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Report

REM Sleep Depotentiates Amygdala Activity to Previous Emotional Experiences

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Summary

Clinical evidence suggests a potentially causal interaction between sleep and affective brain function; nearly all mood disorders display co-occurring sleep abnormalities, commonly involving rapid-eye movement (REM) sleep [1–4]. Building on this clinical evidence, recent neurobiological frameworks have hypothesized a benefit of REM sleep in palliatively decreasing next-day brain reactivity to recent waking emotional experiences [5, 6]. Specifically, the marked suppression of central adrenergic neurotransmitters during REM (commonly implicated in arousal and stress), coupled with activation in amygdala-hippocampal networks that encode salient events, is proposed to (re) process and depotentiate previous affective experiences, decreasing their emotional intensity [3]. In contrast, the failure of such adrenergic reduction during REM sleep has been described in anxiety disorders, indexed by persistent high-frequency electroencephalographic (EEG) activity (>30 Hz) [7–10]; a candidate factor contributing to hyperarousal and exaggerated amygdala reactivity [3, 11–13]. Despite these neurobiological frameworks, and their predictions, the proposed benefit of REM sleep physiology in depotentiating neural and behavioral responsivity to prior emotional events remains unknown. Here, we demonstrate that REM sleep physiology is associated with an overnight dissipation of amygdala activity in response to previous emotional experiences, altering functional connectivity and reducing next-day subjective emotionality.

Results and Discussion

Building on the specific predictions of these neurobiological frameworks [3, 5, 6] and combining functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) sleep recordings, we tested the hypothesis that (1) sleep decreases amygdala and behavioral reactivity in response to previously encountered emotional experiences, associated with reestablished medial prefrontal cortex connectivity and (2) these brain and behavioral sleep benefits are proportional to the extent of decreased central adrenergic levels during rapid-eye movement (REM) sleep, as reflected by reduced gamma (30–40 Hz) EEG activity; a validated proxy indexing reduced central adrenergic activity [7–10]. In short (see Supplemental Experimental Procedures available online), 34 healthy adults (age: 18–30 years) were randomly assigned to one of two groups. Each performed two repeat fMRI tests (test 1, test 2), separated by 12 hr containing a night of EEG-recorded sleep (sleep group, n = 18, ten females) or a waking day (wake group, n = 16, nine females; Figure 1). During each test, participants viewed and rated the subjective emotional intensity of 150 standardized affective pictures [14] on a 1–5 scale, corresponding to increasing intensity. Importantly, participants viewed the same stimuli at both test sessions, affording a measure of change in emotional reactivity to previously experienced affective stimuli (test 2 – test 1), following wake or sleep. Participants additionally performed a circadian control test at the second fMRI session, involving presentation of a novel set of affective stimuli (Supplemental Experimental Procedures). This control test allowed confirmation that behavioral and fMRI differences in reactivity identified following wake and sleep were independent of time of day (Supplemental Results).

Differences in Amygdala Reactivity

We first sought to determine the change in emotional brain reactivity following wake or sleep, focusing a priori on the amygdala [3, 5, 6]. Consistent with the experimental prediction, a significant group (wake, sleep) × test (test 1, test 2) interaction was observed in bilateral amygdala, revealing an overnight decrease in reactivity in the sleep group, yet an increase across the day in the wake group (Figures 2A and 2B). Moreover, and consonant with the proposed function of top-down regulation [13, 15–21], these overnight reductions in amygdala activity were additionally associated with changes in ventromedial prefrontal cortex (vmPFC) functional connectivity. Specifically, a significant group (wake, sleep) × test (test 1, test 2) amygdala connectivity interaction was observed with the vmPFC (Figures 2C and 2D), expressing an overnight increase in the sleep group and converse decrease across the day in the wake group. Thus, a night of sleep decreased amygdala reactivity in response to previously encountered emotional stimuli. Furthermore, this overnight dissipation in amygdala activity was further associated with an increase in vmPFC connectivity.

