



Anterior cingulate volume reduction in adolescents with borderline personality disorder and co-morbid major depression

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ABSTRACT

Borderline Personality Disorder (BPD) is a serious illness characterized by emotional dysregulation, impulsivity, and impaired interpersonal relationships. Prior work shows the anterior cingulate gyrus (ACG)—a region primarily involved in assessing the salience of emotional information and regulating emotional responses—is smaller in adults with BPD. We tested the hypothesis that, similar to adults, adolescents with BPD would have reduced Brodmann area (BA)-24 volume. Thirteen adolescent inpatients with co-morbid BPD and Major Depressive Disorder (MDD) and 13 matched healthy controls received 3T-MRI scans. Using a cytoarchitecturally-derived approach measuring gray and white matter volume, we observed a Group \times Cingulate BA (25,24,31,23,29) \times Matter (gray, white) type interaction indicating the BPD/MDD adolescents had smaller BA24 volume in gray but not white matter. Greater number of suicide attempts and BPD symptom severity measured by the Diagnostic Interview for BPD-revised (DIB-R) total score but not depressive symptoms measured by the Beck Depression Inventory (BDI) was associated with smaller BA24 volume. Our preliminary findings suggest that BPD-related abnormalities in BA24 volume may occur early in the developmental course of BPD with MDD. Future studies examining samples of MDD patients with and without BPD co-morbidity will be needed to clarify whether BA24 volume reductions are specific to BPD.

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Borderline Personality Disorder (BPD), characterized by emotional dysregulation, poor impulse control and impaired interpersonal relationships, is a serious illness with a reported suicide rate 50 times the general population (Skodol et al., 2002). Evidence suggests that early detection of BPD can attenuate the severity of symptoms (Chanen et al., 2008a); however, little is known about early predictors of this disorder. Results from a survey of parents with BPD offspring show that while affective symptoms differentiating BPD patients from their unaffected siblings begin as early as the first year of life, the full manifestation of the syndrome emerges in adolescence (Goodman et al., 2010b). Using diagnostic instruments similar to those used in adults, researchers are diagnosing adolescent presentation of BPD to describe the incidence, phenomenology and negative prognosis for the development of Axis I/II disorders in adulthood (Chanen et al., 2008b; Crawford

et al., 2008). Adolescent BPD symptoms, independent of adolescent Axis I disorders, predict lower academic, occupational and social function, and fewer attained adult developmental milestones (Winograd et al., 2008). The fact the BPD can be diagnosed in adolescents and that this early diagnosis may permit the attenuation of its full manifestation highlights the importance of early detection of this disorder.

Structural MRI studies from our group and others indicate that compared with healthy controls (HCs), adults with BPD have decreased volume in Brodmann Area (BA) 24 (Hazlett et al., 2005; Tebartz van Elst et al., 2003) and subgenual cingulate (Minzenberg et al., 2008). Others have also shown significant volume reduction in orbitofrontal cortex (OFC) in BPD (Tebartz van Elst et al., 2003) but this was not confirmed in a larger sample (Rusch et al., 2003).

To date, two morphometric studies examined anterior cingulate gyrus (ACG) in adolescents with BPD (Brunner et al., 2010; Whittle et al., 2009) and produced conflicting results. Using region-of-interest analysis, Whittle et al. (2009) reported decreased left ACG volume in 15 female BPD adolescents with a wide range of Axis I co-morbidities. More recently, Brunner et al. (2010) compared 20 female adolescents with BPD, 20 psychiatric-ill adolescents

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without BPD and 20 HCs using voxel-based morphology (VBM) and reported no ACG abnormalities. However, both patient groups exhibited gray volume reductions in the dorsolateral prefrontal cortex (DLPFC) as compared with HCs, and BPD adolescents had reduced gray matter volume in OFC.

Other structural MRI findings in adolescent BPD include right-sided OFC gray matter reduction, but no differences in amygdala or hippocampal volumes (Chanen et al., 2008c) (in contrast to the left-sided OFC findings of Brunner et al., 2010) and volume of midline brain structures, a shorter adhaesio interthalamica and large third ventricle in teenage BPD subjects (Takahashi et al., 2009).

This pilot study aimed to test the hypothesis that we would observe BA24 volume reduction in adolescents with BPD similar to our prior report in adults with BPD (Hazlett et al., 2005). Given prior work, we also tentatively hypothesized that we would see volume reductions in DLPFC/OFC. In order to ensure methodological consistency across our adult and adolescent studies, we employed the same image-processing methodology as our first study (Hazlett et al., 2005).

