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Research report

Fear-potentiated startle during extinction is associated with white matter microstructure and functional connectivity

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ABSTRACT

Background: Extinction of conditioned fear is an associative learning process that involves communication among the hippocampus, medial prefrontal cortex, and amygdala. Strength of connectivity between the hippocampus and the anterior cingulate cortex (ACC), and between the amygdala and ventromedial prefrontal cortex (vmPFC), may influence fear-potentiated startle (FPS) responses during extinction. Specific white matter tracts, the cingulum and uncinate fasciculus (UF), serve as primary routes of communication for these areas. Our objective was to investigate associations between FPS during extinction and cingulum and UF connectivity.

Method: Diffusion tensor imaging (DTI) and probabilistic tractography analyses were used to examine cingulum and UF structural connectivity in 40 female African-Americans with psychological trauma exposure. FPS responses during fear conditioning and extinction were assessed via electromyography (EMG) of the right orbicularis oculi muscle. Secondarily, functional connectivity analyses were performed with the seed regions of interest (ROIs) used for tractography.

Results: A significant negative association between cingulum microstructure and FPS during early extinction ($r = -.42$, $p = .01$) and late extinction ($r = -.36$, $p = .03$) was observed after accounting for the effects of age, trauma exposure, and psychopathology (post-traumatic stress disorder symptoms); this pattern was similar for early extinction and functional connectivity between these regions ($p < .05_{corrected}$). No significant correlations were observed between FPS and UF microstructure.

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Conclusions: These data indicate that structural integrity of the cingulum is directly associated with extinction learning and appears to influence functional connectivity between these regions. Decrements in cingulum microstructure may interfere with extinction learning, thereby increasing risk for the development of pathological anxiety.

1. Introduction

Pathological anxiety has been linked to deficits in extinction of learned fear responses, as indicated by data from clinical and animal studies using fear conditioning methods (Delgado, Olsson, & Phelps, 2006; Graham & Milad, 2011). Fear conditioning involves repeated pairings of a neutral (conditioned) stimulus (CS) with an innately aversive (unconditioned) stimulus (US); extinction represents a process by which the CS is repeatedly presented in the absence of the US, with the expectation that defensive, fear-related physiological responses to the cue will attenuate as learning occurs (Myers & Davis, 2007). In high- or pathologically-anxious individuals, this attenuation in fear response may be delayed or diminished. Extinction involves learning to inhibit the conditioned fear response; impairments in this inhibition learning process are thought to be an underlying mechanism of pathological anxiety (Graham & Milad, 2011; Milad et al., 2009; Norrholm et al., 2011). To address this problem, evidence-based approaches to the treatment of pathological anxiety, such as exposure therapy, incorporate techniques that facilitate extinction of cues that trigger anxiety.

Although a number of studies have compared extinction processes between anxious and non-anxious groups of individuals (e.g., Jovanovic et al., 2010; Norrholm et al., 2011) and identified relative deficiencies in anxious groups, it is also valuable to examine extinction learning as a dimensional construct. Examining individual patterns of variation in extinction in association with other neurobiological information, such as neural connectivity (both structural and functional), may give insights into vulnerability for a disorder and likewise inform treatment selection.

A network of limbic and prefrontal brain regions work in concert during extinction learning, including the amygdala, hippocampus, and medial prefrontal cortical regions, particularly, aspects of the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). The amygdala, which includes the central nucleus and basolateral complex, has been consistently associated with the physiological expression of fear during conditioning and extinction (Davis, Myers, Chhatwal, & Ressler, 2006). The amygdala complex receives inhibitory communication from both the hippocampus and ventromedial aspects of the prefrontal cortex (vmPFC; a term that references rostral aspects of the ACC or OFC) during extinction (Hartley & Phelps, 2010; Phelps, Delgado, Nearing, & LeDoux, 2004). The hippocampus is involved with contextual aspects of fear encoding, extinction, and recall of extinction (Maren, Phan, & Liberzon, 2013; Myers & Davis, 2007). This region also has reciprocal connections to the ACC, which regulates inhibition of conditioned fear responses during extinction (Lang et al., 2009).

In general, limbic-prefrontal connections appear to be essential for efficient extinction of conditioned fear-related responses; amygdala, hippocampal and prefrontal regions participate in an integrated manner during this process. The hippocampus engages in the presence of contextual stimuli and signals the need to increase or diminish inhibitory responses by the ACC. Earlier studies have demonstrated involvement of the hippocampus and ACC during extinction learning and recall (Kalisch et al., 2006; Milad et al., 2007), and a recent study highlights the importance of connections between these areas for extinction processes. Lang et al. (2009) applied electrical stimulation as the US in a fear conditioning paradigm that involved colored shapes; they found that dorsal ACC activation positively correlated with activation in the hippocampus, as well as the amygdala and OFC, during extinction (Lang et al., 2009). Animal studies further support the notion that ACC-hippocampal connections directly affect extinction. Griffin and Berry (2004) observed that, compared to rabbits without ACC lesions, ACC-lesioned rabbits continued to demonstrate conditioned responses during extinction trials and did not demonstrate the suppressed hippocampal responses that were characteristic of extinction learning (Griffin & Berry, 2004). A question that remains unexplored is whether these associations were influenced by the integrity of structural/white matter connections. The cingulum is a primary white matter connection between hippocampal and frontal regions; this region has repeatedly shown relevance to learning and memory processes (Charlton, Barrick, Lawes, Markus, & Morris, 2010; van der Holst et al., 2013; Sepulcre et al., 2008; Sexton et al., 2010).

Connectivity between the amygdala and vmPFC also appears to influence extinction, as well as general emotion regulation, as suggested by studies using functional connectivity methods. Delgado, Nearing, Ledoux, and Phelps (2008) employed a fear conditioning paradigm that incorporated an emotion regulation task; participants were instructed to use positive reappraisal strategies when presented with particular conditioned stimuli. The authors found that amygdala activation was positively coupled with activation in the vmPFC during attempts to regulate emotion (Delgado et al., 2008). Compared to anxious individuals, low trait-anxious and psychopathology-free controls have demonstrated heightened amygdala/vmPFC connectivity, whereas highly anxious individuals have shown an opposite pattern (Kim, Gee, Loucks, Davis, & Whalen, 2011; Roy et al., 2013; Stevens et al., 2013). This pattern of (decreased) functional connectivity has characterized individuals with bipolar disorder