NeuroImage: Clinical 3 (2013) 271–278

Contents lists available at SciVerse ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

White matter alterations in antipsychotic- and mood stabilizer-naïve individuals with bipolar II/NOS disorder☆

Sarah W. Yip, Rebecca A. Chandler, Robert D. Rogers, Clare E. Mackay, Guy M. Goodwin *

Department of Psychiatry, University of Oxford, Oxford OX3 7JX, United Kingdom

ARTICLE INFO

Article history:
Received 1 May 2013
Received in revised form 30 July 2013
Accepted 4 August 2013
Available online xxxx

Keywords:
Bipolar II disorder
Bipolar disorder NOS
Diffusion tensor imaging
Voxel-based morphometry
Mood stabilizers
Antipsychotics

ABSTRACT

Structural magnetic resonance imaging (MRI) studies using voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) have been inconsistent in demonstrating impairments in gray matter (GM) and white matter (WM) structures in bipolar disorder (BD). This may be a consequence of significant confounding effects of medication, illness history and selection of controls in existing studies. Study of bipolar II or not-otherwise-specified (BD II/NOS) disorder provides a solution to these confounds and a bridge to unipolar cases across the affective spectrum.

Thirty-eight euthymic, antipsychotic- and mood stabilizer-naïve young adults (mean age = 20.9 years) with BD II/NOS and 37 age-, cognitive ability- and gender-matched healthy controls (HCs) underwent MRI. Voxel-wise and regional gray matter volume comparisons were conducted using voxel-based morphometry (VBM). Tract-based spatial statistics (TBSS) were used to assess whole-brain WM, as indexed using fractional anisotropy (FA), mean diffusivity (MD), parallel and perpendicular diffusion values. No between-group differences were observed for whole-brain VBM comparisons. By contrast, in comparison to HCs, participants with BD II/NOS had significant widespread reductions in FA and increased MD and perpendicular diffusion values in virtually all the major cortical white matter tracts.

These data suggest pathophysiological involvement of WM microstructures – but not GM macrostructures – in high functioning BD II/NOS patients at an early age and before significant clinical adversity has been recorded. We propose that white matter development is a valid candidate target for understanding genetic and environmental antecedents to bipolar disorder and mood disorder more generally.

1. Introduction

In recent years a large number of structural MRI studies have used either voxel-based morphometry (VBM) to look at volumetric differences in gray matter (GM) structures or diffusion tensor imaging (DTI) to assess white matter (WM) microstructure in functional psychiatric disorders. In bipolar I disorder (BD I), alterations in GM volumes have been reported in many studies but there has been little consistency of effect. Thus, two recent meta-analyses have reported significantly *decreased* GM volumes in the temporal and prefrontal cortices (Arnone et al., 2009; Selvaraj et al., 2012), while a recent mega-analysis (i.e., an analysis of individual patient data from multiple studies) reported significantly *increased* temporal lobe, right putamen and right lateral ventricular volumes among BD I patients in comparison to controls (Hallahan et al., 2011). Several factors contribute to this heterogeneity. First, lithium treatment, past and present, has been associated with relatively preserved brain volumes (Hafeman et al., 2012; Hallahan et al., 2011; Mitsunaga et al., 2011; Moore et al., 2000). Second, BD I patients are often treated with antipsychotics in manic episodes, and over the long term, which may influence brain dimensions as in schizophrenia (Ho et al., 2011). Third, the uncertain cumulative effects of physical illness and poor lifestyle choices may produce acquired brain changes in mature patients with BD I. Finally, case control imaging studies frequently use poorly defined methods to recruit controls, which results in excessive heterogeneity between control samples, well illustrated in meta-analyses (Kempton et al., 2008). Cases and controls should be recruited using very similar methods, which is always difficult in clinical case series.

Reports of white matter abnormalities in mood disorder patients date from the early days of CT and MR imaging. So-called WM hyperintensities were frequently attributed to vascular pathology (Brown et al., 1992) and were most noticeable in older patients (Aylward et al., 1994; Dupont et al., 1995) but also described earlier in the disease course (Botteron et al., 1992). More recent studies using quantitative DTI in samples of mature but not elderly patients with BD I (Sexton et al., 2009) have generally described more diffuse differences between cases and controls. As in the case of studies of GM, consistency

* Corresponding author at: Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, United Kingdom. Tel.: +44 1865 226451; fax: +44 1865 204198.
E-mail address: guy.goodwin@psych.ox.ac.uk (G.M. Goodwin).

2213-1582/$ – see front matter © 2013 The Authors. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nicl.2013.08.005

has been lacking across DTI studies. For example, *decreases* in fractional anisotropy (FA) – the most frequently used scalar measure of diffusion – have been reported in regions of the prefrontal cortex (PFC) (Adler et al., 2004), corpus callosum (Wang et al., 2008a), cingulum (Wang et al., 2008b), uncinate fasciculi (McIntosh et al., 2008; Sussmann et al., 2009), superior longitudinal fasciculi (Zanetti et al., 2009) and anterior thalamic radiations (McIntosh et al., 2008; Sussmann et al., 2009), while in other studies, *increases* in FA have been reported in regions such as the corpus genu (Yurgelun-Todd et al., 2007), PFC (Versace et al., 2008), precentral gyrus (Wessa et al., 2009) and uncinate fasciculi (Versace et al., 2008). Variation in findings across studies is potentially due to the confounding factors already described for GM studies above.

Imaging studies have supported the overarching hypothesis that BD I disorder is in some sense a brain disease. Unanswered has been whether the underlying structural differences reflect the consequences of the illness's medium term vascular complications and treatment, relate directly to bipolar psychopathology or are part of a more general developmental brain abnormality seen across the affective spectrum. In order to explore this latter hypothesis, we resolved to assess WM and GM structures in a mood stabilizer- and antipsychotic-naïve group of euthymic individuals with bipolar disorder early in the disease course (i.e., prior to significant clinical intervention). The group in which this approach is most feasible are euthymic, antipsychotic- and mood stabilizer-naïve individuals with BD II or BD not-otherwise-specified (NOS) recruited from the community (as in epidemiological studies) together with healthy control (HC) participants well matched for age, gender, cognitive ability and recruitment route. The further advantage of such cases is the bridge they provide across the affective spectrum between BD I on the one hand and unipolar disorder on the other. We hypothesized that young adults with BD II/NOS would display reductions in FA across the major white matter tracts previously implicated in mature BD I (e.g., callosal, association and limbic fibers).

2. Methods

2.1. Participants and screening

Participants were 38 unmedicated individuals with BD II/NOS (NOS = 13) and 37 HC participants, group-matched on age, gender and cognitive ability. Thirty-three participants (16 BD) were recruited and underwent structural imaging protocols in the first phase between 2006 and 2008. The remaining 42 participants (22 BD) were recruited and scanned in a second phase (2011 and 2012). Case and control numbers were balanced across the two recruitment phases. All participants were scanned on the same 3 T Siemens Trio system using the same image acquisition protocols (details below).

