the arousal strength of such word stimuli can place different demands on the amygdala or the prefrontal cortices (Kensinger & Corkin, 2004), an issue of particular relevance considering the marked hypofrontality commonly reported in sleep deprivation (Chee & Chuah, 2008; Thomas et al., 2000, 2003), yet a hyperactive state of amygdala function following sleep loss (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). Moreover, positive materials may be more associated with relational processing (Kensinger, 2004), which could also account for the susceptibility to interference following sleep deprivation. Additional contributions due to effects of the negative affective state of sleep-deprived individuals, leading to a mood-congruent memory bias of encoding (Lewis, Critchley, Smith, & Dolan, 2005). Subsequent studies combining the assessment of brain activity, mood state and task stimulus properties will be necessary to distinguish between these possibilities.

In summary, studies indicate that prior sleep loss significantly impairs the ability for effective next-day learning of new experi-



**Figure 3.** Sleep deprivation and encoding of emotional and nonemotional declarative memory. Effects of 38 hr 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,  $F = 3.58$ ,  $p < .05$ . Post hoc  $t$ -test comparisons:  $\dagger p < .08$ . \*  $p < .05$ . \*\*  $p < .01$ . n.s. = not significant;  $d'$  =  $d$ -prime (discrimination index).

ences across numerous species. Furthermore, sleep loss appears to disrupt the learning of different affective categories to varying extents, potentially creating an imbalance in negative emotional memory dominance. Most intriguing, animal models indicate that affective learning demonstrates a particular sensitivity to REM sleep deprivation, suggesting a dependency on a specific physiological stage of prior sleep for next-day emotional learning.

### *Sleep and Affective Memory Consolidation*

*Mechanisms of emotional memory consolidation.* In addition to substantial evidence suggesting that emotion facilitates initial memory encoding, emotion is also known to modulate the subsequent stage of latent memory consolidation. A number of behavioral studies in humans have demonstrated diminished forgetting of emotional, as compared with neutral, stimuli. This beneficial influence of emotion on later memory retention increases as the time delay between learning and testing increases. The effect of offline retention has been shown over varying postlearning intervals, including comparisons between recollection at 20 min and 1 week (Kleinsmith & Kaplan, 1963), at immediate recall and 1 hr (LaBar & Phelps, 1998), at immediate recall and 24 hr (Sharot & Phelps, 2004), and at 15 min and 2 weeks (Anderson, Yamaguchi, Grabski, & Lacka, 2006). Furthermore, this latent emotional memory enhancement may be more prevalent for items receiving more detailed remembering than simply a sense of familiarity (Dolcos, LaBar, & Cabeza, 2005; Kensinger & Corkin, 2003; Ochsner, 2000; Ritchey et al., 2008).

With the knowledge that emotion triggers improvements in memory performance over time, elegant work in animal models has substantially characterized the underlying anatomical and neurochemical mechanisms contributing to these effects. The findings of this research have implications relevant to the role of sleep neurobiology in emotional memory processing. A striking finding from a series of early consolidation experiments was that posttraining drug manipulations, such as subcutaneous amphetamine injections, could facilitate memory retention when animals were tested 24 hr after learning. Under these conditions, animals were drug free during the initial learning and subsequent testing, so that pharmacological treatment did not affect performance at encoding or recall but specifically influenced the intervening consolidation phase. Moreover, researchers discovered that administration of certain endogenous compounds could facilitate memory consolidation, namely, peripheral posttraining injections of the stress hormones epinephrine and glucocorticoids (Cahill, 2000; McGaugh, 2000).

It is now proposed that stress hormones constitute a plausible protracted means of modifying latent consolidation by way of emotional arousal, promoting the adaptive reorganization of long-term memory representations. Recent human studies have confirmed these predictions. Using posttraining pharmacological and pain manipulations to elicit responses involving the amygdala (Cahill & Alkire, 2003; Cahill, Gorski, & Le, 2003), Cahill and colleagues have demonstrated that induction of stress hormones can selectively enhance long-term memory of emotional stimuli when retested several days later (and see later sections of the current review). Thus, the hormones adrenaline and corticosterone appear to offer two important adaptive functions in response to arousing experiences: (a) They aid immediate responses to a potentially stressful experience, and (b) they aid future

responses by enhancing consolidation of declarative memory for those arousing events.

In addition to neurohormonal effects, substantial evidence exists that several neurotransmitters, including adrenergic transmitters and acetylcholine, co-regulate the effects of emotion on consolidation. The cholinergic effects are of particular note in relationship to sleep, specifically REM sleep (discussed below). Acetylcholine appears to enhance amygdala-dependent memory consolidation. For example, in rats, posttraining infusions of muscarinic cholinergic agonists and antagonists into the amygdala have been found to enhance and impair, respectively, memory across numerous tasks, including inhibitory avoidance, fear conditioning, and change in reward magnitude (Intorini-Collison, Dalmaz, & McGaugh, 1996; Passani et al., 2001; Power & McGaugh, 2002; Schroeder & Packard, 2002). Furthermore, posttraining cholinergic stimulation of the amygdala, with either muscarinic cholinergic agonists or the acetylcholinesterase inhibitor physostigmine, has been shown to attenuate this emotional memory impairment (Power & McGaugh, 2002).

Collectively, these studies suggest that a cascade system of neurohormonal and neurochemical mechanisms can either jointly act in the endeavor of facilitating consolidation or may independently contribute to this process at different times across the later consolidation period, or during different brain states, such as wake or sleep.

*Sleep and emotional memory consolidation.* The role of sleep after learning in subsequent memory consolidation has now been demonstrated across a range of phylogeny (Walker & Stickgold, 2004, 2006). Here, we focus on affective learning paradigms, especially in humans.

Animal models support a role for sleep in the consolidation of both contextual fear and shock avoidance tasks (for more detailed reviews beyond the scope of the current article, see Smith, 1985; Walker & Stickgold, 2004), which are known to depend on intact hippocampal function. Daytime training on these tasks triggers alterations in sleep-stage characteristics, especially REM sleep (Ambrosini et al., 1993; Ambrosini, Sadile, Gironi Carnevale, Mattiaccio, & Giuditta, 1988; Hennevin & Hars, 1987; Mandai, Guerrien, Sockeel, Dujardin, & Leconte, 1989; Sanford, Silvestri, Ross, & Morrison, 2001; Sanford, Tang, Ross, & Morrison, 2003; Smith, Young, & Young, 1980), possibly reflecting homeostatic demands on REM sleep-dependent mechanisms of consolidation.

