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Unique insula subregion resting-state functional connectivity with amygdala complexes in posttraumatic stress disorder and its dissociative subtype

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ABSTRACT

The insula and amygdala are implicated in the pathophysiology of posttraumatic stress disorder (PTSD), where both have been shown to be hyper/hypoactive in non-dissociative (PTSD−DS) and dissociative subtype (PTSD+DS) PTSD patients, respectively, during symptom provocation. However, the functional connectivity between individual insula subregions and the amygdala has not been investigated in persons with PTSD, with or without the dissociative subtype. We examined insula subregion (anterior, mid, and posterior) functional connectivity with the bilateral amygdala using a region-of-interest seed-based approach via PickAtlas and SPM8. Resting-state fMRI was conducted with (n=61) PTSD patients (n=44 PTSD−DS; n=17 PTSD+DS), and (n=40) age-matched healthy controls. When compared to controls, the PTSD−DS group displayed increased insula connectivity (bilateral anterior, bilateral mid, and left posterior) to basolateral amygdala clusters in both hemispheres, and the PTSD+DS group displayed increased insula connectivity (bilateral anterior, left mid, and left posterior) to the left basolateral amygdala complex. Moreover, as compared to PTSD−DS, increased insula subregion connectivity (bilateral anterior, left mid, and right posterior) to the left basolateral amygdala was found in PTSD+DS. Depersonalization/derealization symptoms and PTSD symptom severity correlated with insula subregion connectivity to the basolateral amygdala within PTSD patients. This study is an important first step in elucidating patterns of neural connectivity associated with unique symptoms of arousal/interoception, emotional processing, and awareness of bodily states, in PTSD and its dissociative subtype.

1. Introduction

It has been argued that the neural circuitry of the insula – a region associated with monitoring internal bodily states, arousal, cognitive emotional evaluation (Critchley et al., 2004; Menon and Uddin, 2010; Craig, 2011; Cloutman et al., 2012), and the processing of homeostatic interactions with sensory-evoked emotions (Meier et al., 2015) – may partly underlie some of the symptoms experienced by individuals with posttraumatic stress disorder (PTSD) (Hopper et al., 2007; Lanius et al., 2010; Pitman et al., 2012; Weston, 2014). Notably, insula activation has been positively correlated to PTSD symptoms in response to script-driven imagery, response inhibition, pain perception, and fear acquisition/extinction (Hopper et al., 2007; Carrion et al., 2008; Mickleborough et al., 2011; Sripada et al., 2013). Previous research investigating the function of the insula in PTSD has found it to be hyperactive in response to trauma reminders (Etkin and Wager 2007; Hopper et al., 2007; Aupperle et al., 2012; Mazza et al., 2013), which has been suggested to be related to heightened detection of bodily

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arousal within PTSD patients (Pitman et al., 2012). By contrast, emerging evidence suggests that the dissociative subtype of PTSD (PTSD+DS) and dissociative symptoms are associated with reduced activation of the insular cortex (Hopper et al., 2007) and increased insula connectivity to the ventrolateral thalamus during symptom provocation (Lanius et al., 2005). The amygdala has also been shown to be a key region in PTSD, where similarly to the insula, hyper/hypoactivation has been associated with symptom modulation in non-dissociative subtype (PTSD−DS) and PTSD+DS patients, respectively (Hopper et al., 2007; Lanius et al., 2010, 2012; Shin and Liberzon, 2010; Mickleborough et al., 2011; Stevens et al., 2013; Weston, 2014). Studies have previously shown that the basolateral (BLA) and centromedial (CMA) amygdala complexes display unique patterns of resting-state functional connectivity between patients with PTSD and controls (Aghajani et al., 2016; Brown et al., 2014), and between PTSD−DS, PTSD+DS, and controls (Nicholson et al., 2015). Crucially, the insula and amygdala have direct structural and functional connections (Baur et al., 2013); however, the functional connectivity of this neural pathway remains poorly understood in PTSD. On balance, Sripada et al., (2012a) found increased functional connectivity between the insula and amygdala among PTSD patients at rest, as compared to trauma-exposed controls. Cisler et al. (2014) also report that repeated exposure to a traumatic memory increased connectivity between the right anterior insula and the amygdala and hippocampus, and Fonzo et al. (2010) report decreased anterior insula-amygdala connectivity during fearful face versus neutral face matching. At present, however, the functional connectivity patterns of insula subregions with respect to PTSD and its dissociative subtype, remains elusive and constitutes a gap in the PTSD literature.

