

Sleep and Affective Brain Regulation

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Abstract

Rapidly emerging evidence continues to describe an intimate and causal relationship between sleep and affective brain regulation. These findings are mirrored by long-standing clinical observations demonstrating that nearly all mood and anxiety disorders co-occur with one or more abnormalities of sleep. This review aims to (1) provide a synthesis of recent human evidence describing affective brain and behavioral benefits of sleep when it is obtained, and conversely, detrimental impairments following a lack thereof, (2) set forth a rapid eye movement sleep hypothesis of affective brain homeostasis, optimally preparing the organism for next-day social and emotional functioning, and (3) outline how this model may explain the prevalent relationships observed between sleep and affective disorders, including relevant treatment mechanisms, with a particular focus on post-traumatic stress disorder (PTSD).

The ability of the human brain to generate, regulate and be guided by emotions represents a fundamental process governing our personal lives, our mental health as well as our societal structure. Advances in cognitive neuroscience over the past two decades have provided important systems-level accounts of the mechanisms underlying affective brain processes (Critchley, 2005; Delgado, Olsson, & Phelps, 2006; Hartley & Phelps, 2010; Ochsner et al., 2009), translationally bridging animal models of emotion regulation and relevant clinical disorders (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Delgado et al., 2006; Drevets, Savitz, & Trimble, 2008; Etkin, 2010; Labar & Cabeza, 2006; Liberzon & Martis, 2006). Upon these empirical foundations, an exciting collection of recent findings has begun to describe a causal role for sleep in the optimal regulation of affective brain function. Moreover, these reports afford tentative neural explanations for the pervasive co-occurrence of sleep abnormalities in psychiatric disorders (Armitage, 2007; Buysse, 2004; Franzen & Buysse, 2008; Gottesmann & Gottesman, 2007; Harvey, Jones, & Schmidt, 2003; Tsuno, Besset, & Ritchie, 2005).

Here, we review evidence in humans suggesting an obligate symbiosis between sleep and affect; both maladaptive consequences caused by the absence of sleep and adaptive benefits following the presence of sleep, especially rapid eye movement (REM) sleep. From these findings, we set forth a neurobiological framework that may account for the observed interactions between sleep and affective brain function. We conclude with comments on the utility of this model in understanding sleep disruption and emotional disturbance in psychiatric disorders, with a specific emphasis on posttraumatic stress disorder (PTSD), and how this REM sleep model may, in part, explain the recent treatment success of specific pharmacological interventions in PTSD. Although this review has a specific focus on human studies a number of animal studies similarly suggest an intimate link between fear conditioning, stress and REM-sleep in animals (DaSilva et al., 2011; Liu et al., 2011; Madan et al., 2008; Sanford, Silvestri, Ross, & Morrison, 2001; Sanford,

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1 Tang, Ross, & Morrison, 2003a; Sanford, Yang, & Tang, 2003b; Sanford, Yang,
2 Wellman, Liu, & Tang, 2010; Wellman, Yang, Tang, & Sanford, 2008; Yang, Wellman,
3 Ambrozewicz, & Sanford, 2011). It should be noted that this focused review addresses 3
4 the relationship between sleep and emotions. In this limited capacity, it does not consider
5 the nonetheless fascinating potential interaction between sleep and mood states, which we
6 and others have considered different to emotions: emotions are short-lived events, often
7 in response to external stimuli, while mood states are more sustained events, often inter-
8 nally generated (for a review, see Mendl, Burman, & Paul, 2010). Although the relation-
9 ship between REM-sleep and mood is an interesting topic as well, we regard it outside
10 of the scope of this review.

11 Neurobiology of the Sleeping Brain

12 Before considering the impact of sleep, and specifically REM sleep, on affective brain
13 function, it is relevant to outline its neurobiological features that help explain a mechanis-
14 tic link with emotional processing. Neuroimaging techniques have revealed significant
15 elevations in activity in affect-related regions including the amygdala, hippocampus and
16 'extended limbic system' throughout the medial prefrontal cortex (mPFC) during REM
17 sleep (Nofzinger, 2005). These dramatic changes in functional brain anatomy are paral-
18 leled by (and likely instigated by) equally profound alterations in neurochemistry
19 (Kametani & Kawamura, 1990; Marrosu et al., 1995). Perhaps most remarkable is the
20 dramatic reduction of noradrenergic activity during REM sleep, showing a marked drop
21 during REM sleep (although not completely absent, as indicated by microdialysis studies
22 (Ouyang, Hellman, Abel, & Thomas, 2004; Park, 2002; Shouse, Staba, Saquib, & Farber,
23 2000). As a consequence, REM sleep represents a brain state largely devoid of adrenergic
24 neurochemistry, while cholinergic activity dominates (Kametani & Kawamura, 1990;
25 Marrosu et al., 1995). EEG waveforms during REM sleep are associated with oscillatory
26 activity in the theta band range (4–7 Hz), together with higher frequency synchronous
27 activity in the 30–80 Hz ("gamma") range (Cantero et al., 2003; Llinas & Ribary, 1993;
28 Steriade, Amzica, & Contreras, 1996). Despite power in the gamma range being the most
29 dominant frequency band present during REM sleep, gamma power is significantly lower
30 than it is during wakefulness (Scheffzuk et al., 2011), likely due to the marked reduction
31 in adrenergic input from the locus coeruleus during REM. These neurobiological features
32 are relevant since many of the neuroanatomical and neurochemical systems altered during
33 REM sleep overlap with the systems supporting waking brain mechanisms of emotion
34 and memory (Dolcos, LaBar, & Cabeza, 2005). Additionally, they further overlap with
35 systems that become disrupted following sleep loss.

36 Impact of Sleep Loss on Emotional Brain Function

37 Emotional reactivity

38 Together with impairments of attention, alertness and memory, sleep loss is commonly
39 associated with subjective reports of irritability and affective volatility (Horne, 1985). For
40 example, sleep restriction to only 5 hours of sleep a night across a 1-week period leads to
41 a progressive increase in emotional disturbance in participants on the basis of question-
42 naire mood scales, together with diary documentation of increasing subjective emotional
43 difficulties (Dinges et al., 1997). Moreover, accumulated sleep loss in medical residents
44 amplifies negative emotional consequences of disruptive daytime experiences while

blunting the benefit associated with goal-enhancing activities (Zohar, Tzischinsky, Epstein, & Lavie, 2005).

