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REM sleep de-potentiates 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 de-potentiate 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** (>30Hz) [7–10]; a candidate factor contributing to **hyper-arousal** and exaggerated **amygdala reactivity** [3, 11–13]. Despite these neurobiological frameworks, and their predictions, the proposed benefit of REM sleep physiology in de-potentiating **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 fMRI and EEG sleep recordings, we tested the hypothesis that (1) sleep decreases amygdala and behavioral reactivity in response to previously encountered emotional experiences, associated with re-established medial prefrontal cortex connectivity, and (2) that these brain and behavioral sleep benefits are proportional to the extent of decreased central adrenergic levels during REM sleep, as reflected by reduced gamma (30–40Hz) EEG activity; a validated proxy indexing reduced central adrenergic activity [7–10]. In short (and see Supplemental Experimental Procedures), thirty-four healthy adults (age:

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18–30 years) were randomly assigned to one of two groups. Each performed two repeat fMRI tests (Test1, Test2), separated by 12hr containing a night of EEG-recorded sleep (Sleep-group, $n=18$, 10 females) or a waking day (Wake-group, $n=16$, 9 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 (Test2 – Test1), 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 Data).

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) \times Test (Test1, Test2) interaction was observed in bilateral amygdala; revealing an overnight decrease in activity in the Sleep-group, yet increase across the day in the Wake-group (Figure 2a&b). 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) \times Test (Test1, Test2) amygdala connectivity interaction was observed with the vmPFC (Figure 2c&d), 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 activity 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) \times Test (Test1, Test2) interaction was observed in intense emotional ratings ($P < 0.05$; Figure 3a&b), 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 (4's and 5's), and a progressive increase in neutral ratings (1's and 2's Figure 3a). In contrast, no significant linear trend or reductions in extreme emotional ratings (4's and 5's) 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 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 *a priori* 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 (Figure 4a–d), 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 Data), 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 NREM sleep and the changes in emotional responsivity.

Taken together, these findings describe an overnight de-potentialization of neural (amygdala) and behavioral (subjective) responsivity to previously encountered affective stimuli [3, 5, 6]. Moreover, the success of this de-potentialization 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 waking salient experiences, orchestrated by 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 post-sleep 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 (de-potentialization, consolidation), while potential constituents of a broader function of REM [3], are conceivably distinct. Nevertheless, either mechanism independently, or their combination, may account for our findings, and represents a clear future target for experimental investigation.

Guided by recent neurobiological models [3, 5], the current study focused on the sleep-dependent differences in emotion reactivity within the central nervous system (specifically the brain). However, these models predict similar downstream adaptive reductions in reactivity with 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 supporting symbiotic emotional homeostasis [31].

Translationally, our results may afford mechanistic insights into a collection of affective disorders where amplified emotion reactivity and sleep disruption are highly co-morbid, particularly the anxiety disorders [1, 2, 4]. Of special relevance in this context is the condition of PTSD, characterized by REM abnormalities [11, 32–35], hyper-arousal [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].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Sleep decreases amygdala activity to prior waking emotional experiences
- The amygdala decrease is associated with re-established prefrontal connectivity
- These neural changes are accompanied by overnight reductions in subjective reactivity
- Reductions in both brain and behavioral reactivity are associated with REM physiology

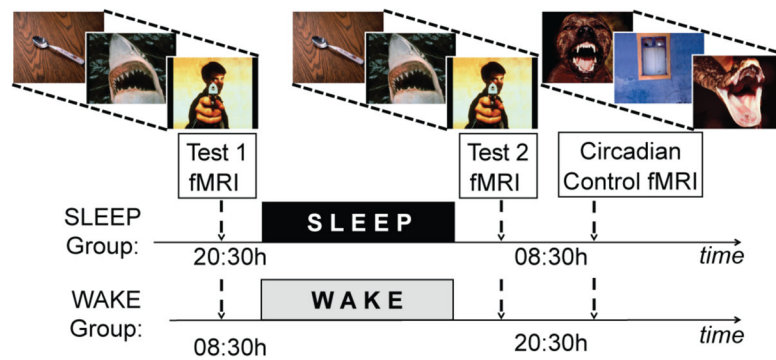


Figure 1.