1. Methods

1.1. Participants

BPD subjects were recruited from the adolescent psychiatric inpatient service at Mount Sinai Hospital in New York City and the HC sample was recruited from the surrounding community via advertisements.

Twenty-six adolescents ($n = 13$ BPD, $n = 13$ HCs) underwent diagnostic and MRI procedures (Table 1 for screening, demographic, and clinical details). All BPD subjects also met criteria for current MDD. Additional BPD subject co-morbidities included, attention deficit hyperactivity disorder (ADHD) (39%), oppositional defiant disorder (39%), any substance abuse diagnosis (15%) and post traumatic stress disorder (PTSD) (8%). The Diagnostic Interview for BPD-revised (DIB-R) total score was used to measure BPD symptom severity and the Beck Depression Inventory (BDI) was used to measure depressive symptomatology. The study was approved by the Mount Sinai School of Medicine's Institutional Review Board. All participants gave assent and written informed consent was obtained from a parent or guardian.

1.2. MRI acquisition and procedures

MRI scans were acquired on a 3-T head-dedicated Siemens Allegra scanner. All participants received a high-resolution T1-weighted MP-RAGE (Magnetization Prepared Rapid Gradient Echo) MRI scan (208 slices with slice thickness = 0.82 mm, matrix size = $256 \times 256 \times 208$, FOV = 210 mm, TR = 2500 ms, TE = 4.38 ms, TI = 1100 ms and an 8° flip angle FLASH acquisition), lasting a total of 20 min.

We conducted a detailed analysis of gray and white matter volume in the prefrontal cortex using a digitized version of an atlas (Perry et al., 1991) that includes 33 coronal slice maps of BAs defined by microscopic examination of one entire postmortem brain (see detailed methods in our earlier study of adults with BPD: Hazlett et al., 2005 and also Mitelman et al., 2003). We conducted two hypothesis driven mixed-design MANOVAs with Diagnostic Group as the between-group factor and all other factors as repeated measures: (1) a Group (HC vs. BPD/MDD) \times Cingulate BA (BA 25, 24, 31, 23, 29) \times Hemisphere \times Matter type (gray, white) MANOVA and (2) a Group (HC vs. BPD/MDD) \times Frontal region (Anterior: BA 8,9,10; Medial: BA 32,25,24; Orbitofrontal: BA11,12,47; Dorsolateral: BA44,45,46) \times BA (1–3) \times Hemisphere (left, right) \times Matter type (gray, white) MANOVA. Our dependent variables were relative

Table 1

Demographics and clinical ratings on Healthy Control (HC) and Borderline Personality Disorder/Major Depressive Disorder adolescent (BPD/MDD) groups.

Group	Healthy adolescents (n=13)	BPD/MDD adolescents (n = 13)
Age (years)	16.2 (0.8)	15.8 (1.1)
Sex	9F, 4M	11F, 2M
DIB-R total	2.5 (1.8)	29.7 (3.9)*
DIB-R Affective	0.9 (0.9)	9.4 (1.2)*
DIB-R Cognitive	0 (0)	2.6 (1.5)*
DIB-R Impulsivity	0.8 (1.0)	6.6 (1.3)*
DIB-R Interpersonal	0.8 (1.1)	11.1 (2.8)*
LSDS-Self-harm	0.0 (0.0)	32.8 (42.5)*
LSDS-Suicide	0.0 (0.0)	1.8 (1.6)*
LHA	7.1 (4.5)	24.2 (9.2)*
BPPS-C	19.6 (10.3)	52.7 (3.1)*
ALS	28.7 (26.1)	86.8 (31.0)*
BIS-11	74.5 (4.3)	73.8 (5.3)
BPAQ	55.7 (13.5)	83.5 (23.1)*
BDI	2.3 (4.1)	25.0 (11.5)*
STAXI-S	15.2 (0.6)	19.8 (10.7)
STAXI-T	13.9 (3.5)	21.2 (6.4)*
ZAN-SA (sexual abuse)	0.0 (0.0)	3.9 (5.3)*
ZAN-OA (verbal/physical abuse)	0.4 (0.8)	1.1 (1.3)
ZAN-N (neglect)	0.2 (0.6)	1.8 (1.6)*

