INTRODUCTION

Differentiating unipolar depression (UD) and depressive episodes in bipolar disorder (BD) is one of the major challenges in psychiatric diagnostics due to the fact that most bipolar patients primarily present with depressive symptoms. Therefore, misdiagnoses are common in BD and lead to poor outcomes and higher health care costs, which may be avoided by appropriate pharmacological treatment.1,2

Diffusion tensor imaging (DTI) is a useful tool with which to study microstructural abnormalities, particularly in white matter tracts, which are likely relevant in the pathophysiology of both neurological and psychiatric disorders, as they point towards altered connectivity in the brain.3

Objective: The absence of neurobiological diagnostic markers of bipolar disorder (BD) leads to its frequent misdiagnosis as unipolar depression (UD). We investigated if changes in fractional anisotropy (FA) could help to differentiate BD from UD in the state of depression.

Methods: Using diffusion tensor imaging (DTI) we employed a voxel-based analysis approach to examine fractional anisotropy (FA) in 86 patients experiencing an acute major depressive episode according to DSM-IV (N=39 BD, mean age 39.2 years; N=43 UD, mean age 39.0 years), and 42 healthy controls (HC, mean age 36.1 years). The groups did not differ in sex, age or total education time. FA was investigated in white matter (FA >.2) and hypothesis-driven anatomically defined tracts (region-of-interest [ROI] analysis). Additionally, an exploratory gray matter FA analysis was performed.

Results: White matter analysis showed decreased FA in the right corticospinal tract in UD vs HC and in the right corticospinal tract/superior longitudinal fascicle in BD vs HC and also in BD vs UD. ROI analysis revealed decreased FA in BD vs UD in the corpus callosum and in the cingulum. Gray matter exploratory analysis revealed decreased FA in the left middle frontal gyrus and in the right inferior frontal gyrus in UD vs HC, and in the left superior medial gyrus in BD vs HC.

Conclusion: This is one of very few studies directly showing differences in FA between BD and UD. Gray matter FA changes in prefrontal areas might be precursors for future prefrontal gray matter abnormalities in these disorders.

KEYWORDS
bipolar disorder, connectivity, diffusion tensor imaging (DTI), major depressive disorder, magnetic resonance imaging (MRI), white matter

*This is to indicate that both authors contributed equally to the present work and should therefore both be regarded as senior authors.
Fractional anisotropy (FA), which can be seen as a quantitative index of white matter coherence, has become the most common DTI measure in psychiatric research. The current belief is that high FA values represent highly organized and normally myelinated axon structure. Therefore, decreased FA can be interpreted as a loss of coherence in the main preferred diffusion direction.

The utility of DTI metrics in gray matter (GM) has been poorly investigated and its meaning is open to debate: reports of changes in FA in GM are rare, as it is primarily seen as a measure of white matter integrity. Nonetheless, there is evidence that decreases in FA within GM structures could be a sign of functionally relevant neurodegeneration before other structural magnetic resonance imaging (MRI) changes are detected. Other studies investigated FA in GM structure, demonstrating FA changes as a marker for brain compression and traumatic brain injury. In a rat model, excess gliosis in GM structures led to increased FA values in these areas. In general, DTI measures in GM could be a potential precursor for future GM atrophy in early Alzheimer’s disease.

There is a growing body of DTI studies in UD and BD patients, with, however, massive heterogeneities regarding DTI methods (e.g., tract-based statistics vs voxel-wise approaches), sample characteristics, and the application of regional restraints (e.g., whole-brain analyses vs region of interest focus). A recent meta-analysis compared FA changes in UD patients, BD patients and healthy controls (HC), including both studies using voxel-based analysis (VBA) and those using tract-based spatial statistics (TBSS) approaches. Results suggest that the corpus callosum and the cingulum bundle, in particular, show significant abnormalities in both disorders.

However, to the best of our knowledge, only three studies are currently available comparing UD to BD directly. In a study with 18 UD, 20 BD, and 21 HC, no differences between the patient groups but reduced FA in callosal fibers for both UD and BD compared to HC were observed. Reduced FA in the superior longitudinal fascicle was detected in BD compared to UD in a study comprising 15 UD, 16 BD, and 24 HC. Finally, in a study including 15 UD, 15 BD, and 21 HC using predefined tracts of interest, decreased FA in BD compared to UD was reported in white matter fiber bundles connecting structures of the anterior limbic network.