Conversely, sleep deprivation after learning of such tasks also has been shown to disrupt consolidation and impair next-day memory retention (Smith, 1985; Walker & Stickgold, 2004). Moreover, these effects are apparent following selective REM sleep deprivation rather than total sleep deprivation (Beaulieu & Godbout, 2000; Fishbein, Kastaniotis, & Chattman, 1974; Hennevin & Hars, 1987; Marti-Nicolovius, Portell-Cortes, & Morgado-Bernal, 1988; Oniani, Lortkipanidze, & Maisuradze, 1987; Pearlman, 1969; Shiromani, Gutwein, & Fishbein, 1979; Smith & Kelly, 1988). Interestingly, the time at which sleep deprivation occurs appears to be important. For example, Graves, Heller, Pack, and Abel (2003) have demonstrated that sleep deprivation 0–5 hr posttraining selectively impairs consolidation of contextual fear conditioning (as measured at a later 24-hr retest; see Figure 4). However, sleep deprivation 5 to 10 hr posttraining did not block consolidation, resulting in similar memory performance at retest (Figure 4). These temporal dynamics appear to overlap with studies investigating the effects of adrenergic antag-

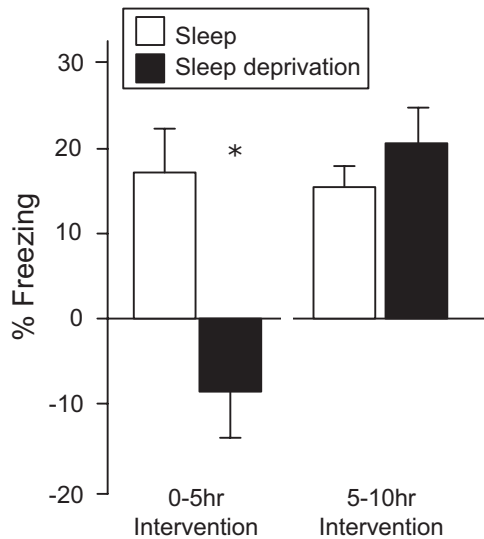


Figure 4. Difference in percentage of freezing during contextual fear conditioning with or without sleep deprivation, across either 0- to 5-hr posttraining or 5 to 10-hr posttraining. \*  $p < .05$ . Error bars represent standard error of the mean. From "Sleep Deprivation Selectively Impairs Memory Consolidation for Contextual Fear Conditioning" by L. A. Graves, E. A. Heller, A. I. Pack, and T. Abel, 2003, *Learning & Memory*, 10, pp. 168–176. Copyright 2003 by Cold Spring Harbor Press. Adapted with permission.

onists on the consolidation of contextual fear conditioning, describing a window of sensitivity several hours postlearning but less effect approximately 6 hr and beyond (depending on the learning paradigm used; Bevilacqua et al., 1997; Izquierdo et al., 1998; Ji, Wang, & Li, 2003).

These findings suggest that the consolidation of fear-associated memory occurs soon after learning, potentially during discreet brain-state time windows. The implications of this temporal sensitivity are informative from a mechanistic standpoint but also from a clinical treatment perspective if the targeted disruption of sleep to negate overnight consolidation becomes a goal, a situation perhaps most pertinent to conditions such as posttraumatic stress disorder (PTSD; discussed below).

In humans, 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 novelty, meaning to extract, and the affective salience of the material. The wealth of evidence demonstrating that human emotional experiences tend to be remembered better than neutral ones (Cahill, 2000; McGaugh, 2004; Phelps, 2004) may help clarify the potential contribution of sleep to episodic memory processing.

Many of these findings describe an offline consolidation benefit (reduction in forgetting) for emotional as compared with neutral information, which appears to persist and even improve over time across periods containing a night of sleep (Kleinsmith & Kaplan, 1963; LaBar & Phelps, 1998; Levonian, 1972; Sharot & Phelps, 2004; E. L. Walker & Tarte, 1963). Several researchers have directly examined whether it is time, with sleep, that preferentially modulates these effects. More specifically, and based on the coincident neurophysiology that REM sleep provides and the neuro-

biological requirements of emotional memory processing (Cahill, 2000; McGaugh, 2004), work has begun to test a selective REM sleep-dependent hypothesis of affective human memory consolidation. For example, Hu, Stylos-Allen, and Walker (2006) compared the consolidation of emotionally arousing and nonarousing picture stimuli following a 12-hr period across a day or following a night of sleep. A specific emotional memory benefit was observed only following sleep and not across an equivalent time awake. Atienza and Cantero (2008) demonstrated that total sleep deprivation the first night after learning significantly impairs later (1-week) retention of emotional as well as neutral visual stimuli. Interestingly, this difference was greatest for neutral relative to emotional items. Such a difference may indicate that emotional items are more resistant to the impact of first-night sleep 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, Gais, and Born (2001) showed that sleep selectively favors the retention of previously learned emotional texts relative to neutral texts and that this affective memory benefit is only present following late-night sleep (a time period rich in REM sleep). This emotional memory benefit was found to persist in a follow-up study performed 4 years later (Wagner, Hallschmid, Rasch, & Born, 2006). The speed of recognizing emotional facial expressions presented prior to sleep has also been demonstrated to be significantly improved the next day, a benefit that is positively correlated with the amount of intervening REM sleep (Wagner, Kashyap, Diekelmann, & Born, 2007).

