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A Comprehensive Tractography Study of Patients With Bipolar Disorder and Their Unaffected Siblings

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Abstract: *Background:* Diffusion tensor imaging studies show reductions in fractional anisotropy (FA) in individuals with bipolar disorder and their unaffected siblings. However, the use of various analysis methods is an important source of between-study heterogeneity. Using tract-based spatial statistics, we previously demonstrated widespread FA reductions in patients and unaffected relatives. To better interpret the neuroanatomical pattern of this previous finding and to assess the influence of methodological heterogeneity, we here applied tractography to the same sample. *Methods:* Diffusion-weighted images were acquired for 96 patients, 69 unaffected siblings and 56 controls. We applied TRACULA, an extension of a global probabilistic tractography algorithm, to automatically segment 18 major fiber tracts. Average FA within each tract and at each cross-section along each tract was compared between groups. *Results:* Patients had reduced FA compared to healthy controls and their unaffected siblings in general, and in particular in the parietal part of the superior longitudinal fasciculus. In unaffected siblings, FA was nominally reduced compared to controls in the corpus callosum. Point-wise analyses indicated that similar effects were present along extended sections, but with variable effect sizes. Current symptom severity negatively correlated with FA in several fronto-limbic association tracts. *Conclusions:* The differential sensitivity of analysis techniques likely explains between-study heterogeneity in anatomical localization of FA reductions. The present tractography analysis confirms the presence of overall FA reductions in patients with bipolar disorder, which are most pronounced in the superior longitudinal fasciculus. Unaffected siblings may display similar, albeit more subtle and anatomically restricted FA reductions. *Hum Brain Mapp 37:3474–3485, 2016.*

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INTRODUCTION

Multiple lines of evidence indicate that white matter integrity and microstructure are implicated in the pathophysiology of bipolar disorder (BD). Post-mortem studies have shown fewer oligodendrocytes [Vostrikov et al., 2007], less myelin [Regenold et al., 2007], and attenuated myelin-associated gene expression [Tkachev et al., 2003] in the brains of patients with BD. Increased volume and number of white matter hyperintensities identified on T_2-weighted magnetic resonance images (MRI) are the most consistent imaging finding in association with BD [Dupont et al., 1987; Kempton et al., 2008]. Based on T_1-weighted MRI, reductions in total [Vita et al., 2009] and callosal [Arnone et al., 2008] white matter have been reported repeatedly in BD patients, although voxel-wise studies are inconsistent with regard to the neuroanatomical locations that are most affected [Kempton et al., 2008; Mahon et al., 2010].

Studies using diffusion tensor imaging (DTI), have corroborated and extended these previous findings. Over 50 case–control studies have been performed using DTI and compared its most common metric, fractional anisotropy (FA), between patients and controls. The majority of these case–controls studies report reduced FA in patients in a wide variety of white matter regions and tracts [Mahon et al., 2010; Nortje et al., 2013; Sexton et al., 2009].

Both BD [Gershon et al., 1982; McGuffin et al., 2003] and white matter microstructure [Jahanshad, 2013; Kochunov, 2015], as quantified by FA, are heritable. In two independent samples we recently reported that FA is also reduced in unaffected relatives of patients with BD, albeit to a lesser extent than in their probands [Sprooten et al., 2011, 2013]. This familiality of the FA reductions indicates that these white matter perturbations are not merely a consequence or direct correlate of the symptoms or disease-associated factors, but that they occur at least to some extent before disorder onset and are likely associated with partly the same genetic risk factors as BD. Such a developmental and possibly genetic role for white matter in BD has implications for genetic research of the disorder, and could ultimately have translational potential in diagnosing, stratifying, and treating patients.

Despite the consistency of DTI findings across independent studies [Sprooten et al., 2011, 2013], in general DTI findings both in patients and unaffected relatives are inconsistent regarding the anatomical specificity of the FA reductions. In patients, hypothesis-driven region-of-interest studies tended to focus on fronto-limbic connections [Caseras et al., 2015; Emsell et al., 2013b; Mahon et al., 2010; Sexton et al., 2009], but unbiased whole-brain analyses do not show a clear overrepresentation of fronto-limbic regions [Nortje et al., 2013; Vederine et al., 2011] but also see [Wise et al., 2016]. In young unaffected relatives Versace et al. [2010] reported age-by-group interactions in the corpus callosum and right temporal lobe, while others found reduced FA restricted to the superior longitudinal fasciculi [Frazier et al., 2007]. In adult unaffected relatives, reduced FA has been reported in the right temporal lobe [Mahon et al., 2013] and posterior corona radiata [Skudlarski et al., 2013]. Genetic liability scores for BD, as continuous measures of genetic risk, have also been inversely correlated with FA in the uncinate and superior longitudinal fasciculi [Emsell et al., 2013a] and with widespread FA [Chaddock et al., 2009]. The largest studies to date are consistent with the notion of subtle but widespread effects in patients [Skudlarski et al., 2013; Sprooten et al., 2013], and in relatives [Sprooten et al., 2011, 2013].

