Chapter 42

REM sleep and emotion regulation

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Summary

Despite substantial research focusing on the interaction between sleep and cognition, especially memory, the impact of sleep and sleep loss on affective and emotional regulation has comparatively attracted much less attention. This might be surprising considering that nearly all psychiatric and neurological disorders with impaired mood express co-occurring abnormalities of sleep, and that many sleep disorders are accompanied by mood disturbances, thus suggesting an intimate relationship between sleep and emotion. Yet, recent studies evaluating subjective as well as objective measures of mood and affect, combined with insights from clinical observations and neuroimaging research, offer new evidence for the emerging role of sleep in regulating emotional brain function. In this chapter, we review clinical and neuroimaging data that support the existence of such complex interactions between sleep and emotion regulation. We report that (1) sleep disorders are frequently associated with affective symptoms; (2) patients with mood disorders often present with sleep disturbances; (3) sleep deprivation may transitorily alleviate depressive symptoms; (4) dream experiences may be highly emotional; (5) brain regions involved in emotion processing and regulation, such as the limbic (e.g., amygdala, anterior cingulate cortex) and ventromedial prefrontal regions, are strongly activated during REM sleep; (6) subjective mood assessments exhibit a circadian modulation. New data also show that some hypothalamic neuropeptides (hypocretin/orexin) play a dual role in the stabilization of sleep–wake states and on mesolimbic dopamine activity, with significant effects on neural plasticity related to emotional learning, reward processing, and addiction. Together, these seemingly disparate observations converge to indicate a physiological interplay between sleep–wake and emotional brain functions serving the modulation, the preparation, and the optimization of waking behavior.

Emotional disturbances in sleep disorders

Insufficient sleep and sleep disorders are often accompanied by daytime complaints, several of them suggesting some form of emotional dysregulation. For example, patients with sleep-onset insomnia or with sleep-maintenance insomnia show increased vulnerability to stress and negative emotions (Waters *et al.*, 1993). Short sleep duration (less than five hours of sleep) is associated with suicidal ideation and attempts among adults in the general population (Goodwin and Marusic, 2008). Sleep deprivation raises anxiety levels, which is independently linked with suicidal ideation and suicide attempts in humans (Friedman *et al.*, 1999). There is also evidence that sleep disturbances may be linked to aggressive and impulsive behavior, as well as mood lability (Pakyurek *et al.*, 2002). In general, these results suggest that insomnia and chronic deprivation of sleep may influence mood, psychological distress, and emotional lability (Benca *et al.*, 1992).

Narcolepsy is another paradigmatic sleep disorder, which presents with an emotional component. Narcolepsy with cataplexy (NC) is a sleep–wake disorder characterized by excessive daytime sleepiness, nocturnal sleep disruption, and several manifestations of so-called "dissociated" or isolated rapid eye movement sleep (REM) features, such as muscle atonia (i.e., cataplexy), sleep paralysis, and hallucinations (Baumann and Bassetti, 2005). The pathognomic symptom of NC is cataplexy, which corresponds to short episodes of muscle tone loss with preserved consciousness triggered by emotions, most often by

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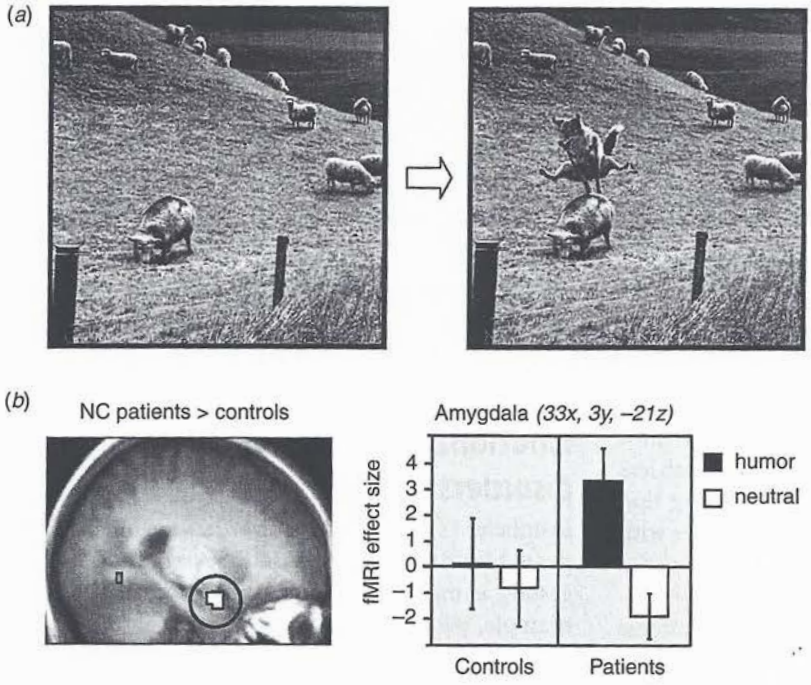