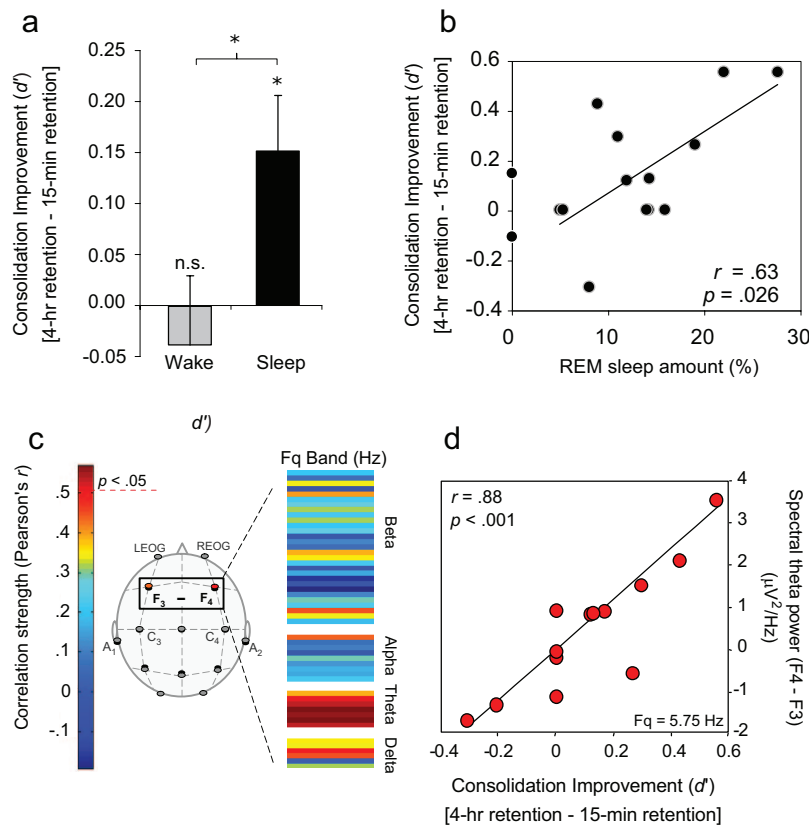
Sleep has been shown to target the consolidation of specific aspects of emotional experiences as well as to mediate the extinction of human fear memories. By experimentally varying the foreground and background elements of emotional picture stimuli, Payne, Stickgold, Swanberg, and Kensinger (2008) demonstrated that sleep can target the strengthening of negative emotional objects in a scene but not the peripheral background. In contrast, equivalent time awake did not afford any benefit to emotional object memory (or the background scene). This 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 et al. (2009) recently investigated the effects of sleep and wake states on fear extinction and the generalization of fear extinction. Concurrent fear conditioning to two different stimuli was followed by targeted extinction of conditioned responding to only one of the stimuli. Participants were then tested following a 12-hr offline delay period across the day or following a night of sleep. Upon their return 12 hr later, generalization of extinction from the target stimuli to the nontargeted stimuli occurred following a night of sleep, yet not across an equivalent waking period. Therefore, sleep may not only modulate affective associations between stimuli but additionally facilitate their generalization across related contexts.

Using a nap paradigm, Nishida, Pearsall, Buckner, and Walker (2009) recently demonstrated that sleep, and specifically REM sleep, neurophysiology may underlie such consolidation benefits. Participants performed two study sessions in which they learned emotionally arousing negative and neutral picture stimuli, one taking place 4 hr prior and one occurring 15 min prior to a recognition memory test. In one group, participants slept (90-min

nap) after the first study session, and in the other group, participants remained awake. Thus, items from the first (4-hr) study sessions passed through different brain states in each of the two groups prior to testing, involving sleep in the nap group and no sleep in the no-nap group. However, items progressed through identical brain-state conditions following the second (15-min) study session prior to testing (a short interval of wake state in each group). 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 (Figure 5a), the extent of which was correlated with the amount of REM sleep (Figure 5b) 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 right-dominant prefrontal theta power during REM sleep

(activity in the frequency range of 4.0–7.0 Hz) exhibited a significant and positive relationship with the amount of emotional memory improvement (Figure 5c and 5d).

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 quantitative and qualitative—and is independent of nocturnal hormonal changes. Corroborating these correlations, researchers have hypothesized and observed that REM sleep represents a brain state that is particularly amenable to emotional memory consolidation, on account of its unique biology (Hu et al., 2006; Pare, Collins, & Pelletier, 2002; M. P. Walker, 2009). Neurochemically, levels of limbic and forebrain acetylcholine are markedly elevated during REM sleep (Vazquez & Baghdoyan, 2001), reportedly quadruple



**Figure 5.** Rapid eye movement (REM) sleep enhancement of negative emotional memories: (a) Offline benefit (change in memory recall for 4-hr versus 15-min old memories) across the day (wake, represented by the gray shaded bar) or following a 90-min nap (sleep, represented by the dark filled bar); (b) correlation between the amount of offline emotional memory improvement in the nap group (i.e., the offline benefit expressed in the dark 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 dark filled bar of Panel 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 (with correlation strength represented by the color range, demonstrating significant correlations within the theta frequency band, i.e., hot colors); and (d) exhibiting a maximum significance at the 5.75-Hz bin. \*  $p < .05$ . Error bars represent standard error of the mean.  $d'$  = d-prime (discrimination index);  $\mu\text{V}^2/\text{Hz}$  = microvolts squared/hertz; REM = rapid eye movement; LEOG = left electrooculogram; REOG = right electrooculogram; Fq = frequency. Adapted from “Prefrontal Theta During REM Sleep Enhances Emotional Memory” by M. Nishida, J. Pearsall, R. L. Buckner, and M. P. Walker, 2009, *Cerebral Cortex*, 19, pp. 1158–1166. Copyright 2009 by Oxford University Press.

the levels seen during NREM and double those measured during quiet waking (Marrosu et al., 1995). In consideration of the known importance of acetylcholine in the long-term consolidation of emotional learning (McGaugh, 2004), this procholinergic REM sleep state may promote the selective memory facilitation of affective memories, similar to that reported with experimental manipulations of acetylcholine (Power, 2004). 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. In this way, REM sleep theta oscillations may afford the ability to strengthen distributed aspects of specific memory representations across related but different anatomical networks (Buzsaki, 2002; Jones & Wilson, 2005).

Together, these results demonstrate that offline time containing sleep, especially REM sleep, may offer a neurobiological state that is especially well suited for the preferential processing of emotional experiences. It should be noted, however, that the majority of studies have principally examined negative and arousing emotional stimuli. An important next step will be the inclusion of positive stimuli of different arousal magnitudes in such paradigms, which may offer an increasingly refined understanding of the interaction between valence asymmetry and sleep-dependent emotional memory consolidation.

### Sleep and Emotional Regulation

Despite substantial research focusing on the interaction between sleep and affective memory, the impact of sleep loss on basic emotional regulation and perception has received limited research attention. This absence of research is also striking considering that nearly all psychiatric and neurological mood disorders express co-occurring abnormalities of sleep, suggesting an intimate relationship between sleep and emotion. Nevertheless, a number of studies evaluating subjective as well as objective measures of mood and affect, combined with insights from clinical domains, offer an emerging understanding for the critical role sleep plays in regulating emotional brain function.