Integrating all evidence to date, we hypothesize that there are widespread subtle reductions in FA in patients as well as unaffected relatives, but that some regions may be more affected than others. In addition to clinical and demographic heterogeneity, the variability in imaging parameters and analyses methods may lead to variance in regional signal-to-noise across studies. This may be responsible for the inconsistencies in the neuroanatomical findings across studies. One such important difference between studies lies in the use of different statistical methods with distinct sensitivities to various types of signals. Studies that have reported regionally specific FA reductions tended to have applied tractography to segment regions of interest, or used conventional voxel-thresholded

Abbreviations

ATR	Anterior thalamic radiations
BD	Bipolar disorder
BPRS	Brief psychiatric rating scale
CAB	Angular part of Cingulum Bundle
CC	Corpus callosum
CING	Cingulum bundle
CST	Corticospinal tracts
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
HAMD	Hamilton Depression Scale
ILF	Inferior longitudinal fasciculus
MPRAGE	Magnetization-prepared rapid gradient-echo
MRI	Magnetic resonance images
SLFP	The parietal part of the superior longitudinal fasciculus
SLFT	Temporal part of the superior longitudinal fasciculus
TFCE	Threshold-free cluster enhancement
UNC	Uncinate fasciculus
YMRS	Young Mania Rating Scale

TABLE I. Clinical and demographic characteristics of the studied sample

	Patients ($N = 96$)	Unaffected siblings ($N = 69$)	Comparison subjects ($N = 56$)	Statistics
	Median (*IQR*)	Median (*IQR*)	Median (*IQR*)	X^2 (*P*)
Age(years)	30 (24–43)	28 (21–39)	25 (22–42)	5.00 (0.08)
IQ estimate[a]	105 (93–117)	107 (96–118)	109 (99–118)	0.77 (0.68)
Symptom scales				
HDRS	4 (1–8)	0 (0–2)	0 (0–0)	79 ($< 10^{-16}$)
YMRS	2 (0–6)	0 (0–1)	0 (0–0)	80 ($< 10^{-16}$)
BPRS	29 (36–33.50)	25 (24–26)	24 (24 25)	64 ($< 10^{-14}$)
LDPS severity score	9 (7–16)	0 (0–0)	0 (0–0)	183 ($< 10^{-16}$)
Age at onset of mania (years)	18 (16–21)	–	–	–
Duration of illness (years)	10 (5–22)	–	–	–
	N (%)	*N* (%)	*N* (%)	X^2 (*P*)/Fisher *P*
Female sex	65 (68%)	36 (64%)	43 (63%)	$X^2 = 0.70$ ($P = 0.70$)
Right-handed[b]	82(85%)	69 (100%)	50 (89%)	$X^2 = 11.18$ ($P = 0.02$)
DSM IV symptoms & diagnoses (SCID)				
Current major depression	13 (14%)	0	0	
Current mania	6 (6%)	0	0	
Past single episode major depression	93 (97%)	4 (6%)	0	
History of psychosis (in sibling)[c]	34 (35%)	31 (45%)	0	
History of anxiety disorder	41 (43%)	4 (6%)	2 (4%)	$P = 1.07*10^{-11}$
History of alcohol use disorder	45 (47%)	10 (14%)	3 (5%)	$P = 6.6*10^{-10}$
History of substance use disorder	45 (47%)	8 (12%)	4 (7%)	$P = 6.59*10^{-10}$
Nicotine dependence (current)[d]	26 (27%)	11 (16%)	2 (4%)	$P = 0.0005$
Medication use				
Lithium	18 (19%)	0	0	
Mood stabilisers	48 (50%)	0	0	
Antidepressants	48 (50%)	10 (14%)	2 (4%)	
Atypical antipsychotics[e]	35 (36%)	0	0	
Anxiolytics/benzodiazepines	34 (35%)	4 (6%)	1 (0.5%)	

IQR = Interquartile Range (1st to 3rd quartile); HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; BPRS = Brief Psychiatric Rating Scale; LDPS = Lifetime Dimensions of Psychosis Scale.
[a]IQ = Full Intelligence Quotient according to WASI.
[b]Hand preference measured using Edinburgh handedness scale.
[c]Patient with history of psychosis or their unaffected sibling.
[d]$\geq$ 2 on the Fagerstorm scale for nicotine dependence.
[e]No patients were currently taking typical antipsychotics.

cluster inference. In contrast, we previously used TBSS combined with threshold-free cluster enhancement (TFCE) [Smith and Nichols, 2009] to detect widespread FA reductions [Sprooten et al. 2011, 2013]. TFCE is extraordinarily sensitive to spatially consistent effects, so that voxels can be detected as significant contributors to between-group differences even if they themselves have very small effect sizes, as long as the effect crosses multiple contiguous voxels [Smith & Nichols, 2009]. In contrast, advantages of tractography are that, as long as the effect is sufficiently consistent within the segmented tract, it should be more sensitive to tract-specific FA differences that may be obscured by normalization to standard space, that it allows for more readily interpretable effect sizes, and that it can generate specific tract and function-specific hypotheses. Thus, tractography is a complementary method to TBSS combined with TFCE, as it is more suitable to identify those tracts that are most meaningful in terms of their effects size, aids the interpretation of the nature of observed effects, and facilitates determination of future research directions across imaging modalities and disciplines. For these reasons, in the present paper we aimed to further examine the neuroanatomical specificity of our previous findings. To this end we applied tractography to the same study in which we previously reported widespread FA reductions in patients and their unaffected siblings.

