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Research paper

Brain structural anomalies in borderline and avoidant personality disorder patients and their associations with disorder-specific symptoms

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ABSTRACT

Background: Borderline personality disorder (BPD) and avoidant personality disorder (AvPD) are characterized by hyper-reactivity to negatively-perceived interpersonal cues, yet they differ in degree of affective instability. Recent work has begun to elucidate the neural (structural and functional) and cognitive-behavioral underpinnings of BPD, although some initial studies of brain structure have reached divergent conclusions. AvPD, however, has been almost unexamined in the cognitive neuroscience literature.

Methods: In the present study we investigated group differences among 29 BPD patients, 27 AvPD patients, and 29 healthy controls (HC) in structural brain volumes using voxel-based morphometry (VBM) in five anatomically-defined regions of interest: amygdala, hippocampus, medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC). We also examined the relationship between individual differences in brain structure and self-reported anxiety and affective instability in each group.

Results: We observed reductions in MPFC and ACC volume in BPD relative to HC, with no significant difference among patient groups. No group differences in amygdala volume were found. However, BPD and AvPD patients each showed a positive relationship between right amygdala volume and state-related anxiety. By contrast, in HC there was an inverse relationship between MPFC volume and state and trait-related anxiety as well as between bilateral DLPFC volume and affective instability.

Limitations: Current sample sizes did not permit examination of gender effects upon structure-symptom correlations.

Conclusions: These results shed light on potentially protective, or compensatory, aspects of brain structure in these populations–namely, relatively reduced amygdala volume or relatively enhanced MPFC and DLPFC volume.

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1. Introduction

Borderline personality disorder (BPD) and avoidant personality disorder (AvPD) are two serious and prevalent disorders marked by great interpersonal sensitivity, anxiety, and affective instability. BPD is a severe, pernicious mental disorder present in an estimated 2.7% of the population (Tomko et al., 2014) and characterized by heightened anxiety, unstable interpersonal relationships, significant affective instability, and a 10% suicide rate (Koenigsberg et al., 2014, 2001; Lieb et al., 2004; Skodol et al., 2002a). In recent years, the underlying neural mechanisms of BPD have begun to be explored using structural and functional neuroimaging modalities (Carpenter and Trull, 2013; Koenigsberg et al., 2014; Krause-Utz

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et al., 2014; Schmahl and Bremner, 2006; Schulze et al., 2016). However, significant questions remain, including the nature of the relationship between inter-individual variation in brain structure and disordered patterns of emotional, cognitive, and behavioral response (Kanai and Rees, 2011).

AvPD, a personality disorder with a prevalence rate comparable to BPD (American_Psychiatric_Association, 2013), is characterized by fears of criticism, rejection, disapproval and embarrassment in interpersonal situations, leading to social avoidance and inhibition. Thus, like BPD, it is marked by interpersonal hypersensitivity and anxiety, but unlike BPD, affective instability, anger and impulsivity are less prominent. The structural features and structural-affective correlates of AvPD have been unexamined. Comparing and contrasting these two disorders, which have important areas of phenomenological overlap and difference, affords a unique opportunity to identify the structural correlates of distinct affective and interpersonal symptoms.

Prior work has identified structural neural anomalies in BPD patients relative to healthy controls (HC), though evidence has been mixed in key frontolimbic regions, including those importantly related to negative emotional experience (e.g. amygdala) and episodic memory (e.g. hippocampus) and those that represent nodes of a network underlying the cognitive control of emotion, including medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC) (Krause-Utz et al., 2014; Ochsner et al., 2012; Schulze et al., 2016). The amygdala is a medial temporal lobe region consistently implicated in processing negative affect in BPD (Krause-Utz et al., 2014), AvPD (Denny et al., 2015), and many other psychiatric illnesses (Denny et al., 2009), as well as in HC given its importance in representing the threat value of a stimulus (LeDoux, 1996; Ochsner et al., 2012). Further, hippocampus, noted for its crucial role in episodic and autobiographical memory consolidation (Squire, 1992), has been shown to differentiate BPD patients from healthy controls in terms of structural volume (Schulze et al., 2016). MPFC, DLPFC, and ACC, by contrast, are associated with diverse cognitive control functions including mental state attribution (MPFC; Ochsner et al., 2012), selective attention and working memory (DLPFC; Curtis and D'Esposito, 2003; Ochsner et al., 2012) and attentional control (ACC; Fan et al., 2005) that each contribute to modulations of emotional intensity (Ochsner et al., 2012).

