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Volume of hippocampal substructures in borderline personality disorder

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ABSTRACT

Borderline personality disorder (BPD) may be associated with smaller hippocampi in comparison to hippocampal size in controls. However, specific pathology in hippocampal substructures (i.e., head, body and tail) has not been sufficiently investigated. To address hippocampal structure in greater detail, we studied 39 psychiatric inpatients and outpatients with a DSM-IV diagnosis of BPD and 39 healthy controls. The hippocampus and its substructures were segmented manually on magnetic resonance imaging scans. The volumes of hippocampal substructures (and total hippocampal volume) did not differ between BPD patients and controls. Exploratory analysis suggests that patients with a lifetime history of posttraumatic stress disorder (PTSD) may have a significantly smaller hippocampus – affecting both the hippocampal head and body – in comparison to BPD patients without comorbid PTSD (difference in total hippocampal volume: −10.5%, 95%CI −2.6 to −18.5, significant). Also, patients fulfilling seven or more DSM-IV BPD criteria showed a hippocampal volume reduction, limited to the hippocampal head (difference in volume of the hippocampal head: −16.5%, 95%CI −6.1 to −26.8, significant). Disease heterogeneity in respect to, for example, symptom severity and psychiatric comorbidities may limit direct comparability between studies; the results presented here may reflect hippocampal volumes in patients who are "less" affected or they may simply be a chance finding. However, there is also the possibility that global effects of BPD on the hippocampus may have previously been overestimated.

1. Introduction

Borderline personality disorder (BPD) has a lifetime prevalence of approximately 6% and more commonly affects women than men. Patients with BPD show high rates of comorbidity with other psychiatric disorders such as affective and anxiety disorders including major depression (MD) and posttraumatic stress disorder (PTSD) – with approximately 20% and 40%, respectively, showing overlapping diagnoses (Grant et al., 2008).

Several studies in the last decade have investigated whether regional brain volumes in patients with BPD differ from corresponding volumes in controls: BPD has been associated with a reduction of right and left hippocampal volumes in most reports (Driessen et al., 2000; Schmahl et al., 2003; Tebartz van Elst et al., 2003; Brambilla et al., 2004; Irle et al., 2005; Zetzsche et al., 2007; Weniger et al., 2009).

Recent meta-analyses (Nunes et al., 2009; Rodrigues et al., 2011; Ruocco et al., 2012) report moderate aggregated effect sizes of volume reduction (e.g. Cohen's *d* of up to 0.7 (Ruocco et al., 2012)); however, there is also substantial variability across studies, signaling heterogeneity of the cohorts studied. Moreover, a putatively smaller hippocampus may not reflect a causal pathogenetic pathway, but be more indirectly associated with the disorder via a variety of factors such as the severity of symptoms over time or treatment effects. Comorbidity may also act as a confounder or mediator: MD (MacQueen et al., 2003) and PTSD (Felmingham et al., 2009) have been shown to be associated with reduced hippocampal volumes. In fact some studies have found that hippocampal volumes are not smaller in BPD patients unless they have comorbid PTSD (Schmahl et al., 2009), while other studies have inconclusive findings.

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Although pathogenesis remains unclear, there is pathophysiologic plausibility that certain pertinent stressors present in, but not specific to, BPD, may act in concert with a given individual susceptibility to culminate in damage to the hippocampus (Geuze et al., 2005).

Also, exposure may differentially interact with specifically vulnerable hippocampal substructures – ventral parts of the hippocampus are predominately involved in behavioral inhibition, emotional memory, and stress processing, while dorsal aspects are thought to be more relevant to spatial and cognitive processing with strong neocortical connections (Fanselow and Dong, 2010) – differential functions that may result in patterns of preferential damage. Studies recruiting patients with other psychiatric disorders have highlighted that the hippocampus shows disease-specific patterns of non-uniform volume reduction (e.g. depression (Maller et al., 2007)). There has been only one previous study that has specifically investigated potential substructural pathology in the hippocampus in patients with BPD (O'Neill et al., 2013), which found reduced volumes in all substructures in the left hippocampus, but affecting only the tail in the right hippocampus, in comparisons with healthy controls.

The study's planned goal was to investigate potential differences in hippocampal substructural volumes associated with BPD using manual volumetry of the hippocampus, extending results from a previous study (Driessen et al., 2000). Additionally, exploratory post-hoc analyses of the effects of comorbidity and a proxy for BPD severity were performed. This study also complements a recent study of our workgroup that looked at group differences in whole-brain and region-of-interest gray matter concentration using a voxel-based morphometry approach in a subset of the population presented here (Labudda et al., 2013).

2. Methods

2.1. Subjects

BPD subjects were recruited as a convenience sample while being treated as inpatients or outpatients at the Department of Psychiatry and Psychotherapy Bethel, Evangelisches Krankenhaus Bielefeld, Germany. BPD was diagnosed by clinical consensus and structured interviews according to DSM-IV criteria. There was no restriction regarding disease duration or age. Control subjects were recruited via local advertisement. The sample comprised 39 patients and 39 controls, with a similar age and gender profile.

All subjects had to be free of any clinically relevant current or previous medical condition (e.g., stroke, ischemic heart disease), and were excluded if there was any history of anorexia, schizophrenia, schizoaffective disorder, major depressive episodes with psychotic symptoms, or substance abuse within the 6 months preceding imaging. Controls had no clinical history of any psychiatric disorder. All subjects were Caucasian and native speakers of German. Written, informed consent was obtained from all subjects. The project, including post-hoc data analysis, was approved by the ethics committee of the University of Münster, Germany.