MATERIALS AND METHODS

Participants

All participants provided informed consent approved by the institutional review boards at Hartford Hospital and Yale University. The present study sample mostly overlaps

with, and is an extension of, the previously described study sample in Sprooten et al. [2013]. Ninety-six patients with DSM-IV bipolar I disorder, 69 of their non-bipolar siblings, and 56 demographically matched healthy volunteers (Table I) participated in the study and provided diffusion weighted scans that passed our visual quality control. Patients were identified through outpatient clinics and community mental health facilities in the Hartford area. Inclusion criteria for patients included: (1) diagnosis of bipolar I disorder as determined by the Structured Clinical Interview [First et al., 2002], administered by experienced research clinicians; (2) no current substance or alcohol abuse/dependence; (3) no history of a major medical or neurological condition; and (4) IQ > 80 [Wechsler, 1999].

Nineteen patients were currently symptomatic (13 depressed, 6 manic), and 77 were in remission. Thirty-four patients had a history of psychosis, whereas 62 patients never had experienced any psychotic symptoms.

Unaffected siblings were within 10 years of age of their probands. Unrelated healthy comparison subjects were recruited through media advertisements and flyers. In the interest of sample validity, history of major depressive episodes, comorbid anxiety disorders, and history of substance abuse/dependence were allowed for all subjects (Table I).

Current mood symptoms were measured using the Hamilton Depression Scale (HAMD) [Hamilton, 1967], the Young Mania Rating Scale (YMRS) [Young et al., 1978] and the expanded version of the brief psychiatric rating scale (BPRS) [Ventura et al., 1993].

Diffusion Weighted and T_1-Weighted Scan Acquisition

All scans were collected at the Olin Neuropsychiatry Research Center, Institute of Living/Hartford Hospital using a research dedicated Siemens Allegra 3T scanner. Diffusion-weighted MR images were acquired using single-shot echo planar imaging (TR/TE = 6300/81 ms, field of view = 22 × 22 cm, acquisition matrix = 128 × 128, voxel size = 1.7 × 1.7 × 3.0mm) with a twice-refocusing spin echo sequence to minimize eddy-current induced distortion. The sequence consisted of 55 non-collinear diffusion weighted directions, two diffusion weighting values ($b = 0$ and 800s/mm^2) and three non-diffusion weighted ($b = 0$) images. The acquisition lasted 6.2 minutes and contained 58 sets of images, with 45 contiguous, interleaved axial slices per volume (slice thickness = 3.0mm) covering the whole brain.

Structural images were acquired using a T_1-weighted, 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR/TE/TI = 2200/4.13/766 ms, flip angle = 13°, voxel size [isotropic] = 0.8 mm, image size = 240 × 320 × 208 voxels), with axial slices parallel to the AC-PC line. To increase signal-to-noise ratio, four volumes were acquired per subject.

Preprocessing

Diffusion-weighted data were converted to NIFTI format using MRIcron, and processed using standard FSL tools (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT). Images were corrected for bulk subject motion and eddy currents by aligning the diffusion-weighted volumes to each subject's first b_0-volume. The b-matrix of the diffusion gradients was rotated using the same transformation, as recommended by [Jones et al., 2013]. FSL's brain extraction tool was applied to remove skull and other non-brain tissue. Diffusion tensor characteristics, including diffusion eigenvectors, eigenvalues and FA were calculated using *dtifit*. *Bedpostx* [Behrens et al., 2007] was applied with a two fiber (ball & stick) model to estimate the distributions (and uncertainty) of the diffusion parameters to enable probabilistic tractography. T_1-weighted scans were reconstructed using MRIcron and visually inspected. For each subject, all volumes were linearly coregistered and averaged. Segmentation of surface-based cortical regions and subcortical volumes were obtained automatically using Freesurfer [Dale et al., 1999; Fischl et al., 1999a; Fischl et al., 1999b].

Tract Segmentation

We applied TRACULA [Yendiki et al., 2011] (http://surfer.nmr.mgh.harvard.edu/fswiki/Tracula), an automated toolbox within Freesurfer to segment 18 major white matter tracts: the anterior thalamic radiations (ATR), the cingulate gyrus part of the cingulum bundle (CING), the medial temporal ("angular") part of the cingulum bundle (CAB), the corticospinal tracts (CST), inferior longitudinal fasciculus (ILF), the parietal part of the superior longitudinal fasciculus (SLFP), the (relatively more) temporal part of the superior longitudinal fasciculus (SLFT), the uncinate fasciculus (UNC), all bilaterally; and the forceps major and minor of the corpus callosum (CC).

TRACULA is an extension of the global probabilistic tractography algorithm developed by [Jbabdi et al., 2007]. This algorithm uses a Bayesian framework to determine the connections (i.e., selection of consecutive voxels) between two pre-defined end points that best fits the preprocessed diffusion data, where the diffusion data is represented by a ball-and-stick model in each voxel [Behrens et al., 2007]. TRACULA extends this algorithm by incorporating anatomical knowledge in the prior probability function, so that the final selected "connection" is not only the best fit given the observed diffusion data within each subject, but also given its similarity to the known and manually verified trajectory of the tract's anatomy in the training set. More concretely, first TRACULA determines the endpoints on both sides of each tract by diluting the endpoints of the tracts in the training data and transforming them to each subject's native space. Next, TRACULA evaluates the location of the probabilistic streamlines (subdivided in spline segments) relative to anatomically labeled regions (Freesurfer segmentations) which are