#### *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 (Horne, 1985). Using a sleep restriction paradigm (5 hr per night), Dinges et al. (1997) reported a progressive increase in emotional disturbance across a 1-week period on the basis of questionnaire mood scales. In addition, subjective descriptions in participants' daily journals indicated increasing complaints of emotional difficulties with reduced sleep. Zohar, Tzischinsky, Epstein, and Lavie (2005) 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.

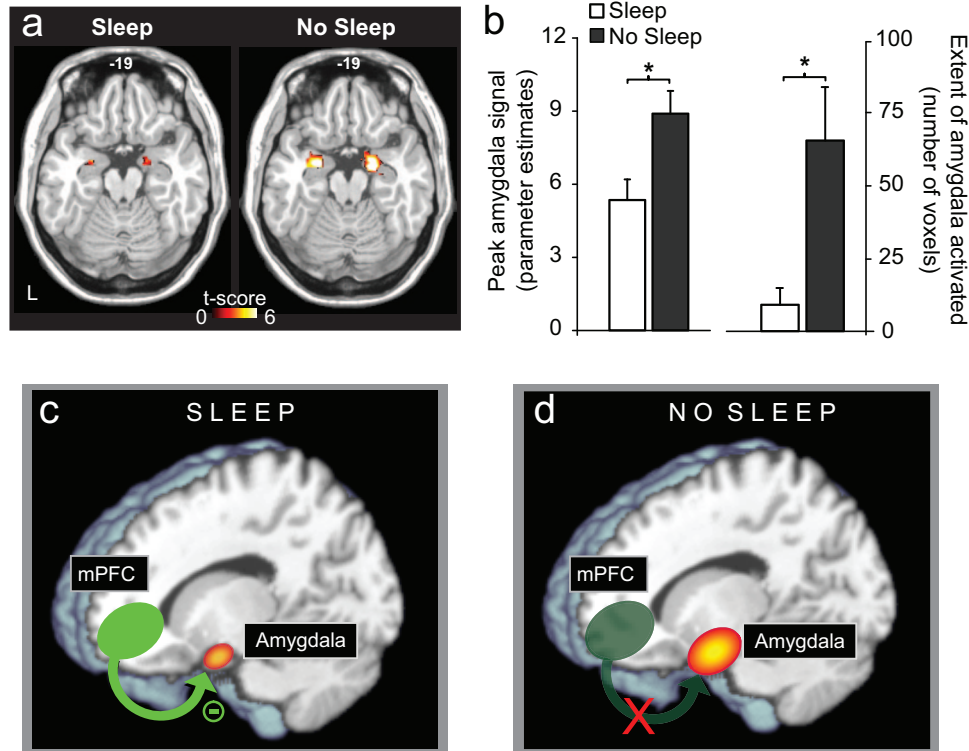
Whereas these findings help to characterize the behavioral irregularities imposed by sleep loss, evidence for the role of sleep in regulating psychophysiological reactivity and emotional brain net-

works is only starting to emerge. To date, only two studies have addressed this interaction. Using functional magnetic resonance imaging (fMRI), Yoo, Gujar, et al. (2007) examined the impact of one night of sleep deprivation on emotional brain reactivity in healthy young adults. During scanning, participants performed an affective stimulus viewing task involving the presentation of picture slides falling along a gradient from emotionally neutral to increasingly negative and aversive. Whereas both groups expressed significant amygdala activation in response to increasingly negative picture stimuli, those in the sleep-deprivation condition exhibited a remarkable 60% greater magnitude of amygdala reactivity relative to the control group (see Figures 6a and 6b). In addition to this increased intensity of activation, there was a threefold increase in the extent of amygdala volume recruited in response to the aversive stimuli in the sleep-deprivation group (Figure 6b). Perhaps most interestingly, relative to the sleep-control group, those who were sleep-deprived experienced a significant loss of functional connectivity between the amygdala and the medial prefrontal cortex (mPFC), a region known to have strong inhibitory projections to the amygdala (Sotres-Bayon, Bush, & LeDoux, 2004; see Figures 6c and 6d of the current article). In contrast, significantly greater connectivity was observed between the amygdala and the autonomic-activating centers of the locus coeruleus in the deprivation group.

Thus, without sleep, an amplified hyperlimbic reaction by the human amygdala was observed in response to negative emotional stimuli. Furthermore, this altered magnitude of amygdala activity was associated with a loss of functional connectivity with the mPFC in the sleep-deprivation condition, implying a failure of top-down inhibition by the prefrontal lobe. It therefore appears that a night of sleep may "reset" the correct affective brain reactivity to next-day emotional challenges by maintaining functional integrity of this mPFC-amygdala circuit and thus govern appropriate behavioral repertoires (e.g., optimal social judgments and rational decisions). Interestingly, a similar pattern of anatomical dysfunction has been implicated in a number of psychiatric mood disorders, which express co-occurring sleep abnormalities (Davidson, 2002; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; New et al., 2007) and directly raises the issue of whether such factors (sleep loss and clinical mood disorders) are causally related. It will be important to identify whether similar dysregulation is observed for positive emotional stimuli, which will allow examination of the full bidirectional impact of sleep loss on affective reactivity.

More recently, Franzen and Buysse (2008) measured the impact 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. Relative to a sleep-control group, a significantly larger pupillary response to negative pictures compared with positive or neutral stimuli was evident in the deprivation group. Furthermore, those in the sleep-deprived condition expressed earlier reactivity to negative images prior to the stimulus onset cue. These data suggest that sleep deprivation not only alters emotional reactivity but may also change the anticipation of these of these events. It is interesting to note the similarity between these findings and those observed in depressed individuals (Siegle, Granholm, Ingram, & Matt, 2001; Siegle, Steinhauer, Stenger, Konecky, & Carter, 2003) as well as the findings from the study by Yoo, Gujar, et al. (2007) reporting





**Figure 6.** The impact 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 two groups (average  $\pm$  standard error of the mean, represented by error bars, 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 inhibitory top-down control. (d) Without sleep, however, amygdala-mPFC connectivity was decreased, potentially negating top-down control and resulting in an overactive amygdala. \*  $p < .01$ ; error bars indicate standard error of the mean.

increased connectivity between the amygdala and autonomic-activating brain-stem centers under conditions of sleep loss.

