Biological Psychiatry: Celebrating 50 Years

Commentary

Fighting the Return of Fear: Roles of Mindfulness-Based Stress Reduction and the Hippocampus

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Although it is crucial to learn which parts of our environment are dangerous, it is also essential to attenuate our threat responses if they turn out to be safe. Learning that stimuli are safe, or the process of extinction, is modeled in the laboratory by taking a stimulus that was previously associated with an aversive outcome and presenting it with no outcome. Although this process informs exposure-based therapies for clinical conditions like anxiety, it has serious shortcomings—often, extinction memories don't last. Even in the controlled setting of the laboratory, people tend to remember the stimulus as dangerous (threat retrieval) rather than safe (extinction retrieval). Thus, there is a pressing need to facilitate the retrieval of extinction memory (1).

In this issue of *Biological Psychiatry*, Sevinc *et al.* (2) take the important step of probing whether mindfulness-based stress reduction (MBSR) could improve extinction retrieval. They collected functional magnetic resonance imaging data while participants underwent a 2-day classical conditioning protocol with threat acquisition and extinction on day 1 and (the focus of their article) presentation of the stimuli again on day 2. Crucially, participants completed this protocol before and after 8 weeks of MBSR (n = 42) or an active control intervention incorporating stress management education and exercise (SME) (n = 25). Strengths of the study include the use of an active control group and random assignment to MBSR versus SME interventions. On the other hand, healthy individuals were studied. Thus, whether the same circuits may underlie extinction processes in individuals with psychiatric illnesses and whether MBSR could improve extinction in psychiatrically ill individuals in whom extinction processes may be compromised remains to be tested in future work.

Sevinc *et al.* (2) reported that MBSR led to decreases in anxiety, self-reported stress, and difficulties with emotion regulation, but SME led to similar changes in the latter two measures as well. Surprisingly, they did not find differences in physiological indices of extinction retrieval (skin conductance response) after MBSR compared with SME. However, they did find distinct neural responses during extinction retrieval after these interventions. Looking throughout the brain, they found that the MBSR group showed a greater increase in blood oxygen level–dependent responses in the supramarginal gyrus (SMG) from pre- to postintervention than the MSE group. Focusing on hippocampal responses in the MBSR group, Sevinc *et al.* (2) observed increased functional connectivity between the left hippocampus and both the SMG and the primary sensory cortex during extinction retrieval when viewing the extinguished cue. Finally, they showed that increases in hippocampal gray matter in the MBSR group were associated with stronger functional connectivity between the hippocampus and the dorsolateral prefrontal and retrosplenial cortices. These results provide insight into the neural mechanisms by which mindfulness interventions could change the retrieval of threat associations. It is important to note that because the measurement of the skin conductance response signal was limited by technical difficulties and because behavioral measures of memory were not collected (e.g., ratings of how much participants expected shock), it remains unclear whether these neural changes promoted the retrieval of threat or safety associations. Future studies will be needed to establish whether the hippocampal changes associated with MBSR drive extinction retrieval.

Why might MBSR promote the retrieval of safety rather than threat associations? While mindfulness training involves increasing attention to the present moment (i.e., greater attention control), it also involves increasing awareness of sensory, motor, and emotional states. This occurs presumably via increased interoceptive processing that results in experiencing expanded perceptual and sensory awareness, which are often reported with mindfulness training (3). Consistent with mindfulness-induced changes in attentional processes, Sevinc *et al.* (2) found that MBSR led to enhanced SMG responses (a region associated with attention) during extinction retrieval and that this signal correlated with reported mindfulness practice. They also report significant increases in hippocampus–SMG connectivity in MBSR but not SME participants. This circuit may contribute to subjective aspects of threat processing, as we recently showed hippocampus–SMG connectivity during stress predicted (sex-specific) subjective stress and arousal (E.V. Goldfarb, Ph.D., *et al.*, unpublished data, July 2019). As subjective and physiological responses can diverge (4), these findings suggest that future investigations will need to parse out the impact of MBSR on subjective aspects of threat conditioning and extinction.