Figure 42.1 Amygdala response to humorous stimuli in narcolepsy–cataplexy (NC) patients. (*a*) Mini-sequence in which a neutral scene was followed by a second picture revealing a new element either neutral or humorous. Here a sequence judged as funny. (*b*) Increased amygdala response to humor in NC patients compared to controls. Parameter estimates show increased fMRI signal to humorous sequences in the patients but not in the controls. (Adapted from Schwartz *et al. Brain* 2008 with permission.) (See plate section for color version.)

laughing, joking, or playing games. Human narcolepsy is associated with a reduction or loss of a hypothalamic peptide called hypocretin or orexin (for a review see Desseilles *et al.*, 2008; Dang-Vu *et al.*, 2009). Interestingly, there is some overlap between brain activity patterns occurring during cataplexy and normal REM sleep (i.e., activation of the brain stem, thalamus, amygdala, and cingulate cortex; deactivation of the prefrontal cortex), suggesting similar brain generators for both conditions (Chabas *et al.*, 2007; Hong *et al.*, 2006; Maquet *et al.*, 1996; Schwartz and Maquet, 2002). A recent fMRI study revealed an increased amygdala (and reduced hypothalamic) response to emotionally positive stimuli (humorous pictures) in NC (Schwartz *et al.*, 2008) (Figure 42.1). Increased amygdala reactivity in NC was confirmed in another fMRI study in which patients could anticipate gains on a game-like task, together with altered responses in mesolimbic reward circuits and ventromedial prefrontal cortex (VMPFC) (Ponz *et al.*, 2010a). These findings are in line with recent animal data showing a link between the hypocretin/orexin system and the expression of motivated behaviors and addiction (Harris and Aston-Jones, 2006), and with the clinical observation that hypocretin-deficient NC patients rarely become addicted to highly addictive pharmacological treatments. Using an aversive conditioning paradigm, Ponz *et al.* (2010b) also demonstrated impaired emotional learning in NC patients, due to the absence of amygdala response to conditioned stimuli, together with an abnormal functional coupling between the amygdala and medial prefrontal cortex. These findings show that brain networks involved in the processing, evaluation, learning, and regulation of emotional signals might rely on neurotransmitters and neural pathways that contribute to the maintenance of sleep–wake states as well. These animal and human imaging data open a new avenue to the study of common brain systems that regulate both sleep, emotion, and reward brain functions.

Sleep alterations in mood disorders

The vast majority of psychiatric disorders, especially those involving mood perturbations, are associated with sleep abnormalities (Benca *et al.*, 1992). For example, sleep difficulties are common among persons with suicidal ideation, suicide attempts, and suicide completion. In depressed patients, in addition to sleep continuity disturbances and SWS deficits, several REM-sleep abnormalities have been reported

(Reynolds and Kupfer, 1987). In endogenous depression, reduced REM-sleep latency was found to co-occur with terminal insomnia, pervasive anhedonia, unreactive mood, and appetite loss. Interestingly, while increased REM-sleep density might be more severe in acute vs. remitted phases, reduced REM-sleep latency can persist even in remitted patients (Giles *et al.*, 1990). Sleep abnormalities might thus be biological markers of mood disorder susceptibility (Benca and Peterson, 2008). Vogel and colleagues hypothesized that an excessive amount of REM sleep and the ensuing decrease in REM-sleep pressure might cause major depression (Vogel *et al.*, 1990). As a consequence, partial REM-sleep deprivation and total sleep deprivation work by suppressing REM sleep and by increasing REM-sleep pressure. Interestingly, increased REM-sleep pressure through repetitive REM-sleep deprivation might be beneficial as an antidepressant treatment, especially for depressed subjects who are able to construct well organized dreams (Cartwright *et al.*, 2003). However, while several antidepressant treatments such as tricyclics increase REM-sleep pressure, REM-sleep suppression is not necessary for an antidepressant response since many antidepressant treatments do not reduce REM sleep (see also next section).

