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Hippocampal and amygdala volumes in borderline personality disorder: A meta-analysis of magnetic resonance imaging studies

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ABSTRACT

Background Structural brain abnormalities have been described in borderline personality disorder (BPD), but previous studies have generally been small and have implicated different brain regions to varying extents.

Method We therefore conducted a systematic review and meta-analysis of published volumetric region-of-interest structural magnetic resonance imaging studies of patients with BPD and healthy controls. We additionally used meta-regression to investigate the modulating effects of clinical parameters, including age, on regional brain volumes.

Results The meta-analysis revealed significant bilateral decreases in hippocampal and amygdala volumes in patients with BPD compared with healthy control participants, in the absence of differences in whole-brain volume. Metaregression demonstrated an association between increasing age and reduced hippocampal volumes in BPD.

Discussion Overall, these findings demonstrate clear structural changes in the medial temporal lobe in BPD, showing similarity to the biological effects of early life stress. Copyright © 2010 John Wiley & Sons, Ltd.

Introduction

Borderline personality disorder (BPD) is a common and disabling condition characterized by impaired regulation of affect, impulsivity and difficulties in interpersonal relationships (Lieb et al., 2004). The exact causes of BPD are not known, but it is strongly associated with early life trauma, and shows a high degree of heritability in twin studies (Lieb et al., 2004). Despite its relatively high prevalence, BPD has attracted less research than other psychiatric disorders, and there is a pressing need for greater understanding of the biological basis of this condition.

A number of studies have investigated brain structure in BPD using magnetic resonance imaging (MRI). Early studies reported decreased volumes of medial temporal lobe structures in BPD, including reductions in the volume of the hippocampus and amygdala (Driessen et al., 2000; Tebartz van Elst et al., 2003). However, there has been considerable disagreement between studies, with a number of investigations failing to find abnormalities of amygdala and hippocampal volumes (Chanen et al., 2008; Schmahl et al., 2009). This apparent heterogeneity may relate to the power of different studies to detect between-group differences, or variation between studies in the clinical characteristics of

the included patients. In particular, previous studies have varied considerably in terms of the age of participants and the presence or absence of comorbid conditions, such as depression or post-traumatic stress disorder (PTSD).

Meta-analysis is a technique that allows quantitative data to be combined from multiple individual studies, increasing the overall power to detect differences and allowing the causes of heterogeneity between studies to be investigated. In the current study, we have conducted a meta-analysis of amygdala and hippocampal, and whole-brain volumes (WBVs), as determined by region-of-interest (ROI) analysis, in BPD. In addition, we have applied meta-regression to determine possible causes of heterogeneity between previous volumetric MRI studies. We demonstrate overall decreases in amygdala and hippocampal volumes across 10 studies of BPD. Furthermore, we extend the results of the only previous meta-analysis of brain volumes in BPD by showing that these reductions in the volume of medial temporal lobe brain regions are not accounted for by differences in WBV, and that the hippocampal volume reductions seen in BPD are associated with increased age (Nunes et al., 2009).

Methods

Literature search

A comprehensive search from the electronic databases EMBASE, PsycINFO and OVID Medline was conducted using the following search strategy: MRI and BPD. The search strategy was supplemented using a cited reference search and by inspecting the reference lists of included articles. The search was conducted in September 2009.

Criteria for inclusion/exclusion

Studies were considered for review by using the following inclusion criteria:

- (1) They were published in English as a peer-reviewed paper (rather than a letter, abstract or case report).
- (2) They compared a sample of formally diagnosed BPD subjects with a group of healthy controls (either related or unrelated to the subjects).
- (3) They utilized ROI volumetric analysis of structural MRI data.
- (4) The means and standard deviations of the volume of the brain region under study were reported (or could be extracted or retrieved from the authors) for both cases and healthy controls.

When results were shown graphically but not given numerically in the text, they were included if the authors were able to supply numerical data. Only brain regions for which at least three separate studies reported data were included in the meta-analysis, restricting the study to amygdala, hippocampal and WBVs.

