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

Marianne Goodman [a,b,*], Erin A. Hazlett [a,b], Jennifer B. Avedon [a], Daniel R. Siever [b], King-Wai Chu [b], Antonia S. New [a,b]

[a] Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA
[b] James J. Peters Veterans Affairs Medical Center, Mental Illness Research, Education, and Clinical Center (MIRECC; VISN 3), USA

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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 × 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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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

* Corresponding author. James J. Peters Dept. of Veterans Administration Medical Center, 130 W. Kingsbridge Road, Office 3B-20b, Bronx, NY 10468. Tel.: +1 718 585 9000x5188; fax: +1 718 364 3576.
E-mail address: Marianne.goodman@va.gov (M. Goodman).

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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.

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)*
BPFS-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; BPFS-C: Borderline Personality Features Scale-Childhood. ALS: Affective Lability 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.

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 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) × Cingulate BA (BA 25, 24, 31, 23, 29) × 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: BA11,12,47; Dorsolateral: BA44,45,46) × BA (1–3) × 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 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 × 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.