Post-traumatic stress disorder (PTSD) is an important psychiatric condition with major sleep disturbances, characterized by frequent nightmares and sleep initiation and/or maintenance insomnia due to recurrent, unwanted re-experiencing of a previous traumatic event. Interestingly, some studies suggested a link between REM-sleep activity (i.e., a more fragmented pattern of REM sleep and increased noradrenergic activity during REM sleep) in the acute aftermath of trauma and the subsequent development of PTSD (Mellman *et al.*, 2002). A recent behavioral study in healthy participants showed that REM sleep-rich late sleep contributes to the long-term consolidation of emotional memories, and suggests that sleep deprivation in the immediate aftermath of traumatic events could be a promising therapeutic measure to prevent PTSD (Wagner *et al.*, 2006). A recent hypothesis also suggests that REM sleep amplifies the abnormal activation of the amygdala and the deactivation of the medial frontal cortex that are observed at baseline in PTSD patients (Germain *et al.*, 2008).

Sleep problems are also reported in schizophrenia. While studies have not shown any differences between healthy subjects and schizophrenic patients for REM-sleep duration and REM-sleep density, decreased REM-sleep latency was found in several studies (Monti and Monti, 2005). In addition, schizophrenic patients do not show any REM sleep rebound after REM-sleep deprivation. It has also been suggested that some features of REM dreaming may overlap with clinical symptoms in schizophrenia, and that dreaming, in particular bizarre features in dreams, could be used as a model for psychosis (Scarone *et al.*, 2008).

Effects of sleep deprivation on emotional responses

We all know that after a night of poor-quality sleep, we may feel in a somewhat unusual mood. We may also react inappropriately, often impulsively, to unforeseen or emotional situations. Reduced emotional control is frequently observed after sleep deprivation in the form of irritability, impatience, childish humor, disregard of normal social conventions, and inappropriate interpersonal behaviors (Horne, 1993). Mood and emotion processing might actually be more affected by sleep deprivation than either cognitive or motor performance (Dinges *et al.*, 1997). Consistent with this observation, decision making that requires the processing of unexpected information, competing distraction, or emotions was found to be affected by sleep deprivation, unlike decision making involving rule-based, convergent, or logical tasks (for a review see Harrison and Horne, 2000). Using a gambling type of task, McKenna and colleagues (2007) recently showed that after one night of sleep deprivation, subjects take more risk than they ordinarily would when they are considering a gain, but less risk when considering a loss. The behavioral effects of sleep deprivation may thus include an (abnormal) augmentation of motivational or "drive-related" behaviors. In animals, REM-sleep deprivation has been reported to enhance appetite, sexual behavior, aggressiveness, and locomotor activity (Velazquez-Moctezuma *et al.*, 1989). In humans, sleep deprivation (in particular REM sleep) was shown to improve mood in patients with endogenous depression and increase appetite and sexual interest in normal subjects (McNamara, 1996). Because these behaviors are thought to involve activation of dopaminergic reward circuits, REM-sleep deprivation may enhance motivational behaviors through an action on dopaminergic functions.