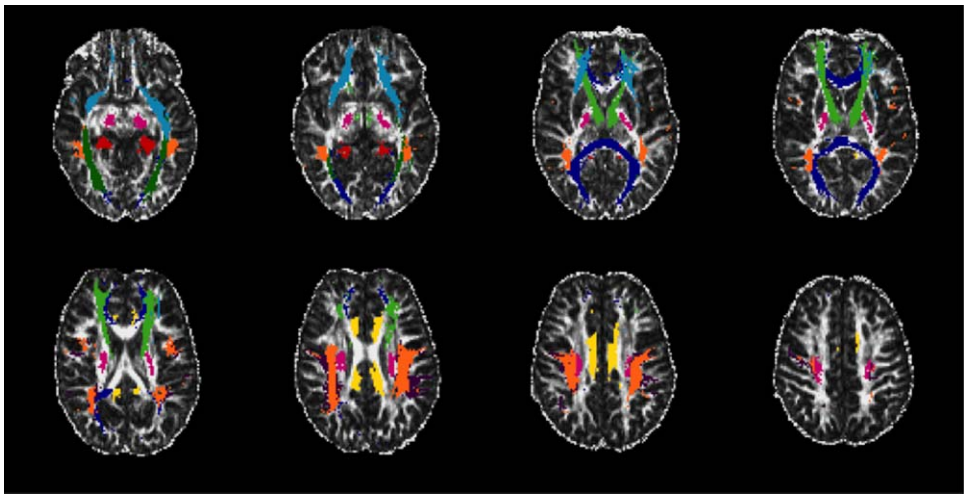

Figure 1.
Example of TRACULA white matter tract segmentations in a single participant. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

known to intersect or neighbor the pathways based on training data, and iteratively creates splines until the similarity in intersecting and neighboring label regions is optimized. Note that all of the segmentation steps are automatically executed by the TRACULA package, which also includes the labeled training data and the results of the training data processing on which the priors are based [Yendiki et al., 2011].

We visually checked the anatomical accuracy of each subject's tract segmentation in fslview. See Figure 1 for an example of a single subject's tract segmentations. For some of the tracts, most notably the UNC, a number of participants were excluded because of truncations, excessive branching into other tracts, for otherwise following unlikely anatomical trajectories, or because the segmentation included a region of poor scan quality (mostly due to orbitofrontal signal loss and/or motion). The numbers of subjects that were excluded for each tract are provided in Supporting Information Table I.

Statistical Analyses

Our main metric of interest was mean FA across all voxels within each tract. All statistical analyses were performed in R 3.0.2 (http://cran.r-project.org/). To test for overall FA differences between groups we applied a large mixed model regression, with hemisphere and tract as within-subject factors (with a random intercept by individual and a fixed slope); diagnostic group and sex as fixed factor; and age and age^2 as covariates. Interactions of group with hemisphere and tract were removed from the model if they were not significant. Tract-by-hemisphere interactions were mostly significant, and retained in all models.

Separate pairwise comparisons between the three groups were performed, and in the comparison of siblings with their probands, family was added as an additional within-subject factor. Effects of family history of psychosis were examined by adding an additional 2-level fixed factor to the regression model used for the sibling-patient comparison.

To explore tract-specific effects, we repeated these regressions for each tract separately (hereafter referred to as "tract-specific models", as opposed to the "large mixed model" above).

Spearman's rank correlation coefficients were computed between average FA and clinical symptom scales within patients, and where possible within siblings, separately. Medication effects were investigated by adding the use of each medication class as a binary factor to the above models. Associations with duration of bipolar illness (years since first manic episode) were assessed by adding this as a continuous variable to the above regression models.

We also performed several post-hoc tests to evaluate the potential confounding effects of imaging-related or demographic factors (see "Additional Tests of Potential Confounds" section): motion parameters, maximum tract length, center tract length, tract volume; and we analyzed mean FA weighted by each voxel's tract-membership probability. The weighted FA was analyzed to asses whether voxels at the edges of the tract may disproportionally influence the results, which could lead to bias given the lower confidence of the segmentation in these voxels and potential inter-subject heterogeneity in these regions. In brief, if the results obtained from average FA within the tracts are similar to the ones obtained using weighted FA, the results are not disproportionally influenced by these low-confidence voxels.

Finally, we also performed point-wise comparisons of FA values along the standard-space mean (common) tract splines, in order to examine whether group differences