*Dreams and Emotion*

The strong emotional tone of mental activity that occurs during sleep (often referred to as *dream mentation*; Hobson, Pace-Schott, & Stickgold, 2000) has long encouraged speculation of sleep-dependent affective processing (for reviews, see Levin & Nielsen, 2009; Stickgold, 2002). Indeed, the notion that dreams are intimately linked to our emotional state is, of course, not new and is perhaps most famously conveyed in the theories of Sigmund Freud, the utility of which is reviewed elsewhere (Hobson et al., 2000; Reiser, 2001). Between 75% and 95% of dreams contain emotional contexts, which largely emerge from REM sleep (Hobson et al., 2000; Hobson, Stickgold, & Pace-Schott, 1998). Furthermore, and discounting the often-stated hypothesis that dreams depict a veridical replay of previous episodic experience, the most apparent link between prior daytime events and subsequent dream content involves current emotional concerns and themes (Fosse, Fosse, Hobson, & Stickgold, 2003). Such findings have taken on added clinical importance in the context of reactive depression. For

example, Cartwright, Kravitz, Eastman, and Wood (1991) have shown that recently divorced women who initially suffered depression dreamed of their ex-spouses more frequently and with stronger emotion than did those who were not depressed. Most remarkable, those who were in remission 1 year later were the same patients who had significantly more such dreams, indicating a potential functional connection between dreaming (and/or the neurophysiological state from which they emerge, i.e., REM sleep) and recovery from emotional conflict or trauma.

*Sleep and Mood Disorders*

The implication of such dream studies raises the more general issue of sleep abnormalities in affective disorders and whether the high degree of co-occurrence is more than epiphenomenal. Indeed, it is difficult to identify any psychiatric mood disorder in which sleep disturbance is not a listed formal symptom or a common feature of the condition (*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [DSM-IV]; American Psychiatric Association, 1994), a relationship that may be bidirectional (for reviews, see Benca, Obermeyer, Thisted, & Gillin, 1992; Bliwise, 2004; Harvey, 2001; Harvey, Jones, & Schmidt, 2003). Here, we

focus on two psychiatric disorders of most relevance to the topic of sleep-dependent emotional information processing: major depression and PTSD.

*Major depression.* As the most prevalent mood disorder, major depression has consistently been linked to sleep abnormalities, found in up to 90% of patients, aspects of which are among the diagnostic criteria for this condition (*DSM-IV*; American Psychiatric Association, 1994). The inability to initiate and maintain sleep (insomnia) is a robust risk factor for the development of both an initial episode of depression and recurrent episodes (Harvey, 2001; Perlis et al., 2006). Polysomnographic recordings of sleep in major depression are often marked by increased sleep latency, wake time after sleep onset, and nocturnal awakenings (Berger, Doerr, Lund, Bronisch, & von Zerssen, 1982; Gillin, Duncan, Pettigrew, Frankel, & Snyder, 1979; Kupfer et al., 1985; Waller et al., 1989). Intriguingly, an additional hallmark feature appears to be a pattern of reduced REM sleep latency (faster entry into REM), a prolonged first REM period, and an increase in REM density (Armitage, 2007; Gottesmann & Gottesman, 2007; Tsuno, Besset, & Ritchie, 2005). Moreover, the normalization of sleep architecture abnormalities has been associated with a reduced risk of relapse into depression, yet the persistence of abnormally short REM sleep latency has been related to an increased risk of relapse (Ohayon, 2007). Short (<65-min) REM sleep latency similarly has been shown to predict both response to antidepressant treatment and risk of relapse in major depression (Giles, Jarrett, Roffwarg, & Rush, 1987; Grunhaus et al., 1994; Kupfer, Frank, McEachran, & Grochocinski, 1990; Rush et al., 1989). Indeed, a recent review by Krystal, Thakur, and Roth (2008) indicated that the likelihood of relapse and/or a more indolent course of both major depression and bipolar disorder (together with alcoholism) were strongly predicted by sleep disruption, including the traits of shorter REM sleep latency, greater REM density, and greater percentage of REM sleep. Furthermore, successful psychological treatments, such as interpersonal therapy and cognitive-behavioral therapy, have been found to decrease REM density (Buysse, Frank, Lowe, Cherry, & Kupfer, 1997; Nofzinger et al., 1994).

Interestingly, depressed patients show increased activity in the midbrain reticular formation and in the anterior paralimbic cortex from waking to REM sleep (Nofzinger et al., 2000). Given the negative affect of depressed patients during waking, Nofzinger et al. have suggested that the overactivation of limbic structures during REM sleep may reflect a susceptibility of depressed patients to experience (and possibly encode) stimuli in a more affectively intense, negative context, findings that are discussed in greater detail in the next section.

*Posttraumatic stress disorder.* Another patient population commonly linked to sleep disturbance is that of individuals experiencing PTSD, which is characterized by intrusive re-experiencing, avoidance, and hyperarousal reactions that persist after exposure to a traumatic event (*DSM-IV*; American Psychiatric Association, 1994). Increasing attention has been paid to the repeated incorporation of emotionally charged waking episodes into sleep mentation—a defining characteristic in the *DSM-IV* criteria for diagnosis. Perhaps not surprisingly, PTSD has also been associated with a dysregulation of REM sleep, together with reports of significantly increased sympathetic autonomic tone (Harvey et al., 2003; Mellman & Hipolito, 2006). In fact, the sleep disruptions that occur following trauma exposure may constitute a

specific mechanism involved in the pathophysiology of chronic PTSD and poor clinical outcome. Subjective and objective sleep disturbances occurring early after trauma exposure, as well as heightened sympathovagal tone during REM sleep, are associated with an increased risk of meeting criteria for PTSD at subsequent assessments conducted up to 1 year later (Koren, Arnon, Lavie, & Klein, 2002; Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002). Whether changes in sleep composition and dream characteristics in PTSD reflect attempted functional or dysfunctional processes remains unclear. However, emotional episodic memory events appear to pervade the mental experiences of dreaming in such patients, which is potentially related to aberrant consolidation mechanisms and the etiology of the disorder itself (issues that are discussed in more detail below).

### A Heuristic Model of Sleep-Dependent Emotional Processing: Explanatory Clinical Insights and Predictive Associations

On the basis of the emerging interaction between sleep and emotion at the basic experimental as well as the clinical level, we next provide a synthesis of these findings, which converge on a functional role for sleep in affective brain modulation. We describe a model of sleep-dependent emotional information processing, offering provisional brain-based explanatory insights regarding the impact of sleep abnormalities in the initiation and maintenance of certain mood disorders and leading to testable predictions for future experimental investigations.

