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Research report

Specificity of abnormal brain volume in major depressive disorder: A comparison with borderline personality disorder

Malte S. Depping [a], Nadine D. Wolf [b], Nenad Vasic [c], Fabio Sambataro [d], Philipp A. Thomann [a], R. Christian Wolf [a,b,*]

[a] Center for Psychosocial Medicine, Department of General Psychiatry, University of Heidelberg, Heidelberg, Germany
[b] Department of Psychiatry, Psychotherapy and Psychosomatics, Saarland University, Homburg, Germany
[c] Department for Forensic Psychiatry and Psychotherapy at the District Hospital Günzburg, Ulm University, Ulm, Germany
[d] Brain Center for Motor and Social Cognition@UniPR, Istituto Italiano di Tecnologia, Parma, Italy

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ABSTRACT

Background: Abnormal brain volume has been frequently demonstrated in major depressive disorder (MDD). It is unclear if these findings are specific for MDD since aberrant brain structure is also present in disorders with depressive comorbidity and affective dysregulation, such as borderline personality disorder (BPD). In this transdiagnostic study, we aimed to investigate if regional brain volume loss differentiates between MDD and BPD. Further, we tested for associations between brain volume and clinical variables within and between diagnostic groups.
Methods: 22 Females with a DSM-IV diagnosis of MDD, 17 females with a DSM-IV diagnosis of BPD and without comorbid posttraumatic stress disorder, and 22 age-matched female healthy controls (HC) were investigated using magnetic resonance imaging. High-resolution structural data were analyzed using voxel-based morphometry.
Results: A significant ($p < 0.05$, cluster-corrected) volume decrease of the anterior cingulate cortex (ACC) was found in MDD compared to HC, as opposed to volume decreases of the amygdala in BPD compared to both HC and MDD. Sensitivity and specificity of regional gray matter volume for a diagnosis of MDD were modest to fair. Amygdala volume was related to depressive symptoms across the entire patient sample.
Limitations: Potential limitations of this study include the modest sample size and the heterogeneous psychotropic drug treatment.
Conclusions: ACC volume reduction is more pronounced in MDD with an intermediate degree of volume loss in BPD compared to HC. In contrast, amygdala volume loss is more pronounced in BPD compared to MDD, yet amygdala volume is associated with affective symptom expression in both disorders.

1. Introduction

Evidence for abnormal brain volume in major depressive disorder (MDD) comes from a multitude of structural neuroimaging studies comparing MDD subjects with healthy controls (Frodl et al., 2008; Cheng et al., 2010; van Tol et al., 2010). Consistently, recent meta-analyses of primary studies employing voxel-based morphometry (VBM) have pointed towards gray matter reductions of the anterior cingulate cortex (ACC) as the most robust structural brain anomaly in MDD relative to healthy participants (Bora et al., 2012; Du et al., 2012; Lai, 2013). These investigations have reinforced existing neuroanatomical models of affective disorder. MDD pathophysiology appears to be characterized by impaired modulation of activity within a cortico-limbic circuitry, along with alterations in the functional organization of multiple brain networks implicated in emotional processes (Diener et al., 2012; Sacher et al., 2012; Wang et al., 2012). Findings from structural and functional neuroimaging methods appear to converge on a similar pattern of brain regions that appears to be relevant for this disorder (Price and Drevets, 2010). So far, however, it is unclear whether brain volume abnormalities in MDD are specific for this disorder since they may also reflect transdiagnostic structural brain alterations. Indeed, in contrast to the extensive literature on differences in brain morphology between MDD patients and healthy controls, neuroimaging studies comparing differences in brain structure between MDD and other diagnostic entities are scarce (Kempton et al., 2011). However, such investigations could beneficially inform both clinical and neurobiological research: Contrasting brain structure between two disorders may facilitate the differentiation of neural substrates specific for different diagnostic categories, if such neural

* Correspondence to: Department of Psychiatry, Psychotherapy and Psychosomatics, Saarland University, Kirrberger Str. 1, 66421 Homburg, Germany. Tel.: +49 6841 16 24305; fax: +49 6841 16 24270.
E-mail address: christian.wolf@uks.eu (R. Christian Wolf).

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substrates would indeed characterize a distinct diagnostic entity. These studies may also help detecting abnormal brain structure that is associated with transdiagnostic psychopathology, i.e. with symptoms common to disorders being compared. Such investigations pertain to the intriguing issue of limited associations between neurobiology and current clinical diagnoses (Cuthbert, 2014).

MDD and borderline personality disorder (BPD) are conceptualized as distinct disorders: BPD is characterized by emotional dysregulation, with additional components of impulsivity and interpersonal sensitivity (Goodman et al., 2010). MDD is characterized by a temporally more stable phenotype including mood bias toward negative emotions, impaired reward function, impaired learning and memory, impaired executive cognitive function, neurovegetative signs, and psychomotor change (Hasler et al., 2004). Affective shifts in BPD are considered to be transient and reactive as opposed to a more sustained alteration of mood in MDD (Goodman et al., 2010). However, symptoms representing enduring aspects of BPD have been shown to specifically include affective alterations, e.g. chronic dysphoria (Zanarini et al., 2007). Furthermore, MDD has been associated with maladaptive emotion regulation strategies (Aldao et al., 2010), as well as with the emotional trait of affective instability (Thompson et al., 2011). Essentially, both disorders share dimensions of negative affectivity and deficits in emotion regulation (Skodol et al., 2002; Chanen et al., 2007; Cheavens and Heiy, 2011). The phenotypical commonalities of both disorders, their high rate of comorbidity (Zanarini et al., 1998; Koenigsberg et al., 1999), and their interactions in case of comorbid presentation (Gunderson et al., 2014) have been interpreted as evidence for common biological features of MDD and BPD (Koenigsberg et al., 1999; Goodman et al., 2010). In this regard, BPD patients constitute a suitable clinical collective to be compared with MDD patients in transdiagnostic neuroimaging research.

