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

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A R T I C L E   I N F O

Article history:
Received 19 August 2010
Received in revised form 9 November 2010
Accepted 12 November 2010

Keywords:
Borderline personality disorder
Adolescent
Structural neuroimaging
MRI, anterior cingulate
Major depression

A B S T R A C T

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 × Cingulate BA (25,24,31,23,29) × 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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without BPD and 20 HCs using voxel-based morphology (VBM) and reported no ACC 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 (Chen et al., 2008) 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 BAZ44 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 × 256 × 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 (1–3) × Hemisphere × Matter type (gray, white) MANOVA and (2) a Group (HC vs. BPD/MDD) × Frontal region (Anterior: BA 8,9,10; Medial: BA 32,25,24; Orbitofrontal: BA11,12,17; Dorsolateral: BA44,45,46) × Hemisphere (left, right) × Matter type (gray, white) MANOVA. Our dependent variables were relative 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 BAZ44 (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 × 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.
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 × Type interaction: F[1,24] = 5.10, p = 0.003). Lastly, there was a significant Group × Cingulate BA × 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 volume 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 × Matter type and the Group × Cingulate BA × Matter type interactions remained significant (both Fs > 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 BDQ) 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 matter (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 inpatient 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 (BA23, 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 co-morbid 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.

Role of funding source

This work was supported by a VA Career Development Grant to MG and NIMH grant R01MH073911 to EAH. Other support came from grant M01-Patient Care RR-0071 from the National Center for Research Resources (NCRR) and the Mental Illness Research and ClinicalCenter, VISN 3 Veterans Heath Administration. These funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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.

Acknowledgments

The authors wish to thank Dr. Monte Buchsbaum for use of the Brodmann area delineation and quantification software.

References