#### *A Nexus of Experimental and Clinical Observation*

The findings discussed above 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.

The reduction of sleep caused by insomnia (Buysse, 2004; Shaffery, Hoffmann, & Armitage, 2003) may predispose patients with depression to an imbalance in memory encoding. Although based on findings from acute sleep deprivation, it is noteworthy that chronic accumulated sleep debt associated with depression may impair the ability to form and retain memories of positive (and neutral) affective valence yet leave preserved the formation, and hence long-term dominance, of negative experiences. Such an encoding bias would result in a perceived autobiographical history dominated by negative life events, despite being potentially filled with both positive and negative daily experiences. Indeed, this imbalance may provide a converse mechanistic explanation for the higher incidence of depression in populations expressing impairments in sleep.

Beyond an imbalance in emotional memory formation, another sleep-dependent mnemonic dysfunction may potentiate disease severity. Mounting data suggest that patients suffering from depression exhibit both a faster progression into REM sleep (reduced REM sleep latency) and an increase in the amount of REM sleep experienced, particularly early in the night (Armitage, 2007; Tsuno et al., 2005). When considered on the foundation of evidence described above indicating a strong positive correlation between

the amplification of negative emotional memories and the amount and speed of entry into REM sleep, this signature alteration of REM sleep in depression may instigate maladaptive and disproportionate consolidation of prior negative affective experiences. This phenomenon would be expected to be especially pronounced when combined with the preexisting dominance of negative memories due to the biased encoding noted above.

Consistent with this hypothesis, many antidepressant medications are known to be REM sleep suppressants (Winokur et al., 2001), which by their action, would curtail such offline emotional memory processing and, in so doing, reduce the strength (consolidation) of associated affective experiences. Indeed, total sleep deprivation is known to be a rapid, yet short-lived, treatment for a subset of depressed patients. Improvement in depressive symptoms has also been shown to occur after a single night of sleep deprivation, although this is apparent in only 40%–60% of patients (Giedke & Schwarzler, 2002; Wirz-Justice & Van den Hoofdaker, 1999) and may be related to the extent of resting baseline overactivity within the amygdala (Clark et al., 2006). Most remarkable, selective deprivation of late night sleep, rich in REM sleep, appears to be particularly efficacious in these subgroup populations (Clark et al., 2006). It is also interesting to note the speed with which symptoms relapse following recovery sleep, likely containing a strong REM sleep rebound, which may contribute to the rapid reversal of this therapeutic effect (Wu & Bunney, 1990). It remains unclear why the efficacy of REM sleep-suppressing antidepressants take a number of weeks to produce clinical improvement, yet the effects of experimental sleep deprivation afford rapid symptom alterations. It may be that different mechanistic routes underlie each effect or that the magnitude of physiological REM sleep suppression induced by antidepressant medications is significantly less than that implied by classical sleep-stage scoring (which is bound by strict criteria and perhaps missing still-present physiological signatures of REM sleep).

Thus, at both stages of early memory processing—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. We note one that has additional implications for mood disorders—that is, sleep to forget.

#### *Emotional-Memory Processing: A Sleep to Forget and Sleep to Remember (SFSR) Hypothesis*

Founded on the emerging interaction between sleep and emotion, a model of affective information processing is outlined below. Our model may offer brain-based explanatory insights regarding the impact of sleep abnormalities, particularly REM sleep, for the initiation or maintenance of mood disturbance.

Although there is abundant evidence to suggest that emotional experiences persist in people's autobiographies over time, an equally remarkable but far less noted change is a reduction in the affective tone associated with their recall. The reason that affective experiences appear to be encoded and consolidated more robustly than neutral memories lies in the autonomic neurochemical reactions that are elicited at the time of the experience (McGaugh,

2004), creating what is commonly termed an *emotional memory*. However, the later recall of such memories tends not to be associated with 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 (the memory) remains.

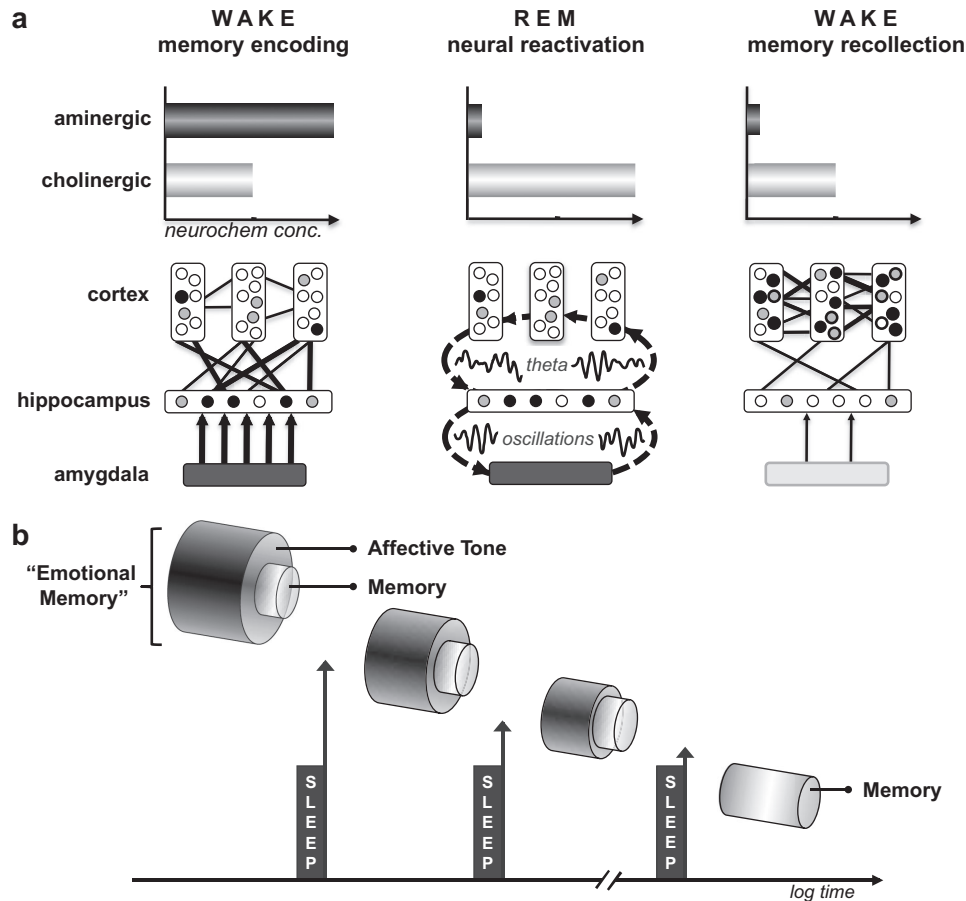
For example, neuroimaging studies have shown that initial exposure to and learning of emotional stimuli is associated with substantially greater activation in the amygdala and the hippocampus relative to that for neutral stimuli (Dolcos et al., 2004, 2005; Kilpatrick & Cahill, 2003). In one of these studies (Dolcos et al., 2004), however, when participants were re-exposed to the same stimuli during recognition testing many months later, a change in the profile of activation occurred (Dolcos et al., 2005). 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 that for neutral items had dissipated over time. This supports the idea that the strength of the memory (hippocampal-associated activity) remains at later recollection, yet the associated emotional reactivity to these items (amygdala activity) is reduced over time.