Studies were excluded if:

- (1) There were insufficient data to extract the number of subjects in each group.
- (2) There were fewer than five subjects in either the BPD group or the control group.
- (3) The comparison groups consisted of patients with minor non-psychiatric illnesses.
- (4) The structure measurement was an area (from a single slice) rather than a volume (i.e. from multiple slices).
- (5) The studies used the voxel-based morphometry, deformation-based morphometry or tensor-based volumetric method for measuring brain regional volumes.
- (6) The data contributed to another publication, in which case the publication with the largest group size for each specific brain region under study was selected.

Data abstraction

Data extracted from the studies included the authors; year of publication; demographic variables

(number, age, years education, gender and handedness); illness variables (diagnosis, comorbid PTSD, comorbid depression); and the mean and standard deviation of the volume of each of the brain regions under study. We calculated the sex and handedness distribution, and the total numbers of subjects according to the original studies. When studies reported data for two separate patient groups and a control group, the pooled means and standard deviations were calculated and used in the analysis, to ensure that the results were not related to one study contributing a disproportionate number of data points to the analysis, and to avoid over-sampling the control groups. Data were largely complete; however, information regarding comorbid major depression was not available for one study, and data on handedness and number of years of education were unavailable for two studies.

Statistical analysis

Standardized mean differences (SMDs) were calculated from each study using Cohen's *d* statistic, and combined using random effect analysis. Publication bias was assessed using Egger's test. The magnitude of between-study heterogeneity was estimated using the I^2 statistic (a measure of the proportion of variance in summary effect size as a result of heterogeneity), and its statistical significance was calculated using Cohen's *Q*. Meta-regression was used to explore age, years of education, lifetime major depression and lifetime PTSD as potential sources of heterogeneity between studies. All statistical analyses were performed using R (<http://cran.r-project.org>). The 'meta' package was used to perform all statistical summaries except for the meta-regression analyses, which were performed using the 'lm' package.

Results

Systematic search

The electronic literature search yielded 189 papers, of which 31 were retrieved in full-text format, and

10 were included in the meta-analysis (Brambilla et al., 2004; Chanen et al., 2008; Driessen et al., 2000; Irle et al., 2005; Schmahl et al., 2003; Schmahl et al., 2009; Tebartz van Elst et al., 2003; Weniger et al., 2009; Zetzsche et al., 2006, 2007). Figure 1 summarizes the study flow and the reasons for exclusion, and Table 1 shows the demographic characteristics of participants from the 10 included studies.

Meta-analysis

The primary findings of the meta-analysis are shown in Table 2 and Figure 2. There was a significant reduction in hippocampal volume in patients with BPD ($n = 148$) compared to healthy controls ($n = 126$) (left hippocampus, $SMD = -0.64$, $p = 0.008$; right hippocampus $SMD = -0.71$, $p = 0.003$). Patients with BPD ($n = 167$) also had bilaterally reduced amygdala volumes compared to healthy controls ($n = 142$) (left amygdala $SMD = -0.54$, $p = 0.009$; right amygdala $SMD = -0.51$, $p = 0.029$). These regional reductions in hippocampus and amygdala volumes did not result from differences in WBV as patients with BPD ($n = 118$) showed no difference from healthy comparison subjects ($n = 126$) in terms of WBV ($SMD = 0.11$, $p = 0.70$).

Publication bias, heterogeneity and meta-regression

There was no evidence of publication bias for any of the measures investigated (Table 2; Figure 2). However, significant heterogeneity between studies was detected for all the regions examined (Table 2). In order to explore the sources of heterogeneity between studies, we conducted a meta-regression for variables that were adequately reported across studies including age, years of education, lifetime diagnosis of major depression and lifetime diagnosis of PTSD. This revealed a significant effect of age on hippocampal volume in BPD with both left and right hippocampi showing greater relative volume reductions in older patients compared to

Figure 1: Flow diagram showing article selection process for volumetric structural MRI studies of BPD

control subjects (left hippocampus, $\beta = -0.10$, $t = -2.49$, $p = 0.049$; right hippocampus, $\beta = -0.11$, $t = -3.19$, $p = 0.018$). This effect derives from a greater reduction in hippocampal volume with age in patients with BPD than in control subjects, as the dependent variable (SMD) represents the difference between the patient and control groups. No other variables showed significant effects in the meta-regression with either hippocampal or amygdala volumes.