To date, very few studies have investigated whether sleep deprivation inappropriately modulates emotional brain reactivity in humans. One study revealed

enhanced amygdala response to emotional stimuli after one night of sleep deprivation, together with reduced functional connectivity between the amygdala and the medial prefrontal cortex (MPFC) (Yoo *et al.*, 2007). The MPFC is known to have an inhibitory influence on amygdala activity, and a disregulation of amygdala–MPFC connectivity is believed to significantly contribute to the neural underpinnings of anxiety and major depression (e.g., Davidson 2002; Johnstone *et al.*, 2007; Desseilles *et al.*, 2009). Using a gambling type of task, Venkatraman and colleagues (2007) provided the first evidence that 24 hours of sleep deprivation can modulate the neural systems associated with decision making. Following sleep deprivation, choices involving higher relative risk elicited greater activation in the right nucleus accumbens, consistent with an elevated expectation of the higher reward after the riskier choice was made. Concurrently, there was less activation for losses in the insular and orbitofrontal cortices suggesting blunted response to losses. By resetting limbic and mesolimbic reactivity to emotional challenges, a good night of sleep may regularize waking affective processing while fostering adapted behavioral responses.

Consolidation of emotional memory during sleep

Compared to the abundant data showing a role for sleep in non-emotional memory processes, the specific contribution of sleep physiology to the consolidation of emotional memories is less clear. Indeed, although several lines of evidence suggest a relationship between sleep and emotional processing, only a few studies investigated how sleep may determine the fate of emotional memories. Wagner *et al.* have contributed a series of behavioral studies demonstrating that REM sleep may enhance emotional memories (Wagner *et al.*, 2001, 2002), and that this emotional memory enhancement may persist for several years (Wagner *et al.*, 2006). Another study confirmed these findings by showing a decrement of memory selectively for highly arousing and negatively valenced pictures after 12 hours of wakefulness as compared to 12 hours of sleep (Hu *et al.*, 2006). On the other hand, Wagner *et al.* (2005) reported that cortisol blockade during sleep interferes with hippocampus-dependent declarative memory formation while it enhances amygdala-dependent emotional memory formation, thus suggesting that the natural cortisol rise during late sleep may dampen emotional memory formation. In consonance with the observation that sleep disturbances frequently follow traumatic experiences (Caldwell and Redeker, 2005), sleep deprivation immediately following a traumatic event has been suggested as a possible therapeutic tool to prevent the consolidation of emotional memories, and potentially thwart the progress of PTSD.

At the brain level, a few studies have started to provide some insights into the cerebral mechanisms underlying sleep-related emotional memory consolidation. Nishida *et al.* (2009) showed that the amount of REM sleep as well as concomitant right prefrontal theta power during a nap correlated with emotional memory facilitation. The authors suggested that increased prefrontal theta may represent the large-scale cooperation between subcortical limbic structures (including amygdala and hippocampal) and prefrontal regions, and that such synchronous activity within limbic and neocortical regions during REM sleep would modulate plastic changes essential for the modulation of affective experiences. A recent study by Sterpenich *et al.* (2007) used fMRI to directly test sleep-dependent emotional memory processing. Subjects who were sleep-deprived during the first night after exposure to arousing emotional pictures and who were retested 72 hours after encoding (including two nights of normal sleep), showed a lack of reduction in amygdala reactivity when re-exposed to these same emotional stimuli unlike subjects who were allowed to sleep during the first night after exposure to the emotional stimuli. The recruitment of the amygdala might allow the recollection of negative information despite the cognitive repercussion of sleep restriction, while retrieval performance deteriorated for neutral and positive stimuli after sleep deprivation. When retested six months after incidental encoding, recollection in the sleep group (compared to the sleep-deprived subjects) was associated with significantly larger responses and increased connectivity in a network encompassing the VMPFC, the extended amygdala, and the occipital cortex (Sterpenich *et al.*, 2009) (Figure 42.2). These results suggest that sleep during the first post-encoding night critically modulates the long-term systems-level consolidation of emotional memory.