Our hypothesis predicts that this 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; see Figure 7). The model further argues that if this process is not achieved, the magnitude of "affective charge" remaining within autobiographical memory networks will persist, resulting in the potential condition of chronic anxiety.

On the basis of the unique neurobiology of REM, we propose an REM sleep hypothesis of emotional brain processing (Figure 7a). We suggest that the state of REM provides an optimal biological theater within which a form of "affective therapy" can be achieved. Specifically, increased activity within limbic and paralimbic structures (including the hippocampus and amygdala) during REM sleep may first offer the capacity for reactivation of previously acquired affective experiences. Second, the neurophysiological 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, and perhaps most importantly, these interactions during REM sleep (and perhaps through the conscious process of dreaming) critically take place within a brain that is devoid of aminergic neurochemical concentration (Pace-Schott & Hobson, 2002), particularly noradrenergic input from the locus coeruleus, the influence of which has been linked to states of high stress and anxiety disorders (Sullivan, Coplan, Kent, & Gorman, 1999).

In summary, the neuroanatomical, neurophysiological, and neurochemical conditions of REM sleep described offer a unique biological milieu in which to achieve a balanced neural facilitation of the informational core of emotional experiences (the memory) while depotentiating and ultimately ameliorating the autonomic-arousing charge originally acquired at the time of learning (the emotion), in effect, negating a long-term state of anxiety (Figure 7).

This model complements previous psychological theories of dreaming by Greenberg and colleagues (Greenberg, Pearlman, &



*Figure 7.* The sleep to forget and sleep to remember (SFSR) 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 amygdala and modulated by high concentrations (conc.) of aminergic neurochemistry (neurochem). During subsequent rapid eye movement (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 the one hand, a depotentiation of the affective tone initially associated with the event(s) at encoding, and on the other hand, 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 event(s) 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 (dark filled), moderate (gray shaded) and weak (open). Color fill of amygdala and arrow thickness represents 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.

Gampel, 1972; Greenberg, Pillard, & Pearlman, 1972) as well as Cartwright and associates (Cartwright, Agargun, Kirkby, & Friedman, 2006; R. Cartwright, Luten, Young, Mercer, & Bears, 1998; Cartwright et al., 1991), which suggest that the process of REM sleep mental activity aids in the resolution of previous emotional

conflict, resulting in reduced next-day negative mood. Moreover, pioneering work by Cartwright et al. has demonstrated that not only the occurrence of dreaming but also the actual content of dreams play an important role in the recovery from emotional trauma and can be predictive of clinical remission months later

(Cartwright et al., 2006, 1998; Cartwright et al., 1991). The current model offers a neurobiological framework for the overnight modulation and alteration of emotional memories and next-day affective brain reactivity. The model does not discount the potential contribution that the mental operation of dreaming itself, beyond the physiological underpinnings of REM sleep, may afford this process.

### *Emotional Memory Processing: Time (Wake) Versus Sleep*

Although many studies have described an enhancement of emotional memory across time periods containing sleep (even when comparing sleep and wake time periods directly), several reports have demonstrated the facilitation of emotional recollection across shorter intervals (up to several hours) that are unlikely to contain sleep (Dolcos et al., 2004; Kensinger, Brierley, Medford, Growdon, & Corkin, 2002; LaBar & Phelps, 1998). This may suggest that sleep represents a preferential, although not exclusive, time during which emotional memories are consolidated and that both time and sleep modulate affective experiences by way of similar underlying mechanisms. For example, theta electrical oscillations throughout subcortical and across cortical areas appear to play an important role in promoting the strengthening and consolidation of emotional memory. Although dominant during REM sleep, such oscillatory activity could occur during the wake state, driven by prior affective learning experience.

Alternatively, emotional memories may be modulated by two different mechanisms, one during wake and one during sleep, which, at a behavioral level (memory recollection), may appear quantitatively similar but, at a mechanistic brain and autonomic-body level, are qualitatively different. The contrasting neurobiology of wake and sleep states, especially REM sleep, supports this latter hypothesis. For example, across time awake, emotional memories may be processed and modulated predominately by adrenergic mechanisms, which are prolific during wakefulness (Saper et al., 2001), enabling more shorter term memory benefits without the necessity of sleep. Therefore, suppression of aminergic systems following affective learning blocks these emotional memory improvements (Cahill & McGaugh, 1998; McGaugh, 2004). The second, REM sleep-dependent process, while also facilitating the consolidation of emotional experience, may take place by way of cholinergic modulation, in the absence of adrenergic influence. It is in this neurochemical distinction that the qualitative difference between wake and sleep mechanisms may emerge. Specifically, by being processed in a network that is now devoid of adrenergic neurochemistry, the visceral autonomic charge associated with the memory at the time of the emotional learning may be depotentiated during the reactivation and reprocessing of information during REM sleep (see Figure 7a). As a consequence, not only is the memory representation more robust, leading to enhanced recall, but the strength of the bound autonomic charge is reduced (see Figure 7b).

