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Amygdala Reactivity and Anterior Cingulate Habituation Predict Posttraumatic Stress Disorder Symptom Maintenance After Acute Civilian Trauma

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ABSTRACT

BACKGROUND: Studies suggest that exaggerated amygdala reactivity is a vulnerability factor for posttraumatic stress disorder (PTSD); however, our understanding is limited by a paucity of prospective, longitudinal studies. Recent studies in healthy samples indicate that, relative to reactivity, habituation is a more reliable biomarker of individual differences in amygdala function. We investigated reactivity of the amygdala and cortical areas to repeated threat presentations in a prospective study of PTSD.

METHODS: Participants were recruited from the emergency department of a large level I trauma center within 24 hours of trauma. PTSD symptoms were assessed at baseline and approximately 1, 3, 6, and 12 months after trauma. Growth curve modeling was used to estimate symptom recovery trajectories. Thirty-one individuals participated in functional magnetic resonance imaging around the 1-month assessment, passively viewing fearful and neutral face stimuli. Reactivity (fearful > neutral) and habituation to fearful faces was examined.

RESULTS: Amygdala reactivity, but not habituation, 5 to 12 weeks after trauma was positively associated with the PTSD symptom intercept and predicted symptoms at 12 months after trauma. Habituation in the ventral anterior cingulate cortex was positively associated with the slope of PTSD symptoms, such that decreases in ventral anterior cingulate cortex activation over repeated presentations of fearful stimuli predicted increasing symptoms.

CONCLUSIONS: Findings point to neural signatures of risk for maintaining PTSD symptoms after trauma exposure. Specifically, chronic symptoms were predicted by amygdala hyperreactivity, and poor recovery was predicted by a failure to maintain ventral anterior cingulate cortex activation in response to fearful stimuli. The importance of identifying patients at risk after trauma exposure is discussed.

Keywords: Amygdala, Arousal, Fear, fMRI, Prospective, Trauma

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The early identification of risk factors that predispose individuals to trauma-related psychopathology, such as posttraumatic stress disorder (PTSD), could help providers prevent or limit symptoms before a disorder develops. Such risk assessment in the peritraumatic period could benefit a significant proportion of the general population; it has been estimated that 50% to 60% experience a potentially traumatizing event (1), and 6% to 8% develop PTSD after trauma exposure (1,2). Markers of brain function may be particularly powerful biomarkers of risk, because they can provide insight into the mechanisms leading to maladaptive responses to trauma and potential targets for treatment. In addition, understanding the intermediate phenotypes of brain function that underlie PTSD development may lead to novel therapeutic approaches.

Findings from studies of chronic PTSD consistently show an association between symptoms and hyperreactivity of the amygdala and dorsal aspects of the anterior cingulate cortex (dACC), key brain regions for emotional expression and appraisal (3–7). In addition, PTSD is associated with underactivity and reduced functional connectivity among regions that regulate amygdala function, including ventral aspects of the anterior cingulate cortex (vACC) (6,8–11). This pattern of abnormalities is thought to contribute to hyperarousal symptoms in PTSD and to impairments in top-down emotion regulation and fear extinction (3,8,9,12). However, most previous research has been conducted cross-sectionally in chronic PTSD and cannot distinguish between risk factors or acquired features of the disorder.

Recent findings from prospective studies of trauma and PTSD implicate amygdala function as a potential predictor of PTSD. For example, studies of military service members before and after combat deployment showed that amygdala and vACC reactivity increased significantly from pre- to postcombat exposure (13,14),

SEE COMMENTARY ON PAGE e85

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and that predeployment amygdala reactivity to emotionally arousing or risk-related stimuli positively predicted postdeployment PTSD symptoms (14,15). Perhaps because these studies recruited individuals from highly trained military samples, participants did not show significant levels of PTSD severity after trauma, and additional studies are needed to determine whether findings generalize to the broader population. A pilot study in a civilian population ($n = 9$) was conducted to assess responses to acute traumas that led to a hospital emergency department (ED) visit, and showed that default mode connectivity between the amygdala and posterior cingulate cortex 6 weeks after trauma was positively related to PTSD symptoms 12 weeks after trauma (16). However, amygdala reactivity has not been investigated as a PTSD predictor in a civilian cohort.

Ideal biomarkers of brain function are those that are reliable and minimally influenced by transient day-to-day changes. Test-retest reliability for functional magnetic resonance imaging (fMRI) measures of reactivity to emotional face stimuli in regions including the amygdala and ACC has been shown to be fair to excellent (17–19). In addition, recent studies indicate that amygdala habituation, or the change over time in the response to a repeated stimulus, shows greater test-retest stability within individuals than reactivity (17,18). Interestingly, individuals with chronic PTSD show an increased initial amygdala response to trauma-related negative stimuli and altered patterns of amygdala habituation relative to controls (20). This heightened initial response, and differences in habituation, may contribute to previous findings of amygdala hyperreactivity in PTSD. However, no prospective study of PTSD has examined habituation of responses to emotional stimuli.

