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Frontolimbic structural changes in borderline personality disorder

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Abstract

Objective: Frontolimbic dysfunction is observed in borderline personality disorder (BPD), with responses to emotional stimuli that are exaggerated in the amygdala and impaired in the anterior cingulate cortex (ACC). This pattern of altered function is consistent with animal models of stress responses and depression, where hypertrophic changes in the amygdala and atrophic changes in the ACC are observed. We tested the hypothesis that BPD patients exhibit gross structural changes that parallel the respective increases in amygdala activation and impairment of rostral/subgenual ACC activation.
Methods: Twelve unmedicated outpatients with BPD by DSM-IV and 12 normal control (NC) subjects underwent a high-resolution T1-weighted structural MRI scan. Relative gray matter concentration (GMC) in spatially-normalized images was evaluated by standard voxel-based morphometry, with voxel-wise subject group comparisons by t test constrained to amygdala and rostral/subgenual ACC.
Results: The BPD group was significantly *higher* than NC in GMC in the amygdala. In contrast, the BPD group showed significantly *lower* GMC than the NC group in left rostral/subgenual ACC.
Conclusions: This sample of BPD patients exhibits gross structural changes in gray matter in cortical and subcortical limbic regions that parallel the regional distribution of altered functional activation to emotional stimuli among these same subjects. While the histological basis for GMC changes in adult clinical populations is poorly-known at present, the observed pattern is consistent with the direction of change, in animal models of anxiety and depression, of neuronal number and/or morphological complexity in both the amygdala (where it is increased) and ACC (where it is decreased).

Keywords: Borderline personality disorder; Frontolimbic; Amygdala; Anterior cingulate cortex; Gray matter; Voxel-based morphometry

1. Introduction

Borderline personality disorder is a serious, chronic disorder characterized by disturbances of impulse control, affect and interpersonal relationships. The neurobiological basis of the last two symptom domains remains poorly-characterized. However, emerging evidence from functional neuroimaging studies suggests that these symptoms are related to dysfunction of fronto-limbic circuits (Posner et al., 2003). Among subcortical limbic structures, the amygdala mediates the most extensive range of social and emotional processes (LeDoux, 2000; Davidson, 2002). Accordingly, BPD patients exhibit exaggerated amygdala responses to social and emotional stimuli (Donegan et al., 2003; Herpertz et al., 2001; Minzenberg et al., 2007). Among frontal cortical areas in BPD, the anterior cingulate cortex (ACC) shows impaired *in vivo* serotonin synthesis capacity (Leyton et al., 2001), impaired serotonergic modulation of metabolic activity (Siever et al., 1999; New et al., 2002), and greater deactivation in response to scripts eliciting memories of interpersonal abandonment (Schmahl et al., 2003a). ACC dysfunction

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in turn may be related to both emotion dysfunction and impaired cognitive control observed in BPD (Posner et al., 2002; Minzenberg et al., in press). Evidence for these reciprocal changes has been found in post-traumatic stress disorder (PTSD) (Shin et al., 2004), depression (Mayberg et al., 1999) and substance abuse (London et al., 2004), which are disorders related to BPD. We have also found elevated amygdala activation, and impaired modulation of task-related ACC deactivation in response to facial emotion, measured by functional MRI (Minzenberg et al., 2007).

