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Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder

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ABSTRACT

Many features of posttraumatic stress disorder (PTSD) can be linked to exaggerated and dysregulated emotional responses. Central to the neurocircuitry regulating emotion are functional interactions between the amygdala and the ventromedial prefrontal cortex (vmPFC). Findings from human and animal studies suggest that disruption of this circuit predicts individual differences in emotion regulation. However, only a few studies have examined amygdala-vmPFC connectivity in the context of emotional processing in PTSD. The aim of the present research was to investigate the hypothesis that PTSD is associated with disrupted functional connectivity of the amygdala and vmPFC in response to emotional stimuli, extending previous findings by demonstrating such links in an understudied, highly traumatized, civilian population. 40 African-American women with civilian trauma (20 with PTSD and 20 non-PTSD controls) were recruited from a large urban hospital. Participants viewed fearful and neutral face stimuli during functional magnetic resonance imaging (fMRI). Relative to controls, participants with PTSD showed an increased right amygdala response to fearful stimuli ($p_{corr} < .05$). Right amygdala activation correlated positively with the severity of hyperarousal symptoms in the PTSD group. Participants with PTSD showed decreased functional connectivity between the right amygdala and left vmPFC ($p_{corr} < .05$). The findings are consistent with previous findings showing PTSD is associated with an exaggerated response of amygdala-mediated emotional arousal systems. This is the first study to show that the amygdala response may be accompanied by disruption of an amygdala-vmPFC functional circuit that is hypothesized to be involved in prefrontal cortical regulation of amygdala responsivity.

1. Introduction

PTSD is a highly debilitating anxiety disorder that develops in some individuals after exposure to trauma. Among the general population, PTSD is estimated to affect approximately 7% (Kessler et al., 2005), and a critical question for the field is why this disorder develops in some, but not others, following severe trauma exposure. An increasing body of evidence shows that in addition to combat veterans, the risk for traumatic life experiences and PTSD is especially high among impoverished individuals living in urban settings with high violence exposure, with trauma rates at nearly 88% and PTSD prevalence at 46% (Alim et al., 2006; Gillespie et al., 2009; Liebschutz et al., 2007; Schwartz et al., 2005).

After a traumatic event, symptoms may develop that interfere with everyday function, including increased emotional arousal and hypervigilance, reexperiencing the traumatic event, and avoidance of trauma reminders. Because these symptoms only persist in a subset of people who experience trauma, one important goal of PTSD research is to identify characteristics that confer resilience or vulnerability for the disorder. Current neurobiological models of PTSD posit that neural circuits typically involved in healthy emotion regulation are disrupted in PTSD (Liberzon and Sripada, 2007; Shin et al., 2006). The goal of the current research was to examine the neural circuits involved in emotion processing in a high-risk urban civilian sample of traumatized African American women.

A wealth of functional neuroimaging evidence has shown that PTSD symptoms are associated with increased activation of the amygdala and insula, brain regions that are involved in initiating and coordinating emotional arousal responses (e.g., Fonzo et al., 2010; Rauch et al., 2000; Shin et al., 2005; Simmons et al., 2011). In addition, PTSD has been associated with decreased activation of prefrontal regions involved in emotion regulation such as the ventromedial prefrontal cortex (vmPFC) and rostral anterior

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cingulate cortex (ACC; Jovanovic et al., 2012; Milad et al., 2009; Rougemont-Bucking et al., 2011; Shin et al., 2001, 2005; Williams et al., 2006). A meta-analysis of neuroimaging studies of anxiety disorders found that reduced vmPFC activation is specific to PTSD, and is not consistently observed in studies of other anxiety disorders (Etkin and Wager, 2007). Evidence from studies of overt emotion regulation and fear extinction in healthy participants suggests that the vmPFC and rostral ACC are involved in decreasing arousal responses to negative emotional stimuli (Etkin et al., 2011; Kim and Hamann, 2007; Milad et al., 2007b; Ochsner et al., 2002).

Examining connectivity between the amygdala and vmPFC can provide a more direct test of the hypothesis that PTSD involves a disruption of medial prefrontal regulation of amygdala responses to emotional stimuli. Recent diffusion tensor imaging (DTI) evidence suggests that white matter integrity is compromised in the cingulum bundle, a major pathway between the amygdala and vmPFC/ACC (Fani et al., 2012b). Similarly, examination of resting state functional connectivity, which often parallels structural connectivity, has shown decreased functional coupling between the amygdala and vmPFC in PTSD (Sripada et al., 2012).

