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Editorial

The Amygdala as a Mediator of Sleep and Emotion in Normal and Disordered States

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Sleep consists of two basic states, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, also known as slow wave sleep and paradoxical sleep, respectively. Good quality sleep may promote higher positive and lower negative affect [1]. Stressful and unpleasant emotional states can disturb sleep [2]. Further, sleep disturbances can reduce the ability to cope with stressful and emotional challenges appropriately, which may contribute to the development of transient emotional disturbances and persistent psychiatric disorders [3]. Traumatic life events virtually always produce at least temporary sleep disturbances that may include insomnia or subjective sleep problems [4], and the persistence of these disturbances may indicate the future development of emotional and cognitive disorders [5–7]. The bidirectional influences of emotion and sleep, and their relevance for both normal and disordered states, demonstrate the need to understand the nature and neural regulation of the relationship between emotion and sleep. Sleep disturbances are common in neuropsychiatric disorders. Although disturbances in both NREM and REM sleep occur, REM sleep, in particular, is thought to play an important role in the adaptive processing of emotionally significant memories in both humans [8,9] and animals [10,11]. Indeed, several authors have made suggestions consistent with this hypothesis, e.g., REM sleep weakens unwanted memory traces in the cortex [12], it aids in the processing of memory for trauma [13,14], and may play a role in consolidating memories for aversive events and in "decoupling" them from their emotional charge [8,9]. However, the relationship between emotion and REM sleep is complex. This is evidenced by the fact that alterations in REM sleep can become fear-conditioned and subject to extinction in much the same way that freezing and other behavioral and physiological responses can become fear-conditioned and extinguished [15–17]. Virtually all animal experimental behavioral assessments evoke emotional responses, and studies have repeatedly demonstrated that stressful experiences while awake can significantly influence subsequent sleep. REM sleep appears to be particularly susceptible to the effects of stress. Increases in REM sleep and changes in other sleep parameters have been reported for a great number of stressors, including avoidable footshock, restraint, water maze, exposure to novel objects, open field, ether exposure, cage change, and social stress (reviewed in [18]). Stressors such as inescapable footshock [19] can produce decreases in REM sleep that may relate to an animal's inability to control or limit its exposure to stress [11]. Alterations in REM-sleep parameters may also be observed: REM sleep EEG theta (REM-θ, 5–8 Hz) amplitude may be reduced after social defeat [20] and alterations in theta amplitude have been linked to fear conditioning and extinction [21]. Thus, different emotional situations have the potential to produce different alterations in subsequent sleep amounts and archtitecture. The amygdala has a long-recognized role in emotion [22–24]. It is directly responsible for associating emotional significance with received information, as well as storing, coding, and recalling emotional memories. In addition, it interacts with the the prefrontal cortex, which is involved in working memory, motivation, planning, and in the diminishing of fear reactions. Additionally, the central nucleus of the amygdala plays a role in the modulation of autonomic phenomena including heart rate, blood pressure, and respiratory-activity patterning [25–27], particularly as related to stress [26]. The amygdala is an important mediator of the effects of emotion, fearful memories, and stress on arousal and sleep and also appears to function in the regulation of physiological sleep. The first suggestion that the amygdala might be involved in the actual regulation of sleep occurred in the early 1960s [28]. In the years since, studies by sleep researchers have reported on the role of the amygdala in regulating the EEG [29], pontogeniculo-occipital (PGO) waves [29], REM sleep [30], and several studies have examined the influence of the amygdala on autonomic variables during wakefulness and sleep (e.g., [25,31,32]). Studies in narcoleptic dogs have also implicated the amygdala in cataplexy, which can be triggered by emotional stimuli [33,34], and a finding of increased blood flow in the amygdala during REM sleep in humans [35] was interpreted as a possible link between emotionality controlled by the limbic system and dream content. Several studies have demonstrated effects of amygdala manipulations on spontaneous [36–38] and stress- and fear-induced [39–41] alterations in sleep. Recent work has shown that the amygdala also regulates REM sleep-specific acitivity

that appears important for emotional learning. For example, REM-dependent physiological events, including θ coherence [42], REM-θ amplitude [21,43], and phasic pontine-waves (P-waves, pontine component of PGO waves) [44] may be more accurate predictors of successful consolidation of fear memory than is the amount of REM sleep. Both REM-θ [43,45] and P-waves [37,46,47] are regulated by the amygdala, which, along with the medial prefrontal cortex and hippocampus, exhibits coordinated θ activity associated with contextual fear conditioning [48]. Brief optic activation of the basolateral amygdala during REM sleep immediately reduced REM-θ without affecting overall amount of, and propensity for, sleep, whereas optic inhibition increased REM-θ [43,45]. The reduction in REM-θ amplitude was associated with subsequent attenuated freezing and altered fear-conditioned REM-sleep responses [43]. Stimulation during NREM sleep did not affect any output measures, suggesting that the effects were REM-sleep specific. In summary, various lines of evidence have demonstrated that sleep and emotional disturbances, and their interactions, play roles in the development of a range of neuropsychiatric disorders as well as being continuing and distressing symptoms. The amygdala has been identified as a critical mediator of emotion and sleep, with significance for both normal function and psychopathology. It is also a clear target for understanding the neural mechanisms that link sleep and emotion. Delineating its role should provide significant insight into the regulation of sleep and emotion in both normal and disordered states.

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