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ORIGINAL ARTICLE

Interhemispheric white matter integrity in young people with bipolar disorder and at high genetic risk

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Background. White matter (WM) impairments have been reported in patients with bipolar disorder (BD) and those at high familial risk of developing BD. However, the distribution of these impairments has not been well characterized. Few studies have examined WM integrity in young people early in the course of illness and in individuals at familial risk who have not yet passed the peak age of onset.

Method. WM integrity was examined in 63 BD subjects, 150 high-risk (HR) individuals and 111 participants with no family history of mental illness (CON). All subjects were aged 12 to 30 years.

Results. This young BD group had significantly lower fractional anisotropy within the genu of the corpus callosum (CC) compared with the CON and HR groups. Moreover, the abnormality in the genu of the CC was also present in HR participants with recurrent major depressive disorder (MDD) ($n = 16$) compared with CON participants.

Conclusions. Our findings provide important validation of interhemispheric abnormalities in BD patients. The novel finding in HR subjects with recurrent MDD – a group at particular risk of future hypo/manic episodes – suggests that this may potentially represent a trait marker for BD, though this will need to be confirmed in longitudinal follow-up studies.

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Key words: Bipolar disorder, diffusion tensor imaging, fractional anisotropy, genetic risk, tract-based spatial statistics.

Introduction

Despite growing evidence for white matter (WM) impairments in bipolar disorder (BD) using diffusion tensor imaging (DTI), findings have been inconsistent (Heng *et al.* 2010; Vederine *et al.* 2011; Nortje *et al.* 2013). Moreover, impaired WM may reflect either genetic liability for the disorder, illness progression or the effects of treatment (Hajek *et al.* 2005). First-degree relatives of patients with BD are at increased risk of developing this condition, and recent research has demonstrated strong heritability of WM morphology (Chiang *et al.* 2012). Consequently, studying WM brain abnormalities in individuals at familial risk of developing BD may facilitate understanding of biological risk factors predicting the later development of BD. A number of studies have revealed both widespread and localized reductions in WM integrity in unaffected relatives of patients with BD, but the spatial distribution and extent of these impairments remains uncertain (Frazier *et al.* 2007; Versace *et al.* 2010; Matsuo *et al.* 2011; Sprooten *et al.* 2011; Linke *et al.* 2013; Mahon *et al.* 2013; Sprooten *et al.* 2013; Emsell *et al.* 2014; Roybal *et al.* 2015). For example, whilst lower fractional anisotropy (FA) in the corpus callosum (CC) of high-risk and BD individuals compared with controls has been reported by Sprooten *et al.* (2013), another study identified this deficit in BD individuals only (Linke *et al.* 2013). Similarly, reduced WM integrity in the superior longitudinal fasciculus of unaffected relatives has been reported, but whether this effect is intermediate or comparable with the decrease observed in BD patients remains unclear (Frazier *et al.* 2007; Sprooten *et al.* 2013), and in the absence of group differences another study reported genetic liability to be associated with FA in this tract (Emsell *et al.* 2014). Among other regions, pathways involved in

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emotion regulation involving fronto-temporal lobes such as temporal associative tracts, left orbital frontal tracts, superior longitudinal fasciculus, cingulum (Frazier *et al.* 2007; Versace *et al.* 2010; Sprooten *et al.* 2011; Mahon *et al.* 2013; Sprooten *et al.* 2013; Emsell *et al.* 2014), pathways connecting fibres to frontal regions such as the internal capsule (Sprooten *et al.* 2011), and intra-hemispheric tracts of the CC responsible for inter-hemispheric communication (Sprooten *et al.* 2013; Roybal *et al.* 2015) have been implicated in subjects at increased familial risk of developing BD.

DTI allows for sensitive exploration of WM microstructural features. FA is perhaps the most widely accepted DTI measure and reflects directionally constrained diffusion of water along nerve fibres (Thomason & Thompson, 2011). Tract-based spatial statistics (TBSS) is a popular means of quantifying FA that restricts the evaluation of diffusion parameters to a WM skeleton (Smith *et al.* 2006) and addresses prior methodological concerns regarding smoothing and normalization (Jones *et al.* 2002; Chao *et al.* 2009). Using TBSS, three previous studies have investigated FA in subjects at increased genetic risk of developing BD compared with controls (Versace *et al.* 2010; Sprooten *et al.* 2011; Roybal *et al.* 2015).

