Emotional arousal and enhanced amygdala activity: New evidence for the old perseveration-consolidation hypothesis

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Commentary

Just a little over a century has passed since Müller and Pilzecker (1900) proposed the "perseveration-consolidation" hypothesis suggesting that neural activity initiated by newly learned information perseverates for a while and that such perseveration is critical for converting new memories into lasting memories and the brain regions essential for such conversion, "perseveration" has been dropped from the hyphenated hypothesis and has not remained an explicit focus of research and theory concerning memory consolidation (McGaugh 1999, 2000).

The essential experimental evidence supporting the memory consolidation hypothesis is that the memory-influencing effectiveness (i.e., impairment or enhancement) of treatments administered after training decreases as the training–treatment interval is increased. Such findings do not require an assumption that the treatments act by altering perseverating neural activity, as many kinds of neural alterations might be (and probably are) responsible for time-dependent effects of post-training treatments. Although it is now generally accepted that memories are formed by the action of processes occurring over time after learning, it is also generally assumed that such processes may involve many sequential cellular events as well as sequential functioning of different brain systems (McClennan et al. 1995; Squire and Alvarez 1995; Izquierdo et al. 2004).

The findings of the study by Pelletier et al. (2005) in this issue of Learning & Memory, provide compelling evidence suggesting that it may now be appropriate to restore "perseveration-" to the consolidation hypothesis. Using extracellular multiple microelectrode arrays, Pelletier and colleagues recorded the activity of neurons in the basolateral amygdala (BLA) of cats before and after a mild footshock administered for inhibitory avoidance training. The firing rate of the neurons, as well as the synchrony of the firing, increased significantly after the footshock, peaked at over half an hour later and did not return to baseline level until over 2 h after the footshock. This general pattern of increased post-footshock activity was observed in approximately half of the BLA neurons that were recorded and was more prominent during slow-wave sleep than during wakefulness. Interestingly, the activity of some neurons peaked shortly after the footshock, whereas the activity of most cells peaked ~40 min after the footshock. As Pelletier et al. (2005) note, this evidence of long-lasting (i.e., perseverating) increased firing of BLA neurons induced by footshock training fits well with the extensive evidence that the BLA is critically involved in modulating the consolidation of emotionally arousing experiences (McGaugh 1990, 2004; Paré 2003).

It is well established that adrenal stress hormones released by emotionally arousing experiences modulate memory consolidation. Systemically administered corticosterone produces dose-dependent and time-dependent enhancement of retention of a wide variety of training tasks, including inhibitory avoidance (McGaugh and Roozendaal 2002). These adrenergic and glucocorticoid treatments are ineffective in influencing memory when administered several hours after training. Importantly, in relation to the findings of Pelletier et al. (2005), adrenergic and glucocorticoid effects on memory consolidation are mediated by actions involving the BLA. Selective lesions of the BLA or adrenoceptor antagonists infused into the BLA block the memory-modulating effects of systemically administered adrenal stress hormones, and infusions of adrenoceptor agonists (e.g., norepinephrine) and glucocorticoid receptor agonists administered selectively into the BLA immediately after training produce dose-dependent enhancement of memory consolidation (McGaugh and Roozendaal 2002). Systemically administered adrenal stress hormones also increase the release of norepinephrine (NE) in the amygdala (Williams et al. 1998; McIntyre et al. 2004). Additionally, in rats given inhibitory avoidance training, NE levels in the amygdala increased immediately after the training and did not decline to baseline level for several hours. NE levels assessed within 90 min after training correlated highly with subsequent retention performance (McIntyre et al. 2002). Such findings support the general hypothesis that the adrenal stress hormones released by training-induced emotional arousal enhance memory consolidation by increasing both the amount and duration of noradrenergic activation within the amygdala (McGaugh and Roozendaal 2002).