Studies assessing physiological and neural measures have provided additional objective verification of emotional dysregulation following sleep deprivation, offering potential explanatory mechanisms of the aforementioned subjective disturbances. Using functional MRI (fMRI) it has been demonstrated that one night of sleep deprivation triggers a 60% amplification in reactivity of the amygdala to negative aversive picture images, relative to a normal night of sleep (Figure 1a,b) (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). Moreover, this increase in amygdala activity following sleep loss was also associated with a significant reduction in functional connectivity of the amygdala with regions of the mPFC believed to exert top-down regulatory control of the amygdala (Figure 1c,d). In contrast, significantly greater amygdala connectivity was observed with a classical fight/flight adrenergic-activating brainstem center of the locus coeruleus under conditions of sleep loss. Congruent evidence has further demonstrated that sleep deprivation results in similar enhanced amygdala reactivity and reduction of connectivity with prefrontal regions during a working memory task that involves emotional distractors (Chuah et al., 2010) and excessive pupil diameter responses (an index of autonomic reactivity) during the passive viewing of negative picture stimuli (Franzen & Buysse, 2008).

Importantly, sleep deprivation is not only associated with enhanced reactivity towards negative stimuli. Growing evidence suggests that sleep loss imposes a bi-directional nature

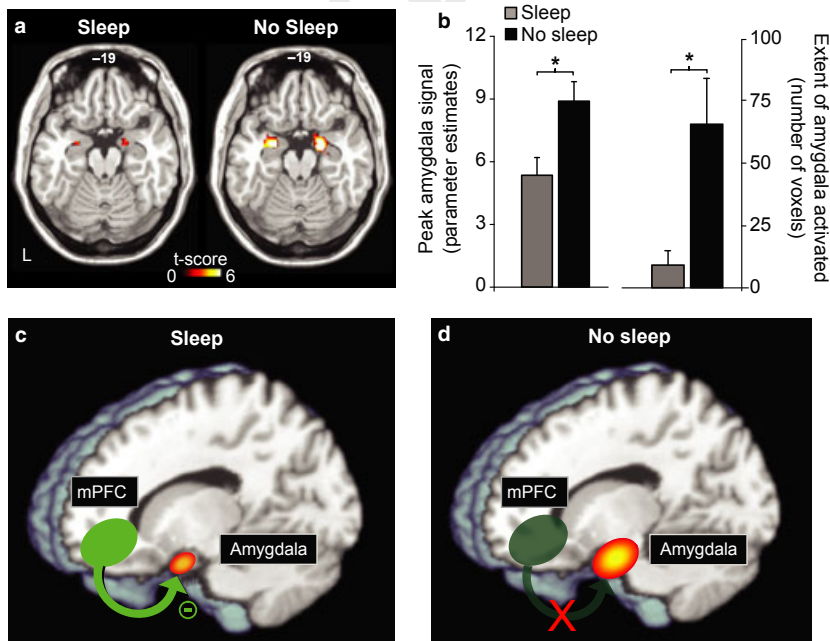


Figure 1 The impact of sleep deprivation on emotional brain reactivity and functional connectivity. (a) Amygdala response to increasingly negative emotional stimuli in the Sleep deprivation and Sleep control groups, and (b) Corresponding differences in intensity and volumetric extent of amygdala activation between the two groups (average $\pm$ s.e.m. of left and right amygdala), (c) 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 s.e.m. Modified from Yoo et al. (2007).

of affective imbalance, also triggering amplified reactivity to positive, reward-relevant picture stimuli. For example, sleep deprivation significantly enhances responsivity throughout regions of the dopaminergic mesolimbic systems in response to pleasure-evoking emotional picture stimuli (Gujar, Yoo, Hu, & Walker, 2011). As with negative emotion reactivity, this enhanced mesolimbic sensitivity to rewarding emotional items was also associated with decreased functional connectivity in regions of the medial and orbital prefrontal cortex. Similar enhanced mesolimbic reactivity following sleep deprivation has also been reported using basic monetary reward incentive paradigms (Libedinsky et al., 2011; McKenna, Dickinson, Orff, & Drummond, 2007; Venkatraman, Chuah, Huettel, & Chee, 2007; Venkatraman, Huettel, Chuah, Payne, & Chee, 2011).

These findings collectively support a framework whereby sleep deprivation exaggerates subcortical limbic and striatal reactivity not only to negative but also to positive affective stimuli, both of which are associated with impoverished prefrontal cortex connectivity. The consequence appears to be a pendulum like, bi-directional reactivity of the brain to both ends of the emotional valence spectrum. Such a model is of clinical relevance for at least two areas of mental health. First, parallel findings of anatomical dysfunction, characterized by altered activity in limbic areas and limbic-prefrontal cortex connectivity, have been reported in a number of psychiatric mood and anxiety disorders that express co-occurring sleep abnormalities, including major depression, bipolar disorder and PTSD abnormalities (Davidson, 2002; Davidson et al., 2002; Drevets et al., 2008; Etkin, 2010; New et al., 2007; Pezawas et al., 2005; Rauch et al., 2000; Rich et al., 2006; Shin, Rauch, & Pitman, 2006; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007; Surguladze et al., 2005). These commonalities directly raise the issue of whether sleep loss plays a causal role in the etiology of these conditions. Second, considering the known disruption of sleep in a number of addiction disorders (Arnedt, Conroy, & Brower, 2007; Brower & Perron, 2010; Ciraulo, Piechniczek-Buczek, & Iscan, 2003; Dimsdale, Norman, DeJardin, & Wallace, 2007; Pace-Schott et al., 2005), this evidence may implicate sleep loss as a predisposing risk factor and therapeutic target in addiction vulnerability to reward-stimulating drugs. They may further intimate a potential role for sleep disruption in the maintenance of addiction habits, especially during attempted withdrawal.

