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Authors
Abramovic, Lucija
Boks, Marco PM
Vreeker, Annabel
et al.

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White matter disruptions in patients with bipolar disorder

Lucija Abramovic[1], **Marco P.M. Boks**[1], **Annabel Vreeker**[1], **Sanne Verkooijen**[1], **Annet H. van Bergen**[1], **Roel A. Ophoff**[1,2,3], **René S. Kahn**[1,4], and **Neeltje E.M. van Haren**[1]

[1]Brain Center Rudolf Magnus, University Medical Center Utrecht, Department of Psychiatry, Utrecht, The Netherlands [2]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA USA [3]Department of Human Genetics, University of California, Los Angeles, CA, USA [4]Icahn School of Medicine at Mount Sinai, New York, USA

Abstract

Bipolar disorder (BD) patients show aberrant white matter microstructure compared to healthy controls but little is known about the relation with clinical characteristics. We therefore investigated the relation of white matter microstructure with the main pharmacological treatments as well its relation with IQ. Patients with BD (N=257) and controls (N=167) underwent diffusion tensor imaging (DTI) and comprehensive clinically assessments including IQ estimates. DTI images were analyzed using tract-based spatial statistics. Fractional anisotropy (FA) and Mean Diffusivity (MD) were determined. Patients had significantly lower FA and higher MD values throughout the white matter skeleton compared to controls. Within the BD patients, lithium use was associated with higher FA and lower MD. Antipsychotic medication use in the BD patients was not associated with FA but, in contrast to lithium, was associated with higher MD. IQ was significantly positively correlated with FA and negatively with MD in patients as well as in controls. In this large DTI study we found evidence for marked differences in FA and MD particularly in (but not restricted to) corpus callosum, between BD patients and controls. This effect was most pronounced in lithium-free patients, implicating that lithium affects white matter microstructure and attenuates differences associated with bipolar disorder. Effects of antipsychotic medication intake were absent in FA and only subtle in MD relative to those of lithium. The abnormal white matter microstructure was associated with IQ but not specifically for either group.

1. Introduction

Converging evidence from magnetic resonance imaging studies suggests that deviations in local white matter volume as well as abnormal structural connectivity play a role in the pathogenesis of BD (O'Donoghue *et al.*, 2017; Bellani *et al.*, 2016 Benedetti and Bollettini, 2014). However, little is known about the influence of clinical characteristics like psychotropic medication on white matter microstructure or whether potential changes in white matter microstructure is related to level of intelligence in patients with Bipolar disorder (BD).

Whereas there is general consensus that lithium has a normalizing or preserving effect on brain volume, leading to attenuated differences between patients and controls (Bearden *et al.*, 2007; Germaná *et al.*, 2010, Singh and Chang, 2012; Hafeman *et al.*, 2012; Abramovic et al., 2016, Hibar *et al.*, 2017), such a role is much less clear for lithium in studies of white matter microstructure. Lithium was positively associated with clusters in the corpus callosum (CC; Walterfang *et al.*, 2009), the left anterior corona radiate and two small peripheral tracts in the frontal orbital cortex (Haarman *et al.*, 2016), however, samples have been small and negative findings have been reported as well (Versace *et al.*, 2008). Also, the effect of other psychotropic medication on brain structure remains unclear. We previously reported that smaller total brain volume in BD patients may be attenuated by lithium, and not by antipsychotic medication use (Abramovic *et al.* 2016). Thus far, few studies reported on the role of psychotropic medication on white matter measurements. To our knowledge, there is only one study showing a lower connectivity in parietal and occipital cortices following antipsychotic treatment (Szeszko *et al.*, 2014). Considering that more than half of patients with BD are prescribed antipsychotic medication (Kessing *et al.*, 2016), the relation of these drugs with white matter microstructure is warranted. A secondary advantage is that such studies may inform on schizophrenia patients as well, where such studies cannot be performed as the number of patients who are not on antipsychotics is usually too small.

A second topic of interest in the context of white matter microstructure is the potential relationship with IQ as both IQ and white matter volume contribute to the clinical phenotype of bipolar disorder (Forcada *et al.*, 2011). Studies in controls have shown that intelligence is positively related to connectivity in the fiber tracts connecting frontal and parietal areas (Schmithorst *et al.*, 2005). In addition, connectivity in the splenium and left-side inferior longitudinal and arcuate fasciculi predicted level of intelligence (Clayden *et al.*, 2011; Barbey *et al.*, 2013; Gläscher *et al.*, 2010; Schmithorst et al., 2005; Navas-Sánchez *et al.* 2014). BD has been associated with lower intelligence (Trotta *et al.*, 2015; Frangou *et al.*, 2005; Vreeker *et al.*, 2016). Therefore, we set out to investigate whether white matter deficits we may find in BD are associated with IQ.

