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Functional reorganization of neural networks during repeated exposure to the traumatic memory in posttraumatic stress disorder: An exploratory fMRI study

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ABSTRACT

Background: Repeated exposure to the traumatic memory (RETM) is a common component of treatments for posttraumatic stress disorder (PTSD). This treatment is based on a fear extinction model; however, the degree to which this treatment actually engages and modifies neural networks mediating fear extinction is unknown. Therefore, the purpose of the current exploratory study was to define the dynamic changes in neural processing networks while participants completed a novel adaptation of RETM.

Method: Participants were adult women ($N = 16$) with PTSD related to physical or sexual assault. Prior to scanning, participants provided written narratives of a traumatic event related to their PTSD as well as a neutral control event. RETM during fMRI consisted of 5 sequential presentations of the blocked narrative types, lasting three minutes each. Self-reported anxiety was assessed after each presentation.

Results: Relative to changes in functional connectivity during the neutral control script, RETM was associated with strengthened functional connectivity of the right amygdala with the right hippocampus and right anterior insular cortex, left amygdala with the right insular cortex, medial PFC with right anterior insula, left hippocampus with striatum and dorsal cingulate cortex, and right hippocampus with striatum and orbitofrontal cortex. Greater PTSD severity generally led to less changes in functional connectivity with the right insular cortex.

Conclusions: These results provide evidence that RETM engages and modifies functional connectivity pathways with neural regions implicated in fear extinction. The results also implicate the engagement of the right insular cortex and striatum during RETM and suggest their importance in human fear extinction to trauma memories. However, comorbidity in the sample and the lack of a control group limit inferences regarding RETM with PTSD populations specifically.

Posttraumatic stress disorder is characterized by re-experiencing, avoidance, and hyperarousal symptoms (APA, 2000) and is associated with marked quality of life impairments (Olatunji et al., 2007). To date, the most evidence-based and widely disseminated psychological treatment for PTSD is prolonged exposure (PE) (Foa et al., 1999; Foa et al., 1991). While PE is a well-supported intervention, it is of limited efficacy with only ~60% of treatment completers entering remission (Foa et al., 1999; Resick et al., 2002; Schnurr et al, 2007). Thus, research efforts directed at improving the efficacy of PE is necessary.

One important treatment component of PE is repeated exposure to the trauma memory (RETM). In PE, this is termed imaginal exposure and takes the form of the individual recounting the trauma narrative repeatedly while providing indices of distress. Therapeutic response to traumatic memory exposure is based on a fear extinction model (Foa and Kozak, 1986; Foa et al., 1991; Rothbaum and Davis, 2003): thoughts and memories of the traumatic event are conceptualized as conditioned stimuli (CS+) that trigger anxiety responses (i.e., the conditioned response) due to their association with the traumatic event (i.e., the unconditioned stimulus, US). Repeated exposure to the traumatic memory (CS+) in a safe context is theorized to weaken the predictive value of the CS + to predict the US and thereby weaken the ability of the

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traumatic memory or reminders to elicit anxiety/distress responses.

The purpose of the present exploratory study was to identify the *in vivo* neural mechanisms engaged and modified during repeated exposure to the traumatic memory. This intent was motivated by the assumptions that this would 1) provide important inferences regarding the mechanisms of treatment action and 2) facilitate development and testing of adjunctive methods to enhance these mechanisms (e.g., pharmacological agonists such as D-cycloserine). We focused on mechanisms of neural functional connectivity changes with neural regions implicated in fear extinction during analogue exposure therapy conducted during fMRI, given that exposure to the trauma narrative is based on a fear extinction model (Foa et al., 1986, 1991; Rothbaum and Davis, 2003). Extensive basic science research has demonstrated that fear extinction involves the interaction between three separate neural structures (Milad et al., 2007; Myers and Davis, 2007; Phelps et al., 2004; Sotres-Bayon et al., 2006). First, the amygdala is critical for the detection and valuation of the CS+ and for motivating the expression of fear-relevant behavioural responding. Second, the hippocampus is involved in contextual modulation of amygdala processing of the CS+, such as learning that the CS + does not predict a shock when a safety signal is present. Third, the medial prefrontal cortex (mPFC) has direct anatomical projections to the amygdala (Ghashghaei et al., 2007) and is critical for regulation of amygdala processing. Indeed, some rodent studies have found that lesion of the mPFC impairs fear-extinction (Morgan and LeDoux, 1995; Morgan et al., 1993; Morgan et al., 2003), albeit inconsistently (Myers and Davis, 2007). Based on this research, we focused our characterization of the neural mechanisms engaged and modified *in vivo* during imaginal trauma exposure on regions of the brain functionally connected with the mPFC, bilateral amygdala, and bilateral hippocampus. One important caveat, though, is that this network of three regions is likely not specific to fear extinction; indeed, these three regions are also generally implicated in salience detection (Davis and Whalen, 2001), memory (Squire, 1992), and emotion regulation (Etkin et al., 2006).