In order to ensure homogeneity across control and BD participant groups, all participants were recruited from the same population and via the same recruitment route: advertisements were published in a local paper, placed in the community and within the University of Oxford. All volunteers expressing interest in participating were given complete details of the study protocols and invited to attend a screening session. Given the difficulty in recruiting our patient population (i.e., unmedicated individuals with BD II/NOS), individuals previously identified as at-risk for BD (or already meeting full DSM-IV criteria) who had previously participated in other research studies at the University of Oxford's Department of Psychiatry (who had also consented to be contacted about future studies) were sent information about the study protocols and invited to take part in the present study via e-mail. Both recruitment methods (advertisement, referrals from other studies) were used to recruit healthy controls and participants with BD II/NOS, in order to ensure the same recruitment route across studies. Following complete description of the study's procedures, all participants provided written informed consent. The study protocols were approved by the National Health Service Research Ethics Committee.

All participants were screened using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). This identified the formal criteria for the diagnosis of bipolar disorder for participants in the BD II/NOS group. HC participants were excluded for: (1) any history of head injury or neurological condition; (2) other contraindication to scanning; (3) current or previous use of psychotropic medication; and (4) current or past psychiatric disorder, including substance use and depression, as assessed using the MINI. Exclusion criteria for BD II/NOS participants were: (1) any history of head injury or neurological condition; (2) other contraindication to scanning; (3) current major depressive, manic or hypomanic episodes at the time of scanning; (4) any current psychotropic medication; (5) any past treatment with an antipsychotic or mood stabilizer (e.g., lithium, anticonvulsants); and (6) any current psychiatric disorder (with the exception of BD and anxiety disorders).

All of the thirty-eight BD II/NOS participants had a history of one or more hypomanic episodes as defined using the MINI. Out of the thirty-eight BD II/NOS participants, 25 participants (10 from phase 1) also had a history of one or more major depressive episodes, and therefore met the criteria for BD II. The remaining 13 BD participants (six from phase 1) were classified as NOS. Among the BD II/NOS participants, four met the criteria for past alcohol abuse, two met the criteria for past marijuana abuse and one met the criteria for past codeine abuse and past anorexia. None of the BD II/NOS or HC participants met the criteria for a current substance or alcohol use disorder. Two of the BD II/NOS participants reported a family history of bipolar disorder. Three of the participants in the BD II/NOS group had received previous SSRI treatment, and all had been medication-free for a minimum of three months prior to scanning.

In addition to the MINI, participants completed psychometric assessments of cognitive ability (phase one: Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1981); phase two: Raven's Matrices (Raven et al., 1998)), current depressive symptoms (Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960)), lifetime and current bipolar symptoms (Mood Disorders Questionnaire (MDQ) (Hirschfeld et al., 2000); Young Mania Rating Scale (YMRS) (Young et al., 1978)), impulsivity (Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995)), and state and trait affect (Positive and Negative Affect Scales (PANAS) (Watson et al., 1988)). Cases and controls were matched on cognitive ability (raw data not shown).

2.2. Image acquisition

All data were acquired using the same 3 T Siemens Trio system (Siemens Medical Systems, Erlangen) at the Oxford Centre for Clinical Magnetic Resonance Research, using a protocol consisting of an axial T1-weighted 3D structural (TR = 2040 ms; TE = 4.7 ms, TI = 900 ms, flip angle = 8°; 1 mm isotropic voxels; acquisition time = 5 min 56 s), and an axial multi-slice diffusion weighted EPI (TR = 9300 ms; TE = 94 ms; B values = 0, 1000 s/mm^2; bandwidth = 1628 Hz/px; directions = 60 [+0]; averages = 3; 2.5 mm isotropic voxels; no. slices = 50 (whole brain); acquisition time: 21 min 2 s).

2.3. Statistical analyses

2.3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of participants in the BD II/NOS and HC groups were analyzed using χ^2 (e.g., gender, handedness) and one-way analysis of variance (ANOVA) analyses, as appropriate.

2.3.2. Global WM, GM and CSF volumes

Individual participant T1-weighted images were brain-extracted (Smith, 2002) and whole-brain segmented into GM, WM and CSF following bias field correction using FMRIB's automated segmentation tool, FAST (Zhang et al., 2001). Total GM, WM and CSF volumes were

calculated for each participant by summing the partial volume estimates in each tissue class, then expressing as a percentage of total brain volume (i.e., the sum of GM, WM and CSF volumes).

2.3.3. Gray matter: Voxel-based morphometry (VBM)

Whole-brain GM was analyzed using FSL-VBM as has been described previously (Douaud et al., 2007). The analysis was conducted in the standard way: A study-specific GM template was created by segmenting individual images into GM, WM and CSF, affine registering to the GM ICBM-152 template and averaging the images to form the template. Individual participant images were then non-linearly registered to the study-specific template, and each voxel divided by the Jacobian of the warp field in order to compensate for any expansion/contraction caused by the non-linear registration. All images were smoothed using FSL-VBM's default 3 mm Gaussian kernel (~7 mm full width half maximum; FWHM). This kernel size was selected in order to maximize sensitivity to volumetric changes in small structures (e.g., thalamus, hippocampus, anterior cingulate) (Honea et al., 2005). Between-group comparisons of whole-brain GM data were conducted using permutation-based non-parametric testing (Nichols and Holmes, 2002) while controlling for phase. No other covariates were included. Whole-brain comparisons were corrected for multiple comparisons across space ($p < .05$) using Threshold-Free Cluster Enhancement (TFCE; Smith and Nichols, 2009).

2.3.4. White matter microstructures: Tract-based spatial statistics (TBSS)

DTI data were analyzed using TBSS (Smith et al., 2006). For each participant, three separate image acquisitions were combined and averaged, then brain extracted and corrected for eddy current distortions and head movements prior to undergoing dti_fit to calculate FA (a scalar index of diffusion where 0 indicates completely isotropic diffusion and 1 indicates completely anisotropic diffusion), MD (a scalar index of the total magnitude of diffusion irrespective of direction), parallel (the dominant (major) direction of diffusion; assumed to represent diffusion in the direction of the fiber tract) and perpendicular (the average of the two orthogonal minor directions of diffusion; assumed to represent diffusion perpendicular to the fiber tract) diffusion values. Diffusion data were aligned to common space using nonlinear registration. Individual participant aligned FA, MD and parallel and perpendicular diffusion data were then projected onto the mean FA skeleton in order to obtain voxel-wise comparisons. Between-group comparisons of whole-brain FA, MD, parallel and perpendicular diffusion data were conducted using permutation-based non-parametric testing (Nichols and Holmes, 2002) and were corrected for multiple comparisons across space ($p < .05$) using TFCE (Smith and Nichols, 2009) while controlling for phase. In order to confirm our primary findings and to explore any possible interactions between study phase and diagnostic group, post-hoc comparisons of regional FA between HC and BD II/NOS participants were conducted.