Discussion

This systematic review and meta-analysis demonstrates that individuals with BPD have reduced volumes of the hippocampus and amygdala in comparison to healthy control subjects, in the absence of differences in WBV. In addition, hippocampal volume decreases were greater with

increased age in the BPD group compared to controls, providing evidence of possible progressive hippocampal pathology in the disorder. These results demonstrate selective reductions in the volumes of medial temporal lobe brain regions in BPD, and help clarify some of the sources of the heterogeneity seen between previous studies (Nunes et al., 2009).

The amygdala plays a primary role in emotion processing, and is especially implicated in the processing of negative affect. Impaired affect regulation is one of the cardinal features of BPD, and the present results suggest that pathology in the amygdala may contribute to the affective symptomatology seen in BPD. The changes in amygdala volume in the disorder may represent part of a broader abnormality in the emotional brain in BPD, with previous studies suggesting a broad impairment in fronto-amygdala systems involved in affect processing in BPD (Silbersweig et al., 2007; Tebartz

Table 1: Demographic characteristics of included study populations

Study (year)	Diagnostic instruments	BPD subjects			Control subjects			Regions under study	
		n	%F	%RH	Age (years)	n	%F		%RH
Driessen et al. (2000)	SCID-II	21	100	86	29.9	21	100	86	29.3
Schmahl et al. (2003)	DIPD-IV	10	100	100	27.4	23	100	87	31.5
Tebartz van Elst et al. (2003)	SCID-II, DIB	8	100	—	33.5	8	100	—	30.5
Brambilla et al. (2004)	DIB, IPDE	10	60	—	29.2	20	30	—	34.9
Irle et al. (2005)	SCID-II	30	100	93	31.0	25	100	100	33.0
Zetsche et al. (2006)	SCID-II, DIB	25	100	100	26.1	25	100	100	27.2
Zetsche et al. (2007)	SCID-II, DIB	25	100	100	26.1	25	100	100	27.2
Chanen et al. (2008)	SCID-II	20	75	90	17.3	20	75	90	19.0
Schmahl et al. (2009)	IPDE	25	100	100	29.0	25	100	100	32.8
Weniger et al. (2009)	SCID-II, DIB	24	100	92	32.0	25	100	100	33.0

n, number of subjects; %F, percentage of female subjects; %RH, percentage of right-handed patients; data for age are expressed as means; Hipp, hippocampus; Amyg, amygdala; SCID, Structured Clinical Interview for DSM; DiPD-IV, Diagnostic Interview for DSM-IV Personality Disorders; DIB, Diagnostic Interview for Borderline Patients; IPDE, International Personality Disorder Examination; —, no data available.

Table 2: Effect sizes and estimates of heterogeneity and publication bias for the regions of interest

Brain region	No. of studies	No. of subjects		Volume difference		Heterogeneity		Publication bias <i>p</i> value	Studies	
		BPD	Controls	SMD	<i>p</i> Value	95% CI	<i>I</i> ² (%)			χ^2
WBV	6	118	126	0.11	0.70	(−0.46, 0.68)	76.8	21.6	0.0006	2, 3, 5, 6, 8, 9
	8	148	167	−0.64	0.008	(−1.12, −0.17)	74.1	27.0	0.0003	1, 2, 3, 4, 5, 7, 8, 9
Hippocampus (L)	8	148	167	−0.71	0.003	(−1.18, −0.24)	73.9	26.8	0.0004	1, 2, 3, 4, 5, 7, 8, 9
Hippocampus (R)	8	167	142	−0.54	0.009	(−0.94, −0.14)	64.2	19.5	0.007	1, 2, 3, 4, 6, 8, 9, 10
Amygdala (L)	8	167	142	−0.51	0.029	(−0.97, −0.05)	72.7	25.7	0.001	1, 2, 3, 4, 6, 8, 9, 10
Amygdala (R)	8	167	142							

CI, confidence interval; R, right; L, left. Studies: 1, Driessen et al. (2000); 2, Schmahl et al. (2003); 3, Tebartz van Elst et al. (2003); 4, Brambilla et al. (2004); 5, Irle et al. (2005); 6, Zetsche et al. (2006); 7, Zetsche et al. (2007); 8, Chanen et al. (2008); 9, Schmahl et al. (2009); 10, Weniger et al. (2009).