One crucial issue that remains largely unaddressed in the study of frontolimbic dysfunction in BPD is the relationship between altered function and altered *structure* of these implicated regions. A variety of rodent models of stress and affective disorders have suggested a morphological basis for the functional alterations found in BPD and related disorders (see Radley and Morrison, 2005 for review). For example, chronic immobilization stress is associated with *hypertrophic* neuronal changes in the basolateral nucleus of the amygdala, including enhanced dendritic arborization (Vyas et al., 2002) and spine density, which parallels the emergence of anxiety-like behavior (Mitra et al., 2005). The dendritic changes may persist after a stress-free period (Vyas et al., 2004). Increased neuronal density in the lateral nucleus of the amygdala is found in adult rats subject to prenatal stress (Salm et al., 2004), and enhanced amygdala neurogenesis may be found in adult rats subject to either social stressors (Fowler et al., 2002) or bilateral olfactory bulbectomy (an established model of depression) (Keilhoff et al., 2006). In contrast, in the ACC and adjacent medial PFC, consistent *atrophic* changes are found in response to stressors. After restraint stress, decreased length and branching of apical dendrites are observed in layer II/III pyramidal cells in ACC and medial PFC (Radley et al., 2004, 2006; Brown et al., 2005; Cook and Wellman, 2004), which may be reversible (Radley et al., 2006). Apical dendritic reorganization of these neurons also occurs in response to chronic exogenous corticosterone administration (Wellman, 2001). Decreased spine density is also observed in layer II/II pyramidal cells of medial PFC after restraint stress (Radley et al., 2006), daily injections (Seib and Wellman, 2003) and social isolation (Silva-Gomez et al., 2003). This literature indicates that a variety of models of anxiety and depression are associated with changes in neuronal number and morphological complexity, which may be variably persistent. These changes can reasonably be expected to have effects, in predictable directions, on measures of both gross structure and function of these respective brain regions in adults who suffer from these symptoms.

Thus far, the findings of volumetric neuroimaging studies of adult populations with these disorders remains varied. Several groups have reported increased amygdala volumes among patients with bipolar affective disorder, relative to healthy control subjects (Altshuler et al., 1998, 2000; Strakowski et al., 1999; Brambilla et al., 2003). Bipolar affective disorder shares many clinical features with BPD, including affective instability, impulsivity and interpersonal disturbances, and may be overrepresented in BPD patients as a comorbid condition (Smith et al., 2004; Magill, 2004). Increases in amygdala volume have also been found in patients experiencing a first episode of major depression, in comparison to both healthy controls (Frodl et al., 2002) and patients with recurrent major depression (Frodl et al., 2003), and in temporal lobe epilepsy patients with comorbid depression (Tebartz van Elst et al., 2000) or dysthymia (Tebartz van Elst et al., 1999), relative to both epilepsy patients without comorbid mood disorders and healthy controls. However, other studies have found no change or reduced volume of the amygdala in major depression and anxiety disorders such as PTSD (reviewed in Anand and Shekhar (2003), Sheline (2000)). In BPD, some studies have found no change in amygdala volume (Brambilla et al., 2004) while others have found reduced volume (Tebartz van Elst et al., 2003; Rusch et al., 2003; Driessen et al., 2000; Schmahl et al., 2003b). Among these latter studies, one excluded parts of the centromedian nucleus of the amygdala from the analysis (Tebartz van Elst et al., 2003), one employed a comparison group with a high incidence of mood, anxiety or substance use disorders (Schmahl et al., 2003b), and one reported stereotactic coordinates for a maximal gray matter volume difference (with voxel-based morphometry) that appears to be clearly posterior to the amygdala proper (and into the hippocampus), by either the MNI coordinate system or using the Brett-transform to Talairach space (Rusch et al., 2003). Therefore, it remains uncertain whether patients with BPD exhibit changes in amygdala volume relative to healthy control subjects. In contrast, ACC volume appears to be decreased in BPD, in both studies in which it has been examined (Tebartz van Elst et al., 2003; Hazlett et al., 2005), as it is in bipolar affective disorder (Lochhead et al., 2004; Lyoo et al., 2004; Sassi et al., 2004).

1.1. The present study

The literature addressing animal models of mood and anxiety disorders therefore suggests a morphological basis for functional changes in BPD, and there is some supportive evidence from volumetric studies of adults with mood disorders as well. Given the findings previously reported in the present study sample, of increases in amygdala activation and decreases in ACC activation to expressions of fear, we set out to test whether these functional changes are accompanied by underlying structural changes in these same brain regions. We employed voxel-based morphometry (VBM) in order to test this hypothesis. VBM offers several advantages in this regard. It is an unbiased, fully-automated procedure that involves the registration of each subject's brain into a standard stereotactic space, to account for global variation in size and shape of individual brains, followed by the segmentation of gray matter from white matter and cerebrospinal fluid (Mechelli et al.,