2.3.4.1. Mean whole-brain FA, MD, parallel and perpendicular diffusion values. For each participant, average whole-brain FA, MD, parallel and perpendicular diffusion values (i.e., mean across the entire skeleton) were calculated using fslstats and entered into SPSS. Between-group comparisons were then conducted using ANOVAs.

2.3.4.2. Medication effects. Targeted region-of-interest (ROI) analyses were conducted to test for the effects of past SSRI treatment on early versus late developing white matter tracts (i.e., the splenium and uncinate fasciculus, respectively). Masks were defined using the ICBM-DTI white-matter labels and JHU white-matter tractography atlases and thresholded using the mean FA skeleton. Individual ROI values were converted to Z-scores and analyzed using multivariate analyses of variance.

3. Results

3.1. Demographic and clinical characteristics

Results of between-group comparisons are shown in Table 1. No significant differences in gender, handedness, age and PANAS positive affect (state and trait) were observed between participants with BD II/NOS, in comparison to HC participants. As expected, BD II/NOS participants scored significantly higher than HC participants on measures of impulsivity, experience of manic symptoms/hypomania (i.e., the MDQ), current depressive affect, state and trait negative affect, and current manic symptoms. However, consistent with previous findings (Chandler et al., 2009), depression and mania scores were low among euthymic participants with BD II/NOS (HAM-D = 6.1; YMRS = 1.8), so all participants were euthymic at the time of scanning.

3.2. Global GM, WM, CSF volumes and VBM

No significant differences in global GM, WM and CSF volumes were found between BD II/NOS and HC participants (Table 1). The study had sufficient power to detect a difference of 2.25%, 3.25% and 5.50% for WM, GM and CSF volumes, respectively (alpha = 0.05; beta = 0.80) (Erdfelder et al., 1996). There were no significant between-group differences in voxel-based GM morphometry.

3.3. Tract-based spatial statistics (TBSS)

3.3.1. BD II/NOS vs. HCs

Findings from whole-brain comparisons of FA, MD and perpendicular diffusion are shown in Fig. 1. Significant widespread reductions in FA, accompanied by increases in MD and perpendicular diffusivity, were observed among BD participants across the mean skeleton including regions of the genu, body, splenium, forceps major and minor, bilateral cingula, anterior thalamic radiations, external capsules, inferior fronto-

Table 1
Demographic, clinical characteristics and mean brain volumes of bipolar II/NOS and healthy control participants.

	Healthy controls (n = 37)	Bipolar II/NOS (n = 38)
Variables	N (%)	N (%)
Study 1	17 (46)	16 (43)
Male	20 (54)	20 (53)
Right-handed	34 (92)	36 (95)
	Mean (St. dev.)	Mean (St. dev.)
Age	21.2 (2.3)	20.9 (3.1)
MDQ	0.1 (.03)	9.5 (1.7)***
HAM-D	2.3 (2.3)	6.1 (5.6)***
YMRS	0.3 (0.5)	1.8 (2.5)**
BIS-11	54.7 (7.0)	69.4 (10.1)***
PANAS-state		
Positive	29.7 (6.8)	30.2 (6.8)
Negative	11.7 (2.3)	13.6 (3.3)*
PANAS-trait		
Positive	33.7 (5.3)	32.1 (6.8)
Negative	13.3 (3.1)	20.4 (7.1)***
Brain volumes (% of total)		
Gray matter	42.8 (1.4)	43.1 (1.4)
White matter	37.3 (1.7)	37.4 (1.8)
CSF	19.9 (1.7)	19.5 (1.4)

MDQ = Mood Disorders Questionnaire; HAM-D = Hamilton Depression Inventory; YMRS = Young Mania Rating Scale; PANAS = Positive and Negative Affect Scales; CSF = Cerebrospinal Fluid.
* $p \leq .005$.
** $p \leq .001$.
*** $p \leq .0001$.

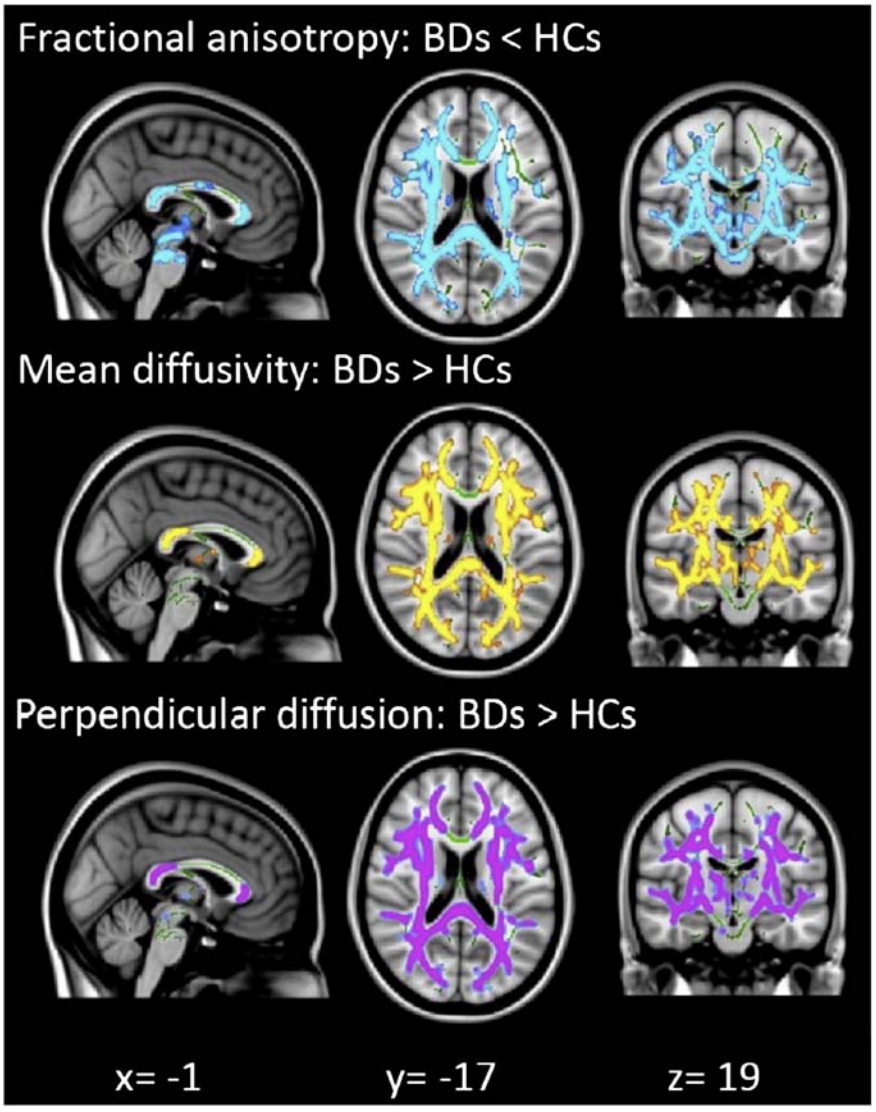

Fig. 1. Results of whole-brain comparisons of FA, MD and perpendicular diffusion. The mean FA skeleton for each group is shown in green, and regions of significantly reduced FA (TFCE-corrected for multiple comparisons across space) are shown in blue. Regions of significantly increased MD and perpendicular diffusion (TFCE-corrected for multiple comparisons across space) are shown in yellow and pink, respectively. BDs = bipolar II/NOS; HCs = healthy controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

occipital fasciculi, inferior and superior longitudinal fasciculi, uncinate fasciculi and brainstem. No significant differences in parallel diffusion were observed between HC and BD II/NOS participants. Across participants, there was no significant effect of study phase on whole-brain FA, MD, parallel or perpendicular diffusion values. Post-hoc comparisons of regional FA revealed no significant main effects of study phase or interaction effects between study phase and group ($p > .05$).