*significantly different from the healthy control group, post-hoc Fisher's LSD, $p < 0.05$; p -values for all clinical variables were Bonferroni corrected. DIB-R: Diagnostic Interview for Borderline Personality Disorder-Revised; total score and subscores (affective symptoms; Cognitive Symptoms; Impulsivity; Interpersonal). LSDS: Life-time Self-Destructiveness Scale; subscales for self-harm and suicide attempts. LHA: Lifetime History of Aggression; BPPS-C: Borderline Personality Features Scale-Childhood. ALS: Affective Liability Scale. BIS-11: Barratt Impulsivity Scale. BPAQ: Buss Perry Aggression Questionnaire. BDI: Beck Depression Inventory. STAXI-2: State-Trait Anger Expression Inventory-2. ZAN Scale: A scale of lifetime frequency of traumatic events, including sexual abuse, verbal/physical abuse and neglect.

BPD subjects were psychiatric inpatients meeting both the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (First et al., 1997) and Revised Diagnostic Interview for Borderlines (DIB-R) (Zanarini et al., 1989) criteria for BPD. Axis I disorders were assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) Subjects were excluded for 1) current psychosis or diagnosis of schizophrenia; 2) current delirium or mania; 3) serious chronic medical condition including pregnancy.

Healthy controls were recruited from advertisements for healthy adolescent volunteers and were age- and sex-matched to BPD/MDD subjects. They did not meet criteria for any Axis I or II disorder.

The SCID-1, SCID-II and DIB-R were administered to both the adolescent and a parent/guardian informant. All clinical data were reviewed in a consensus meeting led by one of the investigators (MG) where diagnostic group was assigned.

volume values (i.e. BA region of interest/whole brain volume). We report univariate F with Huynh-Feldt corrected p values, unadjusted degrees of freedom and epsilon values where necessary. Significant interactions with diagnostic group were followed up with Fisher LSD tests to determine the direction of the effect.

To examine individual differences, we conducted clinical correlations between BPD symptom severity (using the DIB-R total score), number of suicide attempts, and the BDI and volume of BAs which showed significant interactions with group in our MANOVA results.

2. Results

Cingulate volume. BPD/MDD adolescents had smaller relative volume in BA24 (averaged across gray and white matter) compared with the HCs but did not differ in the other cingulate regions (BA25, 31, 23, or 29), Group \times Cingulate BA area interaction ($F[4,96] = 3.43$, $p = 0.029$, epsilon = 0.635; Fig. 1A). Of note, adolescents with BPD/MDD did not differ from HCs in overall relative volume of the cingulate relative to whole brain (main effect of group, $F[1,24] = 0.13$, $p = 0.722$), suggesting that between-group differences in the cingulate were regionally specific.