A limitation of several studies investigating WM abnormalities in unaffected relatives has been the lack of a comparator BD group. The inclusion of such a group enables clarification of whether FA findings in unaffected relatives are similar to, or distinct from, those with the established condition. Hitherto, few studies have investigated (within the same study) FA in patients with established BD, individuals at high genetic risk of developing BD, and controls. To our knowledge, only three previous studies have employed TBSS in all three groups within the same study, each of which had limitations (Linke *et al.* 2013; Mahon *et al.* 2013; Sprooten *et al.* 2013). Two of these three studies had a modest sample size (Linke *et al.* 2013; Mahon *et al.* 2013), and the study with the largest sample (n for all groups = 170) (Sprooten *et al.* 2013) recruited unaffected relatives who had already passed the typical age of illness onset (<30 years). Using voxel-based analysis (Frazier *et al.* 2007; Chaddock *et al.* 2009), tractography (Emsell *et al.* 2014) and TBSS (Skudlarski *et al.* 2013), WM deficits have been detected in both psychotic and non-psychotic BD individuals, as well as their unaffected relatives. In three of these four studies, the mean age of unaffected relatives was over 30 years, again suggesting that many would have already passed the typical onset age of BD illness (Chaddock *et al.* 2009; Skudlarski *et al.* 2013; Emsell *et al.* 2014). Furthermore, DTI findings in studies that included all three groups have been inconsistent in terms of the location and extent of WM abnormalities.

Here, using TBSS, we compared FA in a large young sample of: (i) 'high risk' (HR) first-degree relatives of patients with BD who have not been diagnosed with BD; (ii) patients with BD; and (iii) control (CON) subjects without a family history of BD or other mental illness. As those HR subjects with recurrent major depressive disorder (rMDD) are at greatest risk for later development of a manic or hypomanic episode (Hillegers *et al.* 2005; Duffy, 2010), we also compared this subgroup with both the BD and CON groups. To our knowledge, this DTI study comprises both the largest HR sample, and the largest combined sample, across all three groups to date.

Method

Participants

The sample comprised three groups: (i) 111 CON participants [defined as subjects with no parent or sibling with bipolar I (BD-I) or II (BD-II) disorder, recurrent major depression, schizo-affective disorder, schizophrenia, recurrent substance abuse or any past psychiatric hospitalization; and no parent with a first-degree relative who had a past mood disorder hospitalization or history of psychosis]; (ii) 150 subjects genetically 'high risk' for BD who had not yet developed this condition (HR) [defined as children or siblings of a proband with a confirmed Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of BD-I or BD-II]; and (iii) 63 BD subjects (defined as meeting DSM-IV criteria for either BD-I or BD-II). All participants were aged between 12 and 30 years. Clinical details of the three groups have been described elsewhere (Perich *et al.* 2015). The study was approved by the Human Research Ethics Committee of the University of New South Wales, and complied with the guidelines of the Australian National Health and Medical Research Council.

The lifetime or current presence of psychiatric disorders (including depression and anxiety) besides BD was not an exclusion factor for either HR or CON subjects. This ecological approach has been used by similar studies of individuals at high genetic risk for BD (Nurnberger *et al.* 2011). All participants are involved in an ongoing longitudinal study of individuals at high risk for BD aged 12–30 years. HR and BD participants were recruited from families who had previously participated in a BD pedigree molecular genetics study or a specialized BD research clinic, or were otherwise recruited from clinicians, mental health consumer organizations and other forms of publicity. Control subjects were recruited via print and electronic media, and noticeboards in universities and local communities.

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The subjects aged between 12 and 21 years are involved in a collaborative high-risk study with a US consortium headed by J.I.N. which is based at Indiana University, Johns Hopkins University, Washington University in St Louis and Michigan University (Nurnberger *et al.* 2011). As this US–Australian collaboration involves common clinical assessments for participants aged 12–21 years, we report separately on instruments used for the younger (12–21 years) and older (22–30 years) age groups in this sample. Both groups shared consensus best estimate DSM-IV current and lifetime diagnoses derived from semi-structured diagnostic interviews. Brain imaging studies were only undertaken in the Australian sample. A number of functional imaging studies on this BD HR sample have been previously reported (Roberts *et al.* 2013; Breakspear *et al.* 2015).

Proband consensus DSM-IV diagnosis was determined by two independent raters following best estimate methodology (Leckman *et al.* 1982), using information from the Diagnostic Interview for Genetic Studies (DIGS) version 4, the Family Interview for Genetic Studies (FIGS) and medical records (where available). Confidence rating ranges using the best estimate methodology vary from 1 to 4, where 1 represents criteria not met for a diagnosis and 4 represents a definite diagnosis. All diagnoses reported have a confidence rating of 3 or 4 (probable or definite). Structured diagnostic interviews were also performed on all HR, CON and BD participants. For those aged between 12 and 21 years (CON, $n = 51$; HR group, $n = 92$; BD group, $n = 11$), an adapted version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-BP) was developed specifically for use in the US–Australian collaborative study of young people at genetic risk for BD (Nurnberger *et al.* 2011). The K-SADS-BP combines items from the K-SADS Present and Lifetime Version (Kaufman *et al.* 1997), and uses extended sections on depression, mania and attention-deficit/hyperactivity disorder derived from the Washington University in St Louis K-SADS (WASH-U K-SADS) to elicit detailed information on pre-pubertal mania, rapid-cycling, attentional and subthreshold bipolar symptoms (Geller *et al.* 2001). The K-SADS-BP was administered to both the child and one parent. For participants aged under 21 years, clinicians completed the Children's Global Assessment Scale (CGAS).