3.3.2. Mean whole-brain FA, MD, parallel and perpendicular diffusion values

Given the relatively diffuse nature of white matter alterations observed (i.e., alterations within regions of almost all of the major cortical white matter tracts), we calculated the mean FA, MD, parallel and perpendicular diffusion values across the skeleton as a whole, in order to test the hypothesis of gross alterations in diffusion irrespective of specific anatomical loci (e.g., as might result from artifacts such as excess motion within the patient group). There were no significant between-group differences in FA, MD, parallel or perpendicular diffusion values when averaged across the entire skeleton ($F's < 1$; $p's > .35$) between HC and BD II/NOS participants.

3.3.3. Subtype analyses

Findings from whole-brain comparisons of FA between participants with BD II vs. HC participants and BD NOS vs. HC participants are shown in Fig. 2. In comparison to HCs, both BD II and NOS groups had significant widespread reductions across the mean FA skeleton, including regions of the genu, body, splenium, forceps major and minor, bilateral anterior thalamic radiations, external capsules, inferior fronto-occipital fasciculi, inferior and superior longitudinal fasciculi, uncinate fasciculi and brainstem.

Whole-brain increases in MD and perpendicular diffusion across the mean skeleton were observed among BD NOS participants across regions of genu, body, splenium, forceps major and minor, bilateral anterior thalamic radiations, cingula, external capsules, inferior fronto-occipital fasciculi, inferior and superior longitudinal fasciculi and uncinate fasciculi. Exploratory analyses using a less stringent threshold ($p < .06$, TFCE-corrected) revealed comparable increases

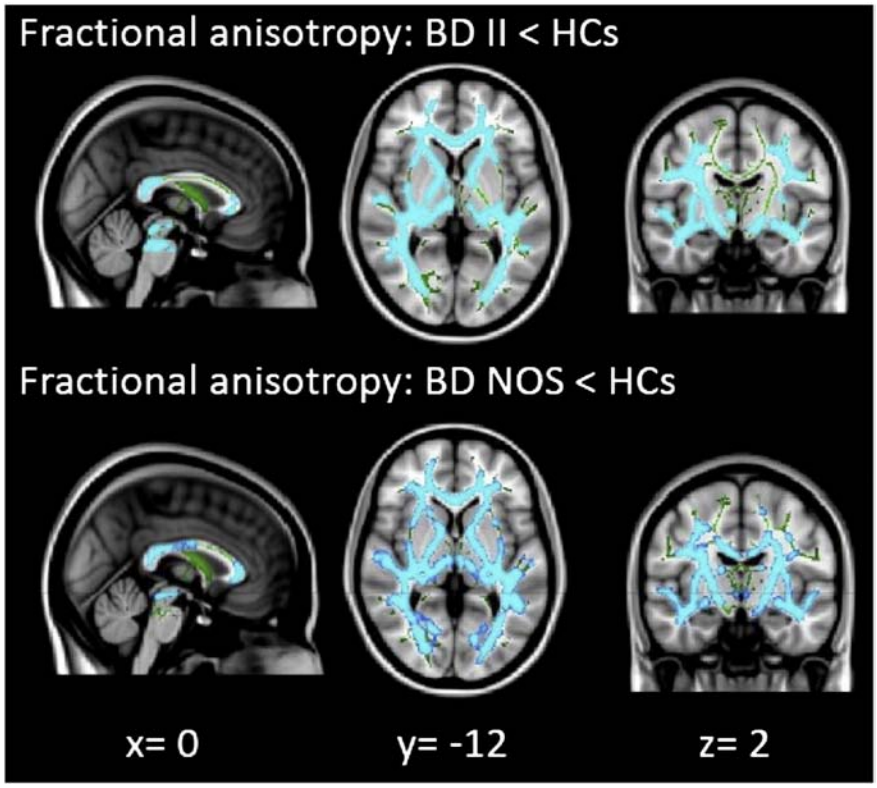

Fig. 2. Results of whole-brain comparisons of FA among participants with BD II and BD NOS in comparison to healthy controls. The mean FA skeleton for each group is shown in green, and regions of significantly reduced FA (TFCE-corrected for multiple comparisons across space) are shown in blue. BD II = bipolar II disorder; HCs = healthy controls; BD NOS = bipolar disorder not-otherwise-specified. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

for BD II participants versus HCs in perpendicular diffusion across the mean skeleton, including regions of genu, body, splenium, major and minor forceps, right cingulum, bilateral anterior thalamic radiations, external capsules, inferior fronto-occipital fasciculi, inferior and superior longitudinal fasciculi and uncinate fasciculi.

No significant differences in whole-brain FA, MD, parallel or perpendicular diffusion values were observed between participants with BD II versus those with BD NOS.

3.3.4. Medication effects: ROI analyses

In comparison to HC participants, participants with BD II/NOS had significant reductions in FA within the splenium ($F = 13.23$, $p = .001$) and uncinate fasciculus (left: $F = 6.99$, $p = .010$; right: $F = 5.91$, $p = .018$) ROIs. After removing the BD II/NOS participants with previous short-term exposure to SSRIs ($n = 3$), these effects remained ($F's \geq 5.98$, $p's \leq .017$). There were no significant differences between BD II/NOS participants with and without previous exposure to SSRIs ($F's \leq .31$, $p's \geq .58$).

4. Discussion

To our knowledge, GM and WM structures have not been assessed previously in an adequately powered study of unmedicated individuals with BD II or BD NOS. There were no differences in voxel-based GM morphometry, global WM, GM or CSF volumes between groups despite sample sizes sufficient to detect differences at previously reported levels (Drevets et al., 1997). In contrast, we found significant widespread differences in WM, as indexed by decreased FA and increased MD and perpendicular diffusion, among euthymic, antipsychotic- and mood stabilizer-naïve individuals with BD II/NOS compared with controls. The reductions observed were more profound and more widespread than those typically observed hitherto within a single study of BD I or BD II disorder.

