Remembrance of Rewards Past

Using event-related fMRI, Wittmann and colleagues report in this issue of *Neuron* that reward value enhances cue memory and that this process is associated with midbrain modulation of hippocampal consolidation. We propose that their findings introduce a novel mechanism by which positive arousal induced by reward anticipation may promote memory.

> "The past is hidden . . . beyond the reach of intellect, in some material object (*in the sensation which that material object will give us*) which we do not suspect."—Proust, 1927 (italics added)

The taste of a tea-soaked madeleine unleashed the torrent of memories that came to fill Marcel Proust's voluminous ode to childhood (Figure 1). There, Proust noted that his memories were resurrected not by force of will, but by the feeling of reward. In contrast, beginning with Ebbinghaus's seminal studies of meaningless syllables (Ebbinghaus, 1913), memory researchers have historically sought to excise emotional influences from their experiments.

All of this changed when neuroscientists discovered a convincing physiological mechanism by which emotion could modulate memory. Most of these experiments began in the animal laboratory and focused on fear. The studies showed that punishment cues could come to elicit fear behavior by changing connections in medial temporal lobe structures including the amygdala (LeDoux, 2000). Brain imaging studies later extended these findings to show that amygdalar activation elicited by punishment cues could modulate hippocampal activity in humans (Buchel and Dolan, 2000). Thus, research implied that anticipatory negative emotions like fear could bolster memory. But what about positive anticipatory emotions like excitement?

On a different front, primate electrophysiologists working with Pavlovian paradigms found that midbrain dopamine neurons preferentially responded to reward cues (Schultz et al., 1997). Soon afterwards, brain imagers discovered that anticipation of rewards (ranging from juice to money) activated deep brain regions associated with the neurotransmitter dopamine in humans, including midbrain regions containing dopamine cell bodies and projection areas in the ventral striatum (Knutson et al., 2001; O'Doherty et al., 2002). Further, activation of these regions correlated not just with salivation in dogs, but also with self-reported excitement in humans. Since midbrain dopamine neurons also project to the hippocampus (Swanson, 1982), the time would seem ripe for a Proustian reunion. Can activation of reward regions enhance memory?

In this issue, Wittmann and colleagues answer "yes" (Wittmann et al., 2005). They show that in humans reward anticipation boosts recognition memory and suggest an underlying neural mechanism. The investigators tackled the question by splicing together two functional magnetic resonance imaging (fMRI) tasks: one designed to evoke reward anticipation, the other to elicit memory encoding. Specifically, they presented pictorial cues (i.e., either living or nonliving things) that signaled whether subjects could earn money or not in an upcoming number judgment task. After a few seconds' delay, subjects attempted to answer whether a rapidly presented target number was greater than 5 before it disappeared. As in prior work, analysis of brain data indicated that reward-predicting cues activated subcortical structures such as the midbrain and ventral striatum.

Immediately after the scan, the investigators surprised subjects with a memory test for the pictorial cues, followed by another test 3 weeks later. Had reward anticipation enhanced cue recognition? Apparently, but only at the 3 week test—implicating long-term consolidation. Analysis of brain data indicated that midbrain activation increased when subjects formed memories of reward cues. Hippocampal activation, on the other hand, increased for both rewarded cues and cues that were subsequently remembered. Together, these findings suggested that reward anticipation modulates, but does not mediate, consolidation. In other words, reward circuits can whisper in the ear of memory circuits, with long-term consequences.

The new brain imaging results support a developing molecular story. Physiological studies suggest that the hippocampus consolidates memories, possibly via long-term potentiation (LTP). Dopamine sustains hippocampal LTP, while dopamine blockade halts it (Huang and Kandel, 1995). Thus, increased dopamine release during reward anticipation might facilitate memory formation. The story appears consistent with the present data, with a few caveats. First, to sustain LTP, dopamine must be available when neurons fire. But in this study, the cue (presumed to initiate firing) preceded anticipation (presumed to elicit dopamine release). Thus, it may turn out that reward anticipation has an even stronger effect on memory for targets than for cues. Second, although the authors focus on the substantia nigra, tract-tracing studies indicate that the ventral tegmental area (VTA) of the midbrain provides more prominent dopaminergic input to the hippocampus. The VTA also modulates the ventral striatum, which showed increased activation during reward anticipation. One cannot distinguish midbrain nuclei at the present study's spatial resolution (6 mm slices), but improved resolution could undoubtedly make such a feat possible.

By bridging reward and memory literatures, these findings open new roads for exploration. First, the results parallel findings that punishment cue-induced amygdalar activation modulates hippocampal consolidation. Are these processes one and the same? While a salience account might predict so, an affective account would not. The present findings raise the interesting possibility that positive and negative anticipatory emotions may modulate memory through different routes. Second, memory for reward cues was clearly associated with activation in the midbrain and ventral striatum during reward anticipation, but not mesial prefrontal cortex activation in response to reward outcomes (Knutson et al., 2003). Thus, it may be that reward anticipation, rather than outcome, enhances cue memory. Finally, the subcortical location of modulatory activation leads one to wonder whether reward anticipation

Figure 1. Tea for Cue?
Credit: Jamil Bhanji.

can "burn in" memories under the radar of consciousness.

Either way, reward cues may clear a path to recollection. Try to remember the last time you tasted moist golden cake, infused with coffee, tea, or milk. Where were you? Who were you with? Of course, recollection is useful not only for generating French literature, but also for foraging (Ikemoto and Panksepp, 1999). One must remember not only the taste of cake, but also where it came from, in order to find more. Such a mechanism might help to explain how animals come to prefer places associated with rewards, how dopaminergic drugs can subvert that process, and even how the entire scope of an author's childhood memories could be resurrected by the taste of a tea-soaked madeleine.

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