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# Running to Forget

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What do ice cream and running have in common? Consuming indulgence foods and running are two actions that typically achieve opposite results: ice cream leads to weight gain and running helps you lose it; high sugar intake is linked to diabetes, cholesterol, blood pressure, and heart disease, while exercise reduces those risks. Ice cream and running do have one thing in common though—both are self-soothing. In response to stress, many people find comfort in food, but some people find it in physical activity. They crave exercise. They simply *must* go out for a run. Running is often described as "self-medicating" and even addictive. In fact, mental health providers often "prescribe" it as an effective routine for coping with depression, stress, and anxiety. The beneficial effects of exercise are widely known but poorly understood. The National Institute of Health recently released a series of calls for studying how exercise affects the body. This initiative seeks researchers that will identify the molecular transducers of physical activity. The goal is to delineate a molecular map to help us understand how physical activity transforms into wellbeing.

One potentially important molecule is the brain-derived neurotrophic factor (BDNF) of the neurotrophic family of signaling proteins. Studies examining exercise in humans and rodents (running on treadmills or swimming) found elevated levels of BDNF (Heijnen et al., 2015). In fact, BDNF appears to be the molecular harbinger of wellbeing. Mitigating cognitive decline, mediating learning and memory, protecting against neuronal death, and encouraging growth of new neurons (Park and Poo, 2013; Weinstein et al., 2014) are only some of BDNF's ascribed beneficial functions. A study by Asthana and colleagues (Asthana et al., 2016), recently published in this journal, reported another possible role for BDNF, which may at first glance appear counterintuitive—the ability to forget. Asthana et al. (2016) investigated whether the BDNF val66met polymorphism (rs6265) plays a role in the ability to prevent fear memories from resurfacing. Memory reconsolidation is the processes in which reactivated long-term memories reenter a state of temporary instability where they are susceptible for disruption (Nader et al., 2000; Sara, 2000). Reconsolidating memories are sensitive to amnesic agents (such as protein synthesis inhibitors, brain insult, etc), which could prevent memory restabilization and persistence. Even without such invasive manipulations, reconsolidation may allow for memory update with information accessible at the time of retrieval (Monfils et al., 2009; Schiller et al., 2010). Asthana et al. (2016) asked whether allelic differences in the BDNF gene might explain individual differences in the ability to update fear memories using reconsolidation mechanisms.

To study this, Asthana et al. (2016) examined 91 participants over 3 consecutive days. During the experiment, the participants sat in front of a computer screen and observed blue or yellow colored squares. Electrodes were connected to their fingers to measure their skin conductance response (indicating arousal as the index of fear) and they had headphones on. On day 1, after almost every presentation of one of the squares (blue for some, yellow for others), a woman's scream was heard. The participants were therefore conditioned to associate one of the squares with an unpleasant outcome (this square was the conditioned stimulus), while the other stimulus remained safe. The next day, the fear memory was reactivated when the participants saw one presentation of the conditioned stimulus (without the scream). This single reactivation trial presumably destabilized the memory and triggered a reconsolidation process. The critical manipulation occurs at this time, during reconsolidation. In pharmacological studies, for example, an amnesic drug is administered to block reconsolidation. Here, instead of a drug, Asthana et al. (2016) introduced a novel behavioral experience, providing new information: 10 minutes after reactivation, the participants underwent extinction training, where they saw repeated presentations of the squares without the scream. On the last day, the squares were presented again (without the scream) to test whether the fear response resurfaced.

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Two groups of participants went through this experimental protocol with the following exception: one group skipped the reactivation trial on day 2 and did extinction training only. In other words, one group had extinction during reconsolidation and another had standard extinction. Within each group, the met allele and non-met allele carriers were compared. What role might BDNF play in reconsolidation update?

Previous studies have actually suggested that BDNF does not participate in fear memory reconsolidation, only in initial consolidation (Lee and Hynds, 2013). A recent study, however, showed that reconsolidation of fear extinction requires BDNF (Radiske et al., 2015). Consistent with the latter findings, Asthana et al. (2016) found that only met allele carriers were affected by reconsolidation: the fear memory did not recover in met allele carriers who were exposed to the reminder prior to extinction. The memory recovered only in met allele carriers that had standard extinction. In contrast, fear memory did not return in non-met allele carriers after extinction regardless of the reminder. Indeed, met allele carriers in previous studies demonstrated impaired fear extinction (Soliman et al., 2010) as well as poor response to exposure-based therapy for posttraumatic stress disorder (Felmingham et al., 2013). Similarly, in the study by Asthana et al. (2016), the met allele carriers who had standard extinction were least affected by extinction training and were unable to retain the diminished fear response. The findings of Asthana et al. (2016) imply that utilizing reconsolidation may rescue the disadvantage that met allele carriers face when attempting to extinguish learned threat responses. Memory reactivation might trigger an alternate molecular cascade that bypasses the ramifications of the BDNF Val66Met mutation, leading to a more permanent reduction of fear.

If BDNF facilitates extinction learning and running elevates BDNF levels, it is not surprising that many people intuitively go for a run to self-sooth daily stressful exposures and perhaps even replace exposure therapy. Indeed, a rodent study found that direct infusion of BDNF into the hippocampus achieved the same results as extinction training without actual extinction (Peters et al., 2010). Perhaps one day there will be a detailed map of the molecular transducers of physical activity and a comprehensive map of memory plasticity. As we gradually put the pieces together, we could begin to design highly precise drugs, target them to specific neural processes, and tailor treatment options based on genetic make-up. But understanding the biology is more than drug development—it is also about behavior. We could design behavioral treatments based on deep understanding of the underlying biological mechanisms. Reconsolidation updating is an excellent case of such behavioral modification. The simple act of memory reactivation and the experiences that coincide with it could have a dramatic effect on what we remember next. Facing our fears, running, meditating, learning, and creating are few of the many ways we could orchestrate our behavior to achieve our best brain state.

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## Statement of Interest

None.

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