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Association among anterior cingulate cortex volume, psychophysiological response, and PTSD diagnosis in a Veteran sample

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ABSTRACT

Posttraumatic stress disorder (PTSD) is associated with fear response system dysregulation. Research has shown that the anterior cingulate cortex (ACC) may modulate the fear response and that individuals with PTSD have abnormalities in ACC structure and functioning. Our objective was to assess whether ACC volume moderates the relationship between PTSD and fear-potentiated psychophysiological response in a sample of Gulf War Veterans. 142 Veteran participants who were associated with a larger study associated with Gulf War Illness were exposed to no threat, ambiguous threat, and high threat conditions in a fear conditioned startle response paradigm and also provided MRI imaging data. PTSD was assessed using the Clinician Administered PTSD Scale (CAPS). Decreased caudal ACC volume predicted greater psychophysiological responses with a slower habituation of psychophysiological magnitudes across trials ($p < 0.001$). PTSD diagnosis interacted significantly with both caudal and rostral ACC volumes on psychophysiological response magnitudes, where participants with PTSD and smaller rostral and caudal ACC volumes had greater psychophysiological magnitudes across trials ($p < 0.05$ and $p < 0.001$, respectively) and threat conditions ($p < 0.05$ and $p < 0.005$). Our results suggest that ACC volume may moderate both threat sensitivity and threat response via impaired habituation in individuals who have been exposed to traumatic events. More research is needed to assess whether ACC size and these associated response patterns are due to neurological processes resulting from trauma exposure or if they are indicative of a pre-morbid risk for PTSD subsequent to trauma exposure.

1. Introduction

Approximately 50–60% of Americans are exposed to traumatic events (Fukuda et al., 1998; Kessler et al., 2005), and 5–20% of these individuals develop Posttraumatic Stress Disorder (PTSD; (Ramchand et al., 2010)). As our understanding of the neurobiology of PTSD continues to develop, research suggests that certain biomarkers may be associated with increased risk for the disorder (Ross et al., 2017) and understanding how these biomarkers are linked to PTSD symptom expression may lead to therapeutically useful findings (Stevens et al., 2017; Yehuda, Neylan, Flory, & McFarlane, 2013). Psychophysiological biomarkers such as exaggerated startle responding have emerged as relatively robust biomarkers of PTSD (Orr, Lasko, Shalev, & Pitman, 1995; Orr, Metzger, & Pitman, 2002). However, the neural underpinnings of exaggerated startle in PTSD are not clearly understood. While several neural structures such as the hippocampus and amygdala have been implicated in the development and maintenance of PTSD, the anterior cingulate cortex (ACC) has garnered considerable interest as a modulator of fear response in PTSD, to our knowledge, no studies have examined associations of ACC structure with psychophysiological responding in PTSD.

In addition to being a key structure for top-down and bottom-up processing sequences, selective attention, and certain social behaviors, the ACC has both afferent and efferent connections to key emotion regulatory limbic structures, such as the amygdala and hippocampus (Lanius, Bluhm, Lanius, & Pain, 2006). Given its proximity and connections to limbic structures, the ACC may impact PTSD susceptibility through its inhibition and resolution of amygdala activation to threatening stimuli (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Shin et al., 2001). Imaging studies of healthy participants have shown that the ACC

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is activated during the processing of significant but non-threatening stimuli (Bush, Luu, & Posner, 2000; Yamasaki, LaBar, & McCarthy, 2002). Conversely, individuals with PTSD were found to have less ACC activation when exposed to distressing stimuli compared to healthy controls (Bremner et al., 1999; Shin et al., 2001). Moreover, studies by our group and others have shown that smaller ACC volume is associated with current chronic PTSD in Veterans (Chao, Weiner, & Neylan, 2013; Woodward et al., 2006). Recent studies also indicate functional heterogeneity within the ACC where the caudal/dorsal ACC, with its projections to the prefrontal cortex is more so associated with cognitive processes compared to the rostral/ventral ACC, with its functional connectivity to limbic structures such as the hippocampus, amygdala, and other subcortical structures such as the insula is more so associated with emotional function (Etkin, Egner, & Kalisch, 2011; Somerville, Heatherton, & Kelley, 2006).

Earlier studies have shown that smaller ACC volume is associated with both abuse and combat related PTSD diagnoses (Kitayama, Quinn, & Bremner, 2006; Woodward et al., 2006), which suggests that reduced ACC volume may linked to PTSD via impaired ACC activation. Given the ACC plays a major role in areas such areas as threat expectancy and emotional regulation (for a review see Etkin et al., 2011), little attention has been given to the ACC – PTSD relationship within the context of established bio-behavioral markers of threat such as psychophysiological reactivity. A body of literature has shown that individuals diagnosed with PTSD exhibit greater fear-potentiated psychophysiological responses to sudden or threatening stimuli (Ramirez-Moreno & Sejnowski, 2012) compared to those who do not have a PTSD diagnosis (Grillon, Morgan, Davis, & Southwick, 1998; Orr et al., 1995; Pole, Neylan, Best, Orr, & Marmar, 2003). Thus, exploring how ACC might be related to psychophysiological response magnitudes may shed light on brain abnormalities that contribute to altered psychophysiological responding in PTSD. And while previous imaging studies that have investigated the relationship between the ACC and PTSD have focused on paradigms such as the Emotional Stroop task, responses to trauma-related distractors, and engaging in a go/no go task (for a review, see Admon, Milad, & Hendler, 2013), very few studies have focused on exploring the relationship between PTSD, the ACC (either functional or structural), and psychophysiological responses. One study has shown that elevated negative affect reactivity to startle was associated with greater ACC and amygdala activation in individuals with snake and spider phobias (Pissiota et al., 2003). Similarly, a more recent study of traumatized women found that greater activation of the prefrontal cortex/ACC region is associated with greater inhibition of fear-potentiated startle responses (Jovanovic et al., 2013). These studies underscore the importance of examining for the first time if abnormal ACC structure can be linked to exagerrated psychophysiological reactivity in PTSD.

