‘Significance and Remembrance’ Revisited

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Throughout 2015, the Observer *is commemorating the silver anniversary of APS’s flagship journal. In addition to research reports, the first issue of* Psychological Science*, published in January 1990, included a general article, “Significance and Remembrance: The Role of Neuromodulatory Systems,” written by neurobiologist James L. McGaugh. In that article, McGaugh — who at that time was President of APS — addressed how stress hormones interact with the brain to consolidate memories. Twenty-five years later, McGaugh, now a research professor at the University of California, Irvine, looks back on how our understanding of memory consolidation has evolved since his article was published.*

I thought that my article published 25 years ago in the first issue of *Psychological Science* was both significant and worth remembering. However, it seems unlikely that any current readers either read it or remember it. As a reminder — or introduction — the paper addressed this central issue:

“…some events are remembered well while other events are remembered poorly, if at all. An adequate neurobiological account of memory must include an explanation of this experiential fact: We need to know how the nervous system selects, from the continuous cascade of sensory events, the specific information that is to be preserved” (McGaugh, 1990).

The article summarized evidence suggesting at least a partial explanation: Stress hormones and brain systems activated by emotionally arousing experiences influence the consolidation of recently acquired memories. The memory “perseveration-consolidation” hypothesis proposed by Müller and Pilzecker (1900) and studies reporting that stimulant drugs administered after training enhance memory consolidation (McGaugh, 1966, 1973) were critical influences suggesting the hypothesis that endogenously activated systems regulate memory consolidation (McGaugh, 1989; McGaugh & Gold, 1989; McGaugh & Roozendaal, 2009).

The central findings discussed in my 1990 *Psychological Science* paper were that

1. the stress hormone epinephrine, normally released from the adrenal medulla in the abdomen in response to emotional arousal, enhanced memory when administered to rats or mice shortly after training; and
2. treatments that impaired the functioning of the amygdala blocked the memory enhancement.

Of particular significance was the finding that infusion of the beta-adrenergic antagonist propranolol into the amygdala blocked the effect of peripherally administered epinephrine. In addition, and importantly, norepinephrine infused into the amygdala after training enhanced memory, and propranolol infused concurrently blocked the enhancement. Thus, the finding of many studies discussed in that paper provided strong evidence that noradrenergic activation of the amygdala is critical in enabling emotional arousal influences on memory consolidation. Findings of recent experiments continue to strongly support this conclusion (McGaugh, 2013, 2015).

Selective Involvement of the Basolateral Amygdala in Memory Modulation

The basolateral nucleus of the amygdala (BLA) is critically involved in the influences of epinephrine and propranolol on memory. Selective lesions of the basolateral nucleus or infusions of propranolol into that nucleus block the memory-enhancing effects of epinephrine. Further, infusing norepinephrine into the BLA after training enhances memory of various learning experiences, including contextual fear conditioning and extinction as well as memory of exposure to novel objects, a task that induces only modest arousal (McGaugh, 2000, 2004).

Glucocorticoid Modulation of Memory Consolidation

The glucocorticoid stress hormone corticosterone (cortisol, in humans) released from the adrenal cortex also enhances memory when administered after training rats on several kinds of learning tasks. Further, as we found with epinephrine, selective lesions of the BLA prevent the memory enhancement provided by corticosterone. Moreover, coactivation of norepinephrine in the BLA is essential for the corticosterone effect. Propranolol infused into the BLA blocks the memory enhancement induced by peripherally administered corticosterone (Roozendaal, 2000; Roozendaal & McGaugh, 2011; Roozendaal et al., 2006).

Assessment of Norepinephrine Within the Amygdala

The interpretations proposed in the 1990 paper were based on studies investigating the effects of drugs or hormones administered systemically or infused into the amygdala shortly after training. In the 1990 study, norepinephrine release was inferred, but not assessed directly. However, more recent studies have directly assessed the amount of norepinephrine released in the amygdala. Drugs that we previously found to enhance memory (picrotoxin, naloxone) increased norepinephrine release, and drugs found to impair memory (muscimol, beta-endorphin) decreased norepinephrine release (Hatfield et al., 1999; Quirarte et al., 1998). Also, mild footshock and peripherally administered epinephrine or corticosterone increased norepinephrine release in the amygdala (McReynolds et al., 2010; Williams et al., 1998). Moreover, when given a single footshock training trial, animals that had the greatest percentage increase in amygdala norepinephrine release shortly after the training showed the best retention of the task 24 hours later (McIntyre et al., 2002).

Amygdala Interactions With Other Brain Regions

Posttraining activation of the amygdala influences the consolidation of memory for many kinds of training. In addition to enhancing the memory of footshock, activation of the amygdala enhances the memory of spatial contexts and objects as well as auditory information. Such findings strongly suggest that amygdala activation modulates memory processes via its projections to brain regions involved in processing different kinds of experiences (Chavez et al., 2013; LaLumiere et al., 2003; Malin & McGaugh, 2006; McGaugh, 2004; Packard et al., 1994). In support of this view, we found that noradrenergic activation of the amygdala that enhanced memory also increased hippocampal expression of the immediate-early gene Arc that is implicated in regulating synaptic plasticity (McIntyre et al., 2005; McReynolds et al., 2010).

Emotional Arousal and Memory in Human Subjects

Studies of human brain imaging have shown that memory for emotionally arousing information is correlated with activation of the amygdala during training. PET and fMRI imaging have yielded comparable results (Cahill et al., 1996; Canli et al., 2000). In addition, several studies reported that emotionally arousing learning experiences induce interactions of the amygdala with other brain regions, including the hippocampus (Dolcos et al., 2004; Kilpatrick & Cahill, 2003).

Many studies have reported that inducing emotional arousal enhances memory of unrelated experiences that occurred prior to the arousal. Postlearning viewing of pleasant or unpleasant videos enhanced memory of a word list (Liu et al., 2008), and viewing an arousing video following a lecture enhanced subjects' performance on a subsequent midterm exam (Nielson & Arentsen, 2012). Human memory also is enhanced by administration of epinephrine or cold pressor stress (induced by having subjects hold an arm in ice water) after learning (Cahill & Alkire, 2003; Mayheu et al., 2004). Further, memory performance correlated with levels of cortisol and alpha-amylase, a biomarker for adrenergic activity assessed after training (Segal & Cahill, 2009; Smeets et al., 2009). In addition, administration of propranolol blocks the memory-enhancing effect of emotional arousal induced by viewing arousing photos associated with an emotionally arousing narrative (Cahill et al., 1994).

Novel Support for an Old Idea

The idea that emotional arousal influences memory is, of course, not new. Four centuries ago Francis Bacon noted that "…memory is assisted by anything that makes an impression on a powerful passion…" (Bacon, 1620/2000). The findings discussed in my paper in *Psychological Science* 25 years ago — and updated and amplified by more recent findings — provide strong support for Bacon's observation as well as for some neurobiological understanding of how emotional arousal assists the preservation of our significant experiences. œ

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