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Persistent amygdala novelty response is associated with less anterior cingulum integrity in trauma-exposed women

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ABSTRACT

Objectives: We investigated the potential role of cingulum and uncinate fasciculus integrity in trauma-related neural hypervigilance, indexed by less discrimination between amygdala activation to novel and familiar affective images.

Participants: 22 women (mean age 21.7 ± 3.9 years) with a history of trauma, and 20 no-trauma controls (mean age 21.9 ± 4.8 years).

Measures: Trauma exposure and trauma-related symptoms were assessed during structured clinical interview. White matter integrity in the anterior cingulum, parahippocampal cingulum, and uncinate fasciculus was measured using diffusion weighted imaging. Amygdala response to novel and familiar affective scenes was measured with functional magnetic resonance imaging.

Results: Trauma-exposed women showed less discrimination between novel and familiar negative images in the amygdala compared to no-trauma controls. In trauma-exposed women, less amygdala discrimination between novel and familiar affective images was associated with less structural integrity in the anterior cingulum, but was not associated with structural integrity of the parahippocampal cingulum or the uncinate fasciculus.

Conclusions: The anterior cingulum might play an important role in impaired novelty discrimination for affective information in the amygdala. This impairment is potentially driven by inefficient habituation and could contribute to persistent behavioral hypervigilance following trauma exposure.

1. Introduction

Exposure to traumatic events can lead to lasting changes in how people respond to affective information in the environment. Many trauma survivors experience chronic hypervigilance, which behaviorally and physiologically is a state of elevated arousal, increased alertness, and constant visual scanning of the surroundings for potential threat (e.g., Dalgleish et al., 2001; Kimble et al., 2010). Hypervigilance can cause significant distress, impair functioning by reducing the attentional resources to focus on the task at hand, and contribute to the maintenance or onset of other symptoms of posttraumatic stress disorder (PTSD) such as re-experiencing and avoidance (e.g., Chemtob et al., 1988; Constans, 2005). Previous neuroimaging work has suggested that abnormal amygdala activation to salient affective information (e.g., Etkin and Wager, 2007; Yoon and Weierich, 2016) and diminished cognitive control by the medial prefrontal cortex (e.g., Bishop et al., 2004) underlie such a hypervigilant state. However, affective and cognitive processes depend on the organization and functional coordination of interconnected brain regions, rather than isolated neural activity. Although a number of studies have investigated variations in the structural connectivity of affective brain regions in trauma-exposed people (e.g., Daniels et al., 2013), as well as beginning to integrate structural and functional connectivity (e.g., Fani et al., 2016), the potential relation between white matter structure and a neural signature of behavioral hypervigilance is still unknown. Taking a multi-method approach that combines structural and functional neuroimaging, we tested a more comprehensive neural model of trauma-related hypervigilance, or over-alertness for threat in the absence of threat.

In hypervigilant states, people show impaired habituation of the affective response to information encountered in daily life, and they remain in a tonic alert and ready state even in the absence of threat. Behaviorally, this state is characterized by heightened attention to the environment, including visual scanning behavior, and heightened physiological readiness to act. Because novel information is affectively salient, by virtue of constituting potential threat, novel information initially activates the brain regions involved in the affective response and anchored by the amygdala (e.g., Balderston et al., 2011; Weierich et al., 2010). However, with repeated presentation of stimuli, this alerting response quickly habituates in healthy people. For example, fMRI studies show that the amygdala response to affective stimuli

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decreases quickly – regardless of valence (i.e., unpleasant, neutral, or pleasant) – when stimuli are presented repeatedly (e.g., Breiter et al., 1996; Fischer et al., 2003; Weierich et al., 2010). This normative reduction in amygdala response to familiar affective information is impaired in hypervigilant and other stress-related states (e.g., Andreano et al., 2014; Blackford et al., 2011; van den Bulk et al., 2016). Similarly and relatedly, people with trauma-related symptoms also fail to show discrimination between novel and familiar negative information in the amygdala (e.g., Protopopescu et al., 2005; Shin et al., 2005; Tuescher et al., 2011), as less habituation to familiar stimuli results in what essentially is a persistent novelty response. Further, PTSD is associated with abnormally persistent responses to familiar trauma-related stimuli in the lateral occipital complex, which is implicated in object recognition and is modulated by the amygdala response (Hendler et al., 2001).

Structurally, the amygdala is connected to the major white matter pathways implicated in affective processing, and in particular the cingulum and the uncinate fasciculus (e.g., Catani et al., 2012). The cingulum is a medial association pathway that connects the frontal, parietal, and temporal lobes (e.g., Beevor, 1891; Schmahmann and Pandya, 2006). Due to its many short fibers, the cingulum is composed of distinct sub-regions that are associated with different neural functions (Heilbronner and Haber, 2014; Jones et al., 2013a; Schmahmann and Pandya, 2006). Heterogeneity within the tract is further shown by minimal correlation between indices of structural integrity (e.g., fractional anisotropy) and cellular composition in distinct cingulum sub-regions (Jones et al., 2013a; Vogt et al., 2001).