Some single studies have argued that BPD patients exhibit abnormalities in brain volume that parallel altered brain morphology in individuals with MDD (Minzenberg et al., 2008). Yet, meta-analyses of structural neuroimaging studies in BPD highlight reductions of hippocampi and amygdalae as the most consistently demonstrated structural abnormality in BPD patients compared to healthy controls (Nunes et al., 2009; Ruocco et al., 2012). The disorder's core symptoms, dysfunctional affect regulation, impulsivity, and interpersonal sensitivity, are in good accordance with the assumed functions of amygdala and hippocampus in emotional and cognitive processing. Discrepant findings between single studies and meta-analyses neuroimaging studies of BPD may essentially be related to clinical heterogeneity of recruited samples, as comorbidity or gender have been identified as potential confounds in this type of research (Niedtfeld et al., 2013).

In this study, we investigated brain volume differences in MDD as compared to both healthy participants and BPD patients. To reduce potential gender bias and to minimize clinical heterogeneity we chose to study female individuals only, and to exclude BPD patients with comorbid posttraumatic stress disorder (PTSD) or bipolar disorder. Exclusion criteria for MDD patients were any lifetime or comorbid Axis I and Axis II disorders according to DSM-IV-TR criteria. The main objectives of this study were twofold: First, in regions consistently identified in meta-analyses of VBM studies in MDD and BPD, i.e. ACC in MDD (Bora et al., 2012; Du et al., 2012; Lai, 2013) and amygdala in BPD (Nunes et al., 2009; Ruocco et al., 2012), we tested the hypothesis that regionally abnormal brain volume would be specific for either disorder category. We predicted that greater cortical volume reductions would be detected in MDD compared to BPD, and that greater medial temporal volume loss, notably amygdala volume reduction, would be present in BPD compared to MDD, as indicated by currently available neuroimaging data linking ACC and amygdala dysfunction to MDD or BDP, respectively (Goodman et al., 2010). Second, we explored the relationship between structural anomalies and affective symptoms, and tested for associations between brain volume and clinical variables and rating scales within and between diagnostic groups. In this regard, we expected an association between depressive symptoms and brain volume in regions showing abnormal neural structure in both MDD and BPD.

2. Methods

2.1. Participants

Twentytwo female patients with MDD, 17 female patients with BPD and 22 female controls participated in this study (Table 1). Patients were recruited among the in- and outpatients treated at the Department of Psychiatry and Psychotherapy III, University of Ulm, Germany. No patient was recruited through study-specific advertising. None of the controls or patients was compensated for participation. Diagnostic assessments for all participants were performed by clinically trained and experienced raters (R.C.W. and N.D.W.) using the German versions of the Structured Clinical Interview for DSM-IV (Axis I and Axis II disorders).

Exclusion criteria for MDD patients were any lifetime or comorbid Axis I and Axis II disorders according to DSM-IV-TR criteria, a past history or the presence of any medical or neurological disorders, presence of drug or alcohol abuse or dependence, a history of head trauma with loss of consciousness and learning disabilities. In addition to a detailed interview conducted by trained clinical psychiatrists (see above), case notes were reviewed to corroborate a definitive diagnosis of MDD.

BPD patients with a past history or the presence of any medical or neurological disorders, a history of head trauma and learning disabilities were excluded from participation. Further exclusion criteria for BPD patients were lifetime diagnoses of schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD) and alcohol and illicit drug abuse within 6 months prior to study participation. Childhood manifestation of ADHD was retrospectively assessed using

Table 1
Demographics and clinical characteristics. MDD: major depressive disorder; BPD: borderline personality disorder; HC: healthy controls; TIV: total intracranial volume (sum of gray matter, white matter and cerebrospinal fluid).

	MDD ($n=22$)		**BPD** ($n=17$)		**HC** ($n=22$)		p-Value
	Mean	*SD*	Mean	*SD*	Mean	*SD*	
Age (years)	33.5	8.9	28.6	7.3	31.4	11.2	0.29[a]
DOI (years)	5.5	4.7	n.a.		n.a.		n.a.
No. of depressive episodes	2.7	1.9	2.0	1.6			0.23[b]
HAMD	28.4	4.7	15.2	5.7	0.7	1.4	<0.0001[a]
BDI	28.7	8.9	33.6	9.7	1.9	2.4	<0.0001[a]
TIV (ml)	1302.3	89.0	1316.6	98.3	1365.7	82.3	0.06[a]

n.a. = Not applicable.

[a] ANOVA.

[b] *t*-Test.