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Anterior cingulate volume in adolescents with first-presentation borderline personality disorder

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ABSTRACT

Reports of volumetric abnormalities in the anterior cingulate cortex (ACC) in adults with established borderline personality disorder (BPD) are inconsistent, and it is not known whether such abnormalities are present early in the disorder. We aimed to investigate ACC volume in a first-presentation teenage BPD sample with minimal exposure to treatment. Fifteen female BPD patients and 15 healthy female control participants underwent magnetic resonance imaging (MRI) scanning. ACC volumes were estimated using a reliable method that accounts for inter-individual variation in sulcal morphology, and measurements were compared between the two groups. Analysis of variance revealed a decrease in volume of the left ACC in BPD patients compared with control participants. This volumetric change was correlated with parasuicidal behavior and impulsivity. A measure of ACC volume asymmetry was also correlated with fear of abandonment symptoms. Our results suggest that ACC volumetric abnormalities early in the course of BPD might be related to clinical correlates of the disorder. Longitudinal studies are needed to examine the nature of this abnormality over the course of the disorder.

1. Introduction

Neuroanatomical abnormalities have been reported in limbic and prefrontal regions in adult patients with borderline personality disorder (BPD) (Lyoo et al., 1998; Schmahl and Bremner, 2006; Lis et al., 2007), and it has been suggested that these abnormalities might be associated with clinical features of the disorder. The anterior cingulate cortex (ACC) is involved in cognitive and affective functions (Bush et al., 2000; Allman et al., 2001; Yücel et al., 2007) that are likely to underpin key borderline features, including affective instability, impulsivity, and cognitive distortions accompanying emotional distress.

Magnetic resonance imaging (MRI) volumetric studies of the ACC in BPD have been inconsistent in their findings. One region-of-interest based study of eight unmedicated adult female BPD patients (Tebartz van Elst et al., 2003) reported a 26% reduction in right cingulate gyrus (grey and white matter) volume. Another reported bilateral reductions in cingulate gyrus grey matter, coupled with increased ACC white matter, in 50 adult patients with various comorbidities (Hazlett et al., 2005). Voxel-based-morphometry studies of unmedicated adult BPD patients with comorbid disorders have reported both left-lateralized reductions (Minzenberg et al., 2008), and an absence of volumetric changes in the ACC (Rüsch et al., 2003).

One explanation for the above inconsistencies might relate to methodological differences in volumetric measurement. The ACC is a region of high morphometric variability, particularly with respect to the presence and extent of the paracingulate sulcus, which runs parallel to the cingulate sulcus along its rostro-caudal extent. We have previously demonstrated that PCS variability can alter the regional distribution of volume in the limbic ACC (ACC_L; callosal sulcus extending to the cingulate sulcus) and the adjacent paralimbic cortex (ACC_P; upper bank of the cingulate sulcus, extending to the paracingulate sulcus when present) by 39–88% (see Fig. 1 and Fornito et al., 2006). For automated voxel-based-morphometry approaches, the morphologically variable nature of this region increases the potential for errors in spatial normalization, making it unclear whether statistically significant findings reflect differences in volume, sulcal and gyral anatomy, or some combination of both (Bookstein, 2001). Consequently, morphometric studies of the region cannot ignore the influence that anatomical variation may have on volumetric estimates.

Another possible explanation for inconsistent findings in the literature is that studies have typically examined samples of adult patients with chronic BPD. Examining younger samples, earlier in the course of the disorder, has the potential to reduce the confounding influences of prolonged illness, treatment, and recurrent or chronic comorbidities (e.g., substance abuse, mood disorders) associated with

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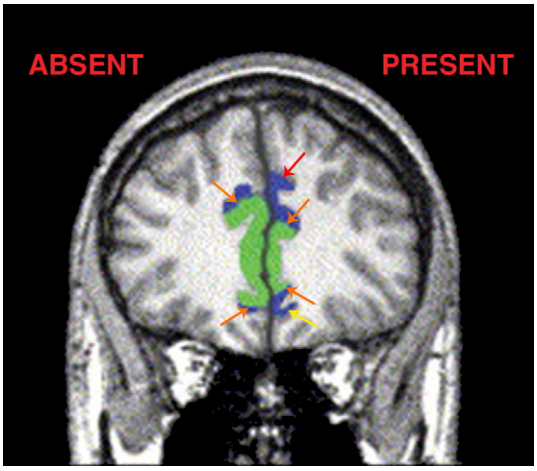

Fig. 1. Example of limbic (ACC_L; highlighted in green) and paralimbic (ACC_P; highlighted in blue) anterior cingulate regions when the paracingulate sulcus (red arrow) and superior rostral sulcus (yellow arrow) are present (right hand side) and absent (left hand side). See text (Section 2.3.1) for description.

