

# The neurogenetics of remembering emotions past

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Even if you have not waded through all seven volumes of Marcel Proust's *Remembrance of Things Past* (1), you are probably familiar with its most famous scene where the narrator bites into a little cake called a madeleine, dipped in tea, and experiences a wash of vivid emotional memories. This literary moment has captured popular imagination (madeleines are now sold by Starbucks) because it so effectively captures the powerful and involuntary nature of emotional memory. Indeed, Proust's novels developed a distinction between voluntary and involuntary memories: The former involve more of our own efforts, but it is the latter, often characterized by emotions, that form the narrative of our life stories. Regarding his own flood of emotional memories Proust asked, "Whence did it come? What did it signify? How could I seize upon and define it?" Almost a century later, memory researchers are asking similar questions about what happens during an emotional event and its later retrieval. What leads us to recall such an event with effortless vividness long afterward? Further, why are some of us more likely to remember emotional memories with Proustian vividness than others or more likely to relive traumatic events? Echoing Proust's thesis that one's emotional memories are closer to the heart than to the mind, a study in this issue of PNAS by Rasch et al. (2) suggests that individual differences in the *ADRA2B* gene that codes the  $\alpha 2B$  adrenoceptor, which plays an important role in vasoconstriction and blood pressure regulation, is also related to brain activation patterns underlying heightened emotional recall.

## Genes, the Amygdala, and Emotional Memories

It has been known for some time that the amygdala is a key brain region for the formation of emotional memories. The modulation hypothesis of emotionally enhanced memory proposes that noradrenaline-related activity in the amygdala influences other brain regions implicated in emotional memory formation (3). According to this model, emotional arousal is associated with the release of norepinephrine from the locus coeruleus in the brainstem, activating adrenergic receptors in the amygdala, which in turn enhances con-

solidation of memory for emotional events. In humans, previous research has shown that pharmacological manipulation of adrenoceptors affects memory for emotional but not neutral events (4), a finding consistent with the role of the amygdala in the formation of memories for arousing events (e.g., ref. 5). Recent research by de Quervain et al. (6) has shown that a variant of the *ADRA2B* gene that codes the  $\alpha 2B$ -adrenergic receptor is linked to individual differences in emotional memory. Moreover, trauma survivors with the *ADRA2B* deletion variant are more likely to re-experience traumatic events (6). Following up on these findings, the results reported by Rasch et al. (2) are the first to tie the deletion variant of the gene to patterns of amygdala activation during the encoding of emotional memories. Across all participants, the most arousing images were most remembered 10 min later in a subsequent free recall task. In addition, deletion variant carriers showed greater amygdala activation than noncarriers when viewing emotionally arousing images and greater functional connectivity between the amygdala and insula at the time of encoding. As the de Quervain et al. (6) study showed, deletion variant carriers were also more likely to remember them vividly. Together, the papers by de Quervain et al. (6) and Rasch et al. (2) break new ground in linking genetic variations in noradrenergic transmission with individual differences in amygdala activation and the enhanced retention of emotional memories.

## Feeling Emotional

The precise aspect of memory formation influenced by these genetic variants remains an open question. Do carriers of the deletion variant experience greater emotional memory because they experience emotional events more acutely and with greater vividness in the first place or because they engrave the traces of memory more deeply after the event? In a study by de Quervain et al. (6), the authors concluded that the genetic variant does not affect initial arousal levels at encoding because participants with the deletion variant did not rate the emotional images as more arousing overall than noncarriers. Rather, they suggested that activation of noradrenergic transmission, associated with emotional arousal, influences memory formation

after the emotional event. Yet self-reported ratings of how arousing an image is may capture more reflective than body-based processes. By contrast, the amygdala is associated with relatively reflexive arousal influences during encoding (7) and emotional memory formation is associated with peripheral sympathetic activation (8). Given the  $\alpha 2B$  adrenoceptor's role in mediating sympathetic influences on peripheral bodily response, greater amygdala response in deletion variant carriers suggests that individual differences in adrenoceptor expression may nevertheless be associated with greater physiologic arousal at the time of encoding.