On the other side of stress reduction, stress induction has been shown not only to diminish extinction retrieval but also to influence threat acquisition and undermine extinction (5). These findings raise several intriguing possibilities. First, MBSR could modulate each of these processes. Sevinc *et al.* (2) state that the effects of MBSR on threat acquisition and extinction will be reported elsewhere, and we are eager to see those results. Second, the fact that stress can modulate threat conditioning suggests that MBSR, which influences stress responses, could more strongly attenuate threat acquisition and retrieval under conditions of stress. Testing the effect of MBSR on learning and retrieval during stress would have significant clinical implications, because stress-related changes in

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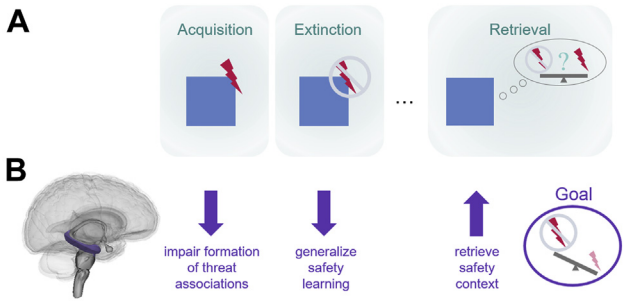

Figure 1. **(A)** Schematic of threat conditioning showing acquisition, extinction, and retrieval of threat or safety associations. **(B)** Proposed mechanisms by which dynamic hippocampal responses throughout threat acquisition, extinction, and retrieval may facilitate the retrieval of "safe" (extinction) rather than "threat" associations. The purple arrow indicating the link between enhanced hippocampal signal during retrieval and stronger extinction retrieval is supported by findings from Sevinc *et al.* (2).

such processes may contribute to the development of psychopathology (6).

As a mechanism by which MBSR could influence extinction retrieval, Sevinc *et al.* (2) focus on enhanced hippocampal responses and connectivity. This is a natural extension of their earlier finding that MBSR enhanced hippocampal gray matter density (7) and aligns with extensive evidence for hippocampal involvement in contextual threat conditioning. In this article, Sevinc *et al.* (2) show that higher hippocampal responses to extinguished cues were associated with stronger skin conductance response indices of extinction recall. Their model proposes that MBSR strengthens hippocampal processes to promote retrieval of the extinction (i.e., safety) context.

While enhancing hippocampal responses and connectivity is one approach to promoting extinction retrieval, evidence from the stress domain indicates that flexible and dynamic hippocampal responses may be crucial to improve extinction retrieval (Figure 1). We have shown that MBSR attenuated hippocampal responses to stress, which was associated with reductions in subsequent maladaptive behavior (8). In addition, dynamically increasing (rather than persistently elevated) hippocampal responses during stress were adaptive (9). Notably, enhanced hippocampal activity and connectivity during threat acquisition and extinction could impede extinction retrieval. For example, higher hippocampal–amygdala connectivity immediately after acquisition was associated with worse extinction retrieval (10). On the other hand, lower hippocampal responses to extinction may enhance extinction retrieval. Impairing hippocampal function during extinction could limit the extent to which this learning is bound to the specific extinction context, thus facilitating extinction retrieval in a wider range of contexts (1). Together, these findings suggest a pathway by which flexible hippocampal responses throughout learning and retrieval would facilitate extinction retrieval. Further research is needed to test this pathway and to specifically delineate the contributions of anterior and posterior hippocampal subregions to these processes. As mindfulness training increases attentional control and expands perceptual and sensory awareness, MBSR may promote flexible updating by increasing awareness of additional stimuli and facilitating dynamic responses in regions including the hippocampus. The current promising findings reported by Sevinc *et al.* (2) will likely motivate future work examining key hippocampal mechanisms by which MBSR may ultimately promote memory for "safe" rather than "threat" associations.

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