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Reduced cortical and subcortical volumes in female adolescents with borderline personality disorder

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ABSTRACT

Volumetric alterations in limbic structures have been detected in adults, but not in adolescents with borderline personality disorder (BPD). We examined adolescents in the early stages of BPD to provide a unique opportunity to investigate which parts of the brain are initially affected by the disorder before confounding factors such as long-term medication or chronicity can mask them. A group of 60 right-handed female adolescents between 14 and 18 years of age (20 patients with BPD, 20 clinical controls, and 20 healthy controls) underwent magnetic resonance imaging (MRI). Focus was on the examination of hippocampal and amygdalar volume differences. Furthermore, a cortical thickness analysis was conducted. FreeSurfer software detected significant group differences in the right and left hippocampus and in the right amygdala. Additionally, significant volume reductions in frontal (right middle frontal gyrus, orbital part of the inferior frontal gyrus bilaterally), and parietal regions (superior parietal gyrus bilaterally) were found in adolescents with BPD compared with controls. No group differences in cortical thickness were revealed.

1. Introduction

Subjects who are affected by borderline personality disorder (BPD) suffer from mood instability and impulsiveness, show dysregulated behaviors such as non-suicidal self-injury, or have a history of multiple suicide attempts (Selby et al., 2009). They have difficulties in maintaining interpersonal relationships or trusting other people, and they may also experience cognitive symptoms such as paranoia or severe dissociative symptoms. The prevalence of BPD in community samples is estimated to be approximately 1% (Paris, 2005) and rises in psychiatric settings to 10% in outpatients and 25% in inpatients (Leichsenring et al., 2011).

Several studies demonstrated that BPD is related to neuroanatomical changes (Schmahl and Bremner, 2006). However, there are differences between adults and adolescents with BPD.

1.1. Neuroimaging findings in adults with BPD

Adults with BPD exhibit structural and functional alterations in limbic structures such as the amygdala and the hippocampus, but also in prefrontal regions, in the cingulate cortex and in the parietal lobule in comparison to healthy controls (HC) (Irle et al., 2005, 2007; Lis et al., 2007).

Limbic structures, the prefrontal regions, and the anterior cingulate cortex (ACC) have functions that are related to the psychopathology of BPD, such as impulsivity, emotional instability, and impulsive aggression (Tebartz van Elst et al., 2003). With regard to limbic structures, studies reported alterations in the hippocampus and the amygdala in adults with BPD (Schmahl and Bremner, 2006; Nunes et al., 2009). A well-replicated result is the finding of a smaller volume in the hippocampus bilaterally in adult patients with BPD in comparison to HC (Driessen et al., 2000; Schmahl et al., 2003; Tebartz van Elst et al., 2003; Nunes et al., 2009; Weniger et al., 2009).

Although the results concerning the amygdala are not as conclusive as the results regarding the hippocampus in adult subjects with BPD, there are several studies indicating alterations in the amygdala in adult samples with BPD. However, the direction of the alteration is not yet established. Some studies and a meta-analysis revealed a volumetric reduction of the amygdala bilaterally (Driessen et al., 2000; Schmahl et al., 2003; Tebartz van Elst et al., 2003; Nunes et al., 2009; Weniger et al., 2009), whereas another study only detected a grey matter loss in the left amygdala (Rüsch et al., 2003). One study even found increased grey matter concentrations in the amygdala bilaterally (Minzenberg et al., 2008). A bilateral enlargement of the amygdala was detected in patients with BPD and comorbid depression (Zetzsche et al., 2006).

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Still under debate is the impact of comorbid post-traumatic stress disorder (PTSD) on limbic grey matter volumes in patients with BPD. Three meta-analyses and a very recently published study examined the influence of PTSD on amygdalar and hippocampal volumes in patients with BPD, but they yielded conflicting findings (no effect of comorbid PTSD: Niedtfeld et al., 2013; Ruocco et al., 2012; decreased amygdalar volume in BPD without comorbid PTSD: de-Almeida et al., 2012; decreased hippocampal volumes in BPD with comorbid PTSD: Rodrigues et al., 2011).

With regard to frontal brain structures and the ACC, a smaller frontal lobe (Lyoo et al., 1998), significant volume reductions of the left orbitofrontal cortex (OFC) and the right ACC (Tebartz van Elst et al., 2003), reduced grey and increased white matter volume of the ACC and the posterior cingulate cortex (Hazlett et al., 2005), and reduced grey matter concentrations in the left rostral/subgenual ACC (Minzenberg et al., 2008) were found in adults with BPD when compared with HC.

In parietal areas, grey matter volume decreases were detected in the right parietal cortex (Irle et al., 2005) and in the right superior parietal cortex in female adults with BPD (Irle et al., 2007), as well as in the left superior parietal cortex and the right inferior parietal lobe in men with BPD when compared with HC (Völlm et al., 2009).

Concerning white matter fiber tracks, findings include a decreased white matter microstructural integrity in the inferior frontal brain region (Grant, et al., 2007), a decreased fractional anisotropy (FA) in the genu and rostral areas of the corpus callosum and of the prefrontal white matter fasciculus bilaterally in adults with BPD (Carrasco et al., 2012), and a reduced interhemispheric connectivity of the left and right dorsal ACCs in patients with BPD and comorbid ADHD compared with HC (Rüsch et al., 2010).