We use diffusion tensor images to estimate fractional anisotropy (FA) and mean diffusivity (MD) in white matter tracts on a voxel level. FA is a measure for directional diffusion, which

is an indication of the distribution of water molecules in the cellular compartments. Because water is more restricted in white matter due to the myelin sheets, FA is usually higher in intact white matter tracts than in grey matter, cerebrospinal fluid or disrupted fibers. MD reflects the average rate of water diffusion, which is usually higher in damaged tissue (Madden *et al.*, 2012). As tissue damage often leads to more free diffusion and less restriction, lower FA is often (but not always) related to higher MD.

The aim of the current study is to investigate differences in white matter microstructure between BD patients and controls and whether they are related to lithium and antipsychotic treatment and IQ. Based on previous studies suggesting abnormalities in the white matter microstructure in patients with bipolar disorder, we expected to find widespread decreases in FA and increases in MD in white matter tracts of patients compared to control subjects. Also, we expected to find less profound deviations in FA in patients on lithium compared to non-using patients.

2. Experimental procedures

Participants

In this cross-sectional study, 262 patients with BD type I and 169 control subjects participated. Control subjects did not have BD, schizophrenia or any other psychotic disorder, nor had their first-degree relatives. Inclusion criteria for all participants were: a minimum age of 18 years old, at least three Dutch-born grandparents, and a good understanding of Dutch language. Subjects with a history of head trauma or a neurological illness were excluded.

The current sample is a subsample of a larger cohort, which was recruited at the University Medical Center Utrecht (UMCU), the Netherlands, as part of a collaboration between the University of California Los Angeles (UCLA) and several Dutch health care institutes. The cohort investigates genetic and phenotypic information of patients with bipolar disorder type I, first-degree relatives and controls. All scans were performed at the same scanner located in the University Medical Center Utrecht. Subjects were scanned between June 2011 and July 2014. The diagnoses of patients were confirmed with the Structured Clinical Interview for DSM-IV (SCID; First *et al.*, 1997). Also, the Questionnaire for Bipolar Illness (QBP-NL; Dutch translation by Akkerhuis, *et al.*, 1997; an adaption of the Enrolment Questionnaire as previously used in the Stanley Foundation Bipolar Network by Leverich *et al.*, 2001; Suppes *et al.*, 2001) was used. Mood status was assessed at inclusion through self-report using the 30-item Inventory of Depressive Symptoms-Self Report (IDS-SR$_{30}$; Rush *et al.*, 1996) and the Altman Self-Rating Mania Scale (ASRM; Altman *et al.*, 1997). Mean and standard deviation of these measures were added to Table 1. We measured substance abuse in patients using the CIDI, while it was assessed in controls with the MINI. None of the subjects was admitted at the moment of assessment. Control subjects were screened for psychiatric diagnoses using the M.I.N.I. (Mini International Neuropsychiatric Interview; Sheehan *et al.*, 1998). Interviews were conducted by at least one well-trained independent rater.

Four subtests of the Dutch version of the WAIS-III (Wechsler D., 1997) were used to estimate current IQ, being Digit Symbol Coding (processing speed), Block Design

(visuospatial capacities), Arithmetic (working memory) and Information (general knowledge). The combination of these four subtests has been shown to reliably estimate IQ in schizophrenia patients (R^2=0.90) and controls (R^2=0.86) (Blyler *et al.* 2000). We have also performed the DART, which is the Dutch version of the National Adult Reading Test (Schmand *et al.*, 1991), as an estimation for premorbid IQ. This data was available for 210 patients and 151 controls. Written informed consent was obtained from all participants. The Humans Ethics Committee of the UMCU and the UCLA Human Subjects review board approved the study.

Image acquisition

Three-dimensional T1-weighted images were acquired on a 3 Tesla Philips Achieva scanner (Philips Healthcare, Best, the Netherlands), equipped with an 8-channel SENSE headcoil. Fast field echo scans with 200 contiguous sagittal slices (TE=4.6 ms, TR=10 ms, flip angle=8°, FOV=240 mm, $0.75 \times 0.75 \times 0.80$ mm^3 voxels) were obtained. In addition, two sets of 30 diffusion-weighted imaging (b-weighting 1000 s/m^2) scans were acquired and five diffusion unweighted scans (TE/TR 7035/68 ms; FOV=240mm, 2 mm isotropic voxel size; 75 slices at 2 mm thickness, no gap).

An independent radiologist evaluated the brain scans of all subjects and those with clinical outcomes were excluded from the analysis. Processing was done on the neuroimaging computer network of the University Medical Center Utrecht – Brain Center Rudolf Magnus, Utrecht, the Netherlands.

Preprocessing

Using the diffusion-weighted imaging data, fractional anisotropy (FA) and Mean Diffusivity (MD) of the tensor were determined as estimates of white matter microstructure.