While changes in FA both in UD and in BD were commonly reported in previous studies, the etiopathological meaning of these lesions remains unclear. It remains to be clarified whether these structural alterations occur after disease onset or whether they represent potential markers of genetic risk (endophenotype). Some studies suggest that the decrease in FA correlates with clinical markers such as the number of depressive episodes, time since onset of disease or severity of illness, which would point towards an effect of disease on the brain. However, other studies have indicated that there may be genetic influences on FA in these patients and groups at risk, which would suggest that FA reductions may be a trait and vulnerability marker of BD.

Hence, the main aim of the present study was to examine FA differences between BD and UD in well-characterized patient samples with a sample size more than double those of the presently available reports. To address differences in the regional foci investigated in previous DTI studies on affective disorders, we used a comparable approach, reporting results of an analysis restricted to white matter only, and restricted to a priori tracts of interests. Additionally, we performed an exploratory whole-brain analysis to detect FA alterations located in GM areas. Finally, we aimed to identify possible clinical variables that influence FA changes to shed more light on the clinical relevance of FA alterations in these disorders.

We expected FA reduction in both UD and BD compared to HC, and reduced FA in BD compared to UD. Due to lack of consistent data, we could not construct a strong a priori hypothesis about specific brain regions, especially in GM areas. For comparing BD to UD, we focused on the corpus callosum and the cingulum bundle, in view of the findings of the recent meta-analysis, and on the uncinated fascicle.

2 | MATERIALS AND METHODS

2.1 | Sample

Forty-three individuals with BD, 43 individuals with UD, and 43 HC were enrolled in the study. Due to extreme outliers on FA maps, as revealed by a homogeneity of covariance test (see below), we had to exclude four BD patients and one HC. The three groups did not differ in age (F(2)= 0.87, P=.42), sex (χ²= 0.32, P=.85), or years of education (F(2)= 1.11, P=.33). On average, UD patients were 34.2 (SD 12.0) years old and BD patients were 29.6 (SD 11.2) years old when first treated for psychiatric symptoms. The age of onset ranged from 13 to 57 years for UD patients and from 14 to 50 years for BD patients.

Eleven BD patients were diagnosed with BD-II and 28 with BD-I. BD patients had significantly more depressive episodes (BD= 6.8; UD= 3.6; t= 3.07, P<.01) and a slightly longer time since the first depressive episode (BD= 151.1 months, UD= 94.0 months, t= 2.17, P=.03) compared to UD patients. For further information, see Table 1. No significant differences in frequencies of comorbid diagnoses were found between patient groups (see Table S2 for further details).

We verified the diagnoses with the structured clinical interview for DSM-IV. All patients were experiencing a current major depressive episode. Patients with additional comorbid life-time diagnoses of any schizophrenic/schizoaffective disorders, substance-related disorders, organic mental disorders, or dementia were excluded from the study. Also, none of the participants had a history of neurological disease or brain injury. This study was approved by the ethics committee of the Medical Faculty of Münster University and was in accordance with the Helsinki Declaration of 1975. The subjects gave written informed consent prior to the examination and received financial compensation for participation.

We used an established strategy to measure the medication load: each psychopharmacologic medication was defined as absent = 0, low = 1 (equal or lower average dose), or high = 2 (greater than average dose). The average dose was defined by the midpoint of the daily dose range recommended by Physician’s Desk. By summing all medication scores, we created a measure that accounted for both the number and the dose of all current psychopharmacological medications taken by the patient.
## Table 1  Sociodemographic and clinical data for study participants

<table>
<thead>
<tr>
<th></th>
<th>BD sample (n = 39)</th>
<th>UD sample (n = 43)</th>
<th>t tests for the two patient groups</th>
<th>HC sample (n = 42)</th>
<th>ANOVA for all three groups</th>
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<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>P-value</td>
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<td>.06&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

<sup>a</sup>P values were obtained using the χ<sup>2</sup> test.

