

The human emotional brain without sleep — a prefrontal amygdala disconnect

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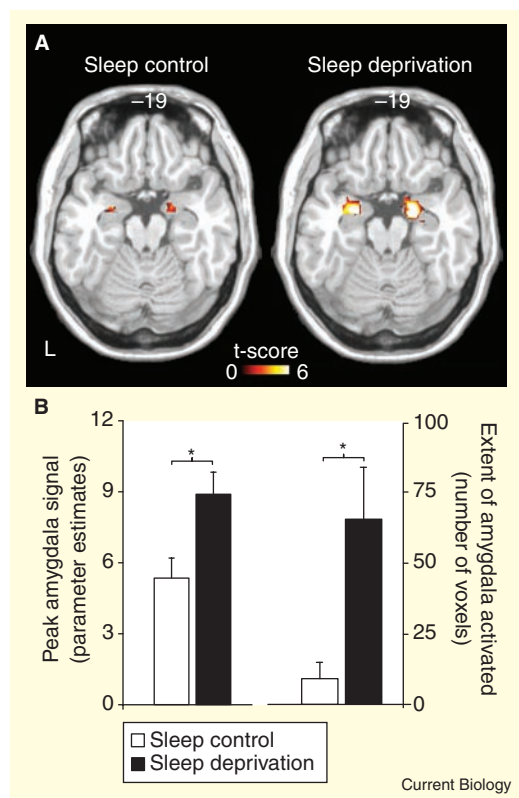
Sleep deprivation is known to impair a range of functions, including immune regulation and metabolic control, as well as neurocognitive processes, such as learning and memory [1]. But evidence for the role of sleep in regulating our emotional brain-state is surprisingly scarce, and while the dysregulation of affective stability following sleep loss has received subjective documentation [2,3], any neural examination remains absent. Clinical evidence suggests that sleep and emotion interact; nearly all psychiatric and neurological disorders expressing sleep disruption display corresponding symptoms of affective imbalance [4]. Independent of sleep, knowledge of the basic neural and cognitive mechanisms regulating emotion is remarkably advanced. The amygdala has a well-documented role in the processing of emotionally salient information, particularly aversive stimuli [5,6]. The extent of amygdala engagement can also be influenced by a variety of connected systems, particularly the medial-prefrontal cortex (MPFC); the MPFC is proposed to exert an inhibitory, top-down control of amygdala function, resulting in contextually appropriate emotional responses [5,6]. We have focused on this network and using functional magnetic resonance image (fMRI) have obtained evidence, reported here, that a lack of sleep inappropriately modulates the human emotional brain response to negative aversive stimuli (see Supplemental data available on-line with this issue).

Twenty-six healthy participants age 18–30 years (mean 24.1, s.d. \pm 2.3) were assigned to either a sleep-deprivation group (n = 14; 7 males) or sleep-control group (n = 12; 6 males). The experimental intervention differentiating the two groups occurred on the night prior to fMRI task-scanning. In the sleep-deprivation group, subjects were awake across Day-1, Night-1 and Day-2, accumulating approximately 35 hours of total sleep deprivation before scanning (5PM, Day-2). In the sleep-control group, subjects slept normally at home across Night-1 prior to scanning on Day-2 (5PM). During scanning, subjects performed an emotional stimulus viewing task in an event-related fMRI design, involving the presentation of 100 images from a standardized picture set [7]. Stimuli ranged in an experimentally controlled gradient from emotionally neutral to increasingly aversive, presented through visual goggles in a pseudorandom order, with subjects providing an emotional classification button-response to verify wakefulness.

Analyses focused on task-specific regions of interest, identifying condition differences specifically within the amygdala (Supplemental Figure S1). To test our experimental hypothesis, we quantified and compared amygdala reactivity between the two groups (Figure 1). While both groups expressed significant amygdala activation in response to increasingly negative picture stimuli, those in the sleep-deprivation condition exhibited a remarkable +60% greater magnitude of amygdala activation, relative to the control group (averaged left and right amygdala, $t_{(24)} = 3.2$, $P = 0.004$; Figure 1A,B; or separately, both $P < 0.05$). In addition to this increased intensity of activation, there was also a three-fold increase in the extent of amygdala volume that was activated in the sleep-deprivation group (averaged left and right amygdala, $t_{(24)} = 2.8$, $P = 0.009$; Figure 1B; or separately, both $P < 0.02$). That these differences were not due to a generalized/non-specific increase in overall amygdala activity in the

Figure 1. Amygdala responses in control and experimental groups.

