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Interactions of noradrenaline and cortisol and the induction of indelible memories

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Abstract: The "Glutamate Amplifies Noradrenergic Effects (GANE)" model emphasizes the role of focal glutamate-noradrenaline interactions in creating functional hotspots for prioritized processing of salient stimuli. Here, we briefly outline current evidence that synergistic action of noradrenaline and cortisol enables emotional stimuli to gain privileged access to amygdala-hippocampal circuits, eventually resulting in the formation of indelible memories and post-traumatic stress disorder (PTSD).

In their superb "Glutamate Amplifies Noradrenergic Effects (GANE)" model, Mather and colleagues (2015) convincingly argue that under conditions of arousal-induced phasic activity of the locus coeruleus (LC), locally elevated glutamate (GLU) levels amplify noradrenergic (Norepinephrine, NE) release from the LC, thus creating functional hotspots of prioritized processing that bias perception and memory. While the focus of the "GANE" model lies on stimulus salience coding through rapid GLU and NE signaling and their focal interactions, it should be emphasized that endocrine signals, including the adrenal stress hormone cortisol (CORT), brain concentrations of which

peak within minutes as a result of hypothalamic-pituitary-adrenal (HPA) axis activation (de Kloet, Joels, & Holsboer 2005), also intimately interact with NE in order to code perceptual and mnemonic priority, especially under conditions of emotional arousal.

In functional magnetic resonance imaging (fMRI) experiments, emotional arousal is frequently operationalized by exposing subjects to facial displays of emotion, which evoke responses in specific functional subdivisions of the amygdala (Goossens et al. 2009, Hurlemann et al. 2008). One established means of segregating the neuromodulatory effects produced by NE, CORT, and their interactions, is pharmacological fMRI (phMRI) (Patin & Hurlemann 2011). By combining phMRI with histoprobabilistic maps of the subregional architecture of the amygdala (Goossens et al. 2009, Hurlemann et al. 2008), it was shown that blockade of β-noradrenergic receptors with the nonspecific antagonist propranolol (40 mg p.o.) desensitized the basolateral amygdala (BLA) (Hurlemann et al. 2010), which is consistent with behavioral data indicating that propranolol (40 mg p.o.) eliminated a facilitation of declarative learning from facial feedback (Mihov et al. 2010). In contrast, enhancement of BLA reactivity with the NE reuptake inhibitor (NARI) reboxetine (4 mg p.o.) produced a response bias towards fearful faces (Onur et al. 2009). Together, these results suggest that increases in NE signaling may be essential for converting the BLA – an area of the brain controlled by powerful inhibitory circuits (Ehrlich et al. 2009) – into a fear module (Onur et al. 2009). One interpretation of these findings is that phasic increases in endogenous NE signaling *per se* might be sufficient to code stimulus salience. However, due to its pivotal role in orchestrating fear memory acquisition and storage via N-methyl-d-aspartate (NMDA) receptor-mediated long-term potentiation (LTP) (Ehrlich et al. 2009), the BLA may be a locus of extensive GLU-NE interactions, such that observations of a reboxetine-induced increase in BLA signals may, in fact, support the "GANE" model (Mather et al. 2015).

In addition to rapid neuromodulatory effects mediated by NE, emotional arousal elicits heightened adrenal release of CORT, which feeds back on the amygdala and hippocampus via activation of mineralocorticoid and glucocorticoid receptors in these regions (de Kloet et al. 2005). Experimentally, this endocrine response can be mimicked

by exogenous administration of synthetic CORT (20-40 mg p.o.), and studies based on this challenge have not only noted a desensitization of the amygdala during fear conditioning (Merz et al. 2010) and reward anticipation (Montoya, Bos, Terburg, Rosenberger, & van Honk 2014), but have also detected timing-dependent changes in hippocampal memory functions. Specifically, when coinciding with declarative memory encoding, stress levels of CORT enhance long-term recall (Buchanan & Lovallo 2001), whereas their occurrence during retrieval impairs performance (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock 2000).

Most importantly, endogenous CORT and NE signals do not act in isolation, and there is accumulating experimental evidence that co-activation of both systems under emotional arousal is crucial for facilitating amygdala-hippocampal interplay during declarative memory formation. The resultant advantage of privileged declarative encoding of salient stimuli, however, comes at the expense of reduced recall of preceding and following information. This peri-emotional amnesia is BLA as well as β-noradrenergic dependent (Hurlemann 2006, Hurlemann et al. 2005, Hurlemann, Wagner, et al. 2007, Strange, Hurlemann, & Dolan 2003) and further amplified, in both magnitude and temporal extent, by combined pre-learning administration of exogenous CORT (30 mg p.o.) and reboxetine (4 mg p.o.), thus suggesting synergistic NE-CORT interactions (Hurlemann 2008, Hurlemann, Matusch, et al. 2007). The same pharmacological intervention was found to induce a negative response bias towards fearful faces in the centromedial nucleus of the amygdala (CMA), an effect that was absent when CORT levels were augmented alone (Kukolja et al. 2008). Evidence indicates that response shifts mediated by CORT, NE, and their interactions are not restricted to the CMA but propagate to interconnected areas including the dorsal striatum, which can be prevented by blockade of mineralocorticoid receptors with spironolactone (400 mg p.o.) (Vogel et al. 2015).

Collectively, these findings argue for a reallocation of neural resources as a function of CORT and NE co-activation under emotional arousal, hence enabling prioritized access to the salience network and memory stores. Obviously, this mechanism confers costs and benefits, evident in a larger devotion of amygdala-hippocampal resources during

encoding (Kukolja, Klingmuller, Maier, Fink, & Hurlemann 2011) and prefrontal cortex (PFC) deactivation (van Stegeren, Roozendaal, Kindt, Wolf, & Joels 2010). It has been conceptualized that such co-occurrence of deficient top-down control from PFC and enhanced amygdala-hippocampal interactions under conditions of heightened CORT and NE release may result in hypermnesia for emotional events, which – when manifest in extreme forms – is pathognomonic of post-traumatic stress disorder (PTSD) (Hurlemann 2008). Converging support for this etiological model comes from preclinical (Bryant, McGrath, & Felmingham 2013) and clinical studies (Nicholson, Bryant, & Felmingham 2014), both suggesting that NE and CORT co-activation predisposes to the development of indelible memories. Future research addressing the mechanistic underpinnings of arousal-induced memory distortions in PTSD should therefore not only focus on neurotransmitter interactions between GLU and NE, as outlined by the "GANE" model (Mather et al. (2015), but also take the interplay of NE and endocrine players including CORT into perspective, which may promote long-term adaptive changes through genomic modifications in addition to rapid nongenomic effects (de Kloet et al. 2005).

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