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Episodic memory after trauma exposure: Medial temporal lobe function is positively related to re-experiencing and inversely related to negative affect symptoms

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ABSTRACT

Hippocampal structure is particularly sensitive to trauma and other stressors. However, previous findings linking hippocampal function with trauma-related psychopathology have been mixed. Heterogeneity in psychological responses to trauma has not been considered with respect to hippocampal function and may contribute to mixed findings. To address these issues, we examined associations between data-driven symptom dimensions and episodic memory formation, a key function of the hippocampus, in a trauma-exposed sample. Symptom dimensions were defined using principal components analysis (PCA) in 3881 trauma-exposed African-American women recruited from primary care waiting rooms of a large urban hospital. Hippocampal and amygdala function were subsequently investigated in an fMRI study of episodic memory formation in a subset of 54 women. Participants viewed scenes with neutral, negative, and positive content during fMRI, and completed a delayed cued recall task. PCA analysis produced five symptom dimensions interpreted as reflecting negative affect, somatic symptoms, re-experiencing, hyper-arousal, and numbing. *Re*-experiencing was the only symptom type associated with hippocampal function, predicting increased memory encoding-related activation in the hippocampus as well as the amygdala. In contrast, the negative affect component predicted lower amygdala activation for subsequently recalled scenes, and lower functional coupling with other important memory-related regions including the precuneus, inferior frontal gyrus, and occipital cortex. Symptom dimensions were not related to hippocampal volume. The fMRI findings for re-experiencing versus negative affect parallel differences in behavioral memory phenomena in PTSD versus MDD, and highlight a need for more complex models of trauma-related pathology.

1. Introduction

Although numerous studies have shown a relationship between traumatic stress and hippocampal structure (O'Doherty et al., 2015; Riem et al., 2015), the role of hippocampal function in trauma-related psychopathology is less clear. The hippocampus is critically involved in the formation of episodic memories (Eichenbaum, 2004; Squire and Zola-Morgan, 1991; Tulving and Markowitsch, 1998), defined as consciously-accessible memories of specific personal experiences (Tulving, 2002). However, relatively few studies have investigated how prior trauma exposure influences episodic memory function in the hippocampus or the amygdala (typically involved in the formation of episodic memories for emotional stimuli), and the existing findings have been mixed (Brohawn et al., 2010; Dickie et al., 2008, 2011; Hayes et al., 2011; Thomaes et al., 2013; Thomaes et al., 2009). Disagreements may be related, in part, to the large heterogeneity in post-traumatic stress disorder (PTSD) symptoms across individuals, and the fact that comorbid depression symptoms are often ignored. In the aftermath of trauma, similar rates of major depressive disorder (MDD) and PTSD diagnoses are observed (Shalev et al., 1998), and the two are highly comorbid (Breslau et al., 2000; Shalev et al., 1998). To address some of these outstanding issues, here we conducted an fMRI study of episodic memory encoding, examining links with continuous symptom dimensions related to PTSD and depression in a trauma-exposed sample.

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Relative to other brain regions, the hippocampus is particularly sensitive to trauma and other forms of stress. Studies of human hippocampal structure indicate reduced volume related to trauma, PTSD, and MDD (Logue et al., 2017; O'Doherty et al., 2015; Riem et al., 2015; Schmaal et al., 2015), particularly in CA3 and the dentate gyrus (Hayes et al., 2017; Teicher et al., 2012), regions of the hippocampus that perform central roles in episodic memory function (Eichenbaum, 2004). Despite similar decreases in hippocampal volume in both PTSD and MDD, these disorders are associated with very different memory-related symptoms. In PTSD, intrusive conscious recollections of the initial trauma are a central feature, consistent with the possibility of an overactive episodic memory system. In contrast, individuals with MDD show less detailed autobiographical memory than healthy individuals (Brittlebank et al., 1993; Williams and Scott, 1988), and impaired episodic memory performance (Bearden et al., 2006; Burt et al., 1995). Such findings suggest that neural processes supporting episodic memory function may differ in trauma-exposed individuals with intrusive PTSD symptoms versus depressive symptoms.

Consistent with this possibility, studies linking hippocampal function with trauma-related pathology have produced mixed results. Among previous studies of episodic memory encoding in PTSD, two found increased encoding-related hippocampal activation (Brohawn et al., 2010; Thomaes et al., 2009), one found decreased hippocampal activation (Hayes et al., 2011), and three found no association (Dickie et al., 2008, 2011; Thomaes et al., 2013). For negative stimuli, PTSD-related differences in encoding were also observed in the amygdala (Brohawn et al., 2010; Dickie et al., 2008; Hayes et al., 2011), a region that coordinates emotional responses and whose activity has been shown to enhance hippocampal encoding-related processes (Cahill and McGaugh, 1998; McGaugh, 2002). These findings have been interpreted as providing a possible neural correlate of PTSD vulnerability, such that vulnerable individuals might more strongly engage the amygdala in memory encoding of negative or threatening experiences, facilitating hippocampal encoding or post-encoding processes, and resulting in longer-lasting or more detailed trauma memories.