Change in Subjective Emotional Reactivity

Next, we tested the prediction that these overnight decreases in amygdala responsivity were accompanied by a corresponding reduction in subjective emotional intensity ratings, specifically for the most intense emotional responses (5-ratings), where the greatest hypothesized benefit of sleep should occur. As with amygdala activity, a significant group (wake, sleep) × test (test 1, test 2) interaction was observed in intense emotional ratings ($p < 0.05$; Figures 3A and 3B), decreasing in the sleep group ($p < 0.05$) while increasing in the wake group. Indeed, within the sleep group, there was a significant linear shift in the profile of change across the 1–5 ratings ($p < 0.001$), with reductions in the most intense ratings (4s and 5s), and a progressive increase in neutral ratings (1s and 2s; Figure 3A). In contrast, no significant linear trend or reductions in extreme emotional ratings (4s and 5s) were observed in the wake group (Figure 3B). Therefore, the overnight decrease in amygdala activity following sleep was additionally accompanied by a concomitant reduction in subjective emotional

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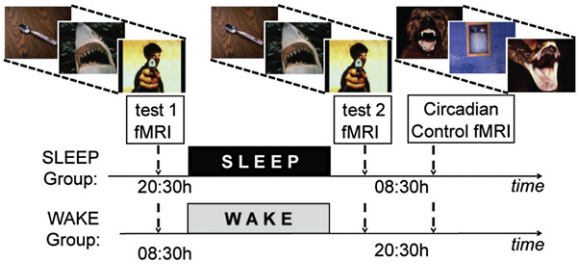

Figure 1. Experimental Design

Both groups performed an emotion reactivity test twice inside the functional magnetic resonance imaging (fMRI) scanner; separated by 12 hr, involving the rating and subsequent rerating of the same standard set of 150 affective picture stimuli (three example images provided). The change in emotional reactivity following sleep (sleep group) or wake (wake group) was assessed by comparing data at test 1 (presleep or prewake) with that at test 2 (post-sleep or postwake); test 2 – test 1. To examine possible time-of-day differences in emotional reactivity, independent of wake or sleep, we performed an additional circadian control test immediately after test 2 (morning in the sleep group, evening in the wake group) was performed by both groups. The circadian control test consisted of a novel set of 150 emotional images not seen before, matched in terms of arousal and valence to the original set used in test 1 and test 2 (sets used counterbalanced as either the experimental set or circadian control set).

reactivity in response to these previously encountered affective stimuli.

Associations with REM Sleep Physiology

We finally sought to test the prediction that the overnight decreases in amygdala and behavioral reactivity in the sleep group were predicted by the extent of reduced REM sleep gamma EEG activity; a validated marker of decreased central adrenergic activity [7–10]. Analysis focused on prefrontal EEG activity, based on this region's dense adrenergic innervation [22, 23] and established role in emotion regulation [24, 25]. Consistent with this prediction, the extent of overnight decrease in both amygdala and behavioral reactivity was significantly correlated with the extent of reduced prefrontal gamma EEG activity during REM (Figures 4A–4D), such that those with the lowest levels of REM-gamma (indicative of lowest central adrenergic activity [7–10]) expressed the largest overnight decrease in emotion reactivity. That this effect was unique to prefrontal REM-gamma was demonstrated by three additional analyses (Supplemental Results), describing specificity at the level of (1) topography: the strength of the predictive relationship between gamma activity and the change in both amygdala and behavioral reactivity decreased from anterior to posterior EEG derivations, (2) frequency: no other frequency band from these same prefrontal EEG derivations correlated with the change in amygdala activity or behavioral reactivity, and (3) brain state: unlike REM sleep, no significant correlation was found between prefrontal gamma power during non-REM (NREM) sleep and the changes in emotional responsivity.

