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Commentary

Forgetting to Be Addicted: Reconsolidation and the Disconnection of Things Past

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Yea, from the table of my memory
I'll wipe away all trivial fond records,
All saws of books, all forms, all pressures past,
That youth and observation copied there,
—William Shakespeare, *Hamlet*, Act 1, Scene 5

Hamlet wanted to wipe away parts of his memories, and once again The Bard has poked at a fundamental feature of human nature. Wouldn't it be useful to select particular memories, change some, and eliminate others altogether? The famed Heisenberg uncertainty principle touched on a similar issue, looking closely at the principle of observation for any physical system—that merely observing a system must necessarily change the answer obtained. This limitation is also a feature of mammalian memory. Merely recalling a memory tends to change it. Wouldn't it be wonderful to control such processes?

One major challenge of addiction neuroscience research has been to better understand the neural mechanisms that support the learning and maintenance of addictive behaviors. One promising direction is memory reconsolidation. Addictive substances, such as nicotine, represent "unconditioned stimuli" with value to addicted smokers. The reward properties of such stimuli and the actions required to obtain them may also come to be associated with "conditioned stimuli" that temporally precede substance use. For example, a smoker may come to associate his favorite pub with smoking a cigarette, and ultimately, nicotine's rewarding properties. This memory gets consolidated and reconsolidated each time the smoker smokes a cigarette at the same pub.

Recent work has suggested that memories that are retrieved are newly labile and susceptible to modification, a process called reconsolidation. Memory strength is dependent not only on the original encoding episode, but on what happens to the memory once it is retrieved. Pharmacological manipulation or new learning during a postretrieval reconsolidation window can act to weaken or strengthen the memory (1). Translating these results to addiction treatment is of obvious benefit and has been the subject of recent work.

Initial attempts at designing behavioral manipulations looked to earlier work targeting fear memories, in which a conditioned stimulus was retrieved to make the memory labile, and was subsequently followed by extinction training (2). In this approach, an A–B association is first learned (e.g., this could be an arbitrary stimulus paired with nicotine, although other drug rewards were used), the A cue retrieved, and A then relearned without B, weakening the original A–B association. However, translating such a paradigm to curtail addictive behavior in the real world is difficult; individuals who suffer from addiction have built up a vast array of associations between a large body of stimuli and their drug of choice (3). Directly targeting one or a handful of them may be feasible, but not all of them, and any remaining cue can act as a trigger for relapse. Going back to our pub example, while it may be possible to directly target the association between a single pub and smoking using this paradigm, it is difficult to target every single pub the patient might regularly visit if we consider the generalization effect of a conditioned stimulus. Of course, this is a problem not only for addiction research, but also for fear learning and other domains where it was hoped that the ability to target problematic memories during the reconsolidation window would help advance treatment.

These initial attempts have subsequently been extended in both fear learning and addiction work by focusing on using the unconditioned stimulus itself as the retrieval cue for reconsolidation, rather than any one individual conditioned stimulus (3,4). Reactivating the unconditioned stimulus (e.g., nicotine rather than the pub in our hypothetical scenario) can simultaneously affect more than one conditioned stimulus. Furthermore, such memories can be modified not only through pharmacological intervention (5), which may be problematic in human participants, but also using behavioral intervention. Retrieving the unconditioned stimulus and then performing extinction for one conditioned stimulus can interfere with the association between a different conditioned stimulus and the unconditioned stimulus (3,4).

In this issue of *Biological Psychiatry*, Xue *et al.* (6) extend this line of work to investigate the neural mechanisms that underpin this phenomenon. Using two different rat models of nicotine addiction, the authors report a series of experiments showing that different conditioned stimuli are coded by separate but possibly overlapping neurons in the basolateral amygdala. Using the unconditioned stimulus (i.e., nicotine) as a reactivation trigger simultaneously activates both groups of neurons, and pharmacologically targeting the basolateral amygdala during the reconsolidation window interferes with both memories. A better mechanistic understanding of what is involved in storing, reactivating, and reconsolidating appetitive drug memories of this type is of obvious benefit, potentially paving the way for developing more targeted pharmacobehavioral interventions in humans. These experiments also raise important new questions, not only about translational issues but also about the basic science involved.

At the core of the latter set of issues is the question of state and reward representation and retrieval dynamics, i.e., how the

SEE CORRESPONDING ARTICLE ON PAGE 781

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brain represents the external world and how it manipulates this information. With notable exceptions (7), the question of representation has suffered from a noticeable degree of segregation from the study of reward-based decision making, with questions about representation largely tackled by memory researchers and questions about reward tackled by decision scientists using tasks with simple state spaces. In reality, however, people (including addicted individuals) encounter complex environments. The work by Xue *et al.* (6) motivates questions about how what we know about each domain may be combined both in the context of nicotine addiction and more generally.

A particularly interesting example concerns why conditioned stimuli seemingly do not act as reconsolidation triggers for one another (3,4). If the unconditioned stimulus can act as a strong retrieval cue for conditioned stimuli, an association that flows backward in time, one would expect an equally strong or stronger forward association between a predictive stimulus (i.e., a conditioned stimulus) and the unconditioned stimulus. Using one conditioned stimulus to retrieve another would then require a single additional step: the unconditioned stimulus would be retrieved first, using what should be a strong connection, and the same retrieval dynamics set in motion when using the unconditioned stimulus as the primary retrieval cue would then follow. This extra step may result in a weaker effect compared to using the unconditioned stimulus as the primary cue, but it is not clear why the effect would be qualitatively different or absent. A related question concerns the nature of what is modified during reconsolidation through extinction training (4). If only one conditioned stimulus is used during extinction, then even if multiple stimuli are retrieved beforehand, why are all of them affected? A better understanding of the representational space within which state and reward information is embedded and the retrieval dynamics governing access to this information is ripe for future work.

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Article Information

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