Depressive symptoms following trauma have not been examined with respect to memory encoding in the hippocampus and amygdala. However, trauma-related depression is likely to share some of the neural abnormalities observed in MDD. Patients with MDD show lower involvement of the hippocampus in memory for positive stimuli (van Tol et al., 2012), and greater involvement of the amygdala for negative stimuli (Ai et al., 2015; van Tol et al., 2012). There is a great need for approaches that consider both PTSD and depression symptoms together. For example, a study of symptom dimensions across several diagnostic categories (PTSD, MDD, healthy controls) showed that depression symptoms predicted impaired resting-state connectivity between the amygdala and dorsolateral prefrontal cortex, dorsal anterior cingulate cortex (ACC), and anterior insula, whereas anxiety symptoms predicted hyperconnectivity between the amygdala and subgenual ACC (Satterthwaite et al., 2016). These associations were observed irrespective of the primary diagnosis. Similar research efforts identifying heterogeneous symptom presentation in the trauma literature have focused on hyper-arousal versus dissociative symptom profiles (Lanius et al., 2010). In complex PTSD, which often involves dissociation, depressive symptoms were found to predict greater hippocampal activation to negative stimuli (Thomaes et al., 2013). Studies of this type can identify cross-cutting risk factors underlying multiple diagnoses, and instances in which abnormalities in brain function do not map cleanly onto diagnostic categories.

Many previous efforts have been made to define trauma-related symptom dimensions. For example, in PTSD, a recent longstanding conceptualization in the DSM-IV-TR outlined three symptom dimensions: re-experiencing, hyper-arousal, and avoidance/numbing symptoms (Association, 2000a). However, studies clustering symptoms in a data-driven manner supported the separation of avoidance versus numbing symptoms (King et al., 1998; Simms et al., 2002) leading to new symptom clusters for PTSD in the DSM-5 (Association, 2013). In depression, a two-factor solution has been observed, separating negative affect from somatic symptoms (Whisman et al., 2000). However, no widely accepted model has yet emerged which considers both PTSD and depression symptoms in a single model of psychological responses to trauma.

Here we constructed symptom dimensions using principal components analysis (PCA) of the individual items on the PTSD Symptom Scale (PSS) and Beck Depression Inventory (BDI). PCA analysis facilitated a parsimonious combined analysis of PTSD and depression symptoms because it: 1) defined symptom dimensions in a hypothesis-neutral manner, 2) allowed for the possibility that similar symptoms from both PSS and BDI might cluster together, and 3) addressed potential confounding effects of score range for scales with different numbers of items (17 items on PSS, 21 items on BDI). Principal components were then used to examine associations with hippocampus and amygdala volume, and function in episodic memory function. Participants completed an episodic memory encoding task during functional magnetic resonance imaging (fMRI), viewing neutral, negative, and positive emotional scenes. Thirty minutes following encoding, participants completed a cued recall task. We hypothesized that PTSD and depression symptom severity would be associated with reduced hippocampal and amygdala volumes. We also predicted that encoding-related hippocampal activity would be positively associated with re-experiencing symptoms, and negatively associated with depressive symptoms. Finally, we predicted that the amygdala's contribution to memory encoding, particularly for negative stimuli, would be positively associated with hyper-arousal, re-experiencing, and depressive symptoms.

2. Materials and methods

2.1. Participants

Participants were drawn from a larger study of risk factors for PTSD conducted in a low-socioeconomic status, urban cohort recruited in the general medical clinics of a large public hospital in Atlanta, GA. This study focused on women because of their higher risk for PTSD relative to men (Kessler et al., 2005). To minimize heterogeneity, we included only African-American women. Additional inclusion and exclusion criteria are listed in the Supplementary Methods. $N = 64$ trauma-exposed women completed the MRI study. MRI data were excluded from two participants for falx calcification leading to EPI signal dropout, two for technical problems with the scanner or stimulus presentation, one who fell asleep during scanning, and five participants due to excessive head motion (> 2 mm/volume). The final sample for fMRI analysis included 54 women; demographics and clinical characteristics are shown in Table 1. 21 participants met for current PTSD, and 33 did not and were considered trauma-exposed controls (TC). Study procedures were approved by the Institutional Review Board of Emory University and the Research Oversight Committee of Grady Memorial Hospital, and all participants provided written informed consent prior to participating.

2.2. Psychological assessment

PTSD symptoms were measured using the PSS (Foa and Tolin, 2000), a 17-item self-report measure of PTSD symptom severity over the last two weeks assessing DSM-IV-TR criteria for PTSD (Association, 2000b). Participants who met for current PTSD endorsed at least 1 re-experiencing symptom, 3 avoidance/numbing symptoms, and 2 hyper-arousal symptoms, following DSM-IV-TR. Depression symptoms were measured using the BDI, a 21-item self-report measure of symptom severity (Beck et al., 1988). Adult trauma exposure was quantified as the number of different types of traumas reported as occurring after the age of 18 on the Traumatic Events Inventory (TEI, Gillespie et al.,