

# Causal role of rapid-eye-movement sleep on successful memory consolidation of fear extinction

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The formation and consolidation of conditioned fear memory is a fundamental mammalian mechanism to adapt to the environment quickly. However, the persistent fear memories failure to extinction can be maladaptive and represent a core symptomatic dimension of fear related disorders such as post-traumatic stress disorder (PTSD) (1-3). An effective model has been successfully developed in humans and animals using the fear conditioning paradigm, in which a neutral conditioned stimulus (CS) is associated with an inherently aversive unconditioned stimulus (US), and fear extinction occurs after repeated exposure to the CS without the US. Sleep is a basic component of physiological process that promotes various cognitive functions, such as learning, memory and emotion regulation (4-6). Sleep may allow the removal of free radicals accumulated in the brain during wakefulness and protect the structural stability of neuronal synapses; the tired nerve cells and the biological characteristics of long-distance signal transmission recover normal physiological function after sleep (7). Recently, more and more researchers paid their attentions to investigate the changes in behavior and neural circuitry of sleep dependent memory consolidation on conditioned fear and fear extinction. However, how sleep, especially specific sleep phase, benefits extinction memory consolidation is still poorly understood.

Sleep is a complex physiological process with different sleep stages, however, the specific roles of different sleep stages and their electrophysiological characteristics

on different styles of memory consolidation are still unclear (4,8,9). There are two hypotheses exist for a long time, one is dual process hypothesis, and the other is sequential hypothesis. The dual process hypothesis holds that non rapid-eye-movement (NREM) sleep consolidates declarative memory, while REM sleep consolidates procedural and emotional memory (4,8). The sequential hypothesis argues that the optimal consolidation of particular types of memories may be required the appearance of slow wave sleep (SWS) and subsequent REM sleep (6,10). Recently, Walker *et al.* proposed a “Sleep to Remember, Sleep to Forget” model, which suggested that REM sleep may be involved in the consolidation of episodic-content and de-potentialization of the emotional component of emotional memory (5). Although the exact mechanism of different sleep stages for different memory consolidation is not yet clear, emerging evidence shows that REM sleep plays a specific role in the consolidation of emotional memory, especially for extinction memory. An animal study found that immediately REM sleep deprivation after extinction training in rat impairs the consolidation of fear extinction memory in the cued fear conditioning task, while deprived REM sleep for 6 hours after extinction training left fear extinction recall intact (11). These results suggested that REM sleep may be specifically important to the memory consolidation of fear extinction. Afterwards, in a human study, Pace-Schott *et al.* (12) first investigated the effects of sleep on extinction memory with classical

fear conditioning paradigm, they found that a total night of sleep promoted the generalization of extinction memory from the extinguished stimulus (CS+E) to the other unextinguished stimulus (CS+U). This study highlights the promising sleep-related interventions to enhance exposure therapy in treating patients with PTSD. However, the potential effect of circadian rhythms cannot be excluded from this study because fear extinction recall was tested at different time points in the sleep group and the wake group. Spormaker *et al.* conducted the first fMRI study to investigate the neurobiological basis of sleep and extinction memory, and found that participants who had REM sleep after fear conditioning and extinction learning exhibited greater extinction recall, accompanied by stronger activation of the ventromedial prefrontal cortex (vmPFC) in response to the extinguished stimulus. Besides the REM sleep, our recent studies showed that NREM sleep, especially SWS, may also involve in the modulation of conditioned fear and extinction memory. Fear extinction can be learned when re-presented prior CS without reinforcement of US during SWS (13). In the sequent study, we re-exposure the extinction associated context cue during SWS, and found the extinction memory recall was impaired (14). However, the results of sleep and extinction memory from different laboratories have so far failed to explain the causal role of different sleep stages on extinction memory with different methodologies.

Recently, Menz *et al.* (15) investigated the effects of different sleep stages on the successful consolidation of extinction memory by a split-night protocol in 80 healthy participants, such paradigm according to the fact that in human the first part of the night is dominated by SWS, whereas REM sleep is more pronounced during the second half (16). This method can disentangle the differential roles of SWS and REM sleep on fear extinction through selectively manipulates the amount of SWS and REM sleep spending on memory consolidation. They found that extinction recall performance displayed an increase of discrimination between a previously extinguished stimulus and a safe stimulus, implying a return of fear and impaired extinction memory recall, while extinction memory recall was intact after an interval of REM-rich sleep, which indicated by a comparable differentiation between the extinguished stimulus and the safety stimulus. These results seem to support a notion that REM sleep is especially important for the safety leaning, and their previous results also showed that REM-rich sleep leads to successful fear recall, which indicated by a better differentiation between

CS+ and CS-, suggesting that REM sleep may contributed to the discrimination of safety and unsafely cues (17). These findings are helpful for us to understand how sleep contribute to successful extinction memory consolidation, which is particular relevant to the augment of extinction based therapy such as clinically exposure therapy.

Furthermore, some factors are worthy of notice concern. First, as mentioned in this study, the hormone levels, such as growth hormone and cortisol, were fluctuated with the circadian. Previous studies showed that cortisol may interact with sleep and play a role in emotional memory consolidation (18,19). Therefore, whether the observed effects attribute to unique sleep stages are still need to be explored. Second, the split-night paradigm artificially isolated the sequential characteristics of SWS and REM sleep in a total night sleep, which may ignore the role of natural sleep on memory processing. Perhaps newly proposed targeted memory reactivation (TMR) paradigm (20), which can selectively reactivate previous learning experience using external reactivation cues (e.g., odors and sounds cues) (21,22), may provide a novel solution to investigate the relationships between the roles of different sleep stages and the extinction memory consolidation. Third, some confounding factors in the control groups should be noticed, such as the elevated cortisol levels after sleep deprivation or interference by other activities when participants stay awake, these factors also can explain the observed differences between the sleep group and the wake group.

In summary, this study by Menz *et al.* provided an innovative method to investigate the role of different sleep stages on human extinction memory. Sleep, especially the REM sleep, may play particular roles in the memory consolidation of fear extinction. Therefore, targeted to improve the sleep quality, especially the REM sleep, may augment the treatment of exposure therapy for anxiety disorders, worthy of exploring in the future.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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