For participants aged between 22 and 30 years (CON, $n = 60$; HR group, $n = 58$; BD group, $n = 52$), the DIGS (version 4) was used to measure the current and lifetime presence of Axis I DSM-IV disorders. Consensus DSM-IV diagnoses of the HR, BD and CON subjects were determined by two independent raters with best estimate methodology (Leckman *et al.* 1982), using the DIGS, the FIGS and medical records (where available). For participants aged between 22 and 30 years, clinicians completed the Global Assessment Scale (GAS).

To assess current mood state, for those aged between 12 and 21 years, the Children's Depression Inventory (CDI) was used, and for participants aged 22–30 years, the Montgomery–Åsberg Depression Rating Scale (MADRS) was administered. To assess current manic symptoms the Young Mania Rating Scale (YMRS) (Young *et al.* 1978) was used for participants aged 22–30 years. Intellectual ability was assessed with the Wechsler Abbreviated Scale of Intelligence. Participants aged 12–30 years completed clinical and neuropsychological assessments on the same day as the scan (McCormack *et al.* 2016). The majority of parental reports using the K-SADS were also completed on the same day as the scan.

Magnetic resonance imaging (MRI) acquisition

Images were acquired with a 3-T Philips Achieva scanner at Neuroscience Research Australia (NeuRA) in Sydney with an eight-channel head coil. Two acquisitions of 32 directional DTI data ($b = 1000$ s/mm^2 with one diffusion weighed b0) were acquired using a single-shot echo planar imaging sequence. The imaging parameters were as follows: repetition time = 7638 ms, echo time = 68 ms, 55 slices, slice thickness = 2.5 mm, gap = 0 mm, field of view = 240 × 138 × 240, acquisition matrix size = 96 × 96, flip angle = 90° with an image time of 4 min 42 s per acquisition.

DTI processing

Details of pre-processing and TBSS processing steps are provided in the online Supplementary Method. For skeletonization and region of interest (ROI) extraction from FA images we followed the ENIGMA-TBSS protocols (http://enigma.ini.usc.edu/wp-content/uploads/2014/01/ENIGMA_TBSS_protocol_USC.pdf). We extracted the mean FA across the full skeleton and subsequently calculated average FA values bilaterally for 21 intra-hemispheric and four inter-hemispheric tracts, yielding a total of 46 ROIs. The regions analysed are listed in online Supplementary Table S1.

Statistical analyses

All statistical analyses were carried out using SPSS v.22 (IBM, USA). Sociodemographic differences between groups were assessed using univariate analysis of variance followed by pairwise comparisons for multiple comparisons using the least significant difference (LSD) method. To compare tracts of interest across

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Table 1. *Demographic data for CON, HR and BD groups*

Demographic data	CON ($n = 111$)	HR ($n = 150$)	BD ($n = 63$)	Difference statistic	p	Pairwise comparisons
Males, n (%)	49 (44.1)	65 (43.3)	21 (33.3)	$\chi^2 = 2.25$	0.32	
Intelligence quotient	117.26 (1.05)	113.73 (0.96)	116.11 (1.52)	$F = 3.11$	0.05	CON > HR, $p < 0.05$
Duration of education, years	15.34 (2.77)	12.59 (3.67)	15.48 (2.46)	$F = 30.95$	<0.01	CON > HR, $p < 0.01$ BD > HR, $p < 0.01$
Age, years	21.83 (3.94)	19.73 (5.59)	24.95 (3.83)	$F = 27.16$	<0.01	CON > HR, $p < 0.01$ BD > HR, $p < 0.01$ BD > CON, $p < 0.01$

Data are given as mean (standard deviation) unless otherwise indicated.
CON, Control; HR, high-risk; BD, bipolar disorder.

diagnostic groups, generalized estimating equations (GEE) models were used as they accommodate within-family correlation arising from the inclusion of siblings from within the same family in either the CON, HR or BD groups (families were not split between diagnostic groups). Each base GEE model was run with FA of the ROI as the dependent variable, hemisphere (right and left) as the within-subject factor, diagnostic group as the between-subject factor (CON, HR, and BD), hemisphere × group as an interaction, and age and gender as covariates. To address whether the relationship between age and FA of ROIs differed between groups, a second set of GEE models was fitted where the age × group interaction was also included as an interaction term in the base model. In order to select the most parsimonious model, for ROIs with no significant age × group interaction ($p > 0.05$) the base model was selected.

Correction for multiple testing of the main effects of group, hemisphere and the group × hemisphere interaction was carried out using false-discovery rate (FDR) q values using the Benjamini & Hochberg (1995) method. For each dependent variable we used the most parsimonious model and ranked group, hemisphere and group × hemisphere comparisons (group, hemisphere and group × hemisphere comparisons for 21 intra-hemispheric tracts, and group comparisons for four inter-hemispheric tracts, yielding a total of 67 ranked comparisons). We also compared HR subjects with rMDD (HR-rMDD) ($n = 16$) against the CON and BD groups where we selected the base models and ranked group, hemisphere and group × hemisphere comparisons for 21 intra-hemispheric tracts, and group comparisons for four inter-hemispheric tracts.

