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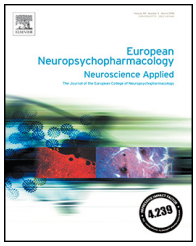

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Common and distinct patterns of abnormal cortical gyrification in major depression and borderline personality disorder

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Abstract
Abnormal gray matter volume has been consistently reported in patients with major depressive disorder (MDD), but markers of cortical neurodevelopment have been rarely investigated. Also, it is unclear whether there exist common versus distinct spatial patterns of abnormal cortical development across different disorders presenting with negative emotions and deficient affective regulation. In this study, we used structural MRI at 3T to investigate the local gyrification index (LGI), a marker of fetal/infant neurodevelopment, in adult female patients with MDD ($n = 22$), in adult female patients with borderline personality disorder (BPD) ($n = 17$), and in controls ($n = 22$). Reduced cortical folding of the precuneus, the superior parietal gyrus and the parahippocampal gyrus was found in both MDD and BPD patients when compared to controls ($p < 0.05$, cluster-wise probability [CWP] corrected). MDD patients showed additional hypogyrification of the middle frontal gyrus and the fusiform gyrus when compared to both controls and BPD patients ($p < 0.05$, CWP corrected). In MDD patients, lower LGI of prefrontal regions was significantly associated with the age of disease onset and with the number of depressive episodes. In BPD patients, lower LGI of orbitofrontal regions was associated with impulsivity.

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Our findings suggest abnormal early cortical development in MDD, affecting brain regions that have been frequently implied in MDD pathophysiology. However, LGI abnormalities may not be specific for MDD, since MDD and BPD patients also exhibited common patterns of hypogyrification. Hypogyrification of cortical regions associated with higher-order cognition appears to be most pronounced in MDD. Abnormal early cortical neurodevelopment may mediate vulnerability to disorders of emotion.

1. Introduction

There is now a well-established pattern of brain volume anomalies in patients with major depressive disorder (MDD). Robust meta-analytic evidence suggests lower gray matter volume of the hippocampus, the cingulate cortex and the dorsolateral prefrontal cortex in patients with acute MDD (Bora et al., 2012; Koolschijn et al., 2009; Zhao et al., 2014). Most of this evidence is based on studies that used voxel-based morphometry (VBM). VBM investigations have also yielded a multitude of structure-symptom correlates (Leung et al., 2009; Mak et al., 2009; Vasic et al., 2008). However, the causality between regional brain atrophy and the clinical onset and/or course of MDD has remained largely unresolved. Only a limited number of longitudinal brain imaging studies are available in MDD research (Arnone et al., 2013; Frodl et al., 2008; Soriano-Mas et al., 2011). At this point, it is largely unknown to what extent brain volume anomalies in MDD patients are present premorbidly, possibly indicating vulnerability to depression, or to what extent they develop as a consequence of the disorder. For now, it has not been possible to establish brain volume measurements as markers for either depression vulnerability or (current) depression severity.

Altered neurodevelopment has been linked to an increased lifetime risk for MDD (Ansorge et al., 2007; Lima-Ojeda et al., 2017). In this view, aberrant maturation of the brain's cognitive and emotional systems may result in a greater likelihood for the occurrence of MDD and/or in a more severe course of MDD. Neuroimaging markers of brain development have been available for some years now (Schaer et al., 2012) and they have been increasingly applied to study neuropsychiatric disorders (Bos et al., 2015; Shaw et al., 2012), including a limited number of investigations in MDD patients (Han et al., 2017; Nixon et al., 2014; Peng et al., 2015; Zhang et al., 2009). Markers of neurodevelopment are associated with a particular stage of brain maturation, i.e. with fetal/intrauterine, infant, childhood or adolescent neurodevelopment. Neurodevelopmental markers promise to capture mechanisms related to disease vulnerability. In neuroimaging research of MDD, for the above-mentioned reasons, such information is highly anticipated.

There is some consensus about the principal brain regions involved in MDD (Bora et al., 2012; Koolschijn et al., 2009; Zhao et al., 2014). However, the candidate regions for depression are also relevant to various other psychiatric conditions, including posttraumatic stress disorder (PTSD) (O'Doherty et al., 2017) and borderline personality disorder (BPD) (Nunes et al., 2009; Ruocco et al., 2012). Indeed, the specificity of neural change to a clinical diagnosis of a psychiatric disorder is often unclear (Goodkind et al., 2015). Current psychiatric nosology and neural underpinnings may not be congruent (Cuthbert, 2014). This disparity has been a major obstacle to the field of biological psychiatry, preventing the translation of neuroimaging advances into clinical practice. Greater consistency between clinical diagnoses and neurobiological changes could be achieved, if neural abnormalities that are distinct for a certain disorder could be differentiated from less specific neurobiological changes found commonly across multiple psychiatric conditions (Goodkind et al., 2015). In this regard, transdiagnostic studies which compare patients that share key clinical symptoms (such as negative emotions and deficient affective regulation) have proven to be of neuroscientific and clinical interest (Depping et al., 2015; Depping et al., 2016).

In this study, we investigated the regional gyrification index (LGI) in patients with MDD and in patients with borderline personality disorder (BPD). The LGI is a measure of the degree of cortical folding, i.e. gyrification, at specific points of the cortical surface (Schaer et al., 2012). The process of gyrification occurs during fetal and infant life (Zilles et al., 2013) and it is closely linked to the early development of cortical connectivity (Tallinen et al., 2016). Higher LGI values reflect higher connectivity, possibly indicating greater "cortical complexity" (Dubois et al., 2008; Tallinen et al., 2016). It has been suggested that the LGI remains stable during childhood, adolescence and adulthood (Zilles et al., 2013). Subsequently, it has been concluded that LGI measurements in adults may capture early, i.e. fetal/infant, neurodevelopment (Han et al., 2017; Nixon et al., 2014; Peng et al., 2015; Shaw et al., 2012; Zhang et al., 2009). Based on this assumption, the LGI has been repeatedly investigated in developmental disorders, including autism (Bos et al., 2015) and attention deficit hyperactivity disorder (ADHD) (Shaw et al., 2012).

Here, we essentially followed a transdiagnostic approach, i.e. we were interested if different disorders of emotion, i.e. MDD and BPD, would show distinct vs. common patterns of abnormal cortical gyrification. Common mechanisms of disease in MDD and BPD are plausible (Goodman et al., 2010; Koenigsberg et al., 1999): First, we could previously demonstrate that there may be common brain atrophy in MDD and BPD (Depping et al., 2015; Depping et al., 2016). Second, while MDD and BPD have distinct clinical features – acute MDD is characterized by persistent sad mood, anhedonia, fatigue, cognitive impairment and neurovegetative signs (Hasler et al., 2004), BPD is characterized by affective shifts, impulsivity and interpersonal sensitivity (Goodman et al., 2010) –, it is noteworthy that the emotional trait of affective instability has also been described in MDD patients (Thompson et al., 2011), as much as BPD patients may show enduring mood changes like chronic dysphoria (Zanarini et al., 2007). MDD and BPD can essentially be

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