Experimental design: Both groups performed an emotion reactivity test twice inside the fMRI scanner; separated by 12hr, involving the rating and subsequent re-rating 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 Test1 (pre wake or sleep) with that at Test2 (post wake or sleep); Test2 – Test1. To examine possible time-of-day differences in emotional reactivity, independent of wake or sleep, an additional circadian control test was performed immediately after Test2 (morning in the Sleep-group, evening in the Wake-group). 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 Test1 and Test2 (sets used counterbalanced as either the experimental set or circadian control set).

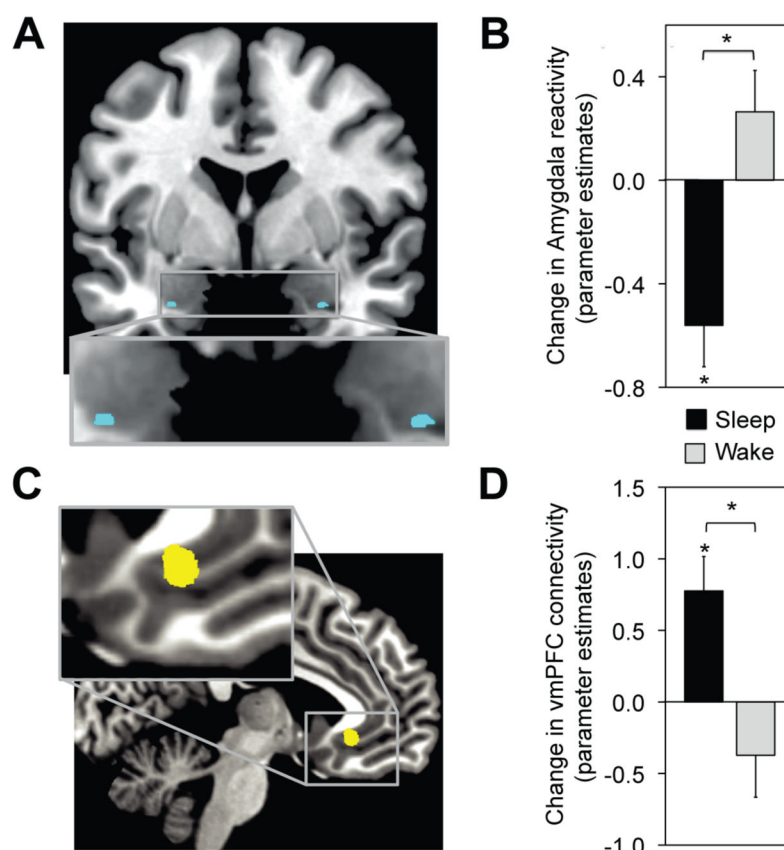


Figure 2.

(A,B) fMRI differences in emotion reactivity: Group \times Test session interaction in bilateral amygdala (blue), demonstrating a significant decrease in activity from Test1 to Test2 in the Sleep-group yet increase in the Wake-group (peak MNI coordinates [x, y, z]; left: -27, 0, -27; Z-score = 3.07; right: 27, 0, -27; Z-score = 3.14). **(C,D)** fMRI differences in functional connectivity: Group \times Test session interaction in amygdala-vmPFC connectivity (yellow), demonstrating increased connectivity from Test1 to Test2 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 $P < 0.05$ family wise error (FWE) corrected for multiple comparisons. $*P < 0.05$, Error bars: S.E.M.

