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Glutamate and Norepinephrine Interaction: Relevance to Higher Cognitive Operations and Psychopathology, Commentary on Mather et al

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Abstract: Mather and colleagues present an impressive interdisciplinary model of arousal-induced norepinephrine (NE) release and its role in selectively enhancing/inhibiting perception, attention, and memory consolidation. This model will require empirical investigation to test its validity and generalizability beyond classic NE circuits as it simplifies extremely complex and heterogeneous actions including NE mechanisms related to higher cognitive circuits and psychopathology.

In the current issue, Mather and colleagues propose a molecular model, termed Glutamate Amplifies Noradrenergic Effects (GANE), through which arousal enhances or inhibits perception, attention, and memory consolidation (Mather, Clewett, Sakaki, & Harley, 2015). In this model, arousal precipitates phasic release of norepinephrine (NE) throughout the brain, but "hot spots" of NE release are generated near activated glutamate circuits, sufficient to engage low affinity β adrenoceptors, which further increase glutamate release and enhance post-synaptic plasticity by increasing cAMP signaling. The model provides an impressive

integration across several fields, but will require empirical investigation to test its validity. Furthermore, although the model is presented as universally applicable throughout brain, NE actually has very heterogeneous actions in different brain circuits. In particular, although the GANE model addresses the effects of normal arousal mechanisms in sensory cortex and hippocampus, it is important to discuss how this model may relate to NE actions in higher cognitive circuits, and to conditions of psychopathology.

The noradrenergic system plays an essential role in the pathophysiology and treatment of psychiatric disorders. For example, noradrenergic dysregulation is associated with posttraumatic stress disorder (PTSD), and α1 antagonists can reduce these symptoms (A. F. T. Arnsten, Raskind, Taylor, & Connor, 2015; Southwick et al., 1999). Many antidepressants target the noradrenergic system (Klimek et al., 1997), and α2A agonists enhance cognition in patients with attention deficit hyperactivity disorder (ADHD) (A. F. T. Arnsten & Wang, 2016). Similarly, accumulating evidence implicates glutamate in the etiology and treatment of mental disorders (Chambers et al., 1999; Krystal, Sanacora, & Duman, 2013). It is not clear whether the GANE model applies to traumatic stress conditions, as the research cited by Mather et al. utilized subtle arousing conditions, e.g. an emotional word. However, it is likely to explain several aspects of PTSD, e.g. enhancing the consolidation of traumatic events that may contribute to flashbacks and intrusive memories. However, additional, higher brain changes during trauma may not be captured by this model, as NE actions in brain are more heterogeneous than described.

Most important for human cognition, the newly evolved circuits in layer III of the dorsolateral prefrontal cortex (dlPFC) that underlie higher cognitive operations are modulated in a unique manner, that is often opposite to classic synapses in sensory cortex, amygdala and hippocampus (A. F. T. Arnsten, Wang, & Paspalas, 2012). Indeed, these newly evolved “Delay cell” circuits in the dlPFC are even regulated differently than sensory/response-related neurons within the dlPFC. For example,

Delay cell persistent firing is mediated by NMDAR with NR2B subunits that are exclusively in the post-synaptic density, not extra-synaptic as they are in classic synapses (Wang et al., 2013). Furthermore, Delay cells are only subtly influenced by AMPA receptors, and show reduced, rather than increased, neuronal firing following systemic ketamine (Wang et al., 2013). In contrast, Response feedback cells in dlPFC (likely layer V) show a more classic profile, with large AMPA receptor influences and increased firing with systemic ketamine (Wang et al., 2013). These marked differences extend to intracellular cAMP signaling events as well. In classic synapses, activation of cAMP signaling, e.g. arising from β-adrenoceptor stimulation, increases glutamate release from axon terminals and strengthens LTP post-synaptically. However, in layer III dlPFC circuits, increased cAMP signaling *weakens* connections by opening cAMP-PKA regulated potassium channels in dendritic spines (A. F. Arnsten, 2015; A. F. T. Arnsten et al., 2012). Instead, it is inhibition of cAMP signaling via post-synaptic α2A-adrenoceptors that strengthens network connectivity by closing potassium channels near the synapse (Wang et al., 2007). There is currently no evidence of NE "hot spots" in these circuits; e.g. blockade of β receptors within the primate dlPFC has no effect on working memory performance (Li & Mei, 1994), even though there are likely high levels of glutamate release in dlPFC arising from the persistent firing of these neuronal networks. Thus, the model shown in Figure 6 of Mather et al. is misleading, as it does not differentiate NE actions in classic synapses versus those in more newly evolved dlPFC circuits.

Mather et al. also provide an over-simplified discussion of NE actions at α1 adrenoceptors. Although they focus on α1 mechanisms that weaken plasticity, there are many synapses where α1 promotes synaptic actions, e.g. in somatosensory cortex (Mouradian, Seller, & Waterhouse, 1991; Waterhouse, Moises, & Woodward, 1981; Waterhouse, Mouradian, Sessler, & Lin, 2000). There are also key circuits where α1 receptor activation potentiates beta receptor actions, e.g. in amygdala, where α1 receptors facilitate β-adrenergic enhancement of memory consolidation (Ferry, Roozendaal, & McGaugh, 1999a, 1999b). These effects are opposite to those described by Mather and colleagues. Their model also does not capture the

important finding that high levels of NE release in PFC during stress decrease persistent firing and working memory abilities through stimulation of α1 receptors (Birnbaum et al., 2004). All of these actions likely have a key effect in switching control of behavior from thoughtful, flexible top-down control by PFC under conditions of safety (moderate levels of arousal), to reflexive, unconscious habits mediated by sensorimotor cortex and subcortical structures during uncontrollable stress (very high levels of arousal).

These mechanisms have particular relevance to the symptoms of PTSD, where there is extensive evidence of elevated noradrenergic activity (Southwick et al., 1999). For example, the α2 antagonist, yohimbine, worsens symptoms and induces hypofrontality in subjects with PTSD at doses that have little effect in control subjects (Bremner et al., 1997; Southwick et al., 1993). These drug actions may arise from a combination of neural events, e.g. loss of dlPFC top-down control from blockade of post-synaptic α2A receptors and increased NE stimulation of α1 receptors in dlPFC, as well as increased NE release in "hot spots" in amygdala, hippocampus and sensory cortex that may exacerbate anxiety and flashbacks (A. F. T. Arnsten et al., 2015). Thus, the GANE model may apply to NE actions in classic brain circuits, but not to higher cortical circuits where circuits are strengthened by α2A- rather than β-adrenoceptor mechanisms.

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