Figure 2: Forest plots showing the effect sizes for studies examining volumetric differences between BPD patients and controls in (A) left hippocampus, (B) right hippocampus, (C) left amygdala and (D) right amygdala. For each study, the square in the forest plot denotes the value of the effect size, and the horizontal lines extending to the right and left of the square indicate the widths of the 95% confidence intervals. The size of the square represents the relative weight of the particular study in the overall meta-analysis, which is also presented numerically. The SMD for each study is also shown. The triangle at the bottom of each graph represents the overall effect as calculated from the combined studies using a random effects model, also shown as the combined SMD

van Elst et al., 2003). The cause of decreased amygdala volumes in BPD remains uncertain, but it is likely that environmental factors, such as early life stress, as well as differences in genetic vulnerability, contribute. In this regard, it is notable that the amygdala and associated limbic circuitry undergo extended post-natal development, and is particularly vulnerable to the effects of early life stress (Cunningham et al., 2002; Tottenham & Sheridan, 2010). The relationship between early life stress and amygdala morphology, however, remains to be fully established, with studies of children subject to stress in the form of institutional care revealing increased amygdala volumes in subjects with a mean age of 8 years, pointing to a complex relationship between stress and the trajectory of amygdala development (Tottenham et al., 2010).

The hippocampus has a key role in regulating hypothalamic–pituitary–adrenal (HPA) responses to stress, and is vulnerable to volume loss in the

context of a sensitized HPA axis (Tottenham & Sheridan, 2010). There is strong evidence of HPA axis dysregulation in BPD (Carrasco et al., 2007), which is most likely a consequence of an interaction between early life stress and genetic vulnerability. Previous animal and human studies have shown that the effects of early life stress on hippocampal volume are most apparent in adulthood, possibly resulting from the long-term consequences of heightened HPA axis responsivity (Tottenham & Sheridan, 2010). The greater relative hippocampal volume reduction seen with advancing age in the current meta-regression is consistent with these earlier findings, and may reflect the pathogenic effects of heightened HPA axis stress responses in the disorder.

The current results help to clarify the differences in brain structure between BPD and other psychiatric disorders. Most notably, the finding of amygdala and hippocampal volume reductions in BPD contrasts with the general lack of significant

medial temporal lobe volume differences in bipolar disorder (Arnone et al., 2009), suggesting that the affective disturbances seen in these conditions involve distinct aetiological processes. The structural brain changes in BPD are more comparable to those seen in patients with depression and PTSD, with all three disorders showing evidence of hippocampal volume loss. However, recent meta-analyses have not revealed amygdala volume loss in depression (Koolschijn et al., 2009), and only marginal unilateral volume decrements in the amygdala in PTSD (Karl et al., 2006). Furthermore, neither co-occurring depression nor PTSD explained the volume reductions seen in medial temporal lobe regions in BPD in the current meta-regression analyses.

A number of limitations of the current study should be noted. Firstly, sufficient data for meta-analysis could only be obtained for the amygdala, hippocampus and WBVs, and, therefore, we cannot comment on the volume of other brain regions in BPD, such as the frontal lobes. Previous studies have provided evidence of volume reductions in other brain areas, including regions of the frontal and parietal lobes (Hazlett et al., 2005; Tebartz van Elst et al., 2003), suggesting that these brain regions may also be affected in the disorder. Secondly, significant heterogeneity was detected in the analyses of both amygdala and hippocampal volumes. This is likely to be derived from methodological and clinical differences between published studies. Where sufficient data were available, we sought to investigate the causes of this heterogeneity using meta-regression, and we were able to identify age as one source of between-study variation in hippocampal volumes. The failure to find an association between PTSD symptoms and amygdala, and hippocampal volumes was surprising, but may reflect loss of volume in these brain regions in BPD whether or not PTSD symptoms are present, potentially reflecting the biological consequences of early life stress.

These limitations notwithstanding, this systematic review and meta-analysis provides clear evidence of structural brain changes in the medial

temporal lobe in BPD and of greater relative hippocampal volume loss in BPD with advancing age. These results clarify and extend previous studies of medial temporal lobe volume in BPD, and provide a striking parallel between medial temporal lobe volume changes in BPD and many previous studies of the effects of early life adversity on hippocampal and amygdala volumes (Nunes et al., 2009; Tottenham & Sheridan, 2010).

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