Emotion recognition and expression

In contrast to the signature of amplified neural reactivity in response to emotional stimuli under conditions of sleep loss, a number of studies have reported what appears to be a paradoxical blunting, rather than over-estimation, in the subjective recognition and rating by sleep deprived participants in response to the expression of emotion by others. For example, sleep loss decreases the perceived intensity of threat-relevant (angry) and reward-relevant (happy) of the deprived individuals in response to static facial expressions, although no differences were observed for ratings of sad faces, an emotion considered low on the arousal spectrum (van der Helm, Gujar, & Walker, 2010). Sleep loss also impairs the degree of perceived emotion felt by deprived participants in response to emotional film clips (Minkel, Htaik, Banks, & Dinges, 2011). Intriguingly, sleep loss also decreased the degree of outward observable emotional expressiveness of the sleep deprived individual themselves. Similarly, a decrease in the vocal expression of positive emotion by deprived participants has been reported after a single night of sleep loss, suggesting multiple routes of emotional expression (facial muscles, vocalization) are compromised by sleep loss (McGlinchey et al., 2011). Of concern, insufficient sleep appears to trigger as much, if not more, of an impact on emotional expression in young children.

Recent evidence demonstrates that three-year-olds who do not obtain an afternoon nap show dysregulation of both positive and negative emotion expression in response to emotional stimuli as well as puzzle solving challenges, relative to those who have obtained a nap (Vandekerckhove et al., 2011).

Such impairments in self-expression of emotion, and the recognition of emotion in others, appear to be at odds with prior evidence describing amplified (rather than impaired) limbic reactivity following sleep deprivation. However, this disparity may be reconciled when considering the concomitant neural impairments in the prefrontal cortex. Not only are prefrontal regions implicated in top-down regulatory control of subcortical limbic networks, they critically *integrate* primary affective signals into second-order maps of the internal state of the organism (Craig, 2010, 2011; Critchley, 2005, 2009; Harrison, Gray, Gianaros, & Critchley, 2010; Medford & Critchley, 2010). It has been argued that only through such mapping and hence appreciation of the current body state, can the brain select appropriate behavioral actions for the organism (actions that include emotion expression) (Craig, 2010, 2011; Critchley, 2005, 2009; Harrison et al., 2010). Set against this evidence, the above disparate findings may be resolved, such that the sleep-deprived brain suffers a mismatch between excessive subcortical reactivity yet impaired higher-order prefrontal function, the latter preventing optimal use and control of the former. As a consequence, there is failure of affectively guided judgments, decisions and, down-stream, emotive (re)actions.

Benefits of Sleep on Emotional Brain Function

Dissipation of emotional reactivity

In contrast to affective dysregulation caused by the absence of sleep, beneficial influences upon emotional perception and regulation have been described following the presence of sleep, and REM sleep in particular. For instance, a daytime nap has been shown to dissipate the intensity ratings of threat-relevant negative emotional face expressions (Fear, Anger), yet increase responsivity towards positive (happy) facial images (Gujar, McDonald, Nishida, & Walker, 2010). Interestingly, however, not all participants who slept demonstrated this resetting of emotional reactivity. Instead, only those who obtained REM sleep during the nap displayed this change in profile of emotional ratings (Figure 2). Similarly, a recent study (described in more detail in later sections) has reported that sleep, and specifically REM sleep, not only dissipates the strength of emotional intensity that participants feel the next day in response to emotional stimuli viewed the night before, but that REM sleep also depotentiates the degree of associated amygdala reactivity while re-establishing connectivity between the amygdala and the mPFC (van der Helm et al., 2011). Also fitting with a sleep-dependent emotion depotentiation model, if participants are deprived of sleep the first night after being exposed to emotional picture stimuli (then given recovery sleep), upon subsequent re-exposure to these same emotional stimuli, no palliative dissipation of amygdala reactivity is observed (Sterpenich et al., 2007). Together, these studies provide neural evidence supporting sleep-dependent emotional depotentiation, demonstrating that the presence of sleep provides a neural dissipation of limbic reactivity to prior emotional memories, while sleep loss results in the persistence of such reactivity, even after several nights of recovery sleep.

Of note, several studies have not reported a significant decrease in emotional reactivity following sleep, all using varied measures of emotional reactivity (Baran, Pace-Schott, Ericson, & Spencer, 2012; Lara-Carrasco, Nielsen, Solomonova, Levrier, & Popova,

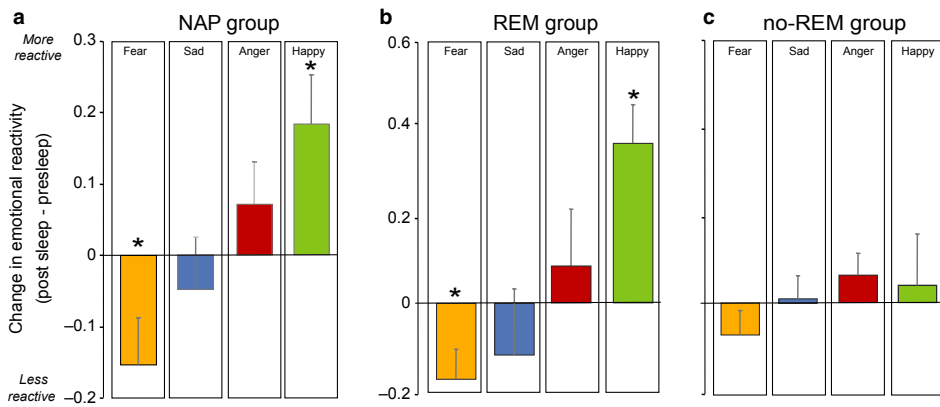


Figure 2 Differential impact of REM sleep on emotional reactivity. Difference in mean ratings between the pre-sleep and post-sleep test sessions across four emotion categories (FEAR, SAD, ANGER, and HAPPY) for (a) the Nap group overall performance, (b) only for those in the Nap group who obtained REM sleep, and (c) only for those in the Nap group who did not obtain REM sleep. Within-group comparisons (symbol above individual bars) reflect paired *t*-test significance (relative to null) at * $p < 0.05$ and ** $p < 0.01$. Error bars represent s.e.m. Modified from Gujar et al. (2010).