Planned comparisons

Planned *post-hoc* comparisons were carried out on tracts that revealed either a significant group effect or group × hemisphere interaction after correction for multiple testing: nine group × hemisphere interaction comparisons (three between-group differences within the left and right hemispheres, respectively, in addition to three between-hemisphere differences within each study group), and three between-group comparisons. Planned comparisons were carried out using the LSD method, and corrected using FDR q values.

Effects of medication and illness severity

Separate analyses were performed to determine whether group differences were related to exposure to lithium, antidepressants or antipsychotics. To assess associations between FA and measures of illness severity and course, relationships between FA and age of onset of first manic, hypomanic, depressive or any mood episode were explored using Pearson's correlations; and relationships between FA and number of episodes of hypomania, mania or depression relationships were explored using Spearman's correlations (as that data were not normally distributed).

Results

Demographic and clinical data

Demographic and clinical data for each group are provided in Tables 1 and 2. The HR participants were slightly younger than both the CON and BD participants, whilst the BD group was older than the CON group. On the MADRS and YMRS, 22- to 30-year-old BD participants scored significantly higher than both their HR and CON counterparts, with no significant differences observed between the latter two groups. Among the 12- to 21-year-old participants, the BD group had significantly higher scores on the CDI than both the HR and CON participants.

Current and lifetime consensus best-estimate DSM-IV diagnoses in all three groups are also detailed in Table 2. It was revealed by χ^2 comparisons that the lifetime occurrence of at least one major depressive

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Table 2. *Clinical and medication data for CON, HR and BD groups*

	CON ($n = 111$)	HR ($n = 150$)	BD ($n = 63$)	Difference statistic	p	Pairwise comparisons
Lifetime DSM-IV diagnosis, *n* (%)						
Any diagnosis	32 (28.8)	75 (50.0)	63 (100.0)	$\chi^2 = 82.31$	<0.01	HR > CON, $p < 0.01$; BD > CON, $p < 0.01$; BD > HR, $p < 0.01$
At least one MDE	12 (10.8)	44 (29.3)	60 (95.2)	$\chi^2 = 131.94$	<0.01	HR > CON, $p < 0.01$; BD > CON, $p < 0.01$; BD > HR, $p < 0.01$
Recurrent MDD	3 (2.7)	16 (10.7)	–	$\chi^2 = 5.99$	0.01	HR > CON, $p < 0.05$
Any anxiety disorder	12 (11.7)	32 (22.1)	30 (49.2)	$\chi^2 = 32.63$	<0.01	HR > CON, $p < 0.05$; BD > CON, $p < 0.01$; BD > HR, $p < 0.01$
Any behavioural disorder	1 (1.0)	16 (11.3)	9 (15.3)	$\chi^2 = 13.33$	<0.01	HR > CON, $p < 0.01$; BD > CON, $p < 0.01$
Any substance disorder	7 (6.3)	13 (18.7)	15 (23.8)	$\chi^2 = 14.10$	<0.01	BD > CON, $p < 0.01$; BD > HR, $p < 0.01$
Current DSM-IV diagnosis, *n* (%)						
MDE	2 (1.8)	3 (2.0)	3 (4.8)	$\chi^2 = 1.61$	0.45	
Hypo/manic episode	0 (0)	0 (0)	0 (0)	–	–	
Symptom severity scales						
22 to 30 years, *n*	54	49	44			
Mean MADRS (S.D.)	2.22 (4.05)	3.00 (4.03)	10.68 (10.65)	$F = 21.41$	<0.01	BD > CON, $p < 0.01$; BD > HR, $p < 0.01$
Mean YMRS (S.D.)	1.00 (1.71)	0.98 (1.51)	4.61 (4.58)	$F = 27.27$	<0.01	BD > CON, $p < 0.01$; BD > HR, $p < 0.01$
12 to 21 years, *n*	37	70	9			
Mean CDI (S.D.)	7.13 (4.26)	8.36 (5.98)	19.89 (7.51)	$F = 19.36$	<0.01	BD > CON, $p < 0.01$; BD > HR, $p < 0.01$
Clinical characteristics						
Global functioning						
Mean GAS/C-GAS (S.D.)	91.01 (5.65)	85.63 (9.88)	78.17 (11.74)	$F = 38.86$	<0.01	CON > HR, $p < 0.01$; CON > BD, $p < 0.01$; HR > BD, $p < 0.01$
Mean age, years (S.D.) at first						
MDE	19.18 (2.96)	16.98 (4.77)	15.45 (3.58)	$F = 5.95$	<0.01	CON > BD, $p < 0.01$
Hypomanic episode	–	–	17.96 (4.18)	–	–	–
Manic episode	–	–	19.48 (4.33)	–	–	–
Elevated mood episode	–	–	18.17 (4.21)	–	–	–
Mood episode	19.18 (2.96)	16.98 (4.77)	15.26 (3.99)	$F = 7.11$	<0.01	CON > BD, $p < 0.01$
Mean number of episodes (S.D.)						
MDE	1.41 (1.23)	2.44 (2.82)	11.93 (11.68)	$F = 20.57$	<0.01	CON < BD, $p < 0.01$
Hypomanic episode	–	–	10.45 (11.2)	–		HR < BD, $p < 0.01$
Manic episode	–	–	3.13 (2.66)	–		–
Any elevated mood episode	–	–	9.95 (11.06)	–		–
Any mood episode	1.41 (1.23)	2.44 (2.82)	21.28 (19.87)	$F = 28.04$	<0.01	CON < BD, $p < 0.01$; HR < BD, $p < 0.01$
Current psychotropic medication, *n* (%)						
At least one psychotropic medication	4 (3.6)	11 (8.0)	46 (76.2)			
Anti-depressants	3 (2.7)	10 (6.7)	36 (57.1)			
Mood stabilizers	–	–	39 (61.9)			
Anti-psychotics	–	–	20 (31.7)			
Benzodiazepines	–	1 (1.1)	2 (1.26)			