Taken together, these findings describe an overnight depotentiation of neural (amygdala) and behavioral (subjective) responsivity to previously encountered affective stimuli [3, 5, 6]. Moreover, the success of this depotentiation was predicted by REM sleep gamma EEG activity, a surrogate marker indexing central adrenergic activity [7–10]. Our data can be interpreted within a recently proposed homeostatic model of REM sleep involving the reduction of emotional tone originally associated with prior waking salient experiences, orchestrated by

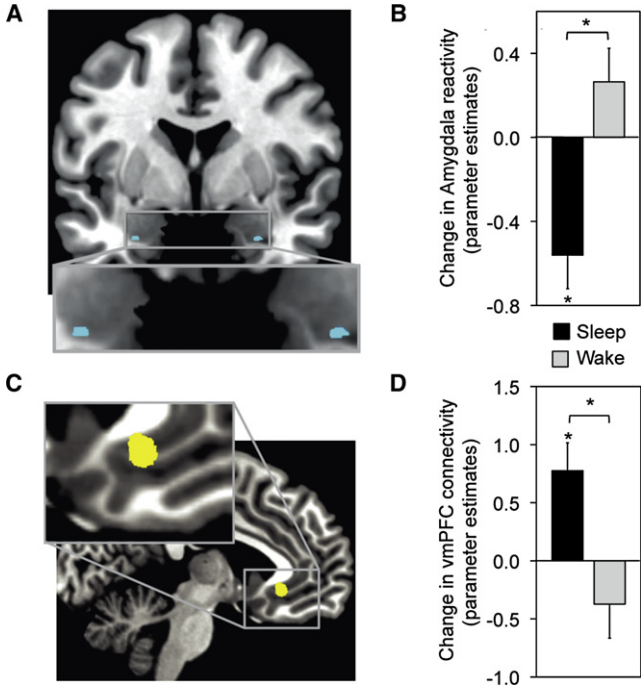

Figure 2. fMRI Differences in Emotional Reactivity and Connectivity

(A and B) Change in emotion reactivity: group × test session interaction in bilateral amygdala (blue), demonstrating a significant decrease in activity from test 1 to test 2 in the sleep group yet increase in the wake group (peak Montreal Neurological Institute [MNI] coordinates [x, y, z]; left: –27, 0, −27; Z score = 3.07; right: 27, 0, –27; Z score = 3.14).

(C and D) Change in functional connectivity: group × test session interaction in amygdala-ventromedial prefrontal cortex (vmPFC) connectivity (yellow), demonstrating increased connectivity from test 1 to test 2 in the sleep group yet decreased coupling in the wake group (peak MNI coordinates [x, y, z]; –6, 30, −7; Z score = 3.22). Differences in activation and connectivity thresholded at $p < 0.05$ familywise error corrected for multiple comparisons. *$p < 0.05$; error bars represent SEM.

the marked reduction in adrenergic activity during REM sleep [3, 5]. Alternatively, or in addition, such findings may be explained by the recognized benefit of REM on emotional memory consolidation [3, 26–28], associated with theta EEG activity [29, 30], thereby decreasing postsleep stimulus novelty and hence emotion reactivity. That the changes in neural and behavioral reactivity reported in the current study correlated with REM gamma activity and not theta activity suggests that each component (depotentiation, consolidation), although potential constituents of a broader function of REM [3], are distinct. Nevertheless, either mechanism independently, or their combination, may account for our findings and represents a future target for experimental investigation.

Guided by recent neurobiological models [3, 5], the current study focused on sleep-dependent differences in emotion reactivity within the central nervous system (specifically the brain). However, these models predict similar downstream adaptive reductions in reactivity within the peripheral nervous system. The consequential impact of such altered central nervous system processing on peripheral nervous system reactivity has potentially important implications, especially considering their respective efferent-afferent interactions known to support symbiotic emotional homeostasis [31].

