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Corpus callosum morphology and relationship to orbitofrontal and lateral ventricular volume in teenagers with first-presentation borderline personality disorder

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ABSTRACT

Previous studies have demonstrated alterations to fronto-limbic circuitry and callosal structure in borderline personality disorder (BPD). We predicted that a first-presentation BPD cohort who demonstrated orbitofrontal cortex (OFC) reductions would show regional reductions in the anterior corpus callosum. *Method:* Twenty teenage first-presentation BPD patients and twenty matched healthy controls underwent Magnetic resonance imaging (MRI) was performed in 20 teenaged first-presentation BPD patients and 20 matched healthy controls. Corpus callosum size and shape and ventricular volume were estimated using established methods and compared between the two groups. The relationship between illness variables and callosal morphology was also examined. OFC volume was correlated with callosal and ventricular variables. *Results:* BPD participants and controls did not differ on measures of callosal size or shape, or ventricular size. BPD participants showed an alteration to the pattern of age-related expansions seen in the callosum. BPD participants with a history of trauma did not demonstrate significant neuroanatomical differences from those without. OFC volumes did not correlate with the thickness of the anterior corpus callosum.*Conclusion:* Gross neuroanatomical changes are not present at the level of the callosum in teenagers with first-presentation BPD. Changes seen in other studies might reflect factors associated with the duration of BPD, such as recurrent comorbidity with axis I disorders, or treatment.

1. Introduction

Structural and functional neuroimaging studies in adults with borderline personality disorder (BPD) have shown alterations in the prefrontal cortex, particularly the orbitofrontal cortex and adjacent ventral medial cortex (including the anterior cingulate gyrus), in addition to the hippocampus and amygdala (Rüsch et al., 2003; Tebartz van Elst et al., 2003; Weniger et al., 2009). This implicates disruptions to prefrontolimbic circuitry as a marker of biological vulnerability to BPD (Lis et al., 2007; Schmahl and Bremner, 2006), or the sequelae of significant childhood trauma that are implicated in the genesis of BPD (Goodman et al., 2004). The characteristic affective dysregulation and impaired impulse control that occur in BPD may be related to altered connectivity between prefrontal and limbic regions (New et al., 2007; Williams et al., 2006). This is supported by two recent studies showing impairments to the structural integrity of white matter in the inferior frontal region (Grant et al., 2007; Rüsch et al., 2007b). It is not clear if these alterations in prefrontal white and grey matter in BPD are related and, if so, whether white matter changes in the disorder occur independently of, or are secondary to, primary grey matter changes.

We have previously demonstrated in a cohort of teenagers with first-presentation BPD that orbitofrontal, but not amygdala or hippocampal, grey matter reductions are present early in the course of BPD (Chanen et al., 2008), and recently these findings have been supported in a sample of female adolescents with BPD (Brunner et al., 2010). However, in our previous study, amygdala volume was related to measures of "state" psychopathology in female participants. We also showed volume reductions at the level of the left anterior cingulate cortex in females from this sample, which correlated with measures of impulsivity and parasuicidal behavior (Whittle et al.,

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2009). These findings suggest that prefrontal-limbic structures, particularly the OFC, are relevant to the early course of BPD in young people. Prefrontal cortical fibres from the orbitofrontal and ventral medial cortex pass between the hemispheres through the corpus callosum (CC), in the region of the genu (Pandya and Seltzer, 1986), whereas amygdala and hippocampal fibres do not. The CC, the brain's largest white matter bundle, connects functionally related interhemispheric regions of the cerebral cortex, predominantly through homotopic connections that connect a given specialized cortical area with its contralateral homolog, but also through heterotopic connections that connect non-homologous areas (Clarke and Zaidel, 1994; de Lacoste et al., 1985; Witelson, 1989). Disorders that produce significant grey matter atrophy such as Alzheimer's disease, vascular dementia and frontotemporal dementia result in regional callosal reductions in the areas connecting atrophic cortical regions (Hallam et al., 2008; Kaufer et al., 1997; Yamauchi et al., 2000); if white matter changes in BPD are indeed secondary to reductions in grey matter regions, subtle alterations at the level of the anterior CC may then be detectable in BPD.

Disrupted interhemispheric connectivity has also been implicated in underlying the mood dysregulation characteristic of major affective disorders (Brambilla et al., 2003, 2004), which can show symptomatic overlap and co-occurrence with BPD (Akiskal, 2004; Paris et al., 2007). Additionally, the corpus callosum appears particularly vulnerable to the effects of childhood abuse and trauma, with children suffering abuse and neglect demonstrating abnormal callosal development and reduced callosal size compared to non-abused children (DeBellis et al., 1999; Teicher et al., 1997, 2004), which may alter the developmental trajectory of interhemispheric integration and functional cerebral laterality (Schiffer et al., 1995). The callosum develops in a non-linear way, and shows quadratic trajectories of micro- and macro-structural changes across the lifespan, particularly in adolescence and early adulthood (Hasan et al., 2008a,b, 2009); these trajectories may be disrupted by the pathophysiology of trauma and major affective illness, which may be reflected in changes in callosal structure.