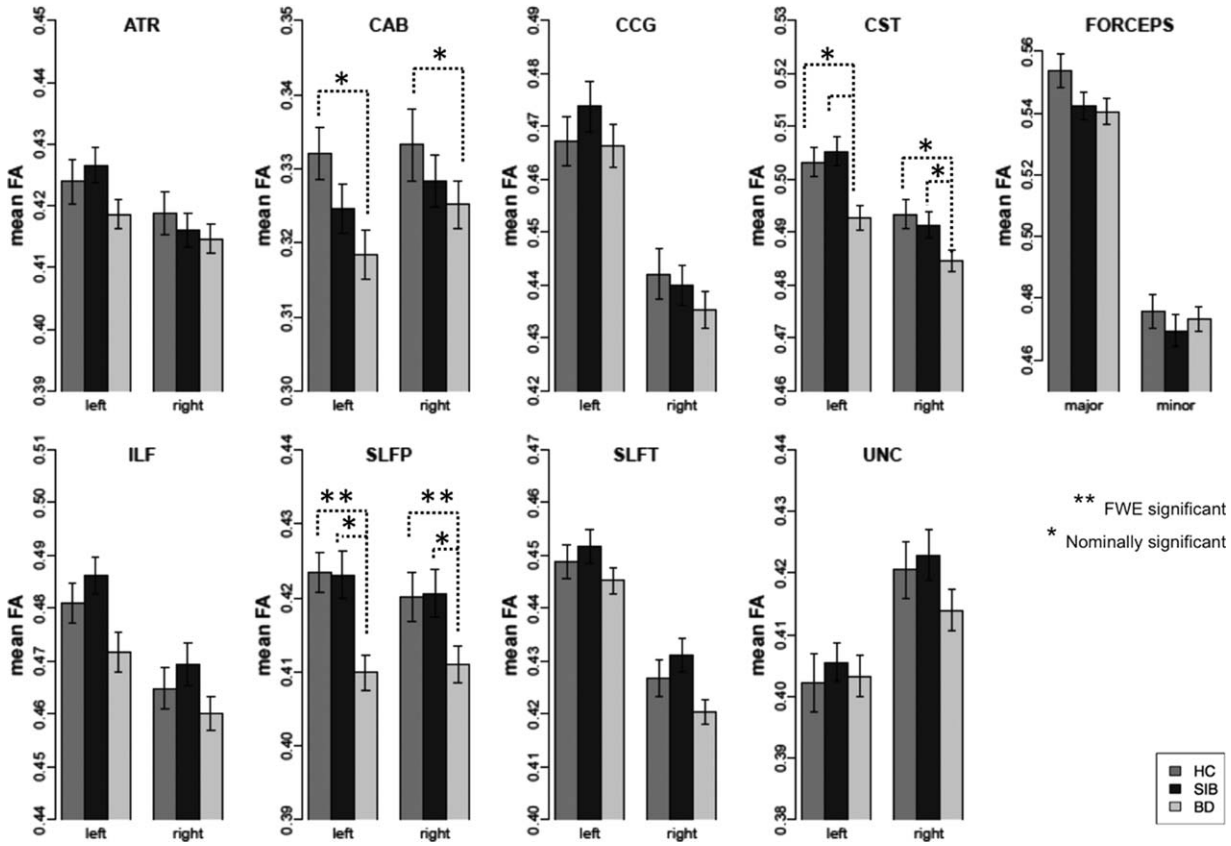

Figure 2.
Mean FA within each tract per group.

were more or less pronounced by sub-sections of the tracts. Each tract contained 40-60 comparison points, and we adopted a liberal, tract-wide Bonferroni corrected α of 0.05 divided by the number of positions along each tract.

RESULTS

All Bipolar Patients Compared to Healthy Controls

In the large mixed model, with all tracts included, there was an overall difference between patients and controls ($P = 0.04$, $t = 2.09$, d$f = 147$), in the absence of any tract-by-diagnosis or tract-by-hemisphere interactions (all $P > 0.16$). There were no tracts in which FA was increased in patients compared to the healthy comparison group (Fig. 2). Means and standard deviations of the extracted FA values per diagnostic group are available in Supporting Information Table II.

In the tract-specific models, considering a Bonferroni-corrected significance level ($P < 0.0056$), only the SLFP was significantly different between patients and controls ($P = 0.005$, $t = 2.95$, d$f = 146$), in the absence of any interactions of diagnosis with age, sex, or age^2. There were also nominal effects in the CST and the CAB ($P < 0.05$; Table II). There were no significant hemisphere-by-diagnosis interactions for any tract-specific model.

Figure 3 shows the point-wise comparison of FA along the SLFP. This figure indicates that the group-difference was mainly driven by the locations in the middle of the left SLFP, where the lowest P-value was 0.0009 (significant at tract-wide corrected α at 0.0011), although similar nominal effects are visible at locations surrounding this tract-wide significant location. Point-wise comparisons along the other tracts did not result in any tract-wide significant effects. The results of point-wise analyses for all tracts are illustrated in Supporting Information Figure 1.

Familiality of Reduced FA In Bipolar Disorder

Next we performed two types of analysis to assess the familiality or genetic components of FA reductions in BD and effects due to illness-specific or uniquely predisposing factors within families. Firstly, comparing unaffected

TABLE II. Pairwise differences between patients, their unaffected siblings and controls for average FA within each tract

	Healthy controls–patients			Healthy controls–siblings			Siblings–affected probands		
TRACT	*T*	*df*[a]	*P*	*T*	*df*[a]	*P*	*T*	*df*[b]	*P*
ATR	1.126	146	0.262	−0.628	118	0.531	0.434	54	0.666
CAB	2.229	145	0.027[c]	−1.280	118	0.203	0.788	56	0.434
CING	0.440	146	0.660	0.096	119	0.923	0.707	55	0.483
CST	2.186	146	0.030[c]	−0.248	117	0.805	2.124	54	0.038[c]
CC	1.026	141	0.307	−1.709	112	0.090	−0.599	51	0.552
ILF	0.960	141	0.339	0.728	114	0.468	1.541	52	0.129
SLFP	2.830	146	0.005[d]	−0.534	117	0.594	2.069	54	0.043[c]
SLFT	1.209	146	0.229	0.190	119	0.850	1.284	55	0.205
UNC	0.615	142	0.540	0.284	117	0.777	0.894	52	0.376

[a]The degrees of freedom (**d*f***) differ between tracts due to variable numbers of cases failing quality control.
[b]The degrees of freedom are different for the sibling-patient contrasts because "family" is modeled as a random factor.
[c]Effect nominally significant (uncorrected $P < 0.05$).
[d]Effect significant at Bonferroni-corrected significance level ($P < 0.0056$).
ATR = Anterior thalamic radiations; CAB = Angular part of Cingulum Bundle; CING = Cingulum bundle (dorsal part); CST = Corticospinal tract; CC = Corpus Callosum (forceps major and minor); ILF = Inferior longitudinal fasciculus; SLFP = Parietal part of superior longitudinal fasciculus; SLFT = temporal part of superior longitudinal fasciculus; UNC = Uncinate fasciculus.