BPD (Chanen et al., 2008c). The present study sought to extend this line of research in the context of a unique sample of young people with first-presentation BPD by investigating measures of ACC_L and ACC_P volume with a region-of-interest based methodology that takes into account individual variability in local sulcal morphology (Fornito et al., 2006).

2. Methods

2.1. Participants

Fifteen female patients meeting Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II, First et al., 1997) criteria for BPD were recruited from the HYPE Clinic (Chanen et al., 2008b), a specialized early intervention program for BPD at ORYGEN Youth Health, Melbourne, Australia. Patients had never received specific treatment for BPD and were physically healthy, based upon medical history. The sample has been described in detail elsewhere (Chanen et al., 2008c). Common comorbid Axis I diagnoses included disruptive disorder ($n=7$), anxiety disorder ($n=6$), mood disorder ($n=6$), and cannabis dependence ($n=2$). Fifteen female control participants were drawn from a pool of healthy volunteers, carefully screened for no personal or family history of psychiatric illness, substance abuse, or neurological disorder. BPD screens were performed by a psychiatrist, clinical neuropsychologist and an experienced graduate research assistant trained in clinical diagnosis, using a checklist derived from the SCID-II. Control participants were matched as closely as possible on a group basis on a number of variables (see Table 1).

Potential BPD participants were excluded from the study if they had a current or lifetime schizophrenia spectrum or affective psychotic disorder, current anorexia nervosa, current alcohol dependence of 2 months or greater duration, or if they had a history of head injury, loss of consciousness for 10 min or more, seizures, thyroid disorder, or other significant medical illness.

The study was approved by local Research and Ethics Committees. Written informed consent was obtained from participants or from a parent or guardian, where appropriate. Patients, but not control participants, were remunerated AUD$50.

2.2. Measures

All diagnoses were made using the Structured Clinical Interviews for DSM-IV Axis I (SCID-I/P, First et al., 1996) and Axis II (SCID-II, First et al., 1997) disorders, supplemented by the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) Disruptive Behavior Disorders section (Kaufman et al., 1997).

The Youth Self-Report (YSR, Achenbach, 1991) and its analogue, the Young Adult Self-Report (YASR, Achenbach, 1997), were used for 11–17 year-olds and 18–30 year-olds, respectively. Consistent with previous literature (Chanen et al., 2007), mean item scores for the YSR and YASR internalizing and externalizing sub-scales were calculated to ensure comparability between the instruments.

The number of parasuicidal episodes (suicide attempts and non-suicidal self-injury, Linehan, 1997) and number of violent episodes (attacks against people, animals or property) over the previous 6 months, along with lifetime exposure to trauma (age of onset, number and duration of episodes or physical, sexual or emotional abuse), were all assessed by semi-structured interview (developed by the investigators and available upon request).

2.3. MRI acquisition and procedures

All participants and controls were scanned using a GE Signa 1.5 T scanner (GE, Milwaukee) at Royal Melbourne Hospital. A three-dimensional volumetric spoiled gradient recalled echo in the steady state sequence (SPGR) generated 124 contiguous 1.5-mm coronal slices. Imaging parameters were TE = 3.3 ms; TR = 14.3 ms; flip angle = 30°; matrix size = 256 × 256; FOV = 24 × 24 cm; voxel dimension = 0.938 × 0.938 × 1.5 mm. MRI data were transferred from DAT tape to a Linux workstation and coded to ensure patient confidentiality and blind rating of data. Volumes were estimated using ANALYZE 7.5 (Mayo Clinic, Rochester, MN, USA; http://mayoresearch.mayo.edu/mayo/research/robb_lab/). The method for estimating whole brain volume has been previously described (Velakoulis et al., 2006).