Table 2 (*cont.*)

	CON ($n = 111$)	HR ($n = 150$)	BD ($n = 63$)	Difference statistic	p	Pairwise comparisons
Stimulants	1 (1.5)	–	1 (0.63)			
Anti-convulsants	–	–	5 (3.15)			

CON, Control; HR, high-risk; BD, bipolar disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MDE, major depressive episode; MDD, major depressive disorder; MADRS, Montgomery–Åsberg Depression Rating Scale; S.D., standard deviation; YMRS, Young Mania Rating Scale; CDI, Children's Depression Inventory; GAS, Global Assessment Scale; C-GAS, Children's Global Assessment Scale.

[a] All participants had an intelligence quotient above 80. A lifetime MDE is defined as meeting DSM-IV criteria for at least one MDE. Confidence rating ranges using the best estimate methodology vary from 1 to 4, where 1 represents criteria not met for a diagnosis and 4 represents a definite diagnosis. All diagnoses listed here have a confidence rating of 3 or higher (i.e. probable or definite). Among the 13 participants with a behavioural disorder, 10 had attention-deficit/hyperactivity disorder (five current), three had oppositional defiant disorder (one current) and three had conduct disorder (none current). The average age of onset of recurrent or single-episode MDD in our sample was 17.9 (S.D. = 5.0) years in the HR group, 19.1 (S.D. = 2.9) years in the CON group and 15.1 (S.D. = 2.8) years in the BD group. For anxiety disorders, the ages were 12.7 (S.D. = 6.5), 11.3 (S.D. = 6.7) and 12.5 (S.D. = 6.1) years, respectively. Of the 39 BD participants taking a mood stabilizer, 15 were taking lithium.

episode (MDE) or any lifetime DSM-IV diagnosis (including rMDD) was significantly higher in the HR ($p < 0.01$) compared with the CON group, consistent with prior reports of high-risk populations (Birmaher *et al.* 2009; Nurnberger *et al.* 2011). There were also significantly higher rates of anxiety ($p < 0.05$) and behavioural disorders ($p < 0.01$) amongst HR individuals.

Of the 150 HR participants, 81.3% had a parent with BD and 18.7% had a sibling with BD. Of the 63 BD subjects, 34 had BD-I (54%) and 29 BD-II (46%). The 324 participants belonged to 262 families.

FA results: group findings

The genu of the CC was the only tract with significant group differences in FA after correction for multiple comparisons (see Fig. 1*a*). Pairwise comparison between the groups showed that this effect was driven by lower FA in the BD compared with the HR and CON groups (BD < HR $p = 0.03$, BD < CON $p = 0.003$, all FDR corrected). There were no FA differences within the BD group between participants with and without current lithium treatment, between those with and without current antidepressant treatment, and between those with and without current antipsychotic treatment (all $p > 0.05$ uncorrected). Further, the FA finding remained significant when those with current lithium and/or antipsychotic treatment in the BD group, and those with current MDE and/or current antidepressant treatment current antidepressant use across all three groups were removed [$n = 107$ CON, $n = 139$ HR, $n = 19$ BD; Wald $\chi^2 = 6.41$, degrees of freedom (df) = 2, $p = 0.040$; BD < CON $p = 0.025$, BD < HR $p = 0.012$; FDR-corrected pairwise comparisons]. Within the BD group, measures of illness severity and course, and mood state did not correlate with FA (all $p > 0.05$). Furthermore, there were no differences between BD-I and BD-II patients (all $p > 0.05$).

To exclude any potential confounding effect of subjects with lifetime major depressive or other DSM-IV disorders in the CON group, we repeated analyses after excluding these subjects. The finding of lower FA in the genu of the CC remained significant when we compared CON participants with no prior or current depressive episode with our total HR and BD samples ($n = 99$ CON, $n = 150$ HR, $n = 63$ BD; Wald $\chi^2 = 8.63$, df = 2, $p = 0.013$; BD < CON $p = 0.003$, BD < HR $p = 0.032$), and when we compared CON participants without any lifetime DSM-IV diagnosis with our total HR and CON sample ($n = 79$ CON, $n = 150$ HR, $n = 63$ BD; Wald $\chi^2 = 8.75$, df = 2, $p = 0.013$; BD < CON $p = 0.003$, BD < HR $p = 0.035$; BD < CON but not BD < HR pairwise comparison survived FDR correction). Further, to exclude any effect of prior depressive episodes in the HR sample, we compared CON and HR