2009; Pace-Schott et al., 2011; Wagner, Fischer, & Born, 2002). In the most recent study, participants rated emotional images on the scales of valence (ranging from sad to happy) and arousal (ranging from calm to excited) (Baran et al., 2012). Twelve hours later, after either a night of sleep or a day of wake, these images were rated again on both valence and arousal, in addition to a memory measure (e.g. “have you seen this picture before?”). No significant differences in valence or arousal ratings were observed between wake and sleep. Several study design differences may contribute to the lack of a sleep-dependent emotional depotentiation effect common to this and the aforementioned reports. First, the scales of “arousal” and “valence” may be less sensitive (due to being more abstract) than asking participants to rate how emotional they innately “feel”, as in earlier studies discussed above. Second, the addition of a memory test in the post-sleep and post-wake sessions in some of these reports, which did not occur in the pre-sleep and pre-wake sessions, may alter the task demands and emotive judgments, which were not included in prior investigations observing emotion depotentiating effects. Finally, no neuroimaging measures were obtained, which leaves open the potential of neural (beyond behavioral) differences present following sleep. Nevertheless, such findings make clear that further research using common methodologies that target both participant subjective feeling states and objective neural assessments are required to build a growing consensus.

Emotional memory consolidation

Beyond basic processes of affective reactivity, recognition and expression, sleep has additionally been demonstrated to play an influential role in emotional memory modulation (for a review, see Payne & Kensinger, 2010; Walker, 2009; Walker & van der Helm, 2009). Most notable is a role for sleep in the “offline” consolidation of salient emotional experiences, including memory for individual words and pictures, selective consolidation of emotional elements within visual pictures, as well as the generalization of fear extinction (Kleinsmith & Kaplan, 1963; Levonian, 1972; Pace-Schott et al., 2009; Payne, Stickgold, Swanberg, & Kensinger, 2008; Spoormaker et al., 2011; Wagner, Hallschmid, Rasch, & Born, 2006; Walker & Tarte, 1963).

Rapid eye movement sleep, in particular, may be especially critical for emotional memory processing. In the case of basic aversive learning, pre-sleep fear conditioning responses, indexed by skin conductance and brainstem reactivity, proportionally decrease the probability of REM sleep occurring during a subsequent nap. This may indicate that excessive fear responses during wake can lead to subsequent disturbances of REM sleep, and with it, the functional affective benefits REM sleep provides (Figure 3a,b). Moreover, those who were able to obtain REM sleep after fear conditioning demonstrated a superior degree of ventromedial prefrontal cortex (vmPFC) activity during post-sleep fear extinction (Figure 3c), consistent with a reestablishment of prefrontal cortex emotional regulatory control permitted by REM, and without any expression of amplification of amygdala reactivity (Spoormaker et al., 2010).

Beyond fear conditioning, emotional fact-based or “episodic” memory similarly demonstrates sensitivity to REM sleep. Early work reported that the overnight retention of emotional details relative to neutral details of a narrative story was superior following late-night sleep (a time period rich in REM sleep) (Wagner, Gais, & Born, 2001). It has subsequently been demonstrated that the speed of recognizing emotional face expressions presented prior to sleep is significantly improved the next day, the amount of which positively correlated with the amount of intervening REM sleep (Wagner, Kashyap, Diekelmann, & Born, 2007). Moreover, not only does the amount of time and speed of entry into REM sleep predict the degree of subsequent strengthening and hence offline consolidation of emotional (and not neutral) memory (Figure 4a,b), but it is specifically the amount of EEG theta activity (4–7 Hz) – a dominant electrical oscillation of REM sleep expressed over the prefrontal cortex – that predicts memory retention (Figure 4c,d; Nishida, Pearsall, Buckner, & Walker, 2009). These findings have led to the proposal that REM sleep represents a neurobiological brain-state particularly amenable to emotional memory processing (Hu, Stylos-Allen, & Walker, 2006; Pare, Collins, & Pelletier, 2002; Walker, 2009; Walker & van der Helm, 2009), with theta oscillations proposed as a carrier frequency that potentially allows disparate brain regions that initially encode information to selectively interact offline. By doing so, REM sleep theta may afford the ability to strengthen distributed aspects of specific emotional memory representations across related

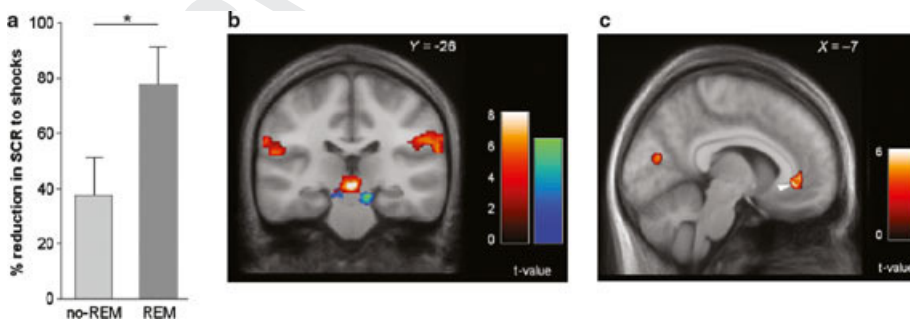


Figure 3 Fear conditioning and extinction related to REM sleep. (a) Significantly greater decreases in skin conductance response across the fear conditioning trials prior to an afternoon nap in those participants obtaining REM sleep relative to the participants who did not enter REM sleep. Error bars represent SEM. (b) fMRI response to mild electrical shocks applied during the conditioning session. Hot colors depict areas of significant activation in response to shock stimuli versus safety, including regions of brainstem, thalamus and bilateral insula, while cool colors depict regions that declined more (linearly) across the conditioning trials in the REM group than in the no-REM group, also including the brainstem. (c) Post-sleep changes in brain fMRI activation during extinction, demonstrating greater ventromedial prefrontal cortex (vmPFC) activity in those who obtained prior REM sleep relative to those who did not, p cluster <0.05 . Modified from Spoormaker et al. (2010).