BD, bipolar disorder; HC, healthy controls; UD, unipolar depression; SD, standard deviation; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; CTQ, Childhood Trauma Questionnaire; YMRS, Young Mania Rating Scale; STAI, State Trait Anxiety Inventory; SSNRI, selective serotonin noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; NDRI, noradrenaline dopamine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; n/a, not applicable; MAO, Monoamine oxidase.
We applied the Beck Depression Inventory (BDI);\textsuperscript{28,29} and the Hamilton Rating Scale of Depression (HAM-D\textsuperscript{30}) for the assessment of depressive symptoms. For manic symptoms the Young Mania Rating Scale (YMRS\textsuperscript{31}) was employed.

\subsection{Data preprocessing}

Diffusion-weighted images were acquired using single-shot echoplanar imaging (EPI) with 20 diffusion directions (two b factors: 0 and 1000 s/mm\(^2\); TR = 9.8 s, TE = 95 ms, acquisition matrix = 128 \times 128, voxel size 1.8 mm \times 1.8 mm \times 3.6 mm, reconstructed to 2.0 mm \times 2.0 mm \times 2.0 mm, 2 averages, 3 Tesla scanner; Gyroscan Intera 3T; Philips Medical Systems, Best, Netherlands). All diffusion-weighted images were effectively corrected for eddy currents and head movements using an established algorithm based on affine whole-brain registration parameters.\textsuperscript{32} We used a freely available, well-validated multi-contrast image registration algorithm, which employs individual-hemisphere registration based on the FA contrast for the optimum spatial pre-processing of DTI data.\textsuperscript{33} All volumes were normalized to the FMRIB58_FA template supplied with FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/FMRIB58_FA.html). Images were mildly smoothed with a 2 \times 2 \times 4 mm full width at half maximum (FWHM) Gaussian kernel to improve the signal-to-noise ratio. The results of this registration approach have been shown to have the best correspondence to tract-based spatial statistics (TBSS) results with the added advantage of whole-brain analysis.\textsuperscript{33}

\subsection{Voxel-based analysis}

Individual FA maps were analyzed using statistical parametric mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK; http://www.filion.ucl.ac.uk/spm). Nuisance regressors for age and gender were added to all models. A one-factorial ANOVA with appropriate post hoc t contrasts was conducted to assess group differences in FA, specifically comparing the two patient groups and also comparing the patient groups with the controls. Due to the heterogeneity of previous DTI studies in affective disorders regarding spatial restrictions and the few available previous findings in meta-analyses and direct comparisons of UD and BD,\textsuperscript{12,23} we opted to analyze three different levels of spatial restrictions: (1) commonly used restrictions to white matter (only voxels with an FA>0.2 were considered\textsuperscript{34–36}), (2) an ROI analysis restricted to the corpus callosum and the cingulum bundle based on previous reports,\textsuperscript{32} and (3) an exploratory whole-brain analysis without any masking, including all GM areas. The corresponding ROIs were generated from three-dimensional registered maps of the topography, course and intersubject variability of major fiber tracts, microscopically defined in human postmortem brains, registered in the Montreal Neurological Institute space\textsuperscript{37} included in the Anatomy toolbox.\textsuperscript{38}

To control for multiple statistical testing, we maintained a cluster-level corrected false-positive detection rate at \(P<0.05\) using a conservative voxel-level threshold of \(P<0.001\) as recommended,\textsuperscript{29} with a cluster extent (k) empirically determined by Monte Carlo simulations (n=5000 iterations). This was performed by means of the AlphaSim procedure which accounted for spatial correlations between GM values in neighboring voxels, implemented in the REST toolbox (http://restfmri.net/forum/index.php). The resulting cluster threshold was \(k=47\) voxels for the entire brain mask and \(k=16\) for white matter. For the ROI analysis, a more lenient cluster-forming threshold (\(P<0.01\) for the corpus callosum and for the cingulum bundle) was applied, yielding \(k=44\) voxels for the corpus callosum and \(k=3\) voxels for the cingulum bundle.

Correlational analyses with disease severity indices (number of depressive episodes, time since first depressive episode, medication load, etc.) and mean FA values from significant clusters were performed for each group separately. Therefore, we extracted the mean FA of all significant clusters from the previous analysis using the SPM eigenvariate function and employed SPSS 21 (SPSS Inc., Chicago, IL, USA) for correlation analyses. These correlation analyses were exploratory and not corrected for multiple comparisons. These data should therefore be treated with caution.