4.1. Gray matter

The absence of any GM abnormalities among individuals with BD II/NOS contrasts with previous reports of significant decreases in GM volumes, whose location varied across studies, among individuals with BD II (Ha et al., 2009; Narita et al., 2011). The likely explanation is the relatively young age of our participants (mean age = 20.9 years) in comparison to previous studies (i.e., 35.2 years (Ha et al., 2009); 40.8 years (Narita et al., 2011)). While some evidence of age-related reductions in GM volumes in BD I already exists (e.g., Doty et al., 2008; Hallahan et al., 2011) very little is currently known about the temporal trajectory in the size of GM structures in BD I or II (reviewed in Selvaraj et al., 2012). Given the relatively large size of our sample, and our recruitment of cases and controls from the same population, the absence of a GM effect provides a strong negative finding. It implies that GM reductions in older samples are acquired as a consequence of illness course. This is compatible with the very limited prospective data available for BD I (Moorhead et al., 2007). Exploring the impact of successful treatment and the relationship between GM changes and cognitive impairment is of obvious clinical relevance for future work (Goodwin, 2009).

4.2. White matter

The reductions in FA encompassed projection, association, callosal and limbic system fibers, just as reported previously in some studies for mature BD I cases (e.g., McIntosh et al., 2008; Sussmann et al., 2009; Wang et al., 2008a). Although the FA reductions were widespread there was no global difference between groups, suggesting some

degree of specificity. Our findings are also consistent with previous reports of reduced FA in callosal, projection, and association fibers among mature, medicated individuals with BD II (Ha et al., 2011; Liu et al., 2010), and with findings from the two previous small scale published studies of antipsychotic- and mood stabilizer-naïve adolescents during first-episode mania (Adler et al., 2006) and manic psychosis (Lu et al., 2011) which also reported relatively large reductions in FA. Nevertheless, previous DTI and VBM studies have reported a range of semi-conflicting findings (see Introduction) with respect to WM and GM structures in BD, and the effects of medication have been identified as a possible confound in this literature (Hafeman et al., 2012). Preclinical data increasingly suggest ameliorative/protective effects of lithium (frequently used to treat patients with BD over the long-term) on WM tissue; e.g., lithium has been shown to increase remyelination (Makoukji et al., 2012). As such, our exclusion of participants with previous exposure to lithium may account for the diffuse nature of the observed reductions in FA. This interpretation is further supported by two recent reports of attenuated FA reductions among lithium-treated patients with BD, in comparison to their non-lithium-treated counterparts (Benedetti et al., 2011; Macritchie et al., 2010). Thus, our study may show more clear-cut differences because we controlled for the confounding factors which have influenced the interpretation of the earlier studies.

Although often considered a less severe form of BD than the paradigm illness, the growing research base suggests comparable levels of impairment across both BD I and II (Jansen et al., 2011; Maina et al., 2007). The prevalence of the two conditions is approximately equal and BD NOS doubles the total rate to 4–5% of the population (Kessler et al., 2005; Merikangas et al., 2007). Only a small number of studies have previously attempted to characterize the neurostructural correlates of bipolar II disorder (BD II) (Ha et al., 2009, 2011; Liu et al., 2010; Narita et al., 2011) using VBM or DTI, or to study cases never treated with antipsychotics or mood stabilizers (Adler et al., 2006; Lu et al., 2011). The two recent studies reporting alterations in WM in BD II showed heterogeneous effects and could not control for the possible confounding effects of medication exposure or duration of illness (Ha et al., 2011; Liu et al., 2010). Nevertheless, using a somewhat different scalar measure of diffusion (apparent diffusion coefficient; ADC), Ha et al. (2011) reported increased diffusivity among individuals with BD II in comparison with both controls and BD I participants across multiple tracts encompassing temporal and frontal regions (Ha et al., 2011). Thus, it is possible that increases in diffusivity may be present across both medicated and unmedicated individuals with BD II.

The BD NOS group remains poorly characterized both clinically and neurobiologically but severity of co-morbidity appears to be less than BD I and BD II (Angst et al., 2010). Given the small number of NOS participants included in this study ($n = 13$) these findings should be interpreted cautiously and require replication in a larger sample.

Three participants with BD II/NOS had previously received short-term SSRI therapy, although all had been medication free for at least three months prior to scanning. After removing these participants with past SSRI treatment, reductions in FA within early and late developing tracts (i.e., the splenium and uncinate fasciculus (Lebel et al., 2008)) remained significant in the BD II/NOS group, in comparison with control participants. No significant between-group differences in FA were observed between BD II/NOS participants with and without previous exposure to SSRIs.

4.3. Limitations

To our knowledge, this is the largest DTI study conducted in antipsychotic- and mood stabilizer-naïve individuals with BD, the largest DTI study of individuals with BD II and the first DTI study of individuals with BD NOS. Our image acquisition protocols and data analysis have been well-validated previously (Smith et al., 2006) and are consistent with previous studies in mature samples of BD I patients (Sexton et al., 2012). Its advantage in controlling for confounds present in most other studies has been described.

These strengths, however, are tempered by the fact that these are not patients as found in clinic samples. While participants from both groups (healthy controls and participants with BD II/NOS) were recruited from the same population (the University of Oxford and surrounding general community) and using closely similar methods, we are not able to report the total number of participants screened and define a true epidemiological sample. Participants were recruited and screened over a number of years and many were first identified as part of separate studies and then referred to this study (see Methods). They meet the criteria for DSM-IV diagnoses and may map well onto populations also discovered at random in epidemiological samples; however how they relate specifically to treatment-seeking individuals with BD (e.g., with respect to long-term outcome) remains unclear. It is therefore critical that Angst has demonstrated in his seminal prospective studies that cases recruited from the general population who meet the criteria for DSM-IV BD in late adolescence have important long-term morbidity (Angst, 1998). Caution should nonetheless be taken when interpreting these findings with respect to mature patients with BD.

The meaning of reduced FA values (and increased MD) remains to be discovered. At the microstructural level, changes in myelination, straightening of fiber orientation and increased fiber density occur in development and may dominate FA measures in normal brains. While most individuals show increases in FA, a small percentage show decreases over time in the relevant adolescent age group (Lebel and Beaulieu, 2011). Diffusion tensor imaging may nonetheless be subject to other macrostructural factors like WM volume (which was not different between our groups on VBM) and aberrant mixing of tracts of different fiber orientations, which we cannot entirely exclude. However, the corpus callosum is composed mainly of uniformly oriented fibers (Basser et al., 2000) so FA values derived from this region are unlikely to be influenced by the presence of crossing fibers. In fact we found reductions in FA in the corpus genu, body and splenium.

Potential artifacts also have to be excluded. We did not employ cardiac gating during diffusion-weighted image acquisition. Intra-individual comparisons of diffusion data obtained with and without cardiac gating demonstrate convincing effects of cardiac pulsation on DTI data (Habib et al., 2010; Kim et al., 2010). However, despite such intra-individual effects, research suggests very minimal effects of cardiac pulsation on FA and MD in group studies (Habib et al., 2010) and previous studies suggest no differences in pulse or blood pressure between control participants and participants with a bipolar phenotype (some of whom already meet the criteria for BD II/NOS) recruited from the same population as the present study (Yip et al., 2012). There were also no significant between-group differences in average FA across the entire FA skeleton (as might occur due to excess motion in the patient group).