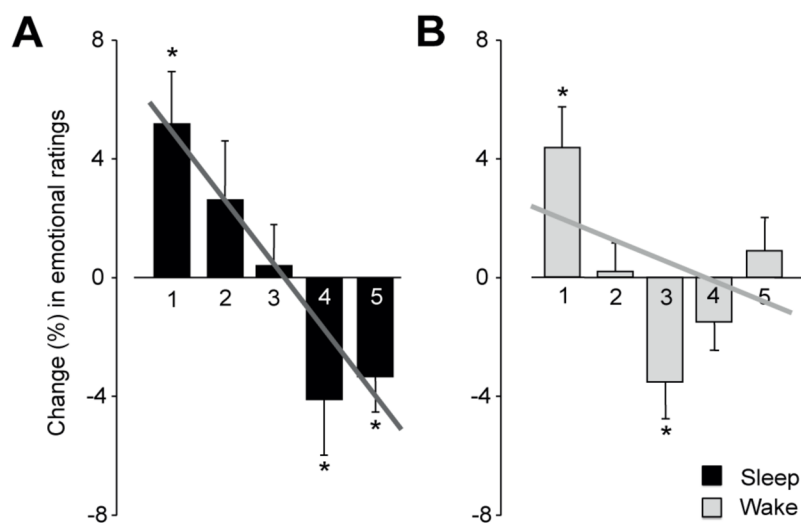


Figure 3. Change in behavioral reactivity between Test1 and Test2 for (A) the Sleep-group, expressing a significant linear shift ($P < 0.001$), and significant decrease in the most intense emotional ratings (4's, 5's) and increase in non-emotional ratings, (B) the Wake-group, resulting in no significant linear profile shift or decrease in the most intense emotional ratings. * $P < 0.05$, Error bars: S.E.M.

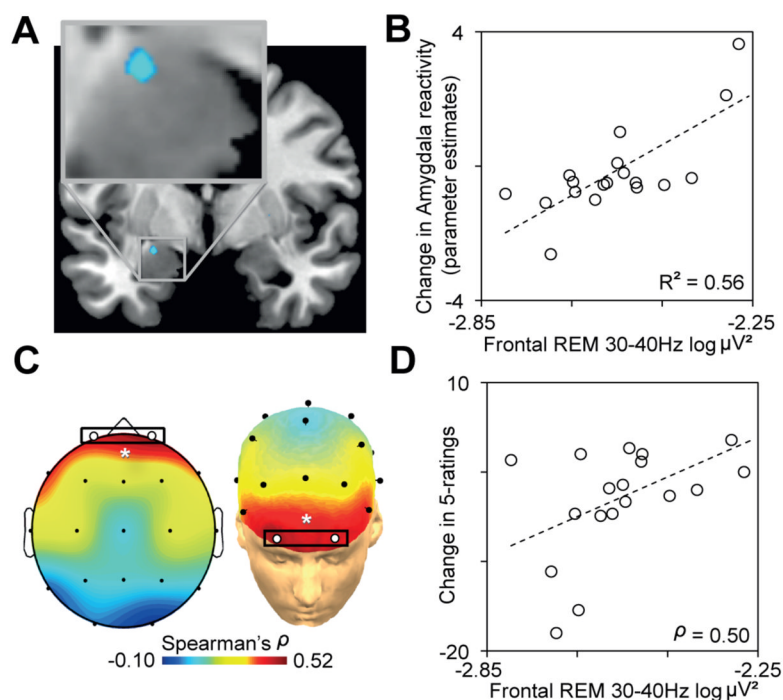


Figure 4.

(A) Pearson's correlation between prefrontal EEG gamma power (average of Fp1-Fp2 EEG derivations) and the extent of overnight decrease in amygdala (blue) activity from Test1 to Test2 (peak MNI coordinates [x, y, z]; -22, -7, -17; Z-score = 3.55), and (B) corresponding scatter plot of this amygdala-gamma power relationship, with R^2 noted only for descriptive purposes [46, 47], with less gamma activity predicting the degree of overnight decrease in emotional activity. (C) Topographical Spearman's correlation (ρ) plot between REM gamma power and the change in emotional reactivity (5-ratings) demonstrating a significant prefrontal relationship (average of Fp1-Fp2, white circles), and (D) corresponding scatter plot and Spearman's ρ value: the extent of reduced gamma EEG activity over prefrontal cortex was proportional to the overnight decrease in emotional reactivity. * $P < 0.05$.