2.2. Psychopathological and clinical assessment

All subjects underwent formal psychopathological assessment using the Structured Clinical Interview for DSM-IV (SCID-I and SCID-II). Unfortunately, we did not use a specific BPD severity rating instrument in the full cohort of BPD patients (e.g. Zanarini Rating Scale for Borderline Personality Disorder (Zanarini et al., 2003)); furthermore, reliable measures of global symptom severity or duration of the disorder were unavailable for a sufficiently large part of the patient population. Rather, the BPD cohort was dichotomized according to the number of DSM-IV criteria fulfilled (5 or 6 criteria vs. 7 and more criteria; i.e., a median split). This resulted in two comparably large groups (18 vs. 21 patients). Though the total number of BPD criteria satisfied is an adequate approximation of BPD severity (Zanarini et al., 2003), a cutoff based approach as above is sensitive to certain aspects of the degree of psychopathology (Asnaani et al., 2007). We therefore pragmatically considered those patients fulfilling five or six DSM-IV criteria only as having a "milder" form of BPD, and those with seven or more as showing "more severe" BPD; see Fig. 1 for further supporting details. Lifetime and current MD and PTSD were diagnosed using the SCID-I. None of the control subjects showed relevant psychopathology.

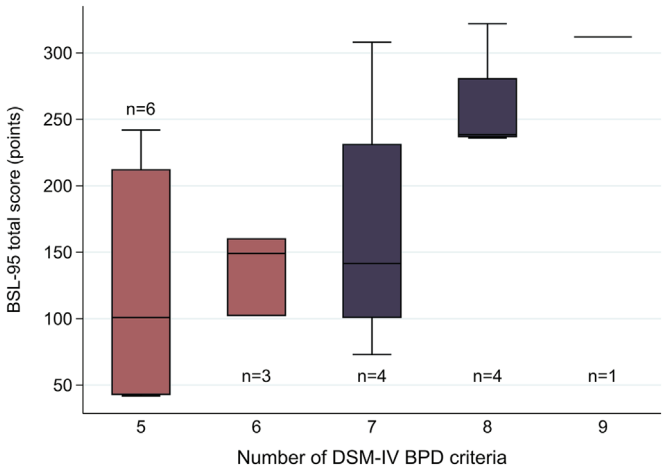

Fig. 1. Severity of borderline personality disorder (BPD) severity. A specific measure of BPD severity was not available for the full population. However, in part of the cohort patients ($n=18$) were rated with the "Borderline Symptom List 95" (Bohus et al., 2007), which summarizes the "extent" of borderline symptomatology. The figure illustrates to what extent the degree of borderline symptoms might be associated with the number of DSM-IV BPD criteria.

Childhood adverse experiences were assessed using the validated German version of the Childhood Trauma Questionnaire (CTQ) (Wingenfeld et al., 2010). The CTQ is a self-report instrument that yields separate indices for emotional, physical and sexual abuse, and emotional and physical neglect. The German version has a similarly high reliability (i.e. Cronbach's alpha coefficient=0.94) and moderate construct validity in comparison to the original American version (Wingenfeld et al., 2010).

Earlier and present medication was quantified into the following substance groups: non-psychiatric medication (e.g., antihypertensive medication, antiarrhythmic agents), antipsychotics, antidepressants and oral contraceptives. Further differentiating the psychiatric drugs, e.g., the antidepressants, into classes of medication, was not feasible due to small numbers per class.

2.3. MRI acquisition

Magnetic resonance imaging (MRI) was performed using a 1.5T scanner system (Siemens MAGNETOM Symphony; Siemens AG, Erlangen, Germany). All subjects underwent a routine protocol to detect any macroscopic pathology that would have led to exclusion (T1-, T2- and proton-weighted sequences, and axial and coronal fluid-attenuated inversion recovery sequences).

The datasets used to perform hippocampal volumetry were generated using a magnetization-prepared, rapid gradient echo T1 3D sequence (MPRAGE; TR 11.1 ms, TE 4.3 ms; FOV 201 × 230 mm; matrix 224 × 256). As previously planned on sagittal T1-weighted images, the axis of acquisition was perpendicular to the anterior–posterior axis of the hippocampus (i.e., resulting in coronal images). A total of 128 coronal non-isotropic slices (in-plane resolution 0.9 × 0.9 mm; slice thickness: 1.5 mm) were acquired.

2.4. Image post-processing and hippocampal volumetry

A single investigator (O.K.), without knowledge of diagnostic status, manually performed hippocampal volumetry. An investigator who was not involved in data processing (M.M.) maintained the imaging database and guaranteed blinding until after the planned comparison had been calculated. Post-hoc exploratory analysis was carried out without blinding. Volumetry was carried out using MRIcron software (Rorden and Brett, 2000).

The area of interest was visualized in all three axes. First, the hippocampal boundaries were coarsely traced on both the axial and sagittal sections. Then, with the resulting mask being used as a guide, the hippocampus was delineated in the coronal plane. Lastly, any discrepancy in the overlap of the final coronal mask and in the axial and sagittal sections was inspected and corrected if warranted.

We followed the proposal by Malykhin et al. (2007) regarding substructural borders. Specifically, on coronal images (a) the superior border of the H_{Head} was represented by the alveus; (b) the posterior border of the H_{Head} – the next slice in the posterior direction marking the beginning of the H_{Body} – was defined as the most posterior slice in which the uncal apex was clearly present; (c) the posterior border of the H_{Body} – the next slice in the posterior direction marking the beginning of the H_{Tail} – was the most posterior slice, before the fornix was seen in full profile.

Note that the division of the hippocampus into these substructures is arbitrary – though methodologically common (Yushkevich et al., 2010) – and does not follow