4.4. Implications

The diffuse reduction in FA observed here occurred in a notably young patient sample and was accompanied by increases in perpendicular – but not parallel – diffusion values, suggesting decreased fiber coherence or myelination (Song et al., 2002) in BD II/NOS. It is consistent with the hypothesis that the abnormality is neurodevelopmental and not acquired as a result of medication or illness course (Lu et al., 2011). FA increases during adolescence as shown by the cross-sectional study of healthy subjects and this occurs at different rates in different brain structures; thus, the splenium stabilizes much earlier (by age 15 years) than the uncinate fasciculus which is probably still changing at age 30 (Lebel et al., 2008). Our findings show effects in both. In the case of the splenium, the age of our subjects (mean age = 20.9 years) suggests that development would be complete, and hence implies that the difference in FA would be enduring. This finding complements and probably

explains the findings of similar differences in mature patients. Data from healthy twins strongly suggest that FA and MD are under genetic control (Brouwer et al., 2012).

The findings generate an important hypothesis — that diffuse WM abnormalities provide a neurodevelopmental marker of vulnerability to affective disorders including but not limited to BD. The BD II/NOS group is intermediate between BD I and unipolar disorder in relation to phenomenology and anxiety co-morbidity (Angst et al., 2010). And there is already a convincing study showing very comparable WM effects in 20 year-olds with first episode major depressive disorder (MDD) (Zhu et al., 2011) as well as in mature patients with MDD (Korgaonkar et al., 2011); preliminary findings have also suggested a link between WM abnormalities in MDD and generalized anxiety disorder (Cullen et al., 2010; Hettema et al., 2012; Korgaonkar et al., 2011). A small study of at risk adolescents with a family history of mood disorder showed the same effect (Huang et al., 2011): other studies in MDD suggest that treatment resistance may be associated with lower FA (Zhou et al., 2011) while resilience to MDD may be related to higher FA measures (Frodl et al., 2012). Future studies should assess the relationship between WM alterations and effective treatment to determine whether FA might be a useful biomarker for stratification in clinical trials.

Alterations in WM microstructural tissues are relatively common across psychiatric disorders, and are therefore implicated in the source pathophysiology of a range of disorders including – but not limited to – BD, attention deficit/hyperactivity disorder (ADHD), schizophrenia and impulse control disorders (Chamberlain et al., 2010; Ellison-Wright and Bullmore, 2009; Sexton et al., 2009; van Ewijk et al., 2012; Yip et al., 2011). Thus, alterations in FA, MD and other indices of WM microstructure may be a very general marker of developmental abnormality with the potential for behavioral pathology, rather than a specific marker of BD, per se. Higher resolution studies may clarify any specificity that does exist by diagnosis.

5. Conclusion

We found widespread impairments in white matter microstructures prior to antipsychotic or mood stabilizer treatment among individuals with BD II/NOS. Together with limited data from previous studies of unmedicated individuals with BD I (Lu et al., 2011) and good studies in unipolar disorder, there is now evidence of pathophysiological involvement of WM microstructures across the mood disorder spectrum. White matter development is a key candidate process for understanding the biological basis of mood disorder and its relationship with related anxiety disorders.

Conflict of interest and financial disclosures

Guy M. Goodwin holds or has held grants from Bailly Thomas charity, Medical Research Council, NIHR, and Servier; has received honoraria from AstraZeneca, BMS, Lundbeck, Sanofi-Aventis, and Servier, holds shares in P1vital Ltd; has served on advisory boards for AstraZeneca, BMS, Boehringer Ingelheim, Cephalon, Janssen-Cilag, Lilly, Lundbeck, Otsuka, P1Vital, Roche, Servier, Shering Plough, Shire, Takeda, and Wyeth and acted as an expert witness for Lilly and Servier. The other authors have no disclosures or conflicts of interest.

Acknowledgments

The authors would like to thank Dr. Corin Bourne for providing statistical advice. MRI scans were funded by a Young Investigator Award (CEM) from the Brain and Behaviour Research Foundation (formerly NARSAD) and the University of Oxford.