In the current study, we conducted a prospective longitudinal investigation of PTSD symptoms after acute trauma, measuring brain function using fMRI at an early timepoint before PTSD diagnosis, approximately 1 month after the index trauma. We investigated neural reactivity and habituation to emotional stimuli as predictors of later PTSD symptom trajectories over the next year. Participants were recruited from an ongoing longitudinal study of biomarkers for PTSD in which individuals who experienced a traumatic event were approached in the ED within 24 hours of trauma and assessed for symptoms at 1, 3, 6, and 12 months after trauma. The fMRI scan took place within 2 to 3 weeks of the 1-month visit (timeline of visits shown in Figure 1B), with a mean (SD) of 57 (14) days after trauma exposure. We hypothesized that heightened reactivity to negative stimuli in the amygdala and dACC, and blunted reactivity in the vACC, would predict later PTSD symptom severity, consistent with the idea that these brain phenotypes reflect vulnerability factors for PTSD. In addition, we assessed the exploratory hypothesis that reduced habituation of the amygdala response to repeated presentations of negative stimuli would predict later PTSD symptoms.

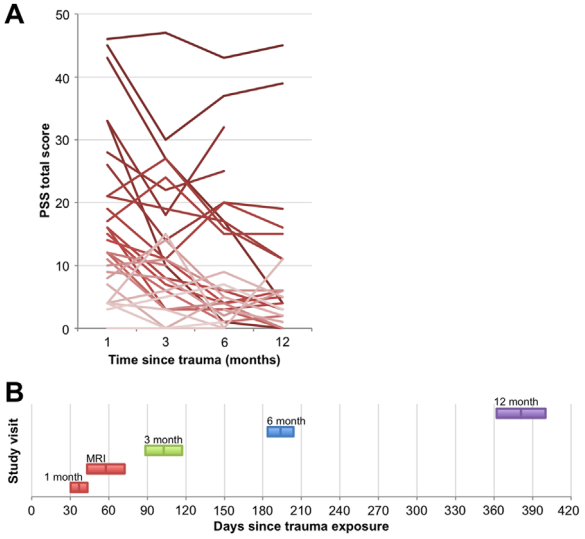

Figure 1. Posttraumatic stress disorder symptom trajectories. **(A)** Line graph shows each participant's posttraumatic stress disorder symptom severity scores (PTSD Symptom Scale total scores) across the four follow-up visits. Line shading (darker to lighter) indicates more severe to less severe symptoms at the 1-month visit. **(B)** Timeline of study visits. Colored bars show mean ± SD in the visit delay, relative to study enrollment in the emergency department. MRI, magnetic resonance imaging.

METHODS AND MATERIALS

Participants

Thirty-eight participants were recruited from a larger study of biomarkers for PTSD. Participants from the parent study who indicated interest in neuroimaging were approached to participate in the neuroimaging study. This add-on study was not designed to be representative of the larger study. Participants were patients in the ED of Grady Memorial Hospital in Atlanta, GA, who had experienced a traumatic event within the last 24 hours. Participants were included if they spoke English, were 18 to 65 years of age, endorsed a criterion A trauma as defined by the DSM-IV-TR (21), and provided contact information for follow-up visits. Exclusion criteria included previous hospitalization for mental health reasons, current suicidal ideation, attempted suicide in the past 3 months, current intoxication, or altered mental status during the ED visit. After fMRI data collection, seven participants were excluded from further analysis because of anatomical abnormalities, such as falx calcification ($n = 3$), head motion >3 mm ($n = 3$), and stimulus presentation malfunction ($n = 1$). Of the final sample of 31 individuals, 22 were in motor vehicle crashes, 4 were pedestrians who were hit by a vehicle, 3 were in motorcycle or bicycle accidents, and 2 were victims of sexual assault.

After the trauma, several participants sought therapy or mental health counseling (unrelated to the current study): 6 within the first month, 4 between 1 and 3 months, 2 between 3 and 6 months, and 2 between 6 and 12 months after trauma. Additional sample characteristics are summarized in Table 1. Supplemental Table S1 lists prescription medication use and comorbid diagnoses identified on a Mini-International Neuropsychiatric Schedule (22) administered during the ED visit. Participants provided written informed consent for all parts of the study, and the Institutional Review Boards of Emory University and Grady Memorial Hospital approved the study procedures.

ED Assessment at the Time of Trauma Exposure

Demographic information and information about the index trauma was gathered using the Standardized Trauma Interview, a 41-item clinician-administered interview gathering information