Similar neural mechanisms for emotion-induced memory impairment and enhancement

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Concerning emotion's influence on memory, the psychologist Henri Piéron observed that "a violent emotion may reinforce memory, and give rise to indelible associations" (1). Our common experience (typically with emotions less intense) also tells us that emotional events tend to be well remembered, and extensive scientific evidence confirms anecdotal observations that emotional arousal can strengthen memory. In the past decade, neuroscience has witnessed a compelling convergence of evidence from human and animal subject studies regarding the neurobiology of emotion-enhanced memory. Key among the neurobiological players so far identified are endogenous stress hormones (in particular, the adrenergic hormones epinephrine and norepinephrine) and an almond-sized structure deep in the medial temporal lobe called the amygdala. The evidence suggests that endogenous stress hormones, released by emotionally arousing events, feed back directly or indirectly to the amygdala to amplify long-term memory storage of the events that induced their release (2).

When it comes to memory, however, emotion is a double-edged sword. It may enhance or impair memory, depending on many factors. Even different aspects of a single emotional experience may be retained very well by the memory, or seemingly lost from it entirely. The amnestic potential of emotional arousal has received less attention from neurobiologists than has its memory-enhancing potential. Into this relative void comes a new report by Strange *et al.* (3) in this issue of PNAS, which combines in a single *tour de force* psychological, pharmacological, and neuropsychological evidence to implicate, in emotion-induced amnesia, mechanisms similar to those involved with emotion-induced memory enhancement.

Strange *et al.* began by establishing an experimental procedure producing both memory-enhancing and -impairing effects reasonably attributable to emotional arousal. Subjects viewed brief lists of nouns presented for 1 s every 3 s. The lists were composed mostly of semantically related, emotionally neutral words. "Emotional oddballs" (aversive words such as "scream," "murder," and "morgue") determined by independent judges to be significantly more emotional than the neutral words were interspersed within the lists. After a short delay, subjects freely recalled as many words as they could from the just-seen list, before continuing with the next list. Results from the lists were pooled. Subjects recalled the emotional words ("E" words) significantly better than they did the neutral words. Furthermore, subjects recalled the words presented immediately before the E words (neutral "E-1" words) significantly worse than they recalled the other neutral words. Control procedures substituting "perceptual oddballs" (words in the same semantic category, but in another font) or "semantic oddballs" (words independently judged to be semantically unrelated to the other words in the list) for the emotional oddballs provided reasonable evidence that both the enhancing effect for the E words and the impairing effect for the E-1 words resulted from the emotional character of the E words. Thus, the experimental procedure establishes both an emotion-related memory enhancement (for the E words) and an emotion-related retrograde amnesia of a few seconds' duration.

Do adrenergic and amygdala mechanisms participate in emotion-induced memory impairment?

Having established this procedure, Strange *et al.* asked whether adrenergic and amygdala mechanisms known to participate in long-term memory enhancement by emotion (4–9) also participate in the mnemonic effects they observed. They addressed the first question by administering the β-adrenergic antagonist propranolol or a placebo to healthy subjects before list learning. They addressed the second question by testing a rare patient with bilateral, apparently selective amygdala damage, resulting from Urbach–Wiethe disease, and matched control subjects. The findings of both experiments were similar: β-adrenergic blockade and bilateral amygdala damage blocked both the enhanced memory of the E words and the impaired memory of E-1 words (and of E-2 words, in the experiment involving propranolol). In both experiments, Strange *et al.* also found in control subjects a significant coupling between the enhancing and impairing effects of seeing an emotional word: the more likely an E word was remembered, the more likely the E-1 and E-2 words were not. Both propranolol and amygdala lesions eliminated this coupling. These results implicate two key neural elements crucial to enhanced long-term memory by emotion (β-adrenergic activation and the amygdala) in relatively short-term enhancement of memory by emotion, as well as in memory impairment by emotion.

It is the strong parallel to prior studies of emotionally influenced, long-term memory that is perhaps most surprising about the new results. In addition to involving relatively short-term memory processes, the experiments of Strange *et al.* involved far less-arousing stimuli than are typically used in studies of amygdala and adrenergic mechanisms in long-term memory in humans (4–8). Also, unlike these prior studies, they involved encoding instructions to the subjects and used procedures making subjects aware throughout that their memory would be tested. Each of these important variables could well influence the outcomes. Thus, it is not at all necessary that propranolol administration and amygdala lesions should produce such similar effects in this study as in the previous studies of their role in long-term, emotionally influenced memory. But they do, and this simple fact should force us to carefully reexamine our ideas about how exactly β-adrenergic and amygdala-based mechanisms participate in memory for emotionally arousing events.

The results of Strange *et al.* raise at least as many interesting questions as

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they answer. For example, animal research involving postlearning administration of β-adrenergic antagonists or amygdala stimulation strongly points to involvement of these mechanisms in consolidation of memory for emotional events (9), and it is for this reason that previous studies with human subjects generally focused on long-term (consolidated) memory (4–8). The findings of Strange *et al.* are consistent with the possibility that at least some of the effects seen at longer retention intervals result from an influence of β-adrenergic blockade and/or the amygdala on short-term memory processes, on encoding processes, or on enhanced attentional processes that may occur during encoding of an emotional event (10, 11). A second issue concerns the fact that propranolol not only abolished the retrograde amnesia associated with the E words, but it reversed it. Subjects under propranolol recalled significantly more E-1 words compared with neutral words. It is not at all clear what this finding may mean. However, if it proves reliable with future experimentation, it should prove theoretically important because no parallel propranolol-induced enhancement of long-term memory for emotional material is known to occur.

The very short time course (a few seconds) of the enhancing and impairing effects of E words also raises a puzzle. As Strange *et al.* note, the time course of peripheral hormone activation is far too "sluggish" to account for the mnemonic effects observed. As a reasonable alternative, they suggest that impaired central nervous system (locus coeruleus) adrenergic activation is likely responsible for the effects of propranolol they observed. In fact, it seems that peripheral adrenergic activation, although likely critical to enhanced memory of more highly arousing events as indicated by extensive animal research (9), may not be critical to memory enhancement in relatively mildly emotionally arousing learning situations (5).

Adding to the importance and timeliness of this new paper is its evidence of significant sex-related differences in retention. Indeed, sex-related influences on both β-adrenergic and amygdala involvement in long-term memory for emotional events exist (12, 13). Strange *et al.* found that the emotion-induced memory decrement was twice as large in women as in men, and that the coupling between the memory-enhancing and memory-impairing effects of the E words was significantly greater in women than it was in men. These data add to a rapidly growing set of findings suggesting that subject sex substantially affects neural mechanisms of emotionally influenced memory (12, 13). Much work needs to be done in this area to delineate and explain sex effects. At minimum, the findings of Strange *et al.* emphasize that understanding the neural underpinnings of emotionally influenced memory now requires that we anticipate, and account for, the influence of sex.

Emotion's influence on memory is highly multifaceted, no doubt with correspondingly intricate neural underpinnings. By focusing on emotion's effects on memory in the short term, and on its ability to impair memory, Strange *et al.* have with a single shot widened the field's current focus considerably. In so doing, they have moved us closer to understanding both the beneficial and harmful effects of emotion on memory.

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