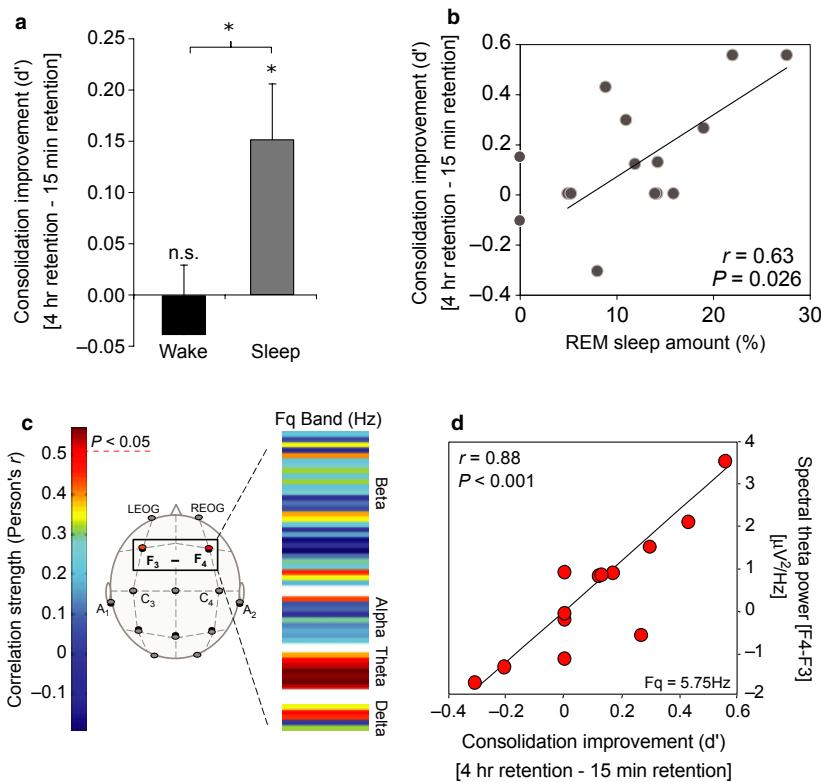


Figure 4 REM sleep enhancement of negative emotional memories. (a) Offline benefit (change in memory recall for 4 hours versus 15 minutes old memories) across the day (wake, gray bar) or following a 90 minute nap (sleep, filled bar); (b) Correlation between the amount of offline emotional memory improvement in the nap group (i.e. the offline benefit expressed in filled bar of a), and the amount of REM sleep obtained within the nap; (c) Correlation (Pearson's r -value) between offline benefit for emotional memory in the sleep group (expressed in filled bar of Figure a) and the relative right versus left prefrontal spectral-band power ([electrode F4 – electrode F3]) within the delta, alpha, theta and beta spectral bands, expressed in average 0.5 Hz bin increments. Correlation strength is represented by the color range, demonstrating significant correlations within the theta frequency band (hot colors), and (d) exhibiting a maximum significance at the 5.75 Hz bin. * $p < .05$; error bars indicate s.e.m. Modified from Nishida et al. (2009).

but different anatomical networks, and/or promote their integration into pre-existing autobiographical memory networks (Cahill, 2000; Jones & Wilson, 2005). However, strengthening of the experience of an emotional event may only be one of two specific functions that REM sleep provides emotional memories, as we next describe.

REM Sleep Homeostasis of Affective Brain Function: A Hypothesis

Although there is abundant evidence to suggest that emotional experiences persist in our autobiographies over time (strengthening of the memory) (Dolcos et al., 2005), an equally remarkable but less noted change is a reduction in the affective tone associated with their recall (depotentiation of emotion). The reason that affective experiences appear to be remembered more robustly than neutral memories is due to well characterized autonomic neurochemical reactions elicited at the time of the experience (McGaugh, 2004). These neurochemical reactions are believed to adaptively prioritize the formation (and hence

long-term retention) of salient information, creating what is commonly termed an “emotional-memory” (Figure 5a). However, the later recall of these 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, overtime, the affective “blanket” (the emotion) that originally tagged the memory at the time of learning has been removed, whereas the information of the experience (the memory) remains (Figure 5b).