siblings to controls, gives an indication of familiality. FA was not significantly reduced in the siblings, in any of the tract-specific models or in the large mixed model, although there was a trend for an effect in the CC ($P = 0.09$; $t = -1.71$, d$f = 112$; Table II). Secondly, comparing patients to their unaffected siblings informs about potential unique environmental factors predisposing to or resulting from illness. Following the tract-specific models, patients showed nominally reduced FA in SLFP($P = 0.04$, $t = 2.07$, d$f = 54$; Table II) and the CST ($P = 0.04$, $t = 2.12$, d$f = 54$), compared to their unaffected siblings, in the absence of interactions of diagnosis with hemisphere or any covariates. None of the other tracts were significantly different between patients and their siblings.

Point-wise comparisons of FA along the trajectory of the tracts indicated that none of these global tract effects were driven by any particular location on the tracts. But, siblings had increased FA compared to controls in a superior section of the left CST, and patients had reduced FA compared to their unaffected siblings in a central part of the left ILF (Supporting Information Fig. 1).

Effects of Personal or Family History of Psychosis

When family history of psychosis was modeled as a fixed factor (in addition to diagnosis, age, age^2 and sex as fixed factors; and family and individual as nested random

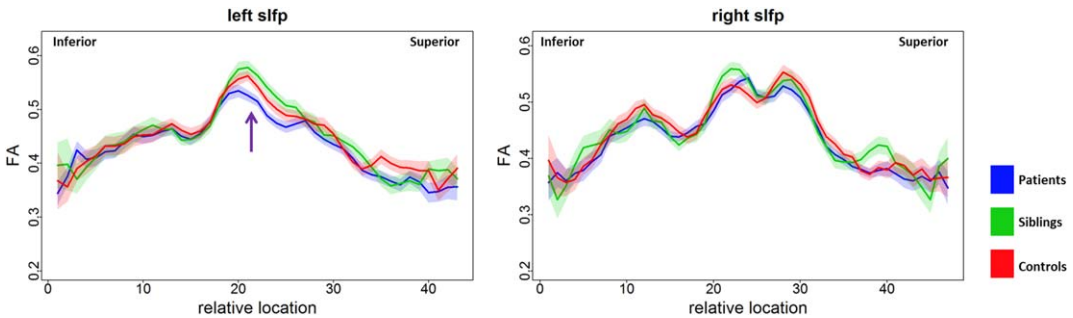

Figure 3.

Point-wise comparison of FA along the SLFP. Solid colored lines show the mean FA at each cross-section along the standard-space tract spline for each group. Shaded colors represent standard errors. The purple arrow indicates the single point at which there was a case-control difference that would be significant under a tract-wide Bonferroni correction ($P < 0.0011$). Of note, towards each endpoint, fewer participants contributed data, as is reflected in the larger standard errors. Equivalent figures for all tracts are available in the Supplementary Materials. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE III. Correlations of current symptom severity with FA in siblings and patients: Spearman *Rho* (*P*)

PATIENTS	HDRS	YMRS	BPRS
ATR	−0.26 (0.009)*	−0.15 (0.15)	−0.19 (0.07)
CAB	−0.11 (0.27)	−0.07 (0.52)	0.04 (0.67)
CING	−0.13 (0.21)	−0.05 (0.66)	0.03 (0.78)
CST	−0.14 (0.18)	0.00 (0.99)	−0.07 (0.49)
CC	0.02 (0.86)	0.22 (0.03)°	0.20 (0.05)°
ILF	−0.16 (0.14)	−0.14 (0.17)	−0.15 (0.15)
SLFP	−0.24 (0.02)*	−0.09 (0.38)	−0.10 (0.41)
SLFT	−0.21 (0.04)*	−0.05 (0.63)	−0.05 (0.64)
UNC	−0.24 (0.02)*	−0.22 (0.03)*	−0.18 (0.08)

SIBLINGS	HDRS	YMRS	BPRS
ATR	−0.35 (0.003)*	−0.22 (0.07)	−0.34 (0.004)*
CAB	0.25 (0.04)	0.06 (0.61)	0.14 (0.27)
CING	−0.22 (0.07)	0.01 (0.92)	−0.13 (0.31)
CST	−0.15 (0.24)	−0.12 (0.33)	0.05 (0.70)
CC	−0.06 (0.62)	0.01 (0.95)	−0.09 (0.48)
ILF	−0.24 (0.06)	−0.11 (0.38)	−0.21 (0.10)
SLFP	−0.25 (0.04)*	0.10 (0.48)	−0.10 (0.43)
SLFT	−0.27 (0.03)*	−0.02 (0.92)	−0.14 (0.27)
UNC	−0.19 (0.13)	−0.11 (0.35)	−0.26 (0.03)*

HDRS = Hamilton depression rating scale; YMRS = Young mania rating scale; BPRS = Brief psychiatric rating scale; ATR = Anterior thalamic radiations; CAB = Angular part of Cingulum Bundle; CING = Cingulum gyrus part of Cingulum bundle; CST = Corticospinal tract; CC = Corpus Callosum (forceps major and minor); ILF = Inferior longitudinal fasciculus; SLFP = Parietal part of superior longitudinal fasciculus; SLFT = temporal part of superior longitudinal fasciculus; UNC = Uncinate fasciculus.

terms) in the large mixed model, there was an overall effect of family history of psychosis ($P = 0.04$; $t = 2.04$; d$f = 103$). Following the tract-specific models, there was a nominal effect of history of psychosis on FA in the CC ($P = 0.03$; $t = 2.20$; d$f = 98$) where patients and their siblings with a history of psychosis had reduced FA compared to those without. There was also a trend for a similar effect of family history of psychosis on FA in the ATR ($P = 0.06$; $t = 1.90$; d$f = 102$). There were no interactions of family history of psychosis with diagnosis, hemisphere, age or age^2.

