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Bidirectional synaptic plasticity can explain bidirectional retrograde effects of emotion on memory

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Abstract: Emotional events can either impair, or enhance, memory for immediately preceding items. The GANE model explains this bi-directional effect by a glutamate "priority" signal that modulates noradrenaline release depending on arousal state. We argue for an alternative explanation: that priority itself evokes phasic noradrenaline release. Thus, contrasting E-1 memory effects are explained by a mechanism based on the Bienenstock-Cooper-Munro theory.

An emotional stimulus is typically well-remembered, but also influences memory for temporally adjacent events. In humans, we demonstrated an emotion-induced retrograde *impairment* of memory in the context of shallow encoding of word lists containing an occasional emotional (E) noun (Strange, Hurlemann, & Dolan, 2003). This retrograde disruption for "E-1" nouns appears to be mediated by the amygdala via a noradrenergic (NE) mechanism, as it is blocked by the β-adrenergic antagonist propranolol (Strange, et al., 2003). However, subsequent studies have shown that, if the encoding task requires that attentional weight be given to each E-1 stimulus, these stimuli show memory

enhancement (Anderson, Wais, & Gabrieli, 2006; Knight & Mather, 2009). In their **Target Article**, Mather et al. propose that for tasks involving attention to E-1 items, this "priority" signal is mediated by glutamate. In a state of arousal, this elevated glutamate level associated with highly active neural representations stimulates greater NE release, leading to enhanced encoding of E-1 stimuli.

We propose that the opposing retrograde effects of emotion on memory can be explained by an alternative, more simple model. We propose that "priority" itself is coded by phasic NE release in the brain. Attending to task-relevant cues has been shown to increase activity in the locus coeruleus (LC) in non-human primates (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994). Thus, high "priority" E-1 encoding is likely to be associated with moderate levels of LC activity (Figure 1a, bottom panel). Given that enhanced memory for emotional items is blocked by propranolol, we assume that these emotional items provoke LC activity (Figure 1a, bottom panel). Because of the aversive nature of the E stimuli, this LC activity is likely to be greater than that evoked by task-relevant E-1 items. By contrast, in the case of low "priority" E-1 encoding, E-1 items trigger minimal LC activity (Figure 1a, top panel).

The bi-directional effects of emotion on memory for E-1 items can then be explained by a non-linear relationship between LC activity to E-1 items and memory encoding. According to the Bienenstock-Cooper-Munro model (Bienenstock, Cooper, & Munro, 1982), when the postsynaptic cell is weakly depolarised by other inputs, active synapses undergo long-term depression (LTD) as opposed to long-term potentiation (LTP). The modification threshold, θ_m, is the measure of post-synaptic activity that determines the direction of synaptic-efficacy change. In this scheme, if postsynaptic activity is below θ_m, but above baseline, synaptic efficacies are weakened. Conversely, if post-synaptic activity exceeds θ_m, synapses are strengthened. In Figure 1b, we apply this model to E-1 memory encoding (red curve). For low priority E-1 items, post-synaptic activity is below θ_m at the time of LC responses to the E noun, leading to a weakening of the efficacy of synapses engaged during E-1 encoding (red curve in Figure 1b). For high priority E-1 items, post-synaptic activity is already relatively high (above θ_m) when the E stimulus is

presented, yielding memory enhancement. Note that the bi-directionality of this proposed effect is dependent on the presentation of E items. The black curve in Figure 1b shows memory for a stimulus that precedes a *neutral* (N) item (*i.e.*, an N-1 stimulus) plotted as a function of the LC activity to this stimulus. Obviously, if for any reason, this "N-1" stimulus evokes LC activity, its memory will be enhanced, but not to the level of enhanced E-1 memory. Importantly, N-1 memory will not be impaired even if it is low priority.

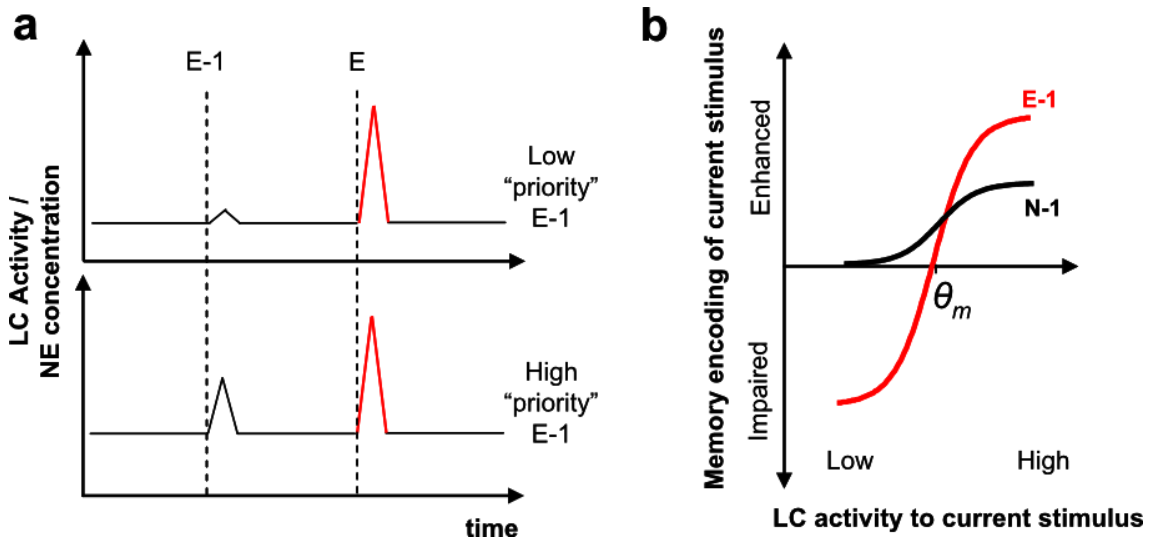

Figure 1. Alternative model for bi-directional retrograde effects of emotion on memory. a. LC responses are illustrated schematically to the presentation of two pairs of E-1 and E items (stimulus onset is indicated by vertical dashed lines). If the E-1 item is of high priority (*i.e.*, the encoding task requires attention to this item), the LC response is higher than to a low priority E-1 item. Subsequent presentation of the E item triggers greater LC activity. b. Hypothesised likelihood of encoding the current neutral stimulus, as a function of LC activity to that stimulus, depending on whether the subsequent stimulus is emotional (red curve) or neutral (black). If the subsequent stimulus is emotional (*i.e.*, triggers large NE release), low E-1 LC activity is more likely to lead to subsequent forgetting of the E-1 stimulus. θ_m : modification threshold.

Thus, applying a well-validated model of the bi-directional nature of synaptic plasticity (Bienenstock, et al., 1982) can fully explain retrograde memory effects of emotion in a parsimonious way. The change in synaptic efficacy most likely occurs within a limited brain circuit involving amygdala and hippocampus (Strange & Dolan, 2004), with NE input from the LC. It will be interesting to test whether contexts proposed to modulate θ_m,

such as stress (Kim & Yoon, 1998), will alter the direction of memory modulation for E-1 items for a given encoding task. Interesting, blocking β-adrenergic receptors with propranolol does not abolish the emotion-induced retrograde amnesia for low priority E-1 stimuli, but actually enhances memory for these E-1 items (Strange, et al., 2003). It is tempting to speculate that propranolol decreases θ_m (*i.e.*, shifts the red curve in Figure 1b to the left), such that low levels of LC activity to low priority E-1 nouns become associated with better memory.

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