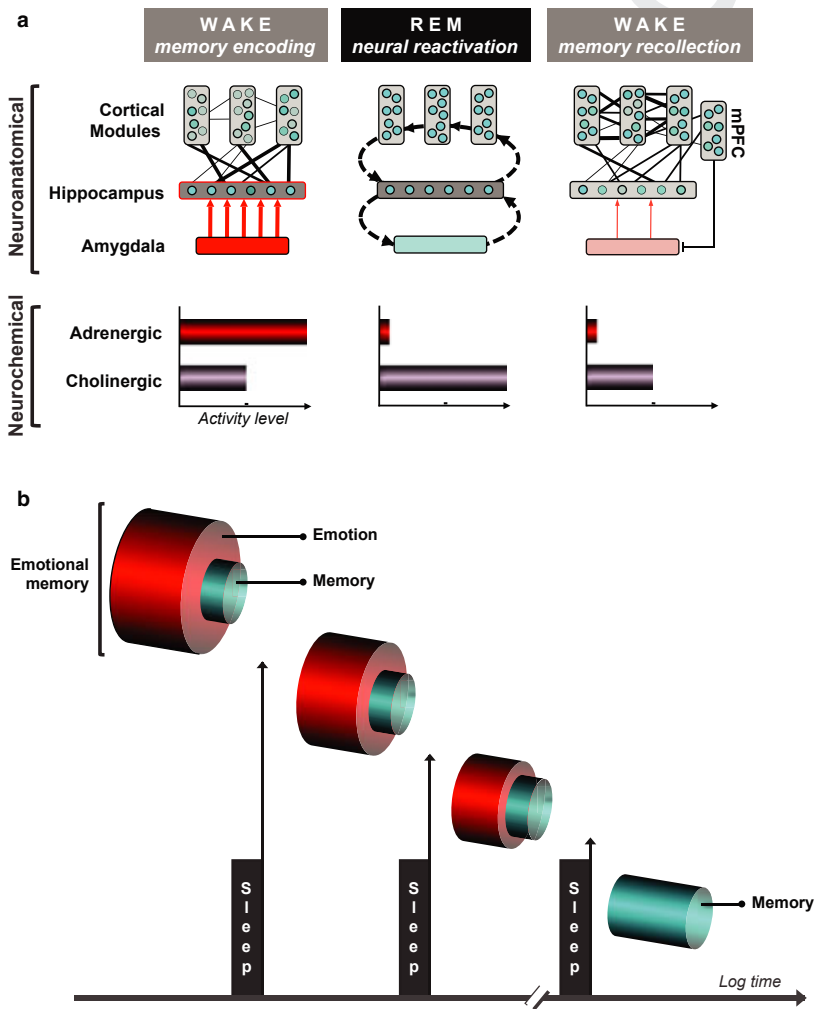


Figure 5 The sleep to forget and sleep to remember (SFSR) model. (a) Neural dynamics. Emotional memory formation involves the encoding of hippocampal-bound cortical information, facilitated by the amygdala and high concentrations of aminergic activity. During REM sleep, these neural structures are reactivated, supporting the reprocessing of emotional memories. However, this occurs in a brain-state with dramatically reduced adrenergic activity, allowing for both cortical strengthening (consolidation), dissipation of previously associated emotion (visceral tone), and re-established mPFC-amygdala regulatory control. Cross-connectivity between structures is represented by number and thickness of lines. Circles within cortical and hippocampal structures represent information nodes; shade strength reflects extent of connectivity. Fill of amygdala and arrow thickness represents influence upon the hippocampus. (b) Conceptual outcome. Through multiple iterations of this REM-mechanism across one or multiple nights, such sleep-dependent reprocessing results in long-term strengthening of salient memories, yet a dissipation of the emotional charge. Thus, sleep transforms an emotional memory into a memory of an emotional event, that itself is no longer emotional.

We offer the hypothesis that such decoupling of emotion from memory preferentially takes place overnight, during the unique neurobiological state of REM, such that we *sleep to forget* the emotional tone, yet *sleep to remember* the tagged memory of that experience. This model further posits that if such a process is not achieved, the magnitude of affective “charge” would persist, resulting in the potential condition of chronic anxiety within autobiographical memory networks.

We suggest that the state of REM sleep provides an optimal biological milieu within which this form of “overnight therapy” can be achieved, based on three associated features: neuroanatomical, neurophysiological and neurochemical (Figure 5a). First, the prominent increase in activity within limbic and paralimbic structures during REM sleep (Nofzinger, 2005) supports the ability for reactivation and hence (re)processing of previously acquired affective memories. Second, the neurophysiological signature of REM sleep involving dominant theta oscillations within subcortical as well as cortical nodes offers large-scale network cooperation during REM for the strengthen of distributed aspects of the emotional memory representation (e.g. perceptual, contextual), across such related but different anatomical networks, resulting in enhanced consolidation and integration of that memory. Third, these interactions during REM sleep (and perhaps through the conscious process of dreaming) critically and perhaps most importantly take place within a brain that is low in aminergic neurochemical concentration (Pace-Schott & Hobson, 2002), particularly noradrenergic input from the locus coeruleus (associated with stress and anxiety responses) and dominated by cholinergic neurochemistry (Itoi & Sugimoto, 2010; Ramos & Arnsten, 2007; Sullivan, Coplan, Kent, & Gorman, 1999; Valentino & Van Bockstaele, 2008). Therefore, REM sleep is proposed to offer a unique biological condition in which to achieve, on one hand, a strengthening and consolidation of the informational core of emotional experiences (the memory), yet additionally depotentiate and ultimately ameliorate the autonomic arousing charge originally acquired at the time of learning (the emotion). Through the process of developing stronger cortico-cortical connections, integration and assimilation of the affective event(s) in the context of past knowledge is supported. As a result, emotional experiences are preferentially retained long-term, but importantly the emotion, which was initially critical to signify salience and priority at the time of learning, has been dissipated. The brain therefore preserves a memory of an emotional event, but which itself is no longer emotional.

This model complements pioneering psychological theories of dreaming by Greenberg and colleagues (Greenberg, Pearlman, & Gampel, 1972a; Greenberg, Pillard, & Pearlman, 1972b) as well as Cartwright and associates (Cartwright, Agargun, Kirkby, & Friedman, 2006; Cartwright, Kravitz, Eastman, & Wood, 1991; Cartwright, Luten, Young, Mercer, & Bears, 1998), 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. In fact, 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; Nielsen & Levin, 2007; Stickgold, 2002).

Specific predictions emerge from this model. As partially demonstrated, the first prediction would be that the degree to which the information of those emotional experiences are retained, long-term, would be proportional to the amount of post-encoding REM sleep obtained, how quickly it is achieved (REM latency), as well as the power of theta oscillations during REM. Evidence for all three of these predictions exists (Nishida et al., 2009; Pare et al., 2002). Second, the inverse REM relationship would hold for the magnitude of emotional depotentiation after sleep. This too appears to be the case; a recent

neuroimaging study involved participants performing two repeat fMRI tests, separated by 12 hours containing either a night of EEG-recorded sleep (sleep group) or a waking day (wake group) (van der Helm et al., 2011). During each test, participants viewed emotional images and rated their subjective intensity of emotional feeling in response to the pictures. Compared to the wake group, the sleep group displayed a significant overnight decrease in amygdala reactivity in response to re-exposure to the pictures (Figure 6a), together with a concomitant increase in amygdala-vmPFC connectivity (Figure 6b). Furthermore, sleep also resulted in a significant dissipation of subjective emotional intensity ratings, relative to the equivalent period of wake.