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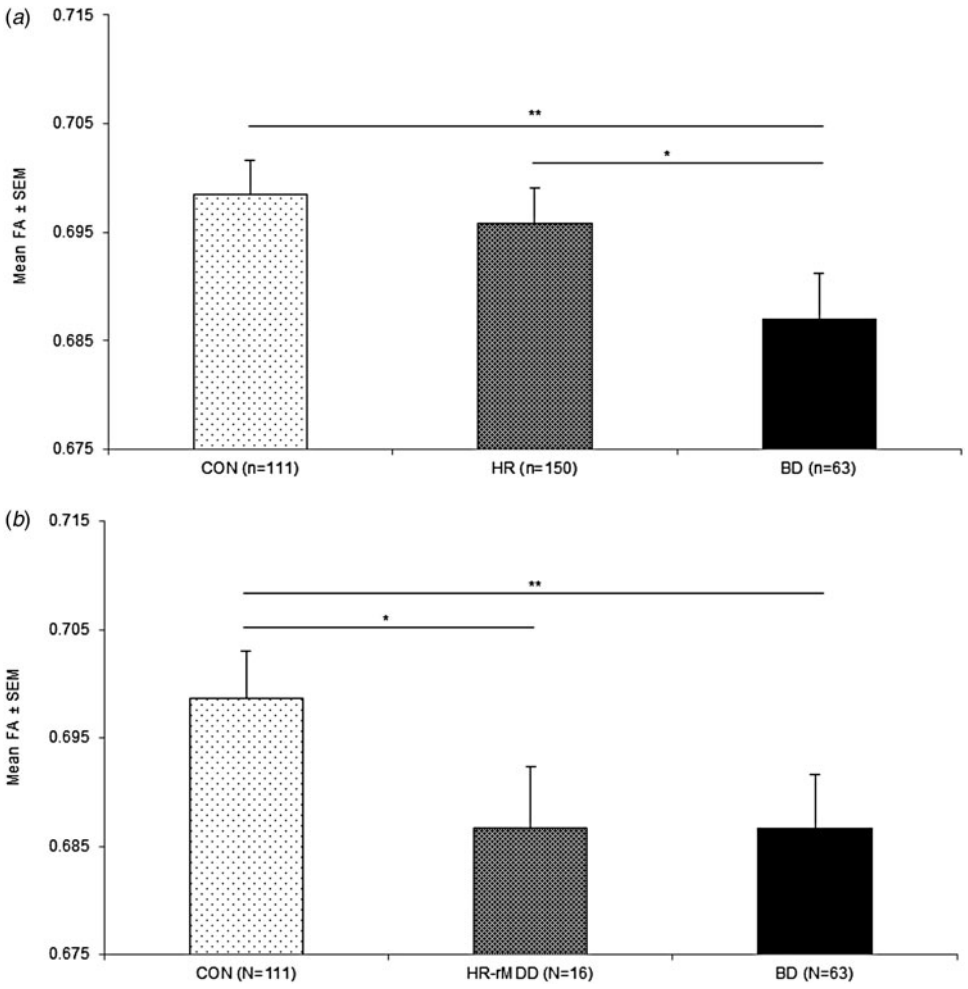

Fig. 1. Group differences in mean fractional anisotropy (FA) in the genu of the corpus callosum (CC). (*a*) The bipolar disorder (BD) group showed lower FA in the genu of the CC compared with high-risk (HR) and control (CON) groups. False discovery rate (FDR)-corrected group effect and pairwise comparisons. (*b*) When HR subjects with a lifetime diagnosis of recurrent major depressive disorder (HR-rMDD) ($n = 16$) were selected from our total HR sample ($n = 150$) and compared against the CON and BD groups, the HR-rMDD group had reduced FA in the genu of the CC compared with CON subjects. FDR-corrected pairwise comparisons. Estimated means are reported after covarying for age and gender, with standard errors (SEM) represented by vertical bars. * $p < 0.05$, ** $p < 0.01$.

subjects with no prior or current depressive episodes with our BD sample; the differences remained significant ($n = 99$ CON, $n = 106$ HR, $n = 63$ BD; Wald $\chi^2 = 10.09$, df = 2, $p = 0.006$; BD < CON $p = 0.002$, BD < HR $p = 0.013$). Additionally, there were no significant differences between those with at least one lifetime depressive compared with those without, both within the CON ($p = 0.798$) and HR ($p = 0.455$) groups. Likewise, there were no significant differences between those with or without a lifetime DSM-IV diagnosis within both the CON ($p = 0.609$) and HR ($p = 0.311$) groups.