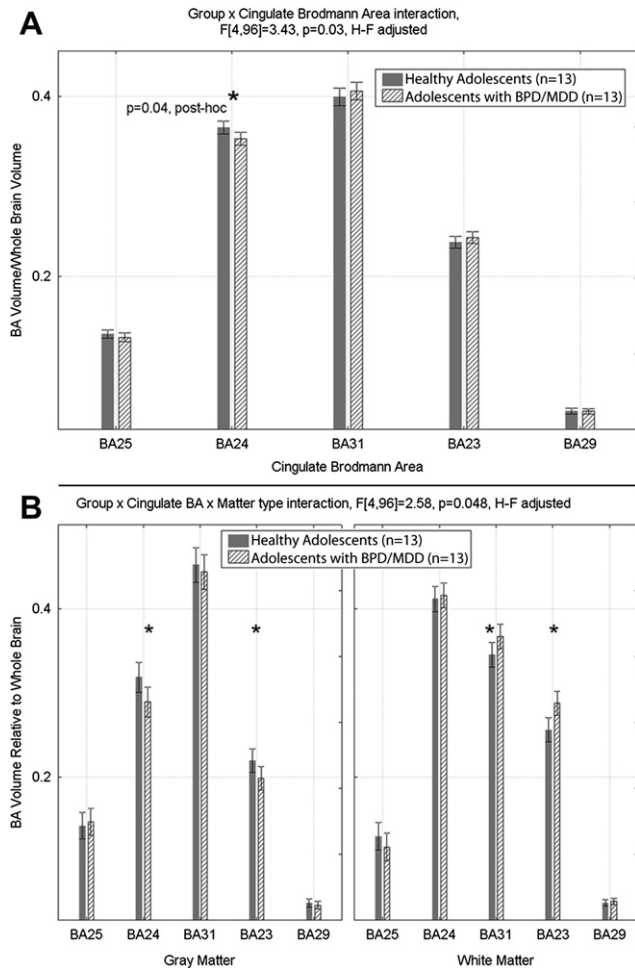


Fig. 1. Mean relative volume for the five cingulate gyrus Brodmann areas (BAs) are shown for healthy adolescents and adolescents with BPD/MDD. A: There was a significant Group \times Cingulate Brodmann area (BA) interaction ($F[4,96] = 3.43, p = 0.029, \epsilon = 0.635$, Huynh-Feldt adjusted degrees of freedom) indicating that adolescents with BPD/MDD have smaller volume in BA24 of the cingulate. *significant post-hoc, $p < 0.05$. B: Compared with the HC group, the BPD/MDD adolescent group showed reduced volume in gray matter but not white matter in BA24. The BPD/MDD group also showed decreased gray matter in posterior cingulate (BA23) and increased white matter volume in posterior cingulate (BAs 31 and 23; significant Group \times Cingulate BA \times Matter type interaction, $F[4,96] = 2.58, p = 0.048, \epsilon = 0.890$).

The BPD/MDD adolescents also differed from HC in the volume of gray and white matter within the ACG. Specifically, the BPD/MDD group had smaller gray (0.23 ± 0.01 vs. HC: 0.24 ± 0.01) and larger white matter (0.25 ± 0.01 vs. HC: 0.24 ± 0.01) volume in the cingulate (averaged across BA and hemisphere; both Fisher's LSD p values < 0.02 ; Group \times Matter type interaction, $F[1,24] = 5.10, p = 0.003$). Lastly, there was a significant Group \times Cingulate BA \times Matter type interaction ($F[4, 96] = 2.58, p = 0.048, \epsilon = 0.890$; Fig. 1B) reflecting that compared with HCs, the BPD/MDD group had smaller gray matter volume in BA24 and 23 and increased white matter in BA31 and 23.

In order to control for any influence gender has on ACG structural measures, we re-ran the cingulate MANOVA with females only. This limited the sample size to 9 HC and 11 BPD/MDD patients but these subgroups did not differ in mean age (HC: 16.22 ± 0.83 ; BPD/MDD: 15.9 ± 1.22). The Group \times Matter type and the Group \times Cingulate BA \times Matter type interactions remained significant (both F s > 3.42 and p values < 0.03).

Prefrontal cortex volume. For our prefrontal cortex MANOVA, the main effect of Group was not significant ($F = 0.65, p = 0.43$) and

none of the interactions with Group were significant (all F -values < 1.85 and $p > 0.14$).

Clinical correlations. Among the 26 adolescents, greater overall BPD symptom severity (DIB-R total scaled score; $r = -0.45, p = 0.022$) and number of suicide attempts ($r = -0.40, p = 0.044$) was associated with smaller overall BA24 volume (averaged across gray and white matter). Interestingly, these measures were not correlated with overall volume for any of the other four cingulate BAs. Lastly, depression, (measured with the BDI) was not correlated with overall volume for any of the cingulate BAs.

We also conducted clinical correlations for volume of gray and white matter (separately) for the three Brodmann areas which showed significant between-group differences (BA24, 23, and 31). Greater overall BPD symptom severity was associated with: smaller BA24 gray ($r = -0.39, p = 0.048$) but not white matter, smaller BA23 Gy ($r = -0.42, p = 0.032$) and larger BA23 white matter ($r = 0.57, p = 0.002$), and greater BA31 white ($r = 0.47, p = 0.015$) but not gray matter. Greater number of suicide attempts was associated with greater white ($r = 0.39, p = 0.049$) but not gray matter in BA23 and greater depression was also associated with greater white matter in BA23 ($r = 0.45, p = 0.026$) and BA31 ($r = 0.42, p = 0.042$).