References

Adler, C.M., Holland, S.K., Schmithorst, V., Wilke, M., Weiss, K.L., Pan, H., et al., 2004. Abnormal frontal white matter tracts in bipolar disorder: a diffusion tensor imaging study. Bipolar Disorders 6 (3), 197–203.
Adler, C.M., Adams, J., DelBello, M.P., Holland, S.K., Schmithorst, V., Levine, A., et al., 2006. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. The American Journal of Psychiatry 163 (2), 322–324.
Angst, J., 1998. The emerging epidemiology of hypomania and bipolar II disorder. Journal of Affective Disorders 50 (2–3), 143–151.
Angst, J., Cui, L., Swendsen, J., Rothen, S., Cravchik, A., Kessler, R.C., et al., 2010. Major depressive disorder with subthreshold bipolarity in the national comorbidity survey replication. The American Journal of Psychiatry 167 (10), 1194–1201.
Arnone, D., Cavanagh, J., Gerber, D., Lawrie, S.M., Ebmeier, K.P., McIntosh, A.M., 2009. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. The British Journal of Psychiatry 195 (3), 194–201.
Aylward, E.H., Roberts-Twillie, J.V., Barta, P.E., Kumar, A.J., Harris, G.J., Geer, M., et al., 1994. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. The American Journal of Psychiatry 151 (5), 687–693.
Basser, P.J., Pajevic, S., Pierpaoli, C., Duda, J., Aldroubi, A., 2000. In vivo fiber tractography using DT-MRI data. Magnetic Resonance in Medicine 44 (4), 625–632.
Benedetti, F., Absinta, M., Rocca, M.A., Radaelli, D., Poletti, S., Bernasconi, A., et al., 2011. Tract-specific white matter structural disruption in patients with bipolar disorder. Bipolar Disorders 13 (4), 414–424.
Botteron, K.N., Figiel, G.S., Wetzel, M.W., Hudziak, J.I.M., Vaneerdewegh, M., 1992. MRI abnormalities in adolescent bipolar affective disorder. Journal of Child and Adolescent Psychopharmacology 31 (2), 258–261.
Brouwer, R.M., Mandl, R.C.W., Schnack, H.G., van Soelen, I.L.C., van Baal, G.C., Peper, J.S., et al., 2012. White matter development in early puberty: a longitudinal volumetric and diffusion tensor imaging twin study. PloS One 7 (4), e32316.
Brown, F., Lewine, R., Hudgins, P., Risch, S., 1992. White matter hyperintensity signals in psychiatric and nonpsychiatric subjects. The American Journal of Psychiatry 149 (5), 620–625.
Chamberlain, S., Hampshire, A., Menzies, L., Garyfallidis, E., Grant, J., Odlaug, B., et al., 2010. Reduced brain white matter integrity in trichotillomania: a diffusion tensor imaging study. Archives of General Psychiatry 67 (9), 965–971.
Chandler, R.A., Wakeley, J., Goodwin, G.M., Rogers, R.D., 2009. Altered risk-aversion and risk-seeking behavior in bipolar disorder. Biological Psychiatry 66 (9), 840–846.
Cullen, K.R., Klimes-Dougan, B., Muetzel, R., Mueller, B.A., Camchong, J., Houri, A., et al., 2010. Altered white matter microstructure in adolescents with major depression: a preliminary study. Journal of Child and Adolescent Psychopharmacology 49 (2), 173-83.
Doty, T.J., Payne, M.E., Steffens, D.C., Beyer, J.L., Krishnan, K.R.R., LaBar, K.S., 2008. Age-dependent reduction of amygdala volume in bipolar disorder. Psychiatry Research 163 (1), 84–94.
Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., et al., 2007. Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. Brain 130 (9), 2375–2386.
Drevets, W.C., Price, J.L., Simpson, J.R., Todd, R.D., Reich, T., Vannier, M., et al., 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386 (6627), 824–827.
Dupont, R.M., Jernigan, T.L., Heindel, W., Butters, N., Shafer, K., Wilson, T., et al., 1995. Magnetic resonance imaging and mood disorders: localization of white matter and other subcortical abnormalities. Archives of General Psychiatry 52 (9), 747–755.
Ellison-Wright, I., Bullmore, E., 2009. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophrenia Research 108 (1–3), 3–10.
Erdfelder, E., Faul, F., Buchner, A., 1996. GPOWER: a general power analysis program. Behavior Research Methods, Instruments, & Computers 28, 1–11.
Frodl, T., Carballedo, A., Fagan, A., Lisiecka, D., Ferguson, Y., Meaney, J., 2012. Effects of early-life adversity on white matter diffusivity changes in patients at risk for major depression. Journal of Psychiatry & Neuroscience 37 (1), 37–45.
Goodwin, G., 2009. Evidence-based guidelines for treating bipolar disorder: a revised second edition — recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology 23 (4), 346–388.
Ha, T.H., Ha, K., Kim, J.H., Choi, J.E., 2009. Regional brain gray matter abnormalities in patients with bipolar II disorder: a comparison study with bipolar I patients and healthy controls. Neuroscience Letters 456 (1), 44–48.
Ha, T.H., Her, J.Y., Kim, J.H., Chang, J.S., Cho, H.S., Ha, K., 2011. Similarities and differences of white matter connectivity and water diffusivity in bipolar I and II disorder. Neuroscience Letters 505 (2), 150–154.
Habib, J., Auer, D.P., Morgan, P.S., 2010. A quantitative analysis of the benefits of cardiac gating in practical diffusion tensor imaging of the brain. Magnetic Resonance in Medicine 63 (4), 1098–1103.
Hafeman, D.M., Chang, K.D., Garrett, A.S., Sanders, E.M., Phillips, M.L., 2012. Effects of medication on neuroimaging findings in bipolar disorder: an updated review. Bipolar Disorders 14 (4), 375–410.
Hallahan, B., Newell, J., Soares, J.C., Brambilla, P., Strakowski, S.M., Fleck, D.E., et al., 2011. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biological Psychiatry 69 (4), 326–335.
Hamilton, M.A., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry 23, 56–61.
Hettema, J.M., Kettenmann, B., Ahluwalia, V., McCarthy, C., Kates, W.R., Schmitt, J.E., et al., 2012. Pilot multimodal twin imaging study of generalized anxiety disorder. Depression and Anxiety 29 (3), 202–209.