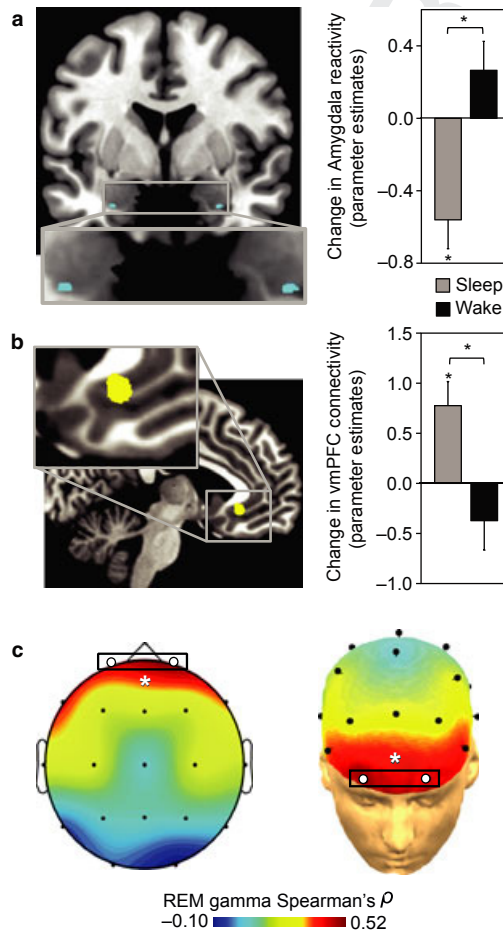


Figure 6 REM sleep depotentiates amygdala reactivity to prior emotional experiences. (a) Change in emotion reactivity: group $\times$ test session interaction in bilateral amygdala (blue), demonstrating a significant decrease in activity across a night of sleep in the sleep group, yet an increase in the wake group across a day of wake. (b) Change in functional connectivity: group $\times$ test session interaction in amygdala-ventromedial prefrontal cortex (vmPFC) connectivity (yellow), demonstrating increased connectivity from after a night of sleep yet decreased coupling after an equivalent time of wake. (c) Topographical Spearman's correlation (ρ) plot of the relationship between electroencephalographic (EEG) gamma power during rapid-eye movement (REM) sleep and the extent of overnight emotional reactivity decrease across a night of sleep, with lower levels of prefrontal gamma activity (marked by white circles) predicting a larger overnight decrease in emotional reactivity. $*p < 0.05$. Modified from van der Helm et al. (2011).

1 Additionally, the effect of REM-sleep physiology on emotional reactivity was investi-
2 gated in this study. The focus was on high-frequency gamma EEG power over the pre-
3 frontal cortex, taken as a validated but indirect measure of central adrenergic activity.
4 Gamma EEG activity has been shown in animal models to proportionally increase and
5 decrease in a dose-dependent manner with corresponding increases and decreases in
6 adrenergic levels (Berridge & Foote, 1991; Cape & Jones, 1998; Keane, Candy, & Brad-
7 ley, 1976). Consistent with the model's predictions, the success of overnight emotion
8 depotentiation at both a brain (amygdala) and behavioral (intensity ratings) level was
9 predicted by gamma EEG activity. Specifically, those participants expressing the lowest
10 REM gamma, showed the greatest beneficial overnight reduction in emotion intensity
11 (Figure 6c). Therefore, the lower the levels of gamma EEG activity, potentially reflect-
12 ing the degree of beneficial decrease in noradrenergic activity during REM sleep, the
13 greater the decrease in next-day emotional brain and behavioral reactivity. That the
14 changes in neural and behavioral reactivity correlated with REM gamma activity and
15 not theta activity further suggest that each component (emotion depotentiation and
16 memory consolidation), although potential constituents of a broader function of REM,
17 are distinct.

18 Without discounting the contribution of other bioamines (Dahan et al., 2007) or
19 NREM sleep (Landsness, Goldstein, Peterson, Tononi, & Benca, 2011; Peterson &
20 Benca, 2006; Plante et al., 2012), it therefore appears that REM sleep and the extent of
21 associated adrenergic reduction, accurately predicts the degree to which sleep dissipates
22 the neural (amygdala) and behavioral strength of emotion from prior affective experi-
23 ences. Furthermore, this depotentiation of subcortical limbic reactivity appears to advanta-
24 geously allow for the next-day reestablishment of amygdala-PFC coupling, offering
25 further regulatory control.

26 27 28 **Implications for Psychiatric Conditions**

29 If the process of decoupling emotion from memory is not achieved across the first night
30 following an affective experience, the model predicts a repeat attempt of the affective
31 demodulation on subsequent nights, since the strength of the emotional "tag" associated
32 with the memory would remain high. If this process fails a second time, the same events
33 will continue to repeat across ensuing nights. It is just such a cycle of REM sleep dream-
34 ing (nightmares) that represents a diagnostic key feature of the anxiety condition of PTSD
35 (Lavie, 2001). We do not believe that it is coincidental that these patients additionally
36 continue to display hyperarousal reactions to associated trauma cues (Harvey et al., 2003;
37 Pole, 2007), suggesting that the process of separating the affective tone from the emo-
38 tional experience has not been accomplished, and is hence consistently re-lived during
39 subsequent cued or deliberate waking recollection (Figure 7a).

40 Supporting this possibility, PTSD has been associated with a dysregulation of REM
41 sleep, together with reports of significantly increased sympathetic autonomic tone (Har-
42 vey et al., 2003; Mellman & Hipolito, 2006). Furthermore, objective sleep disturbances
43 occurring early after trauma exposure, as well as heightened sympathetic vagal tone
44 during REM sleep, are all associated with an increased risk of meeting criteria for
45 PTSD at subsequent assessments conducted up to 1 year later (Koren, Arnon, Lavie, &
46 Klein, 2002; Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002). Indeed, it has been
47 shown in war veterans that the presence of insomnia 4 months post-deployment is a
48 significant predictor of depression and PTSD symptoms 8 months later (Wright et al.,
49 2011).

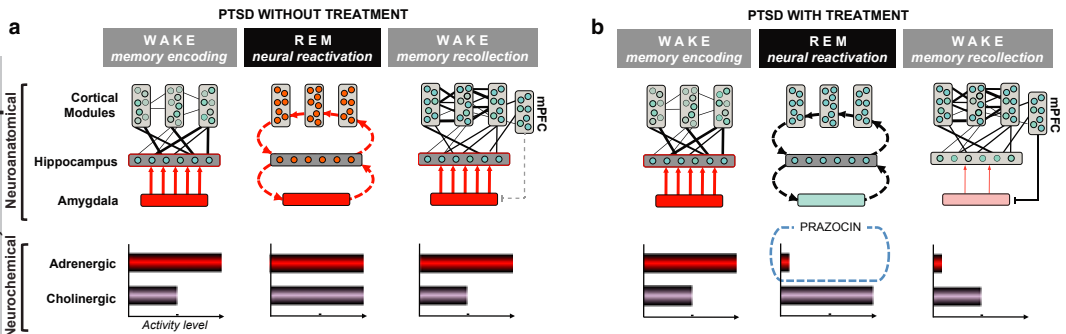


Figure 7 REM sleep model applied to PTSD. (a) REM sleep in PTSD without treatment, characterized by a pathological persistence of central brain adrenergic activity (note difference in middle panel to middle panel of Figure 5a). Elevated adrenergic activity during REM sleep prevents the depotentiation of the emotion tone associated with the salient, including traumatic, experiences. (b) REM sleep in PTSD with treatment by Prazosin, allowing for the reduction in adrenergic levels during REM sleep (note difference in middle panel between a and b). Consequently, there is the restored opportunity for the dissipation of emotion from the prior trauma experiences, preventing hyperarousal reactions during subsequent post-sleep memory recall.