Taken together, these results support a permissive role of sleep – and in particular REM sleep – in the functional brain changes that underlie the formation of enduring emotional memories in humans, and

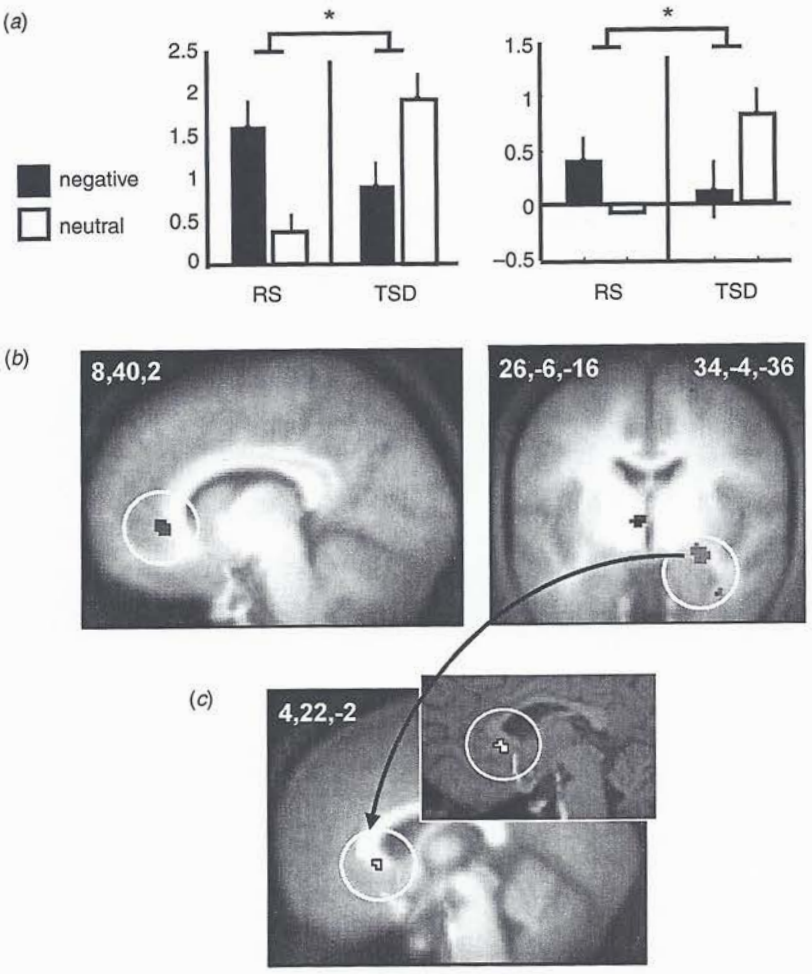

Figure 42.2 Effect of sleep on emotional memory after six months. Sterpenich's fMRI study was performed in three phases: encoding, first retrieval (after three days), and delayed retrieval (after six months). During the incidental encoding session, the subjects rated the valence of 40 negative, 40 positive, and 40 neutral pictures on a seven-point scale (–3, very unpleasant; 0, neutral; +3, very pleasant). During the post-encoding night, one half of the subjects were totally sleep deprived (TSD). The other participants went home and slept as usual (RS). After two additional nights, which allowed sleep-deprived participants to recover, subjects performed a first retrieval session during which 120 previously encoded pictures were presented, randomly mixed with 60 new ones. Six months after the encoding session, the subjects performed a second retest session during which the 120 initially encoded pictures were again mixed with 60 additional new ones. (*a*) Parameter estimates of activity in the MPFC and amygdala, showing increased activity for negative (black bars) than neutral (white bars) pictures for the RS compared to the TSD group after six months. (*b*) The amygdala (in red) was more activated by emotional stimuli during encoding, and the ventral medial PFC (in blue) showed a memory by delay interaction. (*c*) Ventral medial PFC was more connected to the amygdala for negative than neutral correctly recollected pictures and more so in the RS than TSD group (inset, enlarged prefrontal and temporal region in a representative subject). (Adapted from Sterpenich *et al. J Neurosci* 2009 with permission.) (See plate section for color version.)

that may involve a modulation of amygdala-mPFC functional connections.