As Pelletier et al. (2005) note, the duration of increased BLA electrophysiological activity seen after inhibitory avoidance training fits well with the evidence from experiments investigating the effects of stress hormones and training-induced emotional arousal on NE release and memory (Paré 2003). Thus, it is tempting to suggest that the emotional arousal-induced increase in BLA noradrenergic activity and neuronal activity may be causally related. The increase in NE activity may directly affect neuronal firing of GABAergic local-circuit cells as well as projection cells within the BLA. Although it is also possible that the BLA neuronal firing might increase NE release by feedback to presynaptic adrenergic receptors or to brain stem noradrenergic sources (locus coeruleus and/or nucleus of the solitary tract), this seems unlikely, because NE levels increase quickly and peak within 15–30 min after inhibitory avoidance training, whereas the peak of the increase in BLA firing reported by Pelletier et al. (2005) occurred later than that in most cells recorded. However, as the activity of a minority of neurons peaked within seconds after the footshock training, the possibility that such early neuronal ac-
tivity might affect NE release cannot be excluded. This issue might be investigated by infusing lidocaine into the BLA after training. As prior studies have reported that reversible inactivation of the BLA with lidocaine or tetrodotoxin either immediately or within several hours after training impairs memory (Buchere et al. 1992; Parent and McGaugh 1994), it would be of interest to know whether such lidocaine infusions alter NE release within the amygdala.

As noted above, there is considerable evidence that NE activity within the BLA plays an essential role in mediating the influence of emotional arousal and stress hormones on memory consolidation. Does the increase in BLA activity induced by training also play a critical role? Although Pelletier et al. (2005) did not investigate this question, they interpreted their findings as suggesting that the increase in post-training BLA activity may enhance memory consolidation by influencing neuroplasticity in other brain regions. Extensive evidence from pharmacological studies indicates that the BLA modulates memory consolidation via its projections to other brain regions (McGaugh 2002). There is also extensive evidence that the BLA inactivation of neural activity in other brain regions is generally well supported by both electrophysiological and behavioral evidence. The evidence is synchrony of the increased BLA activity following the emotional arousal occurred. It is the first to investigate the sustained time course and increased activity for the induction of long-term potentiation (LTP) in the dentate gyrus (Ikegaya et al. 1994, 1997; Akirav and Richter-Levin 1999; Frey et al. 2001). Lesions of the amygdala also block stress-induced influences on hippocampal LTP (Kim et al. 2001). Electrical stimulation of the BLA enhances LTP in the cortex and dentate gyrus of the hippocampus (Ikegaya et al. 1995; Akirav and Richter-Levin 2002; Dringenberg et al. 2004; Nakao et al. 2004). Previous studies have also reported that post-training electrical stimulation of the amygdala can modulate memory consolidation and that such effects are mediated by projections to other brain regions (Gold et al. 1975; Liang and McGaugh 1983).

Although other investigators have observed effects of averse training (using footshock) on the firing of amygdala neurons after training (Quirk et al. 1995; Maren 2000) and during retention testing (Chang et al. 2005), the study by Pelletier et al. (2005) is the first to investigate the sustained time course and increased synchrony of the increased BLA activity following the emotional arousal induced by inhibitory avoidance training. Evidence from human brain imaging studies suggests that amygdala activity during encoding of emotionally arousing material influences long-term memory via influences involving hippocampal/parahippocampal regions (Cahill et al. 1996; Dolcos et al. 2004; Kilpatrick and Cahill 2003), but such studies have not as yet investigated the involvement of amygdala activity occurring after encoding.

Thus, the proposal by Pelletier et al. (2005) that the arousal-induced increases in BLA neuronal activity may promote plasticity in other brain regions is generally well supported by both electrophysiological and behavioral evidence. The evidence is also consistent with their hypothesis that, "... the memory-modulating role of the BLA would not depend on the specific activation of particular groups of BLA neurons, but on the activity patterns taking place in BLA projection sites when emotional arousal occurred." An important implication of this hypothesis is that training must also induce neuronal processes in other brain regions that continue for several hours after training and remain susceptible to sustained BLA influence. Although this implication is supported by the findings of many studies reporting time-dependent effects of post-training treatments affecting the BLA, the findings reported here by Pelletier et al. (2005) are the first to provide evidence that emotionally arousing training induces perseverating neural activity in the BLA. These novel and important findings suggest that it may be appropriate, perhaps even necessary, to re-hyphenate Müller and Pilzecker’s (1900) “perseveration-consolidation hypothesis” and treatment augmentation hypothesis: Müller and Pilzecker, 1900. Br. J. Psychol. 1: 287–288.
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*Learn. Mem.* 2005 12: 77-79
Access the most recent version at doi:10.1101/lm.93405

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