Recent reviews (Craig, 2009, 2011; Kurth et al., 2010; Gasquoine, 2014) suggest unique functions of the anterior, mid, and posterior insular subregions, where each shows differential structural (Cloutman, 2012) and functional connectivity (Deen et al., 2011), and are involved in separate functional networks (Cauda et al., 2011; Deen et al., 2011). The anterior insula is associated with arousal/interoceptive awareness, cognitive emotional processing (Craig, 2009), heightened alertness, and autobiographical memory (Kurth et al., 2010). By contrast, the mid insula is implicated in the awareness of body movement/ownership, contains somatotopic representations of bodily affect associated with condition of the self, and is involved in integrating homeostatic representations with emotionally salient environmental stimuli (Craig, 2009). Finally, the posterior insular region has been identified as a multimodal convergence zone for sensory information and processing of interoceptive/exteroceptive information including pain, sensorimotor information, and body condition (Craig, 2009; Deen et al., 2011). Here, the functional connectivity patterns of individual insula subregions, which may have unique roles within the neural circuitry of the disorder and its dissociative subtype, remain unexplored. Research with respect to insula subregion-amygdala connectivity is particularly important, as PTSD is characterized by two different phenotypes presenting with contrasting symptoms related to insula and amygdala activation (Hopper et al., 2007; Lanius et al., 2010; Stein et al., 2013; Steuwe et al., 2012; Wolf et al., 2012).

Approximately 70% of PTSD patients exhibit symptoms of emotional undermodulation (Lanius et al., 2012; Weston, 2014). This group (PTSD−DS) is characterized by symptoms of exacerbated arousal and heightened monitoring/detection of bodily states (Lanius et al., 2010, 2015), which may be related to insula and amygdala hyperactivation (Lanius et al., 2010; Pitman et al., 2012), as well as vivid re-experiencing of traumatic memories (Hopper et al., 2007). By contrast, 15–30% of PTSD patients exhibit predominant symptoms of emotional overmodulation (Hopper et al., 2007; Lanius et al., 2012; Stein et al., 2013; Steuwe et al., 2012; Wolf et al., 2012), consisting of depersonalization, derealization, chronic emotional numbing, and attenuated awareness of emotions and interoception of bodily sensations — characteristic of PTSD+DS. These unique PTSD+DS symptoms may be in part mediated by altered neural circuitry and hypoactivation of both the insula and amygdala (Hopper et al., 2007; Lanius et al., 2010; Pitman et al., 2012; Weston, 2014; Nicholson et al., 2015). Accordingly, we compared patterns of anterior, mid, and posterior insular subregion functional connectivity to the amygdala, between controls, PTSD−DS, and PTSD+DS. Relative to controls, both patient groups were expected to show increased insula subregion connectivity to the amygdala, as PTSD has been associated with increased insula-amygdala connectivity at rest (Sripada et al., 2012a). Moreover, we hypothesized that insula subregion-amygdala connectivity would be altered between PTSD−DS and PTSD+DS patients, displaying unique connectivity patterns across the insula subregions

2. Methods

2.1. Participants

The sample consisted of ($n=61$) PTSD patients [($n=44$) PTSD−DS and ($n=17$) PTSD+DS] and ($n=40$) age-matched healthy controls (see Table 1 for descriptive statistics). A portion of the sample's fMRI data was published in a prior report ($n=36$ PTSD-DS, $n=13$ PTSD+DS, and $n=40$ healthy controls) (Nicholson et al., 2015). The exclusion criteria included: noncompliance with 3 T fMRI safety standards, significant untreated medical illness, a history of neurological or pervasive developmental disorders, previous head injury with loss of consciousness, pregnancy, and the use of psychotropic medications (within one month prior to the study). All participants were evaluated using the DSM-IV Structured Clinical Interview (SCID) (First, 1997), the Clinician Administered PTSD Scale (CAPS; PTSD cut-off score ≥ 50) (Blake et al., 1995), the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), Beck's Depression Inventory (BDI) (Beck et al., 1997), and the Multiscale Dissociation Inventory (MDI) (Briere et al., 2005). The CAPS is a structured interview for assessing core and associated symptoms of PTSD (Blake et al., 1995), the CTQ is a screening measure for maltreatment histories (such as abuse and neglect in childhood; Bernstein et al., 2003), BDI is a self-report inventory for measuring depression (Beck et al., 1997), and finally, the MDI is a standard 30-item test of 6 types of dissociative responses (Briere et al., 2005): disengagement, depersonalization, derealization, emotional constriction, memory disturbance, and identity dissociation.

Additional exclusion criteria for both PTSD groups included: diagnosis of bipolar disorder or schizophrenia, and alcohol or substance dependence/abuse within 6 months prior to participation in the study. Dissociative subtype classification consisted of patient scores greater than or equal to 2 on both frequency and intensity for either the CAPS depersonalization or derealization items (Nicholson et al., 2015). Additional exclusion criteria for the control group were current or past Axis-I or Axis-II disorders.

2.2. Procedure

Approval for the current study was received from Western University's ethics board and all participants provided written informed consent. Recruitment took place in London, Ontario through mental health professionals/clinics, and posters/advertisements. Participants took part in a 6-min resting-state scan, being instructed to relax, close their eyes, and let their minds