## Seeing Emotional

The often-quoted "flashbulb" quality of emotional memories refers to their relatively enduring nature, as if they were photographically etched in the brain. Although the permanence of emotional memories has been challenged, growing evidence suggests that the "flash" of the flashbulb, the emotional spotlight cast on salient events, enhances the experience of an emotional event and subsequent memory. This flash arises from the mutually enhancing effects of greater sympathetic arousal (7, 8), amygdala recruitment (7, 9), increased attention (7, 10), and amplified perceptual processing (7, 11, 12). These interacting elements, known as "motivated attention" (11), may produce a more vivid perceptual experience, which in turn may contribute to emotional memory. Indeed, administration of the  $\beta$ -adrenergic antagonist propranolol and agonist riboxetine have opposing effects on attention, suggesting a role of noradrenergic systems in emotional focusing of attention and awareness (13). Greater amygdala recruitment in individuals with the deletion variant of the *ADRA2B* gene may then relate to amygdala-modulated enhancement of attention (7) and, as a consequence, enhanced memory for emotional events.

Beyond the influence of motivated attention at the time of an emotional event, vivid memory is also associated

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with arousal induced after encoding. Arousal during and after encoding interact to influence long-term memory consolidation (14). Building on animal research using post-encoding manipulations of adrenergic activation of the amygdala (3), human studies have shown that memory is enhanced for neutral items when emotional arousal is induced after encoding (15) and is likewise influenced by post-encoding pharmacological manipulations of norepinephrine (16). Thus, as Rasch et al. (2) suggest, variations in the *ADRA2B* gene may also be activating noradrenergic systems influencing longer-term consolidation processes that contribute to enhanced memory (3). Since Rasch et al. (2) examined amygdala responses during encoding, and tested memory recall only 10 min after the encoding task, the role of *ADRA2B* contributions to longer-term consolidation processes remains unclear. The relation between individual differences in variants of the *ADRA2B* gene, amygdala activation related to post-encoding arousal, and long-term memory consolidation is an important area for future research.

### Emotions and Involuntary Memory

Counter to Proust's introspective observations of the nature of memory, there is evidence that encoding of remembered emotional events is not entirely effortless. Although differences in the degree of memory rehearsal have been found insufficient to account for differ-

ences in emotional memory (17), memory for arousing events has been associated with activity in frontal regions that mediate explicit semantic elaboration at encoding (18). Yet convergent evidence suggests that the amygdala-centered systems tapped by the present study are at least partly

## Variations in the *ADRA2B* gene fail to predict memory for neutral items.

independent of frontally mediated voluntary memory. fMRI evidence indicates that activity in frontal-hippocampal networks, associated with controlled encoding processes, predicts memory for less arousing events (19). These networks are functionally distinct from amygdala-hippocampal networks that are active during encoding of highly arousing events (19). Thus, the fate of neutral and even low-arousal emotional memories may be determined more by influences of prefrontally mediated semantic associations on hippocampal activity. The special nature of emotional memory systems is further supported by the finding that variations in the *ADRA2B* gene fail to predict memory for neutral items (6), just as adrenergic antagonists impair

memory selectively for emotional but not neutral events (4). Finally, neurogenetic data further support the view that emotional memory is largely independent of voluntary memory for neutral events. Age-related decline of prefrontally mediated executive functions have been linked to genetic polymorphisms mediating catecholamine availability, such as the *COMT* gene implicated in dopamine metabolism (20). By contrast, emotionally enhanced memory is spared in the face of executive function and memory decline in normal aging (21).

Proust conjectured that emotional memories are more akin to a bodily reflex than to the higher-level meaning-making systems that drive voluntary memory. The finding that genetic polymorphisms in adrenoceptors related to regulating blood pressure are further associated with individual differences in amygdala activation and emotion-enhanced memory is consistent with Proust's view. Such findings point to genetic influences on an evolutionarily older emotional memory system, one that was present in animal brains even before deep semantic elaboration and a complex sense of self came onto the evolutionary scene. Such a genetically endowed motivated memory system ensures that memory retention is modulated by memory importance (3, 4). Genetic variation in this system provides one account of why emotional memories can remain more timeless for some than for others.

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