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Fear not: manipulating sleep might help you forget

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Memory storage is not static – updating is often needed. When it comes to traumatic memories, forgetting may be desired. Two innovative studies recently demonstrated that fear memories can be weakened during sleep using odors associated with fear-learning episodes. New strategies along these lines should be carefully considered for treating unwanted fears.

In the film *Eternal Sunshine of the Spotless Mind* (2004), two ex-lovers attempt to get over a painful breakup through an incredible treatment that erases their memories of each other. Today, this is science-fiction – and very far from scientific fact. However, two recent studies take a step in this direction by successfully attenuating fear memories during sleep. These findings may lead to new hope for people suffering from maladaptive memories, perhaps even traumatic memories at the root of phobia or post-traumatic stress disorder (PTSD).

During sleep, patterns of brain activity elicited during learning are spontaneously reactivated, a process thought to make memories stronger and more enduring [1]. Furthermore, it is possible to externally influence which memories are reactivated during sleep by using sensory cues (e.g., odorants or sounds) as reminders of the previous learning [2]. So far, this 'targeted memory reactivation' (TMR) has been shown to strengthen visuospatial memory, skill learning, and word recall [3–6]. But can TMR suppress or at least weaken painful features of a bad memory?

In a new study conducted by Rolls and colleagues, mice were conditioned to fear amyl acetate, which smells like banana [7]. This odor stimulus was systematically followed by painful foot-shock during conditioning. After a 24-h interval, which ensured sufficient consolidation of the fear memory, the odorant was reapplied during sleep. Paralleling previous studies using TMR, externally reactivating the fear memory in conditioned mice facilitated fear behavior the following day, as indicated by increased freezing when the conditioned stimulus (CS odor) was delivered alone in a new context. However, the goal was to suppress fear memories, not reinforce them. To reverse the effect of the sleep manipulation, the researchers injected a protein-synthesis inhibitor in the amygdala before applying the CS odor during sleep. This manipulation has been successfully used to attenuate fear memory in the awake state [8], based on the idea that enduring memory storage requires protein synthesis during a critical time period after learning. Consistent with expectations, injection of the protein-synthesis inhibitor, combined with subsequent external reactivation of the fear memory during sleep, led to a diminution of fear expression the following day. Appropriate controls confirmed that the fear-memory attenuation was not due to the protein-synthesis inhibitor itself nor to nonspecific effects of odorant presentation.

Hauner and colleagues used different procedures to suppress fear memory in humans [9]. In this study, 15 young subjects underwent contextual fear conditioning, in which face images were associated with an uncomfortable electrical shock while an odor was in the background (e.g., mint, lemon, pine). After conditioning, the faces elicited a fear response demonstrated by increased skin conductance.

Surprisingly, and contrary to Rolls *et al.*'s results, reapplying the odorant during an afternoon nap did not reinforce fear memories. Instead, the odor manipulation reduced fear responses for the corresponding faces relative to other faces for which the corresponding odor context had not been reactivated during sleep. These other faces had the same conditioned association with shock and with a different odor, matched for pleasantness, assuring that TMR effects were specific to the cued association. This targeted fear extinction during sleep was accompanied by a decrease in hippocampal functional MRI activity and a reorganization of ensemble pattern activity in the amygdala from pre- to post-sleep. Whether this fear reduction reflected true erasure of the fear memory, reduction of the emotional salience of the memory, or a new memory trace associated with safety remains unclear.

How can the apparent discrepancy between the two studies – that TMR in the mouse study strengthened fear memory whereas TMR in the human study reduced it – be explained? Aside from species differences, there were also

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procedural differences between the two studies. For one, the reinforcement contingencies differed, in that 50% of the conditioned stimuli were associated with shock in Hauner *et al.*'s study versus 100% in Rolls *et al.*'s study. Also, the level of shock aversion was likely to be greater for mice, and the delay between conditioning and reactivation was much shorter in Hauner *et al.*'s study (a few minutes vs 24 h). Thus, memory storage could have been more labile, such that reactivating the fear memory without the associated punishment readily created a new, 'safe' memory for the CS. The fact that the odor triggered a consistent skin-conductance response during the first period of sleep, before eventually decreasing it, supports the hypothesis that the fear memory was gradually replaced by a safe representation in the human study. Finally, what the odor cue reflected, either the context of the fear experience in Hauner *et al.*'s study or the CS itself in Rolls *et al.*'s study, might be critical for the direction of the TMR effect. Previous findings have shown that when tones were an intrinsic aspect of a finger-tapping task, replaying the tones during subsequent sleep boosted subsequent performance [3]. Conversely, when an odorant was diffused in the background during learning of another, simpler finger-tapping task, re-applying the odorant during sleep had no impact on memory [4]. Additional studies of TMR are needed to understand which parameters of memory can be changed and what neural mechanisms regulate such changes.

Phobia and PTSD can be extremely debilitating. Most current therapies, particularly exposure therapy, require patients to confront their fear or phobia over and over again, which constitutes a highly demanding and stressful experience for them. Lack of compliance with therapy is often a barrier to recovery. Although more research is needed to reveal the mechanisms and the exact conditions by which TMR during sleep can successfully reduce fear, the two studies discussed here introduce a possible alternative (or adjunct) to exposure therapy and possibly other therapies. Research on new treatments for PTSD must be particularly cautious, because there is a potential to create more harm than good. However, targeting fear memories during sleep is all the more interesting because sleep is disturbed in PTSD to the point that it is now considered a core feature of the disorder [10]. Patients may never be treated by the fictional procedures provided by Lacuna Inc. (in *Eternal Sunshine of The Spotless Mind*), but they may someday have novel options that once seemed equally outlandish.

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