The collection of findings linking (REM) sleep abnormalities to the development of PTSD have led to the possibility that sleep, and particularly REM-sleep, may play an important role in the pathophysiology of PTSD (Germain, Buysse, & Nofzinger, 2008; Spoormaker & Montgomery, 2008). Importantly, beyond simple increases or decreases in the total time spent in REM sleep, qualitative features of REM sleep may be more accurate and indicative signatures of functional and dysfunctional affective processing. Such features include the structure of REM (e.g. fragmentation), and physiology (e.g. high frequency EEG activity, the latter potentially reflective of qualitative changes in hyper arousal related to central adrenergic activity).

We offer the thesis that it is the pathological persistence of central brain adrenergic activity during REM sleep in particular, reflected in hyperarousal signals (Harvey et al., 2003; Pole, 2007; Strawn & Geraciotti, 2008), that prevents the capacity of REM sleep for palliatively decreasing the emotion from the traumatic memory, leaving some patients unable to integrate and importantly depotentiate this stored experience. Moreover, the consequential next-day persistent amygdala hyper-reactivity may further prevent the capacity for a return of adaptive amygdala-PFC connectivity and hence regulation. Conversely, the model predicts that treatments that dissipate adrenergic activity during REM sleep would have a beneficial clinical outcome in PTSD. It is precisely this benefit that appears to be represented by the recent pharmacological intervention success in PTSD patients. Nocturnal alpha-adrenergic blockade using prazosin in both patients with combat PTSD (Calohan, Peterson, Peskind, & Raskind, 2010; Raskind et al., 2000, 2002, 2003, 2007) and civilian PTSD (Taylor & Raskind, 2002; Taylor et al., 2006, 2008), has been demonstrated to decrease trauma-dream symptomatology and restore characteristics of REM sleep. Such findings support a proposed functional role for adrenergic changes during REM sleep in affective regulation, and in excess, dysregulation.

Our proposed model offers a putative underlying neurobiological mechanism explaining this pharmacological treatment success (Figure 7b). Specifically, the nighttime blockade of central adrenergic activity during REM sleep in PTSD dissipates levels back to a potentially critical sub-threshold and normative level, allowing the permissive first stages of emotional dissipation of trauma experiences in REM sleep, and by doing so, improve clinical symptomatology associated with the trauma memory.

Conclusion

Evidence to date supports a causal and bi-directional relationship between sleep and emotional brain function. Without sleep, the ability to adequately regulate and express emotions is compromised at both a brain and behavioral level, present for both positive and negative domains of the emotional valence spectrum. In contrast, when sleep is obtained and especially REM sleep, it instigates a restoration of appropriate emotion recognition, reactivity and associated regulation. Beyond processes of reactivity and recognition, reports further implicate sleep, and REM sleep most strongly, in the offline modulation of emotional memories. The majority of findings support a proposed model in which REM sleep is capable of enhancing the memory of prior affective experiences on the one hand, while on the other, dissipating the emotional tone originally associated with such salient experiences at the time of initial exposure. Moreover, this model offers clarifying neurobiological insights underlying the neural mechanisms that contribute to PTSD, as well as explain the recent success of pharmacological intervention using adrenergic blockers in PTSD.

The research field of sleep and affective brain function is, however, only in its infancy, with much yet to understand. We currently know little about the interplay between peripheral and central nervous system mechanisms leading to abnormalities of emotion processing caused by sleep deprivation. Similarly, the precise combination of sleep factors that reset the balance for optimal next-day emotional brain function is unclear. Is it the stages of sleep, their quantity or quality, their brain oscillations, their neurochemistry? Or the cycling nature of sleep, and/or the timing of sleep? Conversely, why do some emotional events we experience while awake impact our sleep at night, while others do not? Is it their intensity, novelty, salience, valence, temporal proximity to sleep, relationship with past experiences or degree of unresolved understanding? We need to look no further than mood disorders to appreciate this wake-sleep reciprocity that modulates affective states. What does seem clear, however, is that the clinical, professional and public health ramifications of this emerging association between sleep and affective brain function are profound. Moreover, and considering the continued erosion of sleep time throughout industrialized nations, particularly in young populations, such evidence perhaps should stir emotions in us all.

Short Biographies

Matthew Walker's research examines the role of sleep in human brain function, focusing on learning, memory and emotional processes. He examines these questions in both normative and clinical populations. He has authored or co-authored empirical research papers in journals including *Nature*, *Neuron*, *Nature Neuroscience*, *PNAS*, *Current Biology* and the *Journal of Neuroscience*. He has also written review articles in *Nature Reviews Neuroscience*, *Trends in Neuroscience*, *Neuron*, *Trends in Cognitive Science* and *Psychological Bulletin*. He earned his PhD in neurophysiology from the Medical Research Council in the UK, and subsequently became an Assistant Professor of Psychology at Harvard Medical School. He is currently an Associate Professor of Psychology and Neuroscience at the University of California, Berkeley, where he directs the Sleep and Neuroimaging Laboratory. He is the recipient of funding awards from the National Science Foundation and the National Institutes of Health, and is a Kavli Fellow of the National Academy of Sciences.

Els van der Helm's research is located at the intersection of sleep, emotion, and memory; she has authored or co-authored papers in these areas for *Current Biology*, *Psychological*

Bulletin, Sleep, PLoS One, PNAS, and the Sleep Medicine Clinics. Current research involves the role of sleep in emotional processing and memory. She is a Fulbright scholar from the Netherlands and has held fellowships from Huygens Talent Program, VSB funds and Prins Bernhard Cultuur Fonds. Before coming to the University of California Berkeley where she pursues her PhD in Psychology working in Professor Matthew Walker's Sleep and Neuroimaging Lab, Els worked with Professor Walker during an internship at Harvard Medical School in Boston and with Professor Eus van Someren during an internship at the Sleep Physiology Lab in Amsterdam. She holds a BA in Psychology and a Masters degree in Clinical Neuropsychology from the University of Amsterdam and a Masters degree in Neurosciences from the VU University in Amsterdam.

Endnote

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