Thus, to expand on previous findings, we investigated whether the interaction between ACC volume and PTSD diagnosis was associated with psychophysiological reactivity to startling sounds over successive trials across three different threat conditions in a sample of Gulf War Veterans. Threat conditions included no threat, ambiguous threat, and high threat. We hypothesized that: (1) smaller ACC volume would be associated with greater psychophysiological response magnitudes across each of the threat conditions and (2) ACC volume would interact with PTSD where individuals who had smaller ACC volumes and were also diagnosed with PTSD would exhibit greater psychophysiological response magnitudes compared to other participants in each of the threat conditions. Based upon prior research that suggests differential caudal and rostral ACC functioning in association to stress response (Admon et al., 2013), we also explored whether or not the caudal and rostral ACC volumes were separately linked to psychophysiological response magnitudes and whether this was moderated by PTSD.

2. Materials and methods

2.1. Participants

We conducted a secondary analysis of data on Veterans from a cross-sectional study that was originally designed to assess the effects of Gulf War deployment on the brain. The original study examined the hypothesis that Gulf War illness was associated with decreased N-acetyl aspartate in the basal ganglia and pons of participants. Gulf War Veterans were recruited between 2002 and 2007 through contacts with physicians at VA clinics in Northern California using methods described elsewhere (Apfel et al., 2011; Weiner et al., 2011). The University of California San Francisco and Committee on Human Research and the Department of Defense Human Research Protection Office approved all research protocols. The sample included both treatment seeking and non-treatment seeking Veterans. Of the 369 Veterans from the original sample, 244 and 172 Veterans engaged in the psychophysiological response task and provided imaging data respectively. Out of those, we had both psychophysiological task and imaging data from 142 Veterans.

Demographic variables including participants' age, sex, education level, race (white versus minority), and whether the participant had a current diagnosis of PTSD were recorded for use in subsequent analyses based upon prior literature linking them to traumatic stress response (Engelhard, Van Den Hout, & Schouten, 2006; Neylan et al., 2005). Current PTSD symptoms (i.e., within the past month) were evaluated by a Ph.D. level clinical interviewer using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). Participants were diagnosed with PTSD based upon frequency and severity of their CAPS scores (e.g. the "1, 2" rule) and the DSM-IV-TR algorithm (for a review, see Weathers, Litz, Herman, Huska, & Keane, 1993). Exposure to child abuse occurring prior to the age of 16 years old was assessed using the last six items of the Trauma History Questionnaire (Green, 1996).

2.2. Psychophysiological response procedure

Three indices of psychophysiological response were collected by trained technicians, who were blind to participants' psychometric status. The participant's left eye blink electromyogram (EMG) activity, skin conductance response (SCR) level, and heart rate (HR) were assessed during a two-minute baseline period. Participants were fitted with headphones and told that they would hear potentially startling sounds. They were asked to focus their eyes on a monitor in front of them. A Coulbourn Instruments Lablinc V Modular System binaurally presented 106-dB(A), 40 ms white noise bursts with nominal 0-millisecond rise and fall times separated by inter-trial intervals of between 30 and 50 s in each threat condition. In the "no threat" condition, participants were instructed that they would not be shocked until later in the study. They were then exposed to ten startling sounds. Only their last five responses were retained. In the "ambiguous threat" condition, participants were fitted with a Coulbourn Instruments Transcutaneous Aversive Finger Stimulator but were told that they would not be shocked. Five additional startling sounds were presented. In the "high threat" condition, Veterans wore the finger stimulator and were told that shocks were imminent. Then five additional startling sounds were presented followed by a 2.5 mA shock. Each condition lasted approximately 4 min and was separated by about 1 min. The medium and high threat conditions were counterbalanced to minimize carry-over effects between these conditions. All physiological signals were sampled at 2 Hz during the resting baseline and at 1000 Hz during the acoustic presentations, digitized, and stored for off-line analysis. EMG, measured in microvolts was captured using three, 4-mm (sensor diameter) In Vivo Metrics Ag/AgCl surface electrodes filled with electrolyte paste according to specifications published elsewhere (Blumenthal et al., 2005). SCR was measured in microsiemens by sending a constant 0.5 V through 9-mm (sensor diameter) InVivo Metrics Ag/AgCl electrodes