Few studies have examined CC in BPD patients and no studies have examined young people early in the course of BPD. Two recent studies have examined CC structure in BPD patients compared with healthy controls (Rüsch et al., 2007a; Zanetti et al., 2007). Zanetti et al. (2007) found no differences in CC structure between patients and controls. Rüsch et al. studied BPD patients with comorbid attention-deficit hyperactivity disorder (ADHD) and found a thinner isthmus of the callosum (connecting parietal and temporal cortices). In this study, BPD patients with an abuse history also demonstrated reductions in the posterior body of the CC compared with those without (Rüsch et al., 2007a). These authors considered that the CC changes identified were consistent with impaired interhemispheric connectivity between parietal and temporal cortices in BPD, but noted that similar regional CC reductions have been seen in ADHD, and could not exclude that these findings were driven by illness processes specific to ADHD rather than BPD.

To investigate the possible role of structural alterations of the CC in this first-presentation BPD sample, we used a sensitive shape analysis method that has previously detected robust changes in the anterior CC in pre-psychotic and first-episode psychosis cohorts (Walterfang et al., 2008b,c, 2009c,e), regional posterior reductions in patients with bipolar disorder (Walterfang et al., 2009a,b) and putative state related expansions in the posterior CC in depressed patients (Walterfang et al., 2009d). In the first instance, we aimed to see if we could replicate the findings by Rüsch et al. (2007a) in a first-presentation BPD group. However, given the previously-demonstrated prefrontal cortical reductions present at first presentation in this cohort, we predicted a reduction in the anterior genu — the callosal region connecting the homotopic orbitofrontal cortex (Pandya and Seltzer, 1986) — in BPD patients compared with controls, and expansions in posterior regions associated with depressive and anxiety symptoms.

2. Methods

2.1. Participants

Twenty 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., 2009), a specialized early intervention program for BPD at ORYGEN Youth Health in Melbourne, Australia. They had minimal exposure to psychiatric interventions and had never received specific treatment for BPD. Potential BPD participants were excluded from the study if they had a schizophrenia spectrum or affective psychotic disorder, anorexia nervosa, and current alcohol dependence with a duration of 2 months or longer. The characteristics of this sample have been previously described (Chanen et al., 2008). Briefly, common comorbidities included disruptive behavior disorders ($N=10$), anxiety disorder ($N=9$, including one case of PTSD), mood disorder ($N=7$, 4 with major depressive disorder, 2 with dysthymic disorder, and 1 with bipolar I disorder), and/or substance abuse or dependence ($N=6$). No participant had comorbid ADHD. Seventeen participants were medication-free; one was taking citalopram, one was taking venlafaxine, and one was on both sertraline and methadone maintenance therapy.

Lifetime trauma exposures (physical, sexual or emotional), along with a number of parasuicidal and violent episodes over the previous 6 months, were assessed by a semi-structured interview (developed by the investigators and available upon request). Interview data on abuse or trauma were available for 19 BPD participants; 10 denied any experience of abuse and 9 reported experience of physical ($N=6$), sexual ($N=5$), and/or emotional ($N=5$) abuse.

Twenty 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, and were recruited via advertisements placed in an employment centre and colleges, and local newspaper advertisements in the community from which the patient group was drawn. Control participants were also subsequently recruited via word-of-mouth from other control participants. BPD screens were performed by a psychiatrist (DV), clinical neuropsychologist and an experienced graduate research assistant trained in clinical diagnosis, using a checklist derived from the SCID-II. Control participants were matched exactly by sex and as closely as possible for age and handedness.

All participants were physically healthy, based upon medical history, and none had a history of serious head injury, loss of consciousness ($\geq$10 min), seizure, neurological diseases, thyroid disorder or other significant medical illnesses. The study was approved by the local Research and Ethics Committees. Written informed consent was obtained from all participants or from a parent or guardian. BPD participants were remunerated AU$50.

2.2. Assessment

Axis I diagnoses were made with the Structured Clinical Interview for DSM-IV patient version (SCID-I/P (First et al., 1996)), supplemented by the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) Disruptive Behavior Disorders section (Kaufman et al., 1997). Axis II diagnoses were made with the SCID-II (First et al., 1997). In common with previous research (Chanen et al., 2007), a PD feature was scored positive if it was present for 2 years and did not occur exclusively in the context of an Axis I disorder, and a total score for the nine borderline personality disorder items on the SCID-II was calculated.

BPD participants less than 18 years old completed the Youth Self-Report (YSR (Achenbach, 1991)) and those 18 years and above completed the Young Adult Self-Report (YASR (Achenbach, 1997)). Consistent with previous research (Chanen et al., 2007), mean scores