The cingulum bundle can be divided into the cingulate part of the cingulum (CGC; also “anterior cingulum”) and the parahippocampal part of the cingulum (PHC; also “posterior cingulum”, although note that some studies parcellate the PHC and the posterior cingulum separately). The CGC fibers extend through the dorsal and ventral prefrontal cortices, the subgenual anterior cingulate cortex (sgACC), and the dorsal anterior cingulate cortex (dACC). Only a small portion of the fibers from the amygdala and other temporal regions terminate in the CGC. On the other hand, the majority of the PHC fibers contain axons projecting to and from the amygdala, parahippocampal gyrus, and other regions in the medial temporal lobe, with fewer fibers connecting to the prefrontal cortex or the sgACC (e.g., Heilbronner and Haber, 2014). Additionally, the uncinate fasciculus (UF) association fiber bundle carries information to and from the limbic affective regions by connecting the temporal lobe with the medial orbital frontal cortex (e.g., von Der Heide et al., 2013). The CGC and UF both are involved in affect regulation, including top-down modulation of affective responses, whereas the PHC is involved in memory creation and recall of visual scenes (e.g., Keedwell et al., 2016; Suzuki, 1996).

Basic structural studies using diffusion weighted imaging (DWI) in trauma-exposed people have been inconsistent. Some show lower structural integrity in the CGC (e.g., Daniels et al., 2013; Hu et al., 2016; Kim et al., 2006; Sanjuan et al., 2013; Schuff et al., 2011), although increased CGC integrity also has been reported (e.g., Abe et al., 2006; Kennis et al., 2015). In addition, several studies have reported that trauma exposure is associated with decreased (Choi et al., 2009; Fani et al., 2014) or increased (Zhang et al., 2012) structural integrity in the PHC. There also have been mixed findings regarding UF integrity, with some evidence for decreased UF integrity in people with trauma-related symptoms (e.g., Costanzo et al., 2016; Eluvathingal et al., 2006) and some evidence for no association (e.g., Fani et al., 2012). These inconsistencies might be attributed to the wide range of post-trauma symptom profiles, the developmental stage of the brain at the time of first trauma exposure, self-report response biases in symptom assessments, and variation among trauma types (e.g., Naifeh et al., 2008). More recently researchers have begun to test the associations between structure (i.e., white matter integrity) and function (i.e., neural activation patterns) in the affective circuitry of trauma-exposed people. For example, people with PTSD were shown to have less structural integrity of the cingulum, and a genetically-differentiated sample subset also showed poorer hippocampus – anterior cingulate functional connectivity at rest (i.e., Fani et al., 2016). Existing DWI studies have not yet tested the relation between structural integrity in the cingulum and task-based function that is consistent with over-alertness or hypervigilance in the brain.

Given that the CGC and the UF are extensively connected to prefrontal cortices and the sgACC, which are implicated in top-down cognitive control (e.g., Shin et al., 2004; Williams et al., 2006), lower structural integrity in the CGC and the UF might be associated with less habituation to affective information as the amygdala response persists for familiar information rather than habituating to repeated stimulus presentation (e.g., Wright et al., 2001). On the other hand, increased structural integrity in the PHC might reflect greater functional connectivity between the amygdala and the adjacent limbic areas (e.g., parahippocampal gyrus, hippocampus), which has been linked to increased threat sensitivity (e.g., Hahn et al., 2010).

Taken together, prior research shows that that normatively the amygdala responds to novelty in much the same way as to other affective properties (e.g., Balderston et al., 2011, Weierich et al., 2010), and also that trauma exposure can be associated with an overly alert salience response. This overactive salience response is anchored in large part by abnormally persistent amygdala activation in the absence of threat, such as when viewing familiar neutral information (Yoon and Weierich, 2016). Our primary objective was to test the relation between novelty discrimination in the amygdala, as one potential neural index of behavioral hypervigilance, and the structural integrity of relevant white matter tracts. We thus integrated diffusion weighted imaging (DWI) to measure cingulum and UF integrity, and task-based functional magnetic resonance imaging (fMRI) to measure of trauma-related “neural hypervigilance”, indexed by less discrimination between novel and familiar affective images in the amygdala. We tested two primary structure-function hypotheses. First, given the need for prefrontal cognitive control in the process of habituation we hypothesized that novelty discrimination for affective information in the amygdala would be associated with less structural integrity in the CGC, and greater integrity in the PHC. Second, we hypothesized that less amygdala habituation to affective information would be associated with less structural integrity in the UF.

2. Method

2.1. Participants

We recruited 22 trauma-exposed (TE) women and 20 women with no trauma exposure (see Table 1 for participant characteristics) from a large urban university in the northeast US. Given known sex differences in affective processing, we restricted our sample to one sex. The presence or absence of trauma exposure was assessed using the trauma exposure criterion (Criterion A) of the posttraumatic stress disorder (PTSD) module of the Diagnostic and Statistical Manual of Mental Disorders IV. All 42 participants were right-handed and eligible for an MRI scan when assessed with a standard MRI safety screen (e.g., no metal in the body, no history of claustrophobia).

2.2. Procedure

Two study sessions were conducted on two separate days. The first study session included the Structured Clinical Interview for DSM-IV (SCID) and a brief set of questionnaires. The second session was scheduled within a week of the first session and included the MRI scan. The MRI scan sequence consisted of T1-weighted structural scans, BOLD T2*-weighted task fMRI scans, and a diffusion-weighted structural scan. All procedures were approved by the Institutional Review Board