Only a small number of studies have examined amygdala functional connectivity in response to emotionally arousing stimuli in PTSD, with mixed findings relating to the strength of connectivity between the amygdala and vmPFC. In response to angry face stimuli, PTSD participants showed decreased connectivity in a circuit involving the amygdala, insula, and dorsal ACC (Fonzo et al., 2010). In contrast, PTSD participants recalling traumatic or emotionally negative autobiographical memories showed *increased* amygdala functional connectivity with the vmPFC relative to controls (Gilboa et al., 2004; St Jacques et al., 2011). The variability in findings may relate to differences in the experimental tasks used, or in the populations examined. Previous studies examined PTSD related to recent intimate-partner violence, accidental injury, and among a general civilian population, respectively. In addition, these studies did not include traumatized controls and thus did not differentiate the effects of trauma versus PTSD on amygdala connectivity (Fonzo et al., 2010; St Jacques et al., 2011), or included participants who were taking psychotropic medications at the time of the scan (Gilboa et al., 2004).

In the present study, we investigated the effects of PTSD on amygdala responses to threat cues (fearful facial expressions) and on the functional coupling of the amygdala with other brain areas, in a highly traumatized sample of African-American women. The primary comparison was between unmedicated participants with or without current PTSD, matched for degree of trauma exposure. Little previous work has examined the neural processing of emotional stimuli in an urban civilian population with very high levels of trauma. We hypothesized that PTSD would be associated with an increased amygdala response, and with decreased functional connectivity between the amygdala and vmPFC/ACC, in response to fearful stimuli.

2. Materials and methods

2.1. Participants

Forty African-American women ages 18–59 were recruited through an ongoing study of risk factors for PTSD. Participants were approached in the general medical clinics of Grady Memorial Hospital, a publicly funded hospital that serves economically disadvantaged individuals in Atlanta, Georgia. High rates of trauma and posttraumatic symptoms have been previously observed within this patient population (e.g., Binder et al., 2008). The hospital population is >85% African-American, and therefore we only included subjects with self-reported African-American race/ethnicity to enhance data homogeneity, in addition to the fact that this is an under-represented group in psychiatric imaging research studies. All participants were screened and met the following inclusion criteria: no neurological disorder, psychosis, current psychotropic medication, or metal clips or implants. Individuals who endorsed a history of bipolar disorder, schizophrenia or any other psychotic disorder were also excluded. Due to the high comorbidity of PTSD and depression, participants with depression were not excluded. Participants had normal or corrected-to-normal vision. Urine tests for pregnancy and illegal drug use (cocaine, marijuana, opiates, amphetamines, methamphetamines) were conducted 24 h prior to the MRI scan, and individuals who showed positive results for pregnancy or drugs were excluded. Men were not included in the current study, as significant sex differences have been observed in the neural processing of emotional stimuli (Stevens and Hamann, 2012). All participants provided written informed consent prior to participating. Participants received monetary compensation for their time. The institutional review board of Emory University approved the study procedures, and testing took place at Grady Memorial Hospital and the Biomedical Imaging Technology Center at Emory University Hospital.

2.2. Psychological assessment

The Modified PTSD Symptom Scale (PSS; Foa and Tolin, 2000) was used to assess PTSD symptoms, and the Traumatic Events Inventory (TEI) was used to assess types and severity of trauma experience. Anxiety levels were assessed using the State Trait Anxiety Inventory (STAI; Spielberger et al., 1970). Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994; Scher et al., 2001). These measures have been used in our previous studies with this population (Binder et al., 2008; Fani, et al., 2012a; Schwartz et al., 2005). Traumatic experiences were assessed using the TEI and CTQ during recruitment, and the additional psychological measures were administered during a laboratory visit one day prior to the MRI scan. PTSD diagnosis was based on DSM-IV-TR criteria (presence of trauma; presence of at least one reexperiencing symptom; presence of at least 3 avoidant/numbing symptoms; presence of at least 2 hyperarousal symptoms; occurrence for at least one month), as assessed by the PSS. All participants had experienced at least one trauma, and PTSD diagnosis was used to classify participants into PTSD and traumatized control (TC) groups. PTSD diagnoses were verified for a subset of participants (55%) using the CAPS. Diagnoses using CAPS and PSS were positively correlated, Spearman's rho $= .57$, $p = .006$. Table 1 lists clinical and demographic characteristics of each group.

2.3. Procedure

Eight fearful and eight neutral (4 male and 4 female) faces were selected from the stimulus set of Ekman and Friesen (1976). Stimuli were projected onto a 24-inch screen at a resolution of 1280×1024 using EPrime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Blocks of fearful and neutral stimuli (15 blocks each) were presented in a pseudorandom order. Each block was composed of all eight faces presented in a random order. Each face stimulus was presented for 500 ms, followed by a 500 ms presentation of a fixation cross. After every 10th block, a 10,000 ms rest period with the instruction "relax and look at the screen" was presented. Face stimuli were presented at a size of $4.3 \times 6.7''$ on a black background, and the fixation cross and instructions were presented in white 18-point Courier New font on a black background. Participants were instructed to pay attention to the faces, but did not make any behavioral response, in order to minimize motion artifacts and neural activation unrelated to processing the visual stimulus.