\section{Results}

\subsection{White matter analysis}

In the t contrast, UD patients showed decreased FA in the right corticospinal tract \((x=28, y=2, z=24, Z=4.34, k=16, P<.001)\) compared to HC. BD patients showed decreased FA in the right corticospinal tract/superior longitudinal fascicle \((x=28, y=−26, z=38, Z=3.91, k=18, P<.001)\) compared to HC. When both patient groups were compared to HC, decreased FA in the right internal capsule \((x=12, y=−18, z=2, Z=3.91, k=20, P<.001)\) was detected. BD patients showed decreased FA in the right corticospinal tract/superior longitudinal fascicle \((x=32, y=−22, z=34, Z=3.87, k=16, P<.001)\) compared to UD patients (see Figure 1).

\subsection{ROI}

BD patients showed decreased FA compared to UD patients in the corpus callosum (Cluster 1: \(x=18, y=26, z=16, Z=3.27, k=61, P<.001;\) Cluster 2: \(x=−14, y=26, z=12, Z=3.57, k=49, P<.001\)) and in the cingulum bundle \((x=8, y=−26, z=34, Z=3.13, k=7, P<.001)\). For further information, see Table 2 and Figure 2. We did not find any group differences in the uncinate fascicle.

\subsection{Whole-brain analysis}

The t test revealed decreased FA in the left middle frontal gyrus \((x=−38, y=16, z=52, Z=4.65, k=58, P<.001)\) and in the right inferior frontal gyrus \((x=42, y=46, z=−6, Z=4.35, k=48, P<.001)\) in UD patients compared to HC. BD patients had decreased FA in the left superior medial gyrus compared to HC \((x=−2, y=42, z=50, Z=3.85, k=48, P<.001;\) see Figure 3). When both patient groups were compared to HC, decreased FA in the superior medial gyrus was detected \((x=−8, y=40, z=52, Z=4.54, k=77, P<.001)\). There were no significant differences between BD and UD patients.

When clinical variables (number of depressive episodes, illness duration and medication load) were added to the model, results for the
two patient groups showed similar patterns (see Table S3). Reversed t tests (patient groups > healthy controls) did not yield any significant results in the white matter analysis. In the GM analysis, we found a cluster with increased FA in the occipital cortex in BD patients compared to HC and in the ROI analysis we found increased FA in the posterior corpus callosum in UD patients compared to HC (see Table S4).

3.4 | Correlation analysis

Correlation analysis showed several significant correlations between the mean FA of significant clusters and disease severity indices. Highly significant (0.01 P-level, two-tailed) positive correlations were found for UD patients between mean FA in the superior medial gyrus cluster (see Table S1) and number of depressive episodes, total sick days due to psychiatric illness and months of paid disability leave. For BD patients, we found highly significant correlations between the mean FA in the internal capsule cluster [Montreal Neurological Institute (MNI): 12, −18, 2] and total time in manic state. Furthermore, we found a highly significant correlation in BD patients between mean FA in the corpus callosum cluster (MNI: 18, 26, 16) and time since first depressive symptoms. For several more significant correlations (0.05 P-level, two-tailed) and further details, please see Table S1.

4 | DISCUSSION

Despite a pressing need to find neurobiological markers that can help to distinguish UD and BD, DTI measures have not yet been employed on a large scale with robust results. Although visible structural changes in psychiatric and neurological diseases have not been detected using conventional neuroimaging, microstructural abnormalities of brain white matter have been discovered using DTI.40–42 In addition, FA maps have been successfully employed to discriminate patients from controls using multivariate analyses in dementia patients, which may indicate the possibility of the clinical application of DTI measures in the future.42,44

To our knowledge, only three studies, with small sample sizes, have directly compared UD and BD patients regarding structural connectivity measures using DTI. We found FA reductions in a white matter cluster (MNI: 32, −22, −34), and using an ROI analysis, and also in the callosum and cingulum in BD patients compared to UD patients. These results show potential for future research into possible biomarkers for affective disorders.