1.2. Neuroimaging findings in adolescents with BPD

Neuroanatomical changes in adult subjects with BPD are probably not only caused by neuroanatomical correlates of the disorder itself, but also by confounding factors such as long-term medication or the process of chronicity. Neuroimaging studies investigating adolescent subjects with BPD are sparse, but they shed light on neuroanatomical changes caused by BPD directly, since adolescents have in most cases not received long-term medication and effects of chronicity are minimized.

In contrast to adult samples with BPD, no volumetric differences in limbic structures have been revealed in adolescents. Only a higher grey matter volume in the left OFC than in the right OFC was reported in adolescents with BPD, indicating a reversal of the normal right-left OFC symmetry in HC (Chanen et al., 2008). Other studies report a reduced grey matter volume of the left ACC (Whittle et al., 2009) and of the ACC bilaterally (Goodman et al., 2011) as well as a shortened adhesio interthalamica (Takahashi et al., 2009) in subjects with BPD when compared with HC. In a very recent diffusion tensor imaging study, reduce FA in the inferior longitudinal fasciculus, in the uncinate, and in the occipitofrontal fasciculi was found in adolescents with BPD compared with HC (New et al., 2013).

In our own voxel-based morphometry (VBM) study using statistical parametric mapping (SPM5) (Ashburner and Friston, 2005, 2000) as the method of analysis, we detected a volumetric reduction in the left OFC and the dorsolateral prefrontal cortex (DLPFC) bilaterally in adolescent females with BPD in comparison to HC, but no changes in any limbic structure (Brunner et al., 2010). Analyzing the same data set with regard to differences in white matter fiber tracks, we found white matter changes in a part of the limbic system, namely the fornix, in inferior frontal brain areas as well as more widespread changes in areas related to the heteromodal association cortex (HASC) (Buchanan et al., 2004; Ross and Pearlson, 1996) in the sample of BPD subjects, indicating an involvement of brain areas related to emotion regulation and emotion cognition (Maier-Hein et al., 2014). Thus, our morphometric study points to alterations in BPD restricted only to prefrontal brain areas, whereas our study analyzing white matter fiber tracks argues for a more widespread involvement of different brain structures in adolescents with BPD, including the limbic system.

1.3. Aims and hypotheses

In our earlier VBM study using SPM5 (Ashburner and Friston, 2005, 2000), we did not only expect volumetric changes in frontal areas, but also in limbic structures, in the BPD group when compared with clinical controls (CC) and HC (Brunner et al., 2010). However, we could not detect alterations in any limbic structure using SPM5. Analyzing the same data set with regard to differences of white matter fiber tracts between the groups, we detected a more widespread involvement of several brain areas, also including a structure of the limbic system (Maier-Hein et al., 2014).

This divergence of the results of our studies, although obtained in the same data set, led us to reanalyze the volumes between the groups using another technique than SPM5. We decided to reanalyze the data using FreeSurfer software (Dale et al., 1999; Fischl et al., 1999) as FreeSurfer is claimed to be an excellent method to analyze subcortical structures. Two earlier studies that compared different analytic methods in adult samples concluded that FreeSurfer displayed the best volumetric results with regard to limbic structures (Tae et al., 2008; Dewey et al., 2010). Assuming that FreeSurfer would show the same high-quality standards when analyzing limbic structures in adolescent samples, we deemed it a suitable method for a reanalysis of the data set. We expected to find alterations in limbic structures, especially the amygdala and the hippocampus, in adolescent girls with BPD when compared with CC and HC. Furthermore, we expected volumetric alterations in frontal areas in the BPD group as already shown by our own VBM study (Brunner et al., 2010) and a study by Chanen et al. (2008). Based on the results of other studies using samples with subjects suffering from BPD, we expected volumetric decreases in the ACC and in the parietal lobe (Irle et al., 2007; Chanen et al., 2008; Takahashi et al., 2009; Brunner et al., 2010; Goodman et al., 2011).

Additionally, we used FreeSurfer to examine whether adolescents with BPD exhibit alterations in cortical thickness in neuroanatomical structures that showed volumetric differences in previous studies (Chanen et al., 2008; Takahashi et al., 2009; Whittle et al., 2009; Brunner et al., 2010; Goodman et al., 2011). Cortical thickness is, together with the cortical surface area, a determinant of the size of grey matter volume (Hutton et al., 2008; Panizzon et al., 2009; Winkler et al., 2010). Thus, an examination of cortical thickness may give a deeper insight into the underlying mechanisms responsible for volumetric changes of neuroanatomical structures in adolescents with BPD.

Due to the results of previous studies, we expected reduced cortical thickness in the BPD group in frontal and cingulate brain areas (Chanen et al., 2008; Takahashi et al., 2009; Whittle et al., 2009; Brunner et al., 2010; Goodman et al., 2011).

2. Methods

2.1. Subjects

The sample consisted of 60 right-handed adolescent girls between 14 and 18 years of age. Patients with a lifetime diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, pervasive developmental disorder, alcohol or drug dependence, or neurological disease were excluded as well as girls with a body