3. Discussion

Our primary finding is that compared with healthy adolescents, those with BPD/MDD have reduced BA24 gray matter volume but no differences in DLPFC or OFC. This preliminary finding raises the possibility of a neurodevelopmental abnormality in BPD. We have previously reported a similar gray matter volume reduction in BA24 in adults with BPD (Hazlett et al., 2005) using identical image-processing methodology. This finding is consistent with reports of decreased left ACG volume in female BPD outpatient adolescents (Whittle et al., 2009) but not with the findings of Brunner et al. (2010). Conflicting results are likely due to small sample size and differences in subject selection, psychiatric co-morbidities and imaging methodology. Our BPD adolescents were all inpatients with co-morbid MDD and may represent a more severely-ill group with greater treatment duration and co-morbid psychopathology. Alternatively, Brunner et al. (2010) employed a whole brain VBM approach which may be less sensitive to group differences than our cytoarchitecturally-derived approach.

Our lack of between-group differences in DLPFC and OFC volumes differs from prior studies reporting reductions in both regions (Chanen et al., 2008c; Brunner et al., 2010). Future work examining larger samples and paying careful attention to comorbidity will help address discrepancies between the preliminary findings to date.

Greater overall BPD symptom severity and number of suicide attempts but not depression was correlated with smaller BA24 volume (averaged across gray and white matter), but not with the other cingulate BAs (BA25, 23, 29 and 31). Smaller anterior cingulate (BA24) gray matter volume was associated with greater BPD symptomatology while larger posterior cingulate (BA 23, 31) white matter volume was associated with depression. Taken together, this pattern of results suggests that anterior cingulate abnormalities are related to adolescent BPD and suicidality and not depression. Larger studies are needed to confirm these preliminary findings regarding the specificity of smaller BA24 gray volume in adolescent BPD.

Subcomponents of the cingulate have been shown to subserve a vast array of functions including emotion, with an affective subdivision (including BA 24 and 25) connected to the amygdala and orbitofrontal cortex, among other regions (Bush et al., 2000). This region of the ACG is primarily involved in assessing the salience of emotional and motivational information and the regulation of emotional responses (Vogt et al., 1992). Our findings of

reduced ACG may be related to alterations in neurochemistry (Hoerst et al., 2010; Rusch et al., 2010a) and structural connectivity (Rusch et al., 2010b) recently reported in adult BPD.

Abnormalities in ACG have also been implicated in other psychiatric disorders, particularly in MDD, a diagnosis present in all the BPD subjects in our sample. MDD and BPD are frequently co-morbid and there exists controversy regarding the precise relationship between MDD and BPD. While the neural circuitry underlying emotion regulation appear common to both disorders, the biology that makes individuals vulnerable to each disorder is as yet poorly understood (Goodman et al., 2010a). Structural MRI data on ACG in adolescent with depressive symptoms is minimal and has yielded mixed results (Boes et al., 2008; Yap et al., 2008). In addition, none of the studies in adolescent, nor adult MDD have controlled for Axis II psychopathology. Future studies examining samples of MDD patients with and without BPD comorbidity will be needed to clarify whether BA24 volume reductions are specific to BPD.

BPD/MDD adolescents were significantly different from HC adolescents in all symptom domains except for self-reported impulsivity, which was similar between groups. This may indicate that our comparison subjects recruited from urban New York are more impulsive than typical samples of healthy adolescents; a notion supported by data indicating higher levels of aggression in healthy control subjects from New York as compared to other cities (Baca-García et al., 2006). However, our clinician-rated instrument for impulsivity, the DIB-R subscale for impulsivity, did find statistically significant differences in the expected direction. This suggests that the BIS may not be the optimal instrument for measuring adolescent impulsivity.

Strengths of this study include the rigorous diagnostic procedure utilizing two instruments and parent informants and the use of the identical methodology to a previous published study in BPD adults. Limitations include our small sample size, presence of additional comorbid Axis I disorders (e.g. PTSD, ADHD) and lack of an MDD group without BPD. Another shortcoming of the present study is that we did not have a large enough sample size to examine sex differences. Future larger-scale studies with a longitudinal design and non-overlapping groups will allow us to determine the developmental course of MDD, BPD, and co-morbid BPD/MDD for both genders.

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Contributors

Drs. Goodman, Hazlett and New conceived the idea for the study. Dr. Goodman recruited, screened, and diagnosed the study participants. Dr. Hazlett conducted the image processing and statistical analysis of the MRI data and drafted sections of the manuscript. Ms. Avedon assisted with recruitment and the MRI data collection for the study participants. Dr. King-Wai Chu and Mr. Daniel Siever provided image-processing support. All authors contributed to and have approved the final manuscript.

Conflict of Interest

There are no conflicts of interest to report for any of the authors.

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