An extensive amount of neuroimaging research has focused on identifying neural mechanisms mediating PTSD (Hayes et al., 2012; Patel et al., 2012; Sartory et al., 2013). In regards to brain function during emotion processing and cognitive tasks, individuals with PTSD demonstrate greater amygdala and dorsomedial PFC activation relative to controls, and less ventral medial PFC activation relative to controls (Hayes et al., 2012). In regards to brain function during symptom provocation, which in the case of PTSD involves a single exposure to a trauma narrative (i.e.,. script-driven imagery), individuals with PTSD demonstrate greater activation of the posterior cingulate, retrosplenial cortex, dorsal anterior cingulate cortex, and striatum compared to controls (Sartory et al., 2013). When collapsed across the type of study (cognitive or emotional task studies and symptom provocation studies), individuals with PTSD demonstrate greater activation in the anterior insula, hippocampus, amygdala, and lateral frontal gyri (Patel et al., 2012). Overall, these results suggest dysfunction in regions implicated in salience detection (amygdala, anterior insula), reward valuation (striatum), emotion regulation (ventral medial PFC), cognitive control (lateral PFC), and autobiographical recall (posterior cingulate cortex). Further, these meta-analyses also implicate dysfunction within the regions implicated in fear extinction noted above (amygdala, hippocampus, and medial PFC). Accordingly, based on 1) the network of regions hypothesized to mediate fear extinction, 2) the conceptualization of RETM as a process of fear extinction, and 3) the meta-analytic findings of dysfunctional activation in amygdala, hippocampus, and medial PFC, we broadly hypothesize that RETM works through engagement and modification of functional connectivity with these three regions implicated in fear extinction.

Note that, because we use a single analogue session of repeated exposure to the traumatic memory (RETM), a therapeutic response is not expected (e.g., psychological treatment for PTSD typically lasts ~12 weeks). Thus, the current investigation is not a probe of the changes in neural mechanisms that underlie therapeutic response to RETM; instead, the current investigation probes the neural mechanisms that are engaged by the therapeutic procedure of RETM. We only examine the neural mechanism changes during RETM among individuals with a current diagnosis if PTSD and we did not recruit a trauma-exposed group without PTSD as a comparison sample. First, RETM as a treatment would not be provided to a trauma-exposed individual without PTSD, thus there would be little clinical utility of identifying neural mechanism changes during RETM among these individuals. Second, trauma-exposed individuals without PTSD exhibited resilience, thus it might expected that they would exhibit significantly different neural responses to RETM that would not necessarily be informative about the neural mechanisms of change among individuals with PTSD, which again limits the clinical utility of this comparison. Accordingly, given that this is the first investigation of the *in vivo* changes in neural mechanisms during RETM among individual with PTSD, this study is exploratory in nature, conducted specifically among individual with a current diagnosis of PTSD, and we broadly hypothesized that RETM engages and modifies functional connectivity with the key nodes implicated in fear extinction.

1. Method

1.1. Participants

Seventeen adult women with PTSD related to either physical or sexual assault were enrolled into the study. One woman moved excessively during the scan causing intractable signal artifact, and her data were subsequently removed from analyses. This resulted in a final sample of 16 participants. Table 1 lists demographic and clinical characteristics of this sample. Inclusion criteria were 1) a history of either physical or sexual assault, 2) a current diagnosis of PTSD, and 3) that participants were stable on any psychiatric medications for at least 4 weeks. Exclusion criteria included psychotic disorders, a primary substance use disorder, or internal metal objects. Participants were recruited from outpatient mental health clinics and from community wide advertisements. All study procedures were approved by the local institutional review board.

Assaultive trauma histories were characterized using the trauma assessment section of the National Women's Survey and National Survey of Adolescents (Kilpatrick et al., 2000, 2003; Resnick et al., 1993), a structured interview used in prior epidemiological studies of assault and mental health functioning among adult women and adolescents. Specific assaultive events were assessed with behaviourally specific dichotomous questions and included: 1) sexual assault (i.e., anal penetration, vaginal penetration, oral sex on the perpetrator, oral sex from the perpetrator, digital penetration, fondling, forced fondling of the perpetrator), 2) physical assault (i.e., attacked with a weapon, attacked with a stick, club, or bottle, attacked without a weapon, threatened with a weapon, attacked with fists), and 3) severe abuse from a caregiver (i.e., beaten with fists or an object to the point where bruising or bleeding occurred).

Psychological disorders were assessed with the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 2002) administered by a trained clinical interviewer and supervised by a licensed clinical psychologist. Participants additionally completed the Posttraumatic Stress Checklist-Civilian Version (Blanchard et al., 1996) and Beck Depression Inventory-II (Beck et al., 1996).