Correlations With Symptom Severity, Duration of Illness and Medication Use

Correlations between FA and clinical symptom scales are presented in Table III and Supporting Information Figure 2. None of the correlations were significant after Bonferroni-corrections for multiple testing. There were nominally significant negative correlations of current symptom severity with FA in the ATR, UNC, SLFP, and SLFT in patients, many of which were also reflected in their unaffected siblings. Unexpectedly, FA in the CC was positively correlated with the YMRS and the BPRS in patients.

When considered as categorical variables, there were no significant effects of current mood (manic, depressed, euthymic) on FA for any tract (all uncorrected $P > 0.09$).

Early age of onset was associated with reduced FA in the SLFP ($P = 0.002$, $t = -3.25$), SLFT ($P = 0.02$; $t = -2.36$) and CING ($P = 0.005$; $t = -2.90$), while correcting for the effects of current age.

Amongst patients, the use of anxiolytics was associated with reduced FA in the CING ($P = 0.0003$; $t = -3.73$) and the CC ($P = 0.016$; $t = -2.46$). Conversely, the use of lithium and antidepressants was slightly associated with increased FA in the CAB ($P = 0.04$; $t = 2.05$; $P = 0.004$; $t = 2.93$), and stimulant use with increased FA in the CST ($P = 0.05$; $t = 1.97$).

Additional Tests of Potential Confounds

We performed additional analyses to assess the effects of any potential confounding variables, for each of the significant results reported. When correcting for 6 motion parameters (3 translations, 3 rotations), the results remained similar, with the reduction in patients in the SLFP ($P = 0.01$; $t = 2.49$), and in siblings in the CC ($P = 0.05$; $t = 2.049$). When weighting average FA by the number of streamlines in each voxel, the results also remained similar although less significant: in patients vs. controls, weighted FA was nominally significant for both the SLFP ($P = 0.02$, $t = 2.48$) and the CST ($P = 0.02$, $t = 2.40$), and contrasting the siblings with the controls, the trend in the CC remained a trend ($P = 0.05$, $t = 1.95$). There were no group differences in terms of tract volume, average tract length, or center tract length, which could indicate differences in tract shape or differences in tractography accuracy. In addition, given the high quality control failure rate for the left UNC, we compared the likelihood of failing quality control for this tract between groups, but there were no differences ($P = 0.91$, $X^2 = 0.18$).

Age, age^2 and sex were included as covariates in all group analyses. There were no significant interactions of age, sex and age^2 with any independent variable of interest (group or clinical scales) for any significant effect reported above. When residualizing FA for age, sex and age^2 before calculating the correlations with clinical symptom scales, the significant results remained similar (all $P < 0.08$).

Patients were significantly more likely to be left handed compared to their unaffected siblings (Fisher $P = 0.02$), but not compared to controls (Fisher $P = 0.45$). There were no significant effects of handedness on FA for any of the tracts (all $P > 0.08$). There were no significant effects of history of anxiety disorders (all $P > 0.19$), substance abuse (all $P > 0.10$), or nicotine addiction (all $P > 0.24$) for any of the

tracts. History of alcohol abuse was associated with increased FA in the UNC ($P = 0.04$; $t = 2.15$) only.

DISCUSSION

The present tractography analysis indicates that BD is associated with reduced FA, at least to some extent, in all major white matter tracts, but that the magnitude of this effect differs between tracts and is most pronounced in the superior longitudinal fasciculus. Unaffected siblings of patients with BD, once they are adults and mostly past the typical age of onset of BD, if anything, show a more anatomically variable pattern of possible, subtle FA reductions, which are most apparent in the CC. The results we show here are consistent with and provide new information on the nature, effect size, and neuroanatomical location of our previous findings from a TBSS analysis in a largely overlapping sample [Sprooten et al., 2013]. In addition, the results are consistent with a recent study using identical tractography methods [Versace et al., 2014], and they extend previous findings of widespread but subtle FA reductions in younger unaffected relatives of patients with BD [Sprooten et al., 2011].