There were no significant differences in FA in the genu of the CC between the total HR and CON groups. However, as detailed in the introduction above, when we compared only HR subjects with rMDD (HR-rMDD) ($n = 16$) against the CON and BD groups, we found that the HR-rMDD group had lower FA in the genu of the CC compared with CON subjects (Wald $\chi^2 = 12.53$, df = 2, $p = 0.002$; BD < CON $p = 0.002$, HR-rMDD < CON $p = 0.012$; all FDR corrected) (see Fig. 1*b*). There was no significant difference in FA in this tract between the HR-rMDD and BD groups. This finding remained significant when those with current lithium and/or antipsychotic treatment in the BD group, and those with current MDE and/or current antidepressant use across all three groups were removed ($n = 107$ CON, $n = 12$ HR, $n = 19$ BD; Wald $\chi^2 = 9.21$, df = 2, $p = 0.010$; BD < CON $p = 0.012$, HR-rMDD < CON $p = 0.038$). Group comparisons of all ROIs are detailed in online Supplementary Table S2.

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Hemisphere results and group × hemisphere interactions

Hemispheric asymmetries are summarized in online Supplementary Table S3 as they are not the focus of this paper. None of the ROI FAs showed a group × hemisphere interaction at either the corrected or uncorrected level. Online Supplementary Table S4 summarizes all group × hemisphere interactions.

Group × age interaction

Only one ROI showed an age × group interaction (for sagittal stratum; $p = 0.046$); hence in the GEE models this interaction was only included for the sagittal striatum tract.

Discussion

We found reduced WM integrity in the genu of the CC of BD patients compared with both CON subject and those at high familial risk (HR group) in a large and relatively young sample, confirming a number of recent reports of reduced WM integrity of the CC in BD (Barysheva *et al.* 2013; Lagopoulos *et al.* 2013; Leow *et al.* 2013; Linke *et al.* 2013; Skudlarski *et al.* 2013; Sprooten *et al.* 2013; Emsell *et al.* 2014; Li *et al.* 2014; Sarrazin *et al.* 2014, 2015; Bauer *et al.* 2015). Furthermore, and of particular interest, we report the novel finding that whilst the overall HR group showed no difference in this tract compared with CON subjects, there was reduced WM integrity in the CC of those HR individuals with rMDD – a finding which remained significant after exclusion of those with a current MDE or antidepressants. This finding is of particular relevance, as rMDD in those at familial high risk for BD is a strong clinical predictor of later development of hypo/manic episodes (Hillegers *et al.* 2005; Duffy, 2010), suggesting the possibility that lower FA in the genu of the CC may represent a trait marker for BD.

Previous DTI studies of subjects with BD have reported abnormalities in the shape, network organization and WM microstructure of the CC (Bellani *et al.* 2009; Bellani & Brambilla, 2011). A meta-analysis of CC findings in BD revealed a volumetric reduction in the CC of patients, when compared with controls (Arnone *et al.* 2008). Prior DTI studies have also reported lower FA throughout the CC, whereas others have reported lower FA in various localized subregions of the CC, in both youth and adults with BD compared with controls (Yurgelun-Todd *et al.* 2007; Barnea-Goraly *et al.* 2009; Chaddock *et al.* 2009; Saxena *et al.* 2012; Barysheva *et al.* 2013; Lagopoulos *et al.* 2013; Linke *et al.* 2013; Skudlarski *et al.* 2013; Sprooten *et al.* 2013; Emsell *et al.* 2014; Li *et al.* 2014; Sarrazin *et al.* 2014, 2015; Bauer *et al.* 2015). In accordance with our finding in the genu, four of these studies found significantly reduced FA in the genu of the CC of BD subjects early in the course of illness compared with controls (Barnea-Goraly *et al.* 2009; Saxena *et al.* 2012; Lagopoulos *et al.* 2013; Leow *et al.* 2013). We found no association in our BD subjects between this FA finding in the genu of the CC and indices of BD illness course and severity, mood state or current psychotropic medications, suggesting that this WM abnormality was not secondary to either illness course or severity, or medication exposure. This is not surprising given that our BD group represented a young population early in the course of their illness, who appeared to be high functioning, as suggested by above-average intelligence quotient scores (Wechsler, 1999) and average GAS scores of over 70 (Endicott *et al.* 1976; Shaffer *et al.* 1983).

Relatively few studies have examined WM integrity in the CC of subjects at high familial risk of BD, and results have been less consistent than those in patients with established BD. Using voxel-based morphometry, genetic liability for BD has been found to be significantly associated with WM deficits in, among other regions, the genu of the CC (McDonald *et al.* 2004). In contrast, in other morphological studies of CC size and shape, abnormalities appeared to be disease-related rather than indicative of genetic vulnerability (Walterfang *et al.* 2009; Bearden *et al.* 2011). In TBSS studies which have included the three groups (controls, those at high familial risk of developing BD, and BD subjects), there have been reports of reduced WM integrity in the CC of BD patients but not in unaffected relatives (Linke *et al.* 2013). However, subtle significant FA reductions in regions such as the splenium and body of the CC have also been observed in unaffected relatives, with more widespread FA reductions evident in BD patients (Sprooten *et al.* 2013). It is noteworthy that the age ranges in the Linke *et al.* (2013) and Sprooten *et al.* (2013) studies were 18–65 and 18–70 years, respectively, suggesting that many participants included as being at familial risk of developing BD may have already passed the peak age of onset for BD. Also, in accord with the direction of our FA findings, a prior TBSS study that did not include a BD comparison group reported lower FA in one large cluster that included the CC in young high-risk individuals aged 12–25 years compared with controls (Sprooten *et al.* 2011), whereas in contrast, another TBSS study that also did not include a BD comparison group reported increased FA in the body splenium and genu of the CC of children at high risk of developing BD compared with controls (Roybal *et al.* 2015).