Hirschfeld, R.M.A., Williams, J.B.W., Spitzer, R.L., Calabrese, J.R., Flynn, L., Keck Jr., P.E., et al., 2000. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. The American Journal of Psychiatry 157 (11), 1873–1875.
Ho, B., Andreasen, N., Ziebell, S., Pierson, R., Magnotta, V., 2011. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Archives of General Psychiatry 68 (2), 128–137.
Honea, R., Crow, T.J., Passingham, D., Mackay, C.E., 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. The American Journal of Psychiatry 162 (12), 2233–2245.
Huang, H., Fan, X., Williamson, D.E., Rao, U., 2011. White matter changes in healthy adolescents at familial risk for unipolar depression: a diffusion tensor imaging study. Neuropsychopharmacology 36 (3), 684–691.
Jansen, K., Ores, LdC, Cardoso, TdA, Lima, RdC, Souza, LDdM, Magalhães, PVdS, et al., 2011. Prevalence of episodes of mania and hypomania and associated comorbidities among young adults. Journal of Affective Disorders 130 (1–2), 328–333.
Kempton, M.J., Geddes, J.R., Ettinger, U., Williams, S.R., Grasby, P.M., 2008. MEta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Archives of General Psychiatry 65 (9), 1017–1032.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Archives of General Psychiatry 62, 593–602.
Kim, S., Pickup, S., Poptani, H., 2010. Effects of cardiac pulsation in diffusion tensor imaging of the rat brain. Journal of Neuroscience Methods 194 (1), 116–121.
Korgaonkar, M.S., Grieve, S.M., Koslow, S.H., Gabrieli, J.D.E., Gordon, E., Williams, L.M., 2011. Loss of white matter integrity in major depressive disorder: evidence using tract-based spatial statistical analysis of diffusion tensor imaging. Human Brain Mapping 32 (12), 2161–2171.
Lebel, C., Beaulieu, C., 2011. Longitudinal development of human brain wiring continues from childhood into adulthood. Journal of Neuroscience 31 (30), 10937–10947.
Lebel, C., Walker, L., Leemans, A., Phillips, L., Beaulieu, C., 2008. Microstructural maturation of the human brain from childhood to adulthood. NeuroImage 40 (3), 1044–1055.
Liu, J.-X., Chen, Y.-S., Hsieh, J.-C., Su, T.-P., Yeh, T.-C., Chen, L.-F., 2010. Differences in white matter abnormalities between bipolar I and II disorders. Journal of Affective Disorders 127 (1–3), 309–315.
Lu, L.H., Zhou, X.J., Keedy, S.K., Reilly, J.L., Sweeney, J.A., 2011. White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia. Bipolar Disorders 13 (7–8), 604–613.
Macritchie, K.A.N., Lloyd, A.J., Bastin, M.E., Vasudev, K., Gallagher, P., Eyre, R., et al., 2010. White matter microstructural abnormalities in euthymic bipolar disorder. The British Journal of Psychiatry 196 (1), 52–58.
Maina, G., Albert, U., Bellodi, L., Colombo, C., Faravelli, C., Monteleone, P., et al., 2007. Health-related quality of life in euthymic bipolar disorder patients: differences between bipolar I and II subtypes. The Journal of Clinical Psychiatry 68 (2), 207–212.
Makoukji, J., Belle, M., Meffre, D., Stassart, R., Grenier, J., Shackleford, G.G., et al., 2012. Lithium enhances remyelination of peripheral nerves. Proceedings of the National Academy of Sciences 109 (10), 3973–3978.
McIntosh, A.M., Maniega, S.M., Lymer, G.K.S., McKirdy, J., Hall, J., Sussmann, J.E.D., et al., 2008. White matter tractography in bipolar disorder and schizophrenia. Biological Psychiatry 64 (12), 1088–1092.
Merikangas, K., Akiskal, H., Angst, J., et al., 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. Archives of General Psychiatry 64 (5), 543–552.
Mitsunaga, M., Garrett, A., Howe, M., Karchemskiy, A., Reiss, A., Chang, K., 2011. Increased subgenual cingulate cortex volume in pediatric bipolar disorder associated with mood stabilizer exposure. Journal of Child and Adolescent Psychopharmacology 21, 149–155.
Moore, G.J., Bebchuk, J.M., Wilds, I.B., Chen, G., Menji, H.K., 2000. Lithium-induced increase in human brain grey matter. Lancet 356 (9237), 1241–1242.
Moorhead, T.W.J., McKirdy, J., Sussmann, J.E.D., Hall, J., Lawrie, S.M., Johnstone, E.C., et al., 2007. Progressive gray matter loss in patients with bipolar disorder. Biological Psychiatry 62 (8), 894–900.
Narita, K., Suda, M., Takei, Y., Aoyama, Y., Majima, T., Kameyama, M., et al., 2011. Volume reduction of ventromedial prefrontal cortex in bipolar II patients with rapid cycling: a voxel-based morphometric study. Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2), 439–445.
Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human Brain Mapping 15 (1), 1–25.
Patton, J.H., Stanford, M.S., Barratt, E.S., 1995. Factor structure of the barratt impulsiveness scale. Journal of Clinical Psychology 51 (6), 768–774.
Raven, J., Court, J., Raven, J., 1998. Raven's Progressive Matrices. Oxford Psychologists Press, Oxford.
Selvaraj, S., Arnone, D., Job, D., Stanfield, A., Farrow, T.F.D., Nugent, A.C., et al., 2012. Grey matter differences in bipolar disorder: a meta-analysis of voxel-based morphometry studies. Bipolar Disorders 14 (2), 135–145.
Sexton, C.E., Mackay, C.E., Ebmeier, K.P., 2009. A systematic review of diffusion tensor imaging studies in affective disorders. Biological Psychiatry 66 (9), 814–823.
Sexton, C.E., Allan, C.L., Mackay, C.E., Ebmeier, K.P., 2012. White matter integrity within the corpus callosum differentiates late-life bipolar and unipolar depression. Bipolar Disorders 14 (7), 790–791.
Sheehan, D., Lecrubier, Y., Sheehan, K., Amorim, P., Janavs, J., Weiller, E., et al., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of Clinical Psychiatry 59 (Suppl. 20), 22–33 (quiz 4-57).
Smith, S.M., 2002. Fast robust automated brain extraction. Human Brain Mapping 17 (3), 143–155.
Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage 44 (1), 83–98.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., et al., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage 31 (4), 1487–1505.
Song, S.-K., Sun, S.-W., Ramsbottom, M.J., Chang, C., Russell, J., Cross, A.H., 2002. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. NeuroImage 17 (3), 1429–1436.
Sussmann, J.E., Lymer, G.K.S., McKirdy, J., Moorhead, T.W.J., Maniega, S.M., Job, D., et al., 2009. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. Bipolar Disorders 11 (1), 11–18.
van Ewijk, H., Heslenfeld, D.J., Zwiers, M.P., Buitelaar, J.K., Oosterlaan, J., 2012. Diffusion tensor imaging in attention deficit/hyperactivity disorder: a systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews 36 (4), 1093–1106.
Versace, A., Almeida, J., Hassel, S., Walsh, N., Novelli, M., Klein, C., et al., 2008. Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. Archives of General Psychiatry 65 (9), 1041–1052.
Wang, F., Kalmar, J., Edmiston, E., Chepenik, L., Bhagwagar, Z., Spencer, L., et al., 2008a. Abnormal corpus callosum integrity in bipolar disorder: a diffusion tensor imaging study. Biological Psychiatry 64 (8), 730–733.
Wang, F., Jackowski, M., Kalmar, J.H., Chepenik, L.G., Tie, K., Qiu, M., et al., 2008b. Abnormal anterior cingulum integrity in bipolar disorder determined through diffusion tensor imaging. The British Journal of Psychiatry 193 (2), 126–129.
Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of Personality and Social Psychology 54 (6), 1063–1070.
Wechsler, D., 1981. WAIS-R Manual: Wechsler Adult Intelligence Scale—Revised. Psychological Corp, San Antonio, Texas.
Wessa, M., Houenou, J., Leboyer, M., Chanraud, S., Poupon, C., Martinot, J.-L., et al., 2009. Microstructural white matter changes in euthymic bipolar patients: a whole-brain diffusion tensor imaging study. Bipolar Disorders 11 (5), 504–514.
Yip, S.W., Lacadie, C., Xu, J., Worhunsky, P., Fulbright, R., Constable, R.T., et al., 2011. Reduced genual corpus callosal white matter integrity in pathological gambling and its relationship to alcohol abuse or dependence. World Journal of Biological Psychiatry Early Online 1–10.
Yip, S.W., Doherty, J., Wakeley, J., Saunders, K., Tzagarakis, C., de Wit, H., et al., 2012. Reduced subjective response to acute ethanol administration among young men with a broad bipolar phenotype. Neuropsychopharmacology 37 (8), 1808–1815.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. The British Journal of Psychiatry 133 (5), 429–435.
Yurgelun-Todd, D., Silveri, M., Gruber, S., Rohan, M., Pimentel, P., 2007. White matter abnormalities observed in bipolar disorder: a diffusion tensor imaging study. Bipolar Disorders 9 (5), 504–512.
Zanetti, M., Jackowski, M., Versace, A., Almeida, J., Hassel, S., Duran, F., et al., 2009. State-dependent microstructural white matter changes in bipolar I depression. European Archives of Psychiatry and Clinical Neuroscience 259 (6), 316–328.
Zhang, Y., Brady, M., Smith, S., 2001. Segmentation of brain MR images through a hidden Markov random field model and the expectation–maximization algorithm. IEEE Transactions on Medical Imaging 20 (1), 45–57.
Zhou, Y., Qin, L.-d., Chen, J., Qian, L.-j., Tao, J., Fang, Y.-r., et al., 2011. Brain microstructural abnormalities revealed by diffusion tensor images in patients with treatment-resistant depression compared with major depressive disorder before treatment. European Journal of Radiology 80 (2), 450–454.
Zhu, X., Wang, X., Xiao, J., Zhong, M., Liao, J., Yao, S., 2011. Altered white matter integrity in first-episode, treatment-naive young adults with major depressive disorder: a tract-based spatial statistics study. Brain Research 1369, 223–229.