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Corpus callosum size and shape alterations in individuals with bipolar disorder and their first-degree relatives

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ABSTRACT

Reductions in the size of the corpus callosum (CC) have been described in patients with bipolar disorder (BD), although the contribution of genetic factors to these changes is unclear. We previously showed a global thinning of the CC in BD patients, and found those with a family history of affective disorders had a larger CC than those without. In this study, we compared callosal size and shape in 180 individuals: 70 with BD, 45 of their first-degree relatives, and 75 healthy controls. The callosum was extracted from a mid-sagittal slice from T1-weighted magnetic resonance images, and its total area, length and curvature were compared across groups. A non-parametric permutation method was used to examine for alterations in width of the callosum along 39 points.

Validating our previous findings, a significant global reduction in callosal thickness was seen in BD patients, with a disproportionate thinning in the anterior body. First-degree relatives did not differ in callosal size or shape from controls. In BD patients, duration of illness and age were associated with thinning in the anterior body; BD patients on lithium treatment showed a thicker anterior mid-body than those on other psychotropics.

Global and regional thinning of the callosum is seen in BD but not in their first-degree relatives. This suggests that CC abnormalities are linked to disease expression in BD and may not represent a marker of familial predisposition.

1. Introduction

The corpus callosum (CC) is the most prominent white matter tract in the brain. It connects the two hemispheres and has a prolonged sequence of maturation through childhood, adolescence and early adulthood. It serves to integrate cognitive and behavioural function across the two cerebral hemispheres to facilitate language, affective and sensorimotor information processing (Clarke and Zaidel, 1994; Hoptman and Davidson, 1994). Impaired information transfer between hemispheres has been implicated in bipolar disorder (Soares and Mann, 1997), and may be mediated by altered callosal structure. Two recent meta-analyses of published studies of mid-sagittal callosal area in bipolar disorder demonstrated a significant reduction in BD patients compared to controls, with an effect size of diagnosis of 0.52 (Arnone et al., 2008) and 0.43 (Kempton et al., 2008), suggesting that widespread disruptions to connectivity affecting the callosum may relate to or reflect functional impairments in the prefrontal and cingulate cortex, the hippocampus and amygdala seen in BD (Soares and Mann, 1997). As the callosum is topographically organized, a differential effect on callosal shape may be seen in areas connecting brain regions disproportionately functionally affected; regional reductions in size and signal intensity have been shown in anterior and posterior callosal regions in both first-episode and established adult BD patients both in our lab (Walterfang et al., 2008a) and by other colleagues (Atmaca et al., 2007; Brambilla et al., 2004; Brambilla et al., 2003).

In addition, we (Walterfang et al., 2008a) reported that patients with a family history of affective disorder showed *increased* total

Abbreviations: CC, corpus callosum; BD, bipolar disorder; DSM, Diagnostic and Statistical Manual for Mental Disorders; UK, United Kingdom; SCID, Structured Clinical Interview for DSM-IV; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale; MRI, magnetic resonance imaging; ANOVA, analysis of variance; ANCOVA, analysis of covariance; BDNF, brain-derived neurotrophic factor.

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callosal area, suggesting that familial factors may moderate callosal structure in BD. We sought to validate and explore further these results, through examination of a larger dataset which included first-degree relatives of BD patients to examine genetic influences on changes to callosal structure, and thus inter-hemispheric connectivity, in BD.

2. Materials and methods

2.1. Subjects

The entire sample was recruited at the Institute of Psychiatry, London, UK. Patients ($n=70$) were identified by clinicians' referrals and were included if they (a) were aged between 17 and 65 years (b) fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised (DSM-IV) criteria for Bipolar Disorder, type I (BDI), (c) had no family history (up to second degree) of schizophrenia or schizophrenia spectrum disorders. Siblings and offspring ($n=45$) were invited to participate, with the patients' consent, if aged 17–65 and without a personal history of Bipolar Spectrum Disorders. Patients were in remission at the time of assessment.

Healthy volunteers ($n=75$) were recruited through an advertisement in the local press and were enrolled if they were (a) aged 17–65 years and (b) had no personal or family history of any Axis I DSM-IV disorder. Healthy volunteers were selected so that they matched both patients and relatives in gender and level of education. Level of education was rated on a 5-point scale ranging from 1 (no educational qualification) to 5 (post graduate university level qualifications).

Exclusion criteria for the entire sample (patients, relatives and controls) included (a) head trauma resulting in loss of consciousness, (b) personal history of neurological or medical disorders, (c) family history of hereditary neurological disorders and (d) fulfilling Lifetime DSM-IV criteria for lifetime drug or alcohol dependence and drug or alcohol abuse in the preceding six months. The study was approved by the Ethics Committee of the Institute of Psychiatry, London, UK. Written informed consent was obtained from all participants.