(A) Amygdala response to increasingly negative emotional stimuli in the Sleep deprivation and Sleep control groups (peak x, y, z Montreal Neurological Institute coordinates: left: -21, -3, -21; right: 24, -3, -21; activation threshold $P < 0.001$, uncorrected; ≥ 5 contiguous voxels), 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).



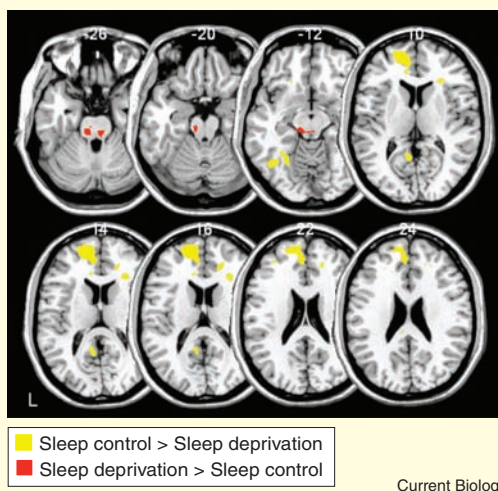


Figure 2. Functional connectivity between amygdala and MPFC in relation to sleep.

Group level differences in amygdala functional connectivity (combined for left and right), including significantly greater connectivity in the medial-prefrontal cortex (green) for the Sleep control group, yet significantly stronger connectivity with autonomic brainstem regions in the Sleep deprivation group (red). Slice number (z-coordinate) displayed on all images (full coordinates provided in Supplemental Table S1). Effects are significant at $P < 0.001$; ≥ 5 contiguous voxels.

sleep-deprivation group was confirmed by a subset analysis of the upper quartile stimulus set (most negative) and lower quartile stimulus set (most neutral). These analyses revealed similar amygdala activation levels between groups for the most neutral pictures, yet highly significant differences for the most negative pictures (Supplemental Figure S2). Thus, a condition-specific amygdala interaction was observed in response to negative stimuli under conditions of deprivation; it is not known, however, to what extent the continued waking activities in the sleep deprivation group contributed to circadian rhythm alterations and subsequent task-specific patterns of brain activity.

Finally, we sought to determine whether these changes in amygdala activity were associated with an altered pattern of functional brain connectivity by examining regions of significant amygdala co-variation within each group, and subsequently compared between groups. Relative to the sleep-deprived group, there was significantly stronger connectivity between the amygdala and the MPFC in those that had slept, evident bilaterally, although was most extensive in the left MPFC (Figure 2; peak Montreal Neurological Institute (MNI) coordinates (x, y, z): -13, 56, 16; Z-score = 4.24, $p < 0.001$; full

coordinates in Supplemental Table S1). This dominance is consistent with the more lateralized activity observed in affective processing and, when dysfunctional, associated with depressive symptoms [5]. In contrast, there was significantly greater amygdala connectivity in the deprivation group with autonomic-activating centers of brainstem, including the locus coeruleus and midbrain (Figure 2; peak MNI coordinates: -8, -27, -26; Z-score = 3.54, $p < 0.001$).

Taken together, these data suggest an amplified, hyper-limbic response by the human amygdala to negative emotional stimuli under conditions of sleep deprivation. Furthermore, this increased magnitude of limbic activity was associated with a loss of functional connectivity with the MPFC in the sleep-deprivation group; suggesting a failure of top-down, prefrontal control. It therefore seems that a night of sleep may 'reset' the correct brain reactivity to next-day emotional challenges by maintaining functional integrity of this MPFC-amygdala circuit, and thus govern appropriate behavioral repertoires.

While the implication of our finding remain speculative, they may provide insights into the pervasive relationship between sleep disruption and mood disorders, including bipolar disorder [4,5,8], which instead of

being viewed as co-occurring, may be more causally related. More generally, these data can offer a neural foundation on which to consider hostile and non-optimal decision-making in sleep-curtailed work personnel (for example military, aviation, medical), as well as circumstances of emotional irrationality in an increasingly sleep-deprived society.

Supplemental data

Supplemental data are available at <http://www.current-biology.com/cgi/content/full/17/20/R877/DC1>

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