REM dreaming and affective processing

Science seems to confirm the traditional belief that dreams are highly emotional. When compared to a real-life spectrum of emotions, the emotional content in dream reports tends to be predominantly negatively loaded with a high proportion of fear- or anxiety-related emotions (e.g., Valli and Revonsuo, 2009) (Figure 42.3). During wakefulness, the amygdala is known to respond to threatening stimuli, stressful situations, or novelty. Its high activity during REM sleep could reflect an elevated intensity of emotions

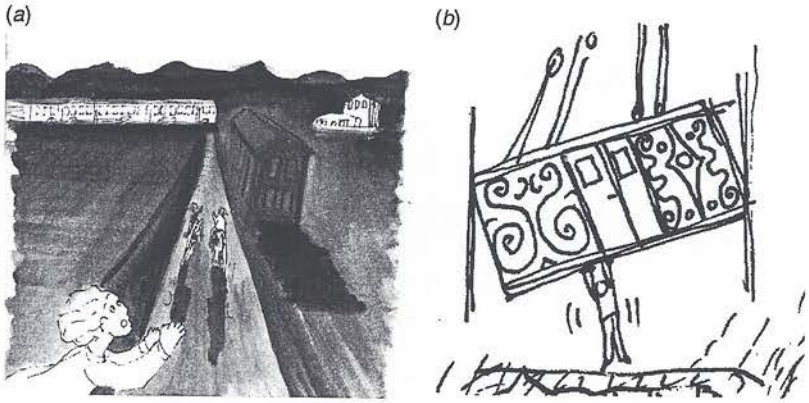

Figure 42.3 Examples of threatening situations associated with strong emotions in dreams. (*a*) Terrified, the dreamer tries to escape a danger by catching a train. (*b*) The dreamer is trapped in a space beneath an elevator, threatened to get crushed by the weight of the elevator. Drawings selected from a dream diary extensively analyzed elsewhere (S. Schwartz, Doctoral thesis). (See plate section for color version.)

in dreams (Maquet *et al.*, 1996; Maquet and Franck, 1997; Schwartz and Maquet, 2002).

Several theories suggest that dreaming may be beneficial for the regulation of emotional states (for a comprehensive review see Nielsen and Levin, 2007). Combining an evolutionary perspective of the function of dreaming with the empirical evidence concerning the frequency of emotionally negative dreams (e.g., nightmares and post-traumatic dreams), Revonsuo and Valli recently suggested that dreaming might serve to simulate responses to threatening events in a totally secure environment (Valli and Revonsuo, 2009). Such active rehearsal would enhance threat-avoidance skills and ultimately help the individual to respond in an adapted and efficient way to dangerous real-life events. A distinct but analogous theoretical explanation for the occurrence of negative emotions in dreams has been proposed by Nielsen and Levin (Levin and Nielsen, 2007; Nielsen and Levin, 2007). They proposed that bad dreams and nightmares would result from a "dysfunction in a network of affective processes that, during normal dreaming, serves the adaptive function of fear memory extinction" (Nielsen and Levin, 2007, p. 300). In short, the "affective network dysfunction" (AND) model stipulates that dreaming may promote the consolidation of fear extinction memories by (1) activating features of fear memories (largely independently from their episodic, real-world contexts); (2) reorganizing these features by creating novel simulated contexts in which the conditioned stimuli are presented without their pairing with the unpleasant unconditioned stimulus, but rather in non-fearful, contexts; and (3) allowing the experience of these modified emotional reactions to such recombined dream features that would foster the extinction of conditioned responses. By identifying an affective network (i.e., hippocampus, amygdala, anterior cingulate, medial prefrontal cortex) whose dysfunction might account for different types of dysphoric dreaming (from occasional bad dreams to non-traumatic nightmares to replicative post-traumatic nightmares), the AND is a sophisticated model that integrates both cognitive and neural explanatory levels.

The suggested cathartic function of dreaming might also relate to the persistence of activity in medial prefrontal regions (MPFC) and orbitofrontal cortex during REM sleep (Maquet *et al.*, 1996; Nofzinger *et al.*, 1997), regions that are known to contribute inhibitory feedbacks on the amygdala. Moreover, the MPFC is also involved in the attribution of intentions, thoughts, and feelings to oneself and to others during wakefulness (Frith and Frith, 2003). We may speculate that MPFC activation during REM sleep may explain why dreamers often attribute thoughts, emotions, and intentions to the dreamed characters, an offline role-play that may ultimately facilitate the resolution of social or emotional conflicts. Conversely, deactivation in the dorso lateral prefrontal cortex (DLPFC) during REM sleep may explain why only very few dream reports represent an exact replay of full memory episodes (Fosse *et al.*, 2003; Schwartz, 2003). Taken together, these observations suggest that isolated episodic elements are reactivated during sleep (most likely via the activation of the hippocampus, limbic structures, and posterior cortical areas), although these elements do not form replicates of real-life episodes (because of the deactivation of the DLPFC among other possible causes). Future research may clarify whether and how exactly such role-play and re-experiencing of waking bits and pieces contribute to emotion regulation.