The finding of FA reductions in the white matter cluster, which is located in a region where the superior longitudinal tract and the corticospinal tract cross, is consistent with a meta-analysis on BD,23 which reported that the superior longitudinal fascicle and the projection tracts were the locations of the most frequently noted aberrations in BD regarding DTI. As our voxel-based analysis of FA does not allow statements about directionality, it remains speculative which tract is affected or if both tracts are affected. This result is in contrast to one study directly comparing UD with BD showing no difference in this region, but with findings of decreased FA in the left superior longitudinal fascicle instead.14 Although the laterality differed, this indicates that the superior longitudinal fascicle may be a key region for future research, with larger samples, on the differentiation of affective disorders.

Furthermore, the more specific localization of our findings in the callosum and the cingulum is consistent with the results of the aforementioned meta-analysis12: the abnormalities in the callosum were located in the frontal part (the genu of the corpus callosum) and the FA reductions in the cingulum were located in the posterior cingulate cortex (PCC). The genu of the corpus callosum is a crucial area through which commissural fibers pass. These fibers, including the forceps minor, connect the hemispheres of the prefrontal cortex, which are central to current concepts of emotional dysregulation in UD and BD.26,45,46 Disturbed structural connectivity in the callosum may thus provide a structural basis for abnormal emotion processing in these areas. The FA reductions in the posterior cingulum in BD, which is known to be involved in neurocognitive functions such as attention, planning and memory, could be interpreted as a correlate of worse cognitive deficits in BD compared to UD.47,48 Moreover, the findings of this study are consistent with previous research directly comparing UD and BD showing no FA differences, but differences in mean diffusivity and radial diffusivity in the posterior cingulate between UD and BD.15

The FA reductions in the frontal gyri in both UD and BD compared to HC were at least partly localized in GM. The prefrontal cortex is commonly affected in both structure,49–51 and function,52,53 in BD and UD. While decreased GM volumes suggest the presence of irreversible neuronal degeneration, FA changes are harder to interpret.
in GM: microstructural tissue alterations as assessed by DTI can be caused by axonal damage or temporary tissue alterations due to inflammation, edema or temporary changes of the blood–brain barrier. In multiple sclerosis, a brain disease associated with abnormal immune system functioning and inflammation, DTI is used to detect microstructural changes before lesions are spotted in T1 MRI sequences. Therefore, these DTI changes may be interpreted as a possible link between immune system abnormalities in affective disorders and
As expected, BD and UD patients differed in clinical variables, with more depressive episodes and an earlier onset of disease in the BD group, which makes interpreting results more difficult, especially considering the apparent influence of disease severity on FA changes. In addition, medication differs in these two groups. Thus, the possibility cannot be excluded with certainty that the differences in FA between these groups were only a reflection of disease severity and/or medication effect and that such differences are not of any value in helping to distinguish between these disorders. When adding clinical covariates that differed between UD and BD patients (number of depressive episodes, medication index and illness duration) to the general linear model, a similar pattern of results comparing UD and BD was still found (Table S3), indicating an effect of diagnosis and rather a representation of clinical severity.

One of the strengths of our study is the direct comparison of the two patient groups. In addition, whereas in current literature samples were mixed and heterogeneous (depressed, manic, remitted, etc.), all our patients were experiencing a depressive episode, excluding state as a possible explanation for differences between patient groups.

ACKNOWLEDGEMENTS

The study was supported by grants from the German Research Foundation (DFG; grant FOR 2107; DA1151/5-1 to UD), Innovative Medizinische Forschung (DA120903 to UD, DA111107 to UD, and DA211012 to UD), and Rolf-Dierichs-Stiftung (ZUW80037 to UD).

DISCLOSURE

V. Arolt is a member of the advisory board of, or has given presentations on behalf of, the following companies: Astra-Zeneca, Janssen-Organon, Lilly, Lundbeck, Servier, Pfizer, Otsuka, and Trommsdorff. These affiliations are of no relevance to the work described in the paper. H. Kugel has received consultation fees from MR:comp GmbH, Testing Services for MR Safety. This cooperation has no relevance to the work that is covered in the paper. The other authors declare no conflict of interest.

REFERENCES


SUPPORTING INFORMATION

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