To integrate these results with other, similar DTI studies, two important factors should be considered. Firstly, studies that extract mean FA values from regions of interest or that use more conventional methods of inference such as cluster extent tend to find case–control differences in more confined, but overall variable, white matter tracts [Bauer et al., 2015; Emsell et al., 2013a; Emsell et al., 2013b; Frazier et al., 2007; Sussmann et al., 2009; Versace et al., 2010]. In contrast, studies using TFCE as method of inference tend to detect more global FA reductions [Roybal et al., 2015; Skudlarski et al., 2013; Sprooten et al., 2013; Sprooten et al., 2011]. As hypothesized, a comparison of the present tract-wide results to the point-wise analysis and our previous TBSS results suggests that this is likely a consequence of the distinct sensitivity of these different methods. Many voxels that are contributing to the spatial consistency of TFCE-significant clusters may have effect sizes below conventional significance thresholds, and will not pass significant thresholds adjusted for multiple comparisons across voxels. Our point-wise analysis of FA along the trajectories of the tracts and inspection of Figure 3 directly illustrates this interpretation. Our Bonferroni-corrected point-wise comparison within the SLFP would only consider a single point in the center of the tract different between patients and controls, while similar, but less pronounced effects were present along a much wider section of the SLFP. At the same time, few new suggestive, localized group differences were detected in our large-scale univariate point-wise comparisons, which we interpret with more caution because of the relatively liberal significance levels considered given the total number of pairwise comparisons that were performed.

A second methodological consideration for studies of unaffected relatives concerns the sample characteristics. Younger samples include a subset of individuals who will continue to develop BD or a genetically associated psychiatric disorder. As a consequence, these studies tend to report more significant effects of familiality [Frazier et al., 2007; Roybal et al., 2015; Sprooten et al., 2011; Versace et al., 2010] compared to studies of mature unaffected relatives [Chaddock et al., 2009; Emsell et al., 2013a; Skudlarski et al., 2013; Sprooten et al., 2013], who may represent some resilience to psychiatric disorders in addition to genetic risk factors.

Although our data are consistent with global FA reductions in BD, the most pronounced group differences were located in the SLFP, a large fiber bundle connecting the posterior and superior temporal cortices with the frontal and parietal lobes. Although the SLFP is relatively reliable to segment, it is difficult to distinguish from other parts of the superior longitudinal fasciculus or the arcuate fasciculus using DTI. In the present analysis, certainly, there was a high degree of overlap between the segmentations of the SLFT and the SLFP (see Fig. 1), and both arched into the temporal lobe to also include fibers of the arcuate fasciculus [i.e., Thiebout de Schotten et al., 2012; Catani & Thiebout de Schotten, 2008]. Hence, some caution is required in attributing the observed effect to any particular subdivision of the superior longitudinal fasciculus, and more precise high-resolution imaging or post-mortem studies would be required to do so. We discuss this finding therefore in the context of the superior longitudinal fasciculus in general. Historically, the arcuate fasciculus was the first fiber bundle with a known role in cognition (i.e., Wernicke's aphasia), and is best known for its role in language. More generally, however, the superior longitudinal fasciculus bilaterally is important for a multitude of cognitive functions and behaviors including attention, sensorimotor functions and visuospatial perception and manipulation [Sarubbo et al., 2015]. Despite these predominantly non-affective functions described in the literature, the superior longitudinal fasciculus has repeatedly been associated with BD [Emsell et al., 2013a; Lin et al., 2011; Versace et al., 2014]. In our sample, FA in the SLFP was also negatively correlated with severity of depressive symptoms, implying that the SLFP is relevant for mood and affective temperament aside from cognition. Finally, the negative association of SLFP FA and duration of illness and the significant differences between patients and their non-affected siblings, tentatively suggest that there may be a progressive, illness-associated component to this phenotype.

Although the effects of diagnosis were most pronounced in the SLFP, some other tracts showed more evidence for correlations with clinical dimensions. The strongest associations between FA and ratings of current (subclinical or clinical) mood symptoms were in the ATR, which as main connection of the thalamus and striatum with the

prefrontal cortex, is important in motivation and mood regulation and is thought to mediate treatment response of deep-brain stimulation in depression [Riva-Posse et al., 2014]. Other tracts showing correlations with symptom severity were the UNC and SLFT. Taken together, these associations with current affective symptoms suggest that there may be a dynamic, state-dependent component to white matter microstructure in fronto-limbic association fibers, in addition to the well-known genetic component [Jahanshad, 2013; Kochunov, 2015].

Despite the accumulating and largely consistent evidence for a role of white matter in BD across the literature, it should be noted that all effect sizes remain small. More sensitive, multi-modal imaging techniques, as well as multidisciplinary approaches need to be explored before this knowledge reaches translational potential. In addition, it is pivotal to have a better understanding of the clinical relevance and causality of white matter perturbations in BD, including their associations with predisposing as opposed to progressive factors, which will require the investigation of longitudinal cohorts.

As a methodological limitation, it is noteworthy that our diffusion-weighted images have an anisotropic resolution, with the voxels being larger in the z-direction, which can bias the estimation of the diffusion tensor distribution, as it will be less accurate, and potentially larger spread, in the z-direction. On the other hand, in most clinical studies a trade-off between spatial and angular resolution has to be made to keep the scan time manageable, and our angular resolution is relatively high, which benefits the tensor estimation. Further, our careful visual quality control of the tract segmentations and the use of a previously validated, probabilistic tractography method, should protect against the influence of tractography biases on our extracted FA values.

In conclusion, this tractography study corroborates our own and others' previous evidence that white matter microstructure is altered in patients with BD. The differential sensitivity of different analysis techniques can explain previous inconsistencies in the anatomical locations of white matter alterations in BD, especially for those studies that are less well-powered. While many regions appear to be affected to some extent, our findings indicate that the most pronounced effects are located in the superior longitudinal fasciculus. There is a familial and most likely genetic component to these white matter perturbations, which is, across studies, most apparent in young unaffected relatives. In addition, some fronto-limbic white matter alterations may be state-related, a hypothesis that warrants more direct investigation in longitudinal and in-depth clinical studies.

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