Several prior studies have indicated anomalous concentrations of gray matter in BPD relative to healthy controls in amygdala (Krause-Utz et al., 2014; Schulze et al., 2016), though there is mixed evidence as to the direction of the anomaly. *Reduced* (Depping et al., 2015; Niedtfeld et al., 2013; Soloff et al., 2008) and *greater* amygdala volume in BPD patients relative to healthy controls (Minzenberg et al., 2008) have both been reported. Still other work has examined structural differences between BPD patients and healthy controls with amygdala as a particular region-of-interest and reported no group difference in amygdala volume (Brambilla et al., 2004; Kuhlmann et al., 2013; Zetzsche et al., 2006). Importantly, some of this work has shown that greater BPD amygdala volumes predict *less* BPD symptom severity (Niedtfeld et al., 2013), while somewhat more evidence exists showing that greater amygdala volumes predict *greater* symptom severity (Depping et al., 2015; Zetzsche et al., 2006). Thus, the question of volumetric differences in amygdala between BPD patients and healthy controls–and, crucially, the clinical significance of such differences–is unresolved.

Hippocampal evidence, however, has been more consistent in implicating reduced structural volume in BPD patients relative to healthy controls (Driessen et al., 2000; Sala et al., 2011; Schmahl et al., 2009; Schulze et al., 2016). However, the relationship between individual differences in hippocampal volume and self-reported anxiety and affective instability is less clear, although some evidence has shown that, among BPD patients, relatively reduced hippocampal volume predicts greater aggressiveness (Sala et al., 2011; Zetzsche et al., 2007). Thus, we were motivated to examine hippocampus as a region-of-interest in this study.

Further, evidence has been mixed with regard to volumetric differences between BPD patients and healthy controls in MPFC, DLPFC, and ACC. In MPFC, evidence for or against volume differences is scarce. One study has shown ventral MPFC gray matter reductions in BPD patients relative to healthy controls (contiguous with volumetric reductions in ACC), though the same study also reported greater gray matter volumes in BPD patients relative to healthy controls in dorsal MPFC (Soloff et al., 2008). In DLPFC, a recent multimodal meta-analysis has shown evidence of *increased* gray matter volume in BPD patients relative to HC (Schulze et al., 2016), though some individual studies have found no significant group difference in gray matter volume (Brambilla et al., 2004; Sala et al., 2011) as well as an inverse relationship between DLPFC volume and impulsiveness in BPD patients (Sala et al., 2011). In ACC, several studies have indicated that BPD patients show reduced volumes relative to healthy controls (Goodman et al., 2011; Hazlett et al., 2005; Minzenberg et al., 2008; Niedtfeld et al., 2013; Soloff et al., 2008), including one study where greater ACC volume in BPD patients predicted less BPD symptom severity (Niedtfeld et al., 2013). However, other recent reports have specifically examined volumetric differences in ACC and have not found evidence for a difference between BPD patients and healthy controls (Depping et al., 2015; Kuhlmann et al., 2013; Labudda et al., 2013). Thus, similar to amygdala, studies examining structural abnormalities in MPFC, DLPFC, and ACC in BPD relative to healthy controls have reached varying conclusions.

With regard to AvPD patients, to our knowledge there are only two published neuroimaging reports in the literature, both of which were functional neuroimaging studies (Denny et al., 2015; Koenigsberg et al., 2014). Denny and colleagues (2015) found evidence for amygdala hyper-reactivity in AvPD patients relative to healthy controls when anticipating engaging in explicit emotion regulation via cognitive reappraisal, whereas Koenigsberg et al. (2014) did not find evidence of greater amygdala recruitment in AvPD patients relative to healthy controls when repeatedly viewing negative emotional pictures. However, structural differences in AvPD have remained unexplored. Moreover, a direct comparison between the neural structure of BPD and AvPD, two personality disorders with different phenotypic presentations, could help to better understand the relationship between brain structural volume and personality disorder symptoms.

Thus, the present study sought to examine structural differences in gray matter volume among BPD patients, AvPD patients, and healthy controls using voxel-based morphometry (VBM) in a priori-motivated, unbiased, anatomically-defined regions-of-interest. Importantly, we further investigated the relationship between observed structural differences and inter-individual variation in disorder-relevant measures of anxiety and affective instability. Given the varied structural neuroimaging evidence reviewed above in a priori regions of interest including the amygdala, hippocampus, MPFC, DLPFC, and ACC, we did not make predictions regarding the direction of volumetric main effects. However, greater gray matter volume in regions strongly linked to processing negative affect (i.e. amygdala) was expected to predict greater self-reports of negative affect within and across groups, and greater gray matter volume in regions linked to cognitive control (i.e. MPFC, DLPFC, and ACC) was expected to predict diminished self-reports of negative affect within and across groups.