2.3.1. Anterior cingulate cortex (ACC)

Prior to regional volumetric measurement, the variability of sulcal patterning in the ACC was documented. The presence and extent of the paracingulate sulcus was measured (three categories: 'absent', 'present', 'prominent'), and an asymmetry index was assigned to each individual based on the combination of left and right paracingulate sulcus morphology, in accordance with previously published methods (Yücel et al., 2001). An asymmetry was indicated by a greater degree of folding in one hemisphere than the other. For example, a 'prominent' paracingulate sulcus indicates a greater degree of folding than a 'present' paracingulate sulcus, which in turn indicates a greater degree of folding than an 'absent' case. Thus, an asymmetry direction of leftward (left>right), rightward (right>left), or symmetric (left = right) could be assigned to each individual. Previous work by our group has shown that paracingulate sulcus asymmetry influences ACC volume such that an asymmetry in favour of one hemisphere is associated with a relatively larger ACC_P than ACC_L in that hemisphere (Fornito et al., 2008).

Secondly, limbic and paralimbic portions of the ACC (ACC_L and ACC_P, respectively) were demarcated by taking into account individual differences in morphology of the cingulate, paracingulate and superior rostral sulci, as described in detail by Fornito et al. (2006). The anterior ACC_L contained all grey matter in the gyrus bound by the callosal sulcus and the cingulate sulcus. The ACC_P contained all grey matter in the gyrus bound by the cingulate and paracingulate sulci, except in cases where the paracingulate sulcus was absent, for which the ACC_P contained only the grey matter on the upper bank of the cingulate sulci (see Fig. 1 for illustration). Dorsally, the posterior border for both regions was a straight vertical line drawn on the coronal plane passing through the anterior commissure. Ventrally, the posterior border for both regions was the appearance of the internal capsule separating the caudate nucleus from the putamen on the coronal plane.

Thirdly, volumetric asymmetry measures were calculated for the ACC_L and ACC_P using the formula $100 \times (\text{left} - \text{right}) / [0.5 \times (\text{left} + \text{right})]$, such that positive values indicate left larger than right volumes. Such measures have been shown to have significant associations with aspects of cognitive and affective functioning (Fornito et al., 2008; Whittle et al., 2008b).

All measurements for this study were made by one rater (SW). Intra-rater reliability was assessed by means of the intraclass correlation coefficient (ICC; absolute agreement) using 15 brain images from a separate MRI database established specifically for this purpose. Measurements made by a second rater also enabled the establishment of inter-rater reliability. ICC values for paracingulate sulcus classifications and volumetric measures were all 0.90 or greater.

2.4. Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 16 (Chicago, Ill.). A mixed-model multivariate analysis of covariance (MANCOVA) was carried out on the left and right ACC_L and ACC_P volume measures. Group (BPD versus control) was the between-subject factor, and hemisphere (left versus right) and region (limbic versus paralimbic) were the within-subject factors. Whole brain volume and age were used as covariates. We also tested for group differences in ACC volumetric asymmetry using a MANCOVA with one within-subjects factor: region (limbic versus paralimbic).

To examine the relationships between ACC structure and clinical and other features of BPD, partial correlations, controlling for age and whole brain volume, were calculated between ACC asymmetry measures and total SCID-II BPD score, each of the nine BPD criteria, internalizing and externalizing scores on the YSR/YASR, and numbers of parasuicidal and violent episodes in the past 6 months. Asymmetry measures were

Table 1
Sample characteristics.

	BPD ($n=15$)	Control ($n=15$)	$t(1,28)$	P
Age (years)	17.39 ± 1.15	19.65 ± 2.18	3.555	0.002
Height (cm)	161.21 ± 7.74	163.71 ± 6.23	0.942	0.355
Handedness	13 right (87), 1 left (7), 1 mixed (7)	14 right (93), 1 left (7)	$\chi^2 = 1.037$	0.595
FSIQ	100.73 ± 5.81	101.14 ± 9.92	0.137	0.892

Data are given as mean ± S.D. or number (percentage). BPD = borderline personality disorder. FSIQ = full-scale IQ as estimated by the National Adult Reading Test (NART).