Commentary on Mather, M., Clewett, D., Sakaki, M., & Harley, C.W. (in press). Norepinephrine ignites local hot spots of neuronal excitation: How arousal amplifies selectivity in perception and memory. Behavioral and Brain Sciences.

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Importance of amygdala noradrenergic activity and large-scale neural networks in regulating emotional arousal effects on perception and memory

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Abstract: Mather and colleagues postulate that norepinephrine promotes selective processing of emotionally salient information through local “hotspots” where norepinephrine release interacts with glutamatergic activity. However, rodent and human findings show that norepinephrine is ineffective in modulating mnemonic processes in absence of a functional amygdala. We therefore argue that emphasis should shift towards modulatory effects of amygdala-driven changes at the network level.

Emotional arousal enhances memory of currently relevant, i.e., salient, information, whereas it can impair memory of irrelevant information (Mather & Sunderland, 2011; Bennion et al., 2013). Mather et al. formulate the interesting hypothesis that when norepinephrine (NE) release coincides with high glutamatergic activity within an activated brain region or neuronal ensemble, NE release is further increased, resulting in locally enhanced neuronal activity and better memory. In contrast, when NE release does not coincide with high glutamate levels, NE suppresses neuronal activity, resulting in memory impairment. Although their model incorporates interactions at the systems level, it puts strong emphasis on local processes, creating NE "hotspots". Here, we argue that such primarily local effects underestimate the importance of modulatory influences of the amygdala on encoding and consolidation of information throughout the network, and that without a functioning amygdala, such NE hotspots might be unable to affect local mnemonic processes.

According to the widely accepted 'amygdala modulation hypothesis', basolateral amygdala (BLA) activity enhances memory of emotionally arousing experiences by influencing neural plasticity mechanisms in target regions elsewhere (McGaugh, 2002). In rodents, pharmacologically enhancing or reducing noradrenergic activity within the BLA, i.e., mimicking different arousal conditions, is sufficient to alter training-associated neural plasticity in distal brain regions (McIntyre et al., 2005; Beldjoud, Barsegyan, & Roozendaal, 2015) and to determine whether neural representations in these other areas are being strengthened (Roozendaal & McGaugh, 2011). Recent evidence suggests that such BLA interactions with other brain regions not only modulate the strength of memory, but are also importantly involved in regulating memory precision (Ghosh & Chattarji, 2015), and that NE activity in particular may be the driving force behind improved accuracy (Barsegyan, McGaugh, & Roozendaal, 2014). Human neuroimaging research corroborates these findings by showing that amygdala activity during encoding of emotionally arousing stimuli predicts enhancement of hippocampus-dependent memory (Hamann, et al., 1999; Canli et al., 2000). ß-Adrenoceptor blockade during encoding abolishes the emotional memory enhancement effect (Cahill et al., 1994) and suppresses memory-related amygdala activity (Strange & Dolan, 2004). Amygdala-

hippocampal connectivity, furthermore, is stronger for emotionally arousing than for neutral stimuli (Dolcos, Labar, & Cabeza, 2004), and the dominant directionality of this connectivity is indeed from amygdala toward hippocampus (Fastenrath et al., 2014).

Critically, amygdala-NE interactions *selectively* enhance memory for emotionally arousing as compared to neutral stimuli (e.g., Cahill et al., 1994). Mather et al. posit that the amygdala modulation hypothesis explains this selectivity in terms of a trade-off in which resources are shifted toward the emotional stimuli. However, recent findings indicate that there may be more to it than a simple trade-off. For instance, Lovitz & Thompson (2015) show that intra-BLA infusion of the β-adrenoceptor agonist clenbuterol induces a long-term increase in excitability of hippocampal neurons when administered after emotionally arousing inhibitory avoidance training, but that clenbuterol decreases hippocampal excitability in non-trained control animals. These findings strongly support the idea that the impairing effects of amygdala-NE interactions on memory of non-salient/non-arousing information involve an *active* process that is dependent on the amygdala.

Converging human evidence for this notion comes from patients with damage to the amygdala. For instance, patients with Urbach-Wiethe disease (UWD), who exhibit selective calcifications in the BLA (Terburg et al., 2012), fail to show emotional enhancement of episodic memory (Cahill et al., 1995). Studies in patients with other forms of amygdala pathology furthermore revealed a deficit in up-regulating processing of emotional stimuli in higher-order visual cortices (Vuilleumier et al., 2004) as well as an impairment in increasing encoding-related hippocampal activity for emotional items (Richardson, Strange, & Dolan, 2004). Critically, UWD patients also exhibit *enhanced* memory for neutral information encountered in close temporal proximity to emotionally arousing stimuli (i.e., diminishing the impairment for such information observed in healthy controls; Strange, Hurlemann, & Dolan, 2003). One could argue that such findings remain consistent with an interpretation in terms of local hotspots of NE activity if amygdala damage would lead to a general impairment of NE signaling. However, UWD patients, although they fail to acquire conditioned responses, appear to exhibit

normal arousal responses, as evidenced by normal skin conductance and startle responses to unconditioned stimuli (Bechara et al., 1995; Klumpers et al., 2015). Thus, findings from amygdala-lesioned patients agree with animal work in suggesting that due to BLA damage, NE is ineffective in modulating local memory processes elsewhere in the brain.

Other studies have shown that stress-related hormones such as glucocorticoids also contribute to selective enhancement of emotional memories. For instance, in humans, elevating stress hormone levels after learning generally leads to consolidation benefits for emotionally arousing as compared to neutral information (Abercrombie et al., 2006; Kuhlmann, & Wolf, 2006). Rodent work has shown that NE activity within the amygdala also crucially determines the modulatory effects of stress hormones on neural plasticity and memory in distal brain regions (Roozendaal et al., 1999). The synthetic glucocorticoid dexamethasone given immediately after inhibitory avoidance training enhances long-term memory of this training in rats with an intact BLA, but dexamethasone impairs inhibitory avoidance memory if noradrenergic activity in the BLA is blocked with a β-adrenoceptor antagonist (Quirarte, Roozendaal, & McGaugh, 1997). Thus, these findings again support a critical role for BLA noradrenergic activity in determining enhancements or impairments of information storage in other brain regions.

In conclusion, local hotspots of NE activity at sites where mnemonic operations take place alone cannot explain the selectivity afforded by amygdala-driven modulatory processes. This observation, of course, begs the question what mechanism underlies these distant modulatory effects. Important clues have come from functional connectivity studies in humans, showing that modulated regions are part of distinct large-scale neural systems, such as the “salience” and “default mode” networks (Hermans et al., 2011; Hermans et al., 2014). Novel technologies for electrophysiological recordings and optogenetics in rodents are beginning to make it possible to study such networks in unprecedented spatiotemporal detail. We predict that these developments will ultimately lead to the conclusion that selective processing of arousing material results primarily from amygdala-driven changes in network properties of large-scale neural systems, rather than NE-induced local hotspots of activity.

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