Translationally, our results may afford mechanistic insights into a collection of affective disorders where amplified emotion

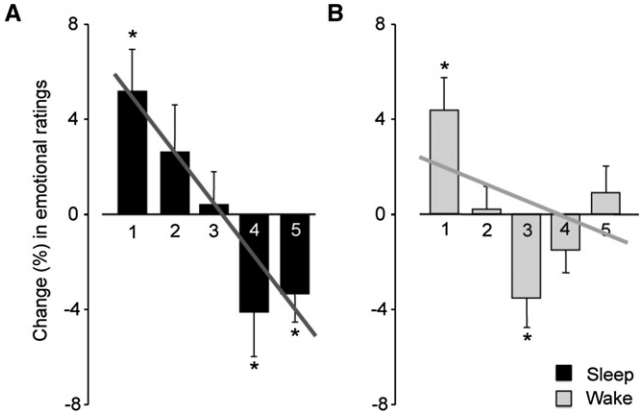

Figure 3. Change in Behavioral Reactivity between Test 1 and Test 2 after a Period of Sleep or Wake

(A) The sleep group expressed a significant linear shift ($p < 0.001$) and significant decrease in the most intense emotional ratings (4s, 5s) and increase in nonemotional ratings.

(B) The wake group showed no significant linear profile shift or decrease in the most intense emotional ratings. *$p < 0.05$; error bars represent SEM.

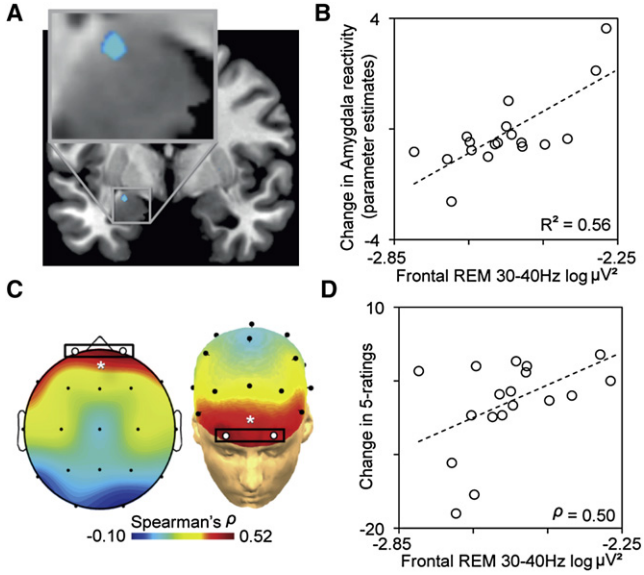

Figure 4. Association between Gamma Power and Emotional Reactivity

(A) Relationship between prefrontal electroencephalographic (EEG) gamma power (average of Fp1-Fp2 EEG derivations) during rapid-eye movement (REM) sleep and the extent of overnight decrease in amygdala (blue) activity from test 1 to test 2 (peak MNI coordinates [x, y, z]; –22, −7, −17; Z score = 3.55).

(B) Corresponding scatterplot of the amygdala-gamma power relationship shown in (A), with R^2 noted only for descriptive purposes [46, 47], with lower levels of gamma activity predicting the degree of overnight decrease in emotional activity.

(C) Topographical Spearman's correlation (ρ) plot between gamma power during REM sleep and the change in emotional reactivity (5-ratings) demonstrating a significant prefrontal relationship (average of Fp1-Fp2, white circles).

(D) Corresponding scatterplot and Spearman's ρ value: the extent of reduced gamma EEG activity over prefrontal cortex was proportional to the overnight decrease in emotional reactivity. *$p < 0.05$.

reactivity and sleep disruption are highly comorbid, particularly the anxiety disorders [1, 2, 4]. Of special relevance in this context is the condition of post-traumatic stress disorder (PTSD), characterized by REM abnormalities [11, 32–35], hyperarousal [36–40], and exaggerated amygdala reactivity [41–43]. Indeed, the current findings offer a putative neurobiological explanation for the recent pharmacological treatment success involving nighttime suppression of adrenergic activity in PTSD, restoring REM sleep features and improving clinical symptomatology [12, 44, 45].

Supplemental Information

Supplemental Information includes three figures, five tables, Supplemental Results, and Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.cub.2011.10.052.

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