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Research report

Reduced neural activation during an inhibition task is associated with impaired fear inhibition in a traumatized civilian sample

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ABSTRACT

Introduction: Impaired inhibition of fear in the presence of safety cues and a deficiency in the extinction of fear cues are increasingly thought to be important biological markers of Posttraumatic stress disorder (PTSD). Other studies have suggested that there may be altered neural activation during behavioral inhibition tasks in subjects with PTSD. The current study aimed to see whether neural activation during inhibition was reduced in a highly traumatized civilian population, and whether atypical activation was associated with impaired fear inhibition.

Methods: The participants were 41 traumatized women (20 PTSD+, 21 PTSD−) recruited from Grady Memorial Hospital in Atlanta, GA. We used a Go/NoGo procedure with functional magnetic resonance imaging (fMRI) in a high-resolution 3T scanner. Participants were instructed to press a button whenever an "X" or "O" appeared on the screen, but not if a red square appeared behind the letter. Participants were assessed for trauma history and PTSD diagnosis, and completed a fear-potentiated startle and extinction paradigm.

Results: We found stronger activation in the ventromedial prefrontal cortex (vmPFC) in traumatized subjects without PTSD compared to those with PTSD in the NoGo greater than Go contrast condition. Activation in the vmPFC was negatively correlated with fear-potentiated startle responses during safety signal learning ($p = .02$) and fear extinction ($p = .0002$).

Conclusions: These results contribute to understanding of how the neural circuitry involved in inhibitory processes may be deficient in PTSD. Furthermore, the same circuits involved in behavioral inhibition appear to be involved in fear inhibition processes during differential fear conditioning and extinction.

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1. Introduction

Posttraumatic stress disorder (PTSD) can develop in some individuals after exposure to an event that causes extreme fear, horror, or helplessness (APA, 1994). PTSD is characterized by three primary symptom clusters following a traumatic experience: (a) the first cluster of symptoms includes re-experiencing of the traumatic event through intrusive thoughts, nightmares, flashbacks, and related phenomena that are often produced by reminders of the traumatic event; (b) the second cluster is characterized by avoidance symptoms including loss of interest in social situations and emotional detachment; and (c) the third cluster includes psychophysiological reactivity in response to trauma-related stimuli including exaggerated startle, hypervigilance, elevated perspiration, and shortness of breath (APA, 1994). Dysregulation of the fear processing system appears to be central to many of these symptoms of PTSD. Studies with combat and civilian trauma populations have shown that inhibition of fear-potentiated startle is impaired in PTSD compared to controls (Jovanovic et al., 2012). Inhibition of fear responses involves learning to discriminate between danger and safety cues and to suppress fear responses in the presence of safety cues (Jovanovic and Norrholm, 2011). Fear responses are acquired through a Pavlovian conditioning model in which a neutral stimulus (CS+) is paired with an aversive unconditioned stimulus (US). After several pairings, the association is formed so that the CS+ alone elicits the conditioned response (CR) (Pavlov, 1927). In differential conditioning, a separate cue that is never paired with the US (CS−, safety signal) does not elicit the CR if the fear response is appropriately inhibited. An additional paradigm used to investigate fear inhibition is extinction, in which the previously fear-conditioned CS+ is repeatedly presented without the US, until the subject learns that it no longer predicts danger.

There are several lines of evidence that implicate the prefrontal cortex (PFC) as an anatomical substrate for fear inhibition (Jovanovic and Norrholm, 2011). For example, functional magnetic resonance imaging (fMRI) data indicate increased activation of the ventromedial (vm)PFC during an extinction recall task that is presented after extinction learning has occurred (Phelps et al., 2004; Milad et al., 2007). Furthermore, morphometric MRI analyses suggest that the thickness of vmPFC cortical tissue is correlated with extinction retention (Milad et al., 2005; Hartley et al., 2011). The PFC is also activated during response inhibition tasks in the absence of fearful stimuli. In such tasks, the participant is presented with a "Go" signal indicating that a response is required, for example, to press a button when a letter appears on the monitor. On a fraction of trials, however, the participant is required to withhold a response during a "NoGo" signal (the Go/NoGo task) (Eagle et al., 2008; Hester et al., 2004). Go/NoGo tasks used in subjects with PTSD with fMRI (Carrion et al., 2008; Falconer et al., 2008) have found decreased activation in the PFC in PTSD subjects compared to controls.

A hallmark of PTSD neurobiology is exaggerated amygdala activity during fearful stimulation coupled with reduced top–down control of the amygdala by the PFC, indicating dysregulation of this inhibitory neurocircuit (Rauch et al., 2000, 2006; Shin et al., 2004; Liberzon and Martis, 2006; Etkin et al., 2006). A recent meta-analysis of imaging studies during emotion processing in PTSD, social anxiety, and specific phobia indicated that the vmPFC (including the rostral anterior cingulate cortex – rACC) is less active in PTSD patients relative to controls (Etkin and Wager, 2007). Additionally, a recent fMRI study of extinction recall demonstrated decreased activation of the vmPFC in PTSD patients (Rougemont-Bücking et al., 2010). Finally, structural MRI data indicate that greater rACC volume predicts positive treatment outcomes in PTSD patients (Bryant et al., 2008). This area has been found to differ in PTSD patients compared to controls in shape and size (Corbo et al., 2005).

Differential fear conditioning and extinction paradigms in a highly traumatized civilian population (Jovanovic et al., 2010b, 2010a; Glover et al., 2011; Norrholm et al., 2011) suggest that participants with PTSD show higher fear-potentiated startle to the CS+ (danger signal) and CS− (safety signal) than trauma controls (Glover et al., 2011). Data from our study on extinction suggest that a high degree of fear during late extinction is related to impaired inhibition, as it is best predicted by higher fear responses to the safety signal at the end of conditioning (Norrholm et al., 2011). In the current study, we investigated the neurocircuitry of response inhibition using an fMRI Go/NoGo task in a sample of traumatized women from inner-city Atlanta with and without PTSD. We hypothesized that women with PTSD would have less activation of the vmPFC/rACC during the inhibition condition compared to trauma controls. Furthermore, we examined inhibition of fear-potentiated startle in relation to neural activation to the response inhibition task. We hypothesized that impaired inhibition of fear would be associated with decreased activation in the vmPFC during the NoGo condition.

2. Methods

2.1. Participants

A total of 53 African American females aged 20–62 years were recruited through an ongoing study of risk factors for PTSD from the primary care medical clinics of a publicly funded hospital that serves a low-income minority population in inner-city Atlanta (Bradley et al., 2008; Schwartz et al., 2005). After complete description of the study to the subjects, written informed consent was obtained. Study procedures were approved by the institutional review boards of Emory University and Grady Memorial Hospital.

Women were considered eligible for participation if they were able and willing to give informed consent. Participants were screened with a short questionnaire to assess for the presence of these exclusion criteria: current psychotropic medication use, medical or physical conditions that preclude MRI scanning (e.g., metal implants), a history of schizophrenia or other psychotic disorder, history of head injury or loss of consciousness for longer than 5 min, or a history of neurological illness. Participants were also screened for pregnancy using a urine test. Of the 53 women recruited, data from 12