As our HR group has not yet passed the peak age of onset for developing BD (<30 years), this group is more

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likely than samples of older subjects to include a higher proportion of individuals who will later convert to BD. Although it is not known at the time of this study which of these individuals may later develop BD, those who have already developed rMDD have been found in other studies to be at greater risk of conversion (Hillegers *et al.* 2005; Duffy, 2010). Our novel finding of reduced WM integrity in the genu of the CC in those who have already developed rMDD in the HR group raises the question of whether this may represent a biological as well as clinically distinct phenotype that may be at particular high risk of ultimately developing BD.

As the CC is the largest WM fibre tract that connects the brain hemispheres, facilitating communication between left- and right-side brain structures (De Lacoste *et al.* 1985), our findings support the proposition that abnormal interhemispheric connectivity may represent a trait marker for BD (Bellani *et al.* 2009). Little is known about the functional role of each subregion of the CC. However, anterior regions such as the genu connect the frontal cortices (Aboitiz *et al.* 1992) which play an important role in higher-order cognitive and emotional processing (Davidson & Irwin, 1999; Galinowski *et al.* 2015). Given the frontal abnormalities frequently reported in BD (Phillips, 2014), it is conceivable that microstructural disturbances in the genu of the CC may contribute to the cognitive and emotional deficits characteristic of BD. Bearden *et al.* (2011) has reported a significant association between the genu of the CC and response inhibition, as well as verbal processing speed, in BD probands and their unaffected twins. Recent studies have identified associations between the genu of the CC and multiple neurocognitive domains including working memory, processing speed and psychomotor coordination in BD subjects compared with controls (Ajilore *et al.* 2015; McKenna *et al.* 2015; Poletti *et al.* 2015). Taken together, these findings support the postulation that reduced WM integrity in the genu of CC in our BD and HR-rMDD subjects may be linked to impulsivity and cognitive disturbances.

Limitations

Several methodological issues require consideration. Employment of complementary techniques such as tractography, a technique used to visually represent neural tracts, and whole-brain voxel-based analyses, would contribute to a fuller understanding of possible WM microstructural abnormalities in this population. Furthermore, while FA is widely accepted to be an index of general WM integrity, specific microstructural defects – such as myelin damage, axonal disorganization, or fibre incoherence – which may underlie changes in this metric, remain to be elucidated (Assaf & Pasternak, 2008). Whilst the current study derived average FA per tract, the majority of the cited TBSS BD high-risk papers have used voxel-based TBSS or whole-brain voxel-based analyses, making direct comparison between the present results and previous findings difficult. Further, as the study groups differed on age, we covaried for the potential effects of age, and age × group interactions, in our statistical models. In contrast to a report by Versace *et al.* (2010), we found no evidence of age × group interactions in CC FA. However, as typical WM cortical development is non-linear (Imperati *et al.* 2011; Lebel *et al.* 2012) and non-linear effects of age could not be incorporated into our model, we cannot exclude the possibility of non-linear effects of age on our findings.

Our results need to be interpreted with caution given the absence of differences between CON subjects and our total cohort of HR subjects ($n = 150$). Although it is likely that a substantial proportion of our HR individuals with rMDD will develop BD, the time course for this is unknown. With all the current participants enrolled in an ongoing longitudinal study, follow-up data will improve our understanding of the underlying mechanisms that contribute to trajectories that result in BD. As our MRI scans are repeated at multiple time points, in future years we will be able to investigate whether abnormalities in the genu of the CC are more frequent in those who subsequently develop BD. Further, in view of recent studies (Xu *et al.* 2013; Bessette *et al.* 2014) and a meta-analysis (Liao *et al.* 2013) which have reported abnormalities in the genu and body of the CC of patients with MDD not at familial risk of BD, it is not possible at present to distinguish between our finding representing a specific risk to future BD or a broader generic risk to mood disorders including MDD.

Conclusions

These results from a large sample provide further evidence that the genu of the CC may play a role in the pathophysiology of BD. Furthermore, in a novel finding, we extend previous CC findings by showing that lower FA in the genu of the CC was also present in those at high familial risk who have rMDD. While it need be acknowledged that the number of those with rMDD was relatively small, and that longitudinal data are needed to definitively determine trajectories that result in BD, our findings nonetheless raise the tantalizing possibility that WM integrity of the CC may represent a potential trait marker for BD.

Supplementary material

The supplementary material for this article can be found at http://dx.doi.org/10.1017/S0033291716001161

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Declaration of Interest

J.I.N. is an investigator for Assurex on a study of the clinical efficacy of pharmacogenetic screening and has consulted with Janssen Pharmaceuticals regarding high-risk studies in BD. All other authors report no biomedical financial interests or other potential conflicts of interest.

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