2.2. Assessment

Diagnostic assessments for all participants were conducted by personal interview with two trained psychiatrists, who were initially blind to diagnostic but not family status (BD family member or unrelated control), using the Structured Clinical Interview for DSM-IV (SCID) for Axis I (First et al., 1998) and the SCID-II Personality Questionnaire for Axis II diagnoses (First et al., 1997). Inter-rater reliability was kappa >0.92 for both instruments. Where applicable, further information about age of onset, previous episodes and hospital admissions as well as current medication (type, dose and duration) was collected from medical notes. Family history of psychiatric disorders was assessed using the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) supplemented by medical notes as necessary.

All participants were rated using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Prior to scanning patients were assessed weekly over a minimum period of one month to ensure that they (a) continued to fulfil DSM-IV criteria for remission requiring a minimum period of six months of remission since the last syndromal episode (b) scored below 7 in the HDRS and YMRS and (c) had remained on the same type and dose of medication for a minimum period of six months.

For all participants an estimate of current full-scale intelligence quotient (FSIQ) was obtained on the day of scanning using the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1981).

2.3. MRI scanning

Structural images were acquired using a 1.5-T General Electric Signa System scanner (GE, Milwaukee, USA) at the Maudsley Hospital, London. Images were acquired in the axial plane using a T_1 weighted, 3D Spoiled Gradient Recalled Echo (SPGR) protocol (TE = 5.1 ms, TR = 18 ms, flip angle = 20°, slice thickness = 1.5 mm, in plane resolution = 0.9375 mm × 0.9375 mm, Nex = 1.

2.4. Image processing

All images were checked manually for gross structural abnormalities prior to analysis.

The brain was automatically segmented from the rest of the head (Smith 2002). Images were registered to a template image comprising the average of 152 normal T1-weighted MRI scans previously placed in a stereotaxic coordinate space (Woods et al., 1998). A 9-parameter linear transformation was used which allowed translation, rotation and scaling along each of the three principal axes; this method accounts more robustly for differential effects of gender and illness between callosal shape and brain size than simply covarying for brain volume (Bermudez and Zatorre, 2001). The mid-sagittal slice was identified and interpolated to a voxel dimension of 0.5 mm × 0.5 mm in the y and z planes. The mid-sagittal slice was confirmed by an experienced rater (SB) via identification of the slice which showed minimal white matter in the cortical mantle adjacent to the callosum,

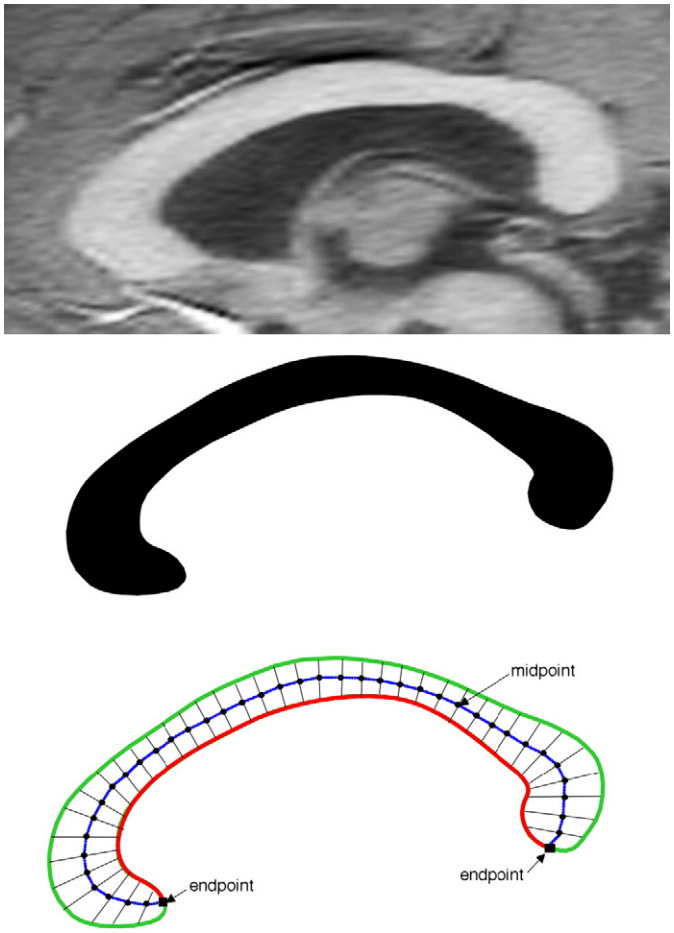

Fig. 1. Callosal extraction and segmentation. The mid-sagittal image, top, is then binarised to select out the callosum (middle). The mid-spline is then generated, and divided into 40 equidistant sections, with orthogonal lines generated from the 39 points along the callosum between the endpoints.