### *Predictions of the Model*

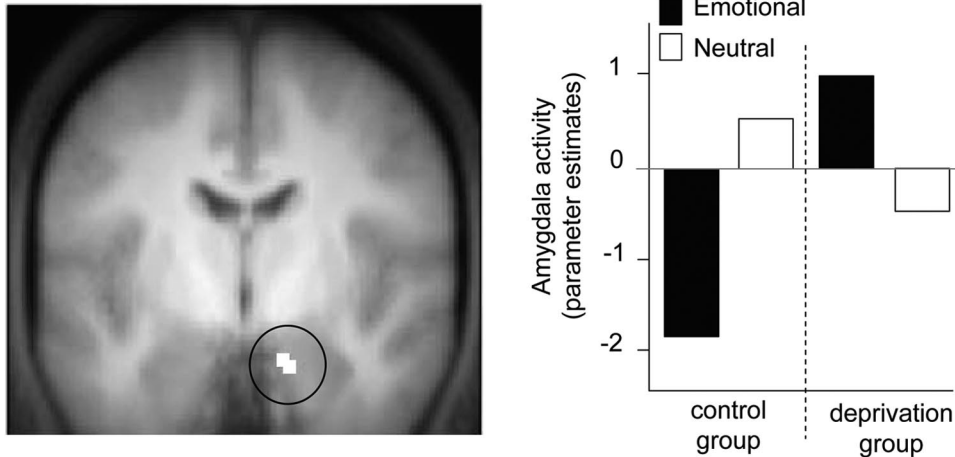
The model predicts that if this process of divorcing emotion from memory is not achieved across the first night following such an experience, a repeat attempt of affective demodulation will occur on the second night, as the strength of the “emotional tag” associated with the memory will remain high. If the process fails a second time, the same events will 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 (Lavie, 2001). It may not be coincidental, therefore, that such patients continue to display hyperarousal reactions to associated trauma cues (Harvey et al., 2003; Pole, 2007) and may indicate that the process of separating the affective tone from the emotional experience has not been accomplished. The reason why such an 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 and/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 (Harvey et al., 2003; Pole, 2007; Strawn & Geraciotti, 2008), potentially suggestive of insufficient aminergic demodulation, that prevents the processing and separation of emotion from memory.

This model also makes specific experimental predictions as to the fate of these two components: the memory and the emotion. As partially demonstrated, the first prediction is that, over time, the veracity of the memory itself will be maintained or improved, and the extent to which these (negative) emotional experiences are strengthened will be proportional to the amount of post-experience REM sleep obtained as well as how quickly it is achieved (REM latency).

Second, with physiological measures, these same predictions are expected to 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 (Sterpenich et al., 2007). Relative to a control group who 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 hr later (the sleep to remember component of the hypothesis) but also exhibited a lack of reduction in amygdala reactivity when re-exposed to the same negative emotional picture slides at recognition testing (Figure 8; 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. In contrast, those who did not sleep the first night after the emotional learning session, despite obtaining two full recovery nights of sleep, exhibited no such depotentiation of subsequent amygdala reactivity.

Findings of a related study, however, do not conform to these trends. Wagner, Fischer, and Born (2002) instructed participants to subjectively rate and re-rate emotional picture slides after 3 hr of early-night sleep or 3 hr of late-night sleep. Valence ratings of unpleasantness actually increased following sleep, specifically late night sleep (rich in REM), as compared with new picture slides not seen before. This was also true in a group that was allowed to sleep the entire night. The difference between this finding and those describing a decrease in emotional reactivity remains unclear. It is of note that when compared with the same items before sleep (baseline ratings, instead of new items), no increase in valence rating was evident. This discrepancy may also be due to the dimension of valence not being sensitive to changes in autonomic emotional reactivity. In fact, participants also rated these picture



**Figure 8.** Impact of sleep deprivation on limbic brain activity during subsequent emotional memory retrieval. (a) Higher degree of amygdala reactivity during delayed (72-hr) recollection of previously learned negative emotion picture slides in participants that were sleep deprived the first night after learning in comparison with a control group that slept the first night after learning and (b) the associated magnetic resonance signal from the amygdala in both groups of participants, 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. Adapted from “Sleep-Related Hippocampo-Cortical Interplay During Emotional Memory Recollection” by V. Sterpenich, G. Albouy, M. Boly, G. Vandewalle, A. Darsaud, E. Balteau, et al., 2007, *PLoS Biology*, 5, e282. Copyright 2007 by the Public Library of Science.

stimuli on the basis of arousal strength. There was no such amplification of arousal reactivity following sleep, demonstrating a numerical but nonsignificant decrease over time relative to baseline measures. Alternatively, it may be that the assessment of valence is associated with the veracity of the memory, which is strengthened overnight, thereby promoting the recall of perceived pleasantness (or unpleasantness). Arousal (the visceral, autonomic dimension of emotion), in contrast, appears to be reduced over time, despite the beneficial strengthening of memory recall.

The third tenet of the model predicts that a pathological increase in REM sleep, as commonly occurs in depression (Armitage, 2007; Gottesmann & Gottesman, 2007; Tsuno et al., 2005), may disproportionately amplify the strength of negative memories. This may occur so much so that, despite individuals’ concomitant attempts at ameliorating the associated affective tone through increased REM sleep, such REM sleep would still create a perceived autobiographical history dominated by negative memory excess (which may also facilitate disadvantageous waking rumination). In contrast, the selective decrease of REM, as occurs with many antidepressants, would predict a reduction of such negative memory consolidation and bias, although it may curtail the degree of affective decoupling that can occur. Over the long term, the balanced extent of accumulated REM should therefore correlate not only with the persistence, in memory, of the emotional experience but also with a decreased magnitude of autonomic response associated with recall, all of which are testable experimental questions.

### Conclusion

When viewed as a whole, findings at the cellular, systems, cognitive, and clinical levels all point to a crucial role for sleep in the affective modulation of human brain function. On the basis of

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, next-day reactivity throughout limbic and associated autonomic systems. However, if the canonical architecture and amount of sleep is disrupted, as commonly occurs in mood disorders, particularly major depression and PTSD, this symbiotic alliance of sleep-dependent emotional brain processing may fail. The predicted consequences of this failure appear to support the development and/or maintenance of a number of clinical symptoms expressed in mood disorders, whereas the changes in sleep associated with common pharmacological treatments of these cohorts support a relief of these aberrant overnight processes, all of which lead to experimentally testable hypotheses. Ultimately, the timeless wisdom of our parents may never have been more relevant—that is, when troubled, “get a good night’s sleep, and you’ll feel better in the morning.”

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Received July 15, 2008

Revision received April 12, 2009

Accepted April 28, 2009 ■