Chronobiology of emotions

While the previous sections highlighted some intricate links between sleep and emotion regulation, circadian modulations of affective processes suggest that chronobiological factors should also be considered. In healthy individuals, subjective mood exhibits a remarkable circadian rhythmicity (Birchler-Pedross *et al.*, 2009; Boivin *et al.*, 1997). One recent study suggested that mood changes after sleep deprivation may depend on morningness–eveningness chronotypes (Selvi *et al.*, 2007). Moreover, sleep abnormalities in depression have been found to relate to chronobiological disturbances (e.g., Germain and Kupfer, 2008; Lewy *et al.*, 2006; Wirz-Justice, 2008). Consistent with a circadian modulation of affective regulation, the most widely documented rapid-onset antidepressant therapy is sleep deprivation, which acts within 24 to 48 hours in 40 to 60% of depressed patients (Wu *et al.*, 2009). Indeed, one putative mechanism that may mediate such rapid antidepressant effects is the activation of the hypocretin/orexin system by sleep (or REM sleep) deprivation (Mignot, 2001). In line with this hypothesis, dampened diurnal variations in hypocretin-1 were observed in depression (Salomon *et al.*, 2003), and may thus underlie the contribution of sleep–wake physiology to the maintenance or treatment of depression (Benca *et al.*, 1992).

The vulnerability to the effect of sleep loss and its consequence on mood markedly differs between persons in a trait-like manner and may relate to some genetic predisposition (Van Dongen *et al.*, 2004). In particular, it was recently proposed that clock genes, which regulate circadian and seasonal rhythms, with allelic variants modulating individual rhythms at both the cellular and behavioral levels, may underlie these various phenotypes. In particular, in patients suffering from mood disorders, rare genetic variants of Period3 (Per3) were found to be associated with higher novelty seeking, marginally better response to antidepressant treatments (SSRIs), worse mood in the evening, worse family and spare-time social adjustment (Artioli *et al.*, 2007). In addition, $Per3^{5/5}$ variant is associated with morningness (Archer *et al.*, 2003), as well as with increased slow-wave activity during non-REM sleep, increased theta and alpha activity during wakefulness and REM sleep, and greater decrement of cognitive performance in response to sleep loss (Viola *et al.*, 2007). Moreover, $Per3^{5/5}$ might correlate with earlier age at onset of bipolar disorder (Benedetti *et al.*, 2008), which is a predictor of worse evolution of the disease. A recent fMRI study revealed that, after staying awake all night, $Per3^{5/5}$ carriers showed widespread reduction of brain activity in prefrontal, temporal, parietal, and occipital areas, when compared to individuals with the short allele $Per3^{4/4}$ (Vandewalle *et al.*, 2009). While these data suggest that circadian genes impact strongly on sleep-loss vulnerability and cognition, it remains to be tested if the long variant directly impairs emotion regulation, independently of the effect of mood induced by sleep deprivation. "Chronobiotics" (i.e., the treatment of circadian rhythm disorders) such as melatonin administration might be used in order to prevent mood or emotional disruption in conditions where circadian regulation is compromised, such as sleep disorders, mental disorders, jet lag, or shift work.

It is well established that sleep- and circadian-related factors affect waking cognition. The studies reviewed in this chapter provide an emerging view that the neurobiology of sleep, REM sleep in particular, may promote the regulation of affective processes and optimize waking emotional functioning. Moreover, recent brain imaging findings as well as dream data suggest that an offline rehearsal and consolidation of emotional experiences may occur during sleep. Therefore, sleep may serve complementary and vital functions by fostering adapted defense mechanisms against past and future psychological (and physical) threats and by renewing our daily portion of motivation and good mood.

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