All DWI images were pre-processed using FSL's FMRIB's Diffusion Toolbox. First, with *Topup* the images were realigned and corrected for possible susceptibility distortions using two non-diffusion weighted (b-value=0) images with opposite phase-encoding directions. Second, Eddy correction was used to correct for eddy-current distortions and possible head movements. Then, the Brain Extraction Tool (*BET*) was used to exclude all non-brain tissue (Smith, 2002). The diffusion tensor model was then fitted to each voxel using *dtifit*. Quality control was performed by visual inspection of the raw DTI and FA images.

Tract Based Spatial Statistics (TBSS)

We performed group comparisons solely on the white matter skeleton, in order to minimize the chance that results are driven by partial volume effects or confounded by morphological differences, and to increases the statistical power of the analysis.

Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics; Smith *et al.*, 2006), part of FSL (Smith *et al.*, 2004; http://www.fmrib.ox.ac.uk/fsl). First, FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson

2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. This white matter skeleton was thresholded at FA=0.2 to exclude nonwhite matter and voxels in extremities where there is too much cross-subject variability in alignment. Each subject's aligned FA data was then projected onto this white matter skeleton, and the maximum FA value is searched along the normals to the skeleton and dragged onto the skeleton for group-level comparisons.

To investigate how MD varies between groups, the original nonlinear registration was applied to the MD data, and the warped MD data was projected onto the original mean FA skeleton.

Statistical analyses

Demographic and clinical variables—Data were examined for normality of the distribution, outliers and extreme values. Demographic and clinical variables were compared for the different group comparisons described below, using Student's t tests and χ^2-tests as appropriate.

We compared patients with bipolar disorder and control subjects on age, gender distribution, handedness and IQ. In addition, in separate analyses we compared patients on and off lithium, and patients on and off antipsychotic medication on number of episodes, history of psychotic episodes (yes/no), and age at onset. Age at illness onset is defined as the age of first manic or depressive episode. The sample largely overlapped with the samples described in Abramovic *et al* (2016) and Vreeker *et al.* (2017), except for 9 patients and 4 controls for whom the DTI scans were not obtained.

FA and MD differences between groups—First, we investigated the correlation between white matter microstructure and diagnosis, by comparing patients with BD and control subjects on FA and MD in each voxel. Secondly, we investigated the role of lithium and antipsychotic medication intake by performing two separate group analyses: 1) by splitting up the patients with bipolar disorder into two subgroups, depending on current lithium use or not, and compare FA and MD betweenpatients on (Li+) and off lithium (Li−) and 2) by splitting up the patients with bipolar disorder into two subgroups, depending on current antipsychotic use or not, and compare FA and MD between patients on (AP+) and off antipsychotic medication (AP−). Also, each medication group was compared with controls. Third, we investigate the role of IQ in the comparison between BD patients and controls.

A general linear model was used to test differences between groups (BP vs HC; Li+ vs Li−, AP+ vs AP−) in FA and MD, with age and gender as covariates. To investigate the effect of IQ in the comparison between patients and controls, IQ and group-by-IQ interaction were added. The analyses were imbedded in Randomise, which is a tool for permutation-based non-parametric testing. Threshold-free cluster enhancement (TFCE) was applied to a permutation analysis. TFCE is a method for enhancing cluster-wise structures corrected for multiple testing, while the image remains voxelwise. A *p*-value is calculated for each voxel, corrected with family-wise error (FWE) correction via permutation testing with 5000

random permutations. The TFCE corrected *p*-maps were thresholded at pFWE<0.05 and only the clusters above this threshold are reported. The anatomical regions of these clusters were identified using the 'JHU ICBM-DTI-81 White-Matter Labels' atlas.

3. Results

Demographic and clinical variables

No significant differences were found between patients and controls on gender and handedness distribution. BD patients were slightly, but significantly, older than controls, i.e. 3.1 years (p=0.03). The majority of patients used lithium (65.8%) and 42.0% used antipsychotic medication at the time of scanning. Nine patient used typical antipsychotic medication, and among these nine patients one patient also used atypical antipsychotic medication.

As expected, current IQ was significantly lower in patients than in controls (Vreeker *et al.*, 2016). Patients on lithium had significantly lower IQ than patients who were not on lithium (p=0.04). Patients on antipsychotics were significantly younger than patients who were not on antipsychotics (p=0.01). For further demographic and clinical information, see Table 1 and Table 2.

FA and MD differences between groups

Global—See Figure 1 for mean FA and MD for the different groups. Mean FA was significantly lower and mean MD was significantly higher in patients than in controls (respectively, F(1,421)=12.50, p<0.001; F(1,421)=10.61, p=0.001). Mean FA was significantly higher and mean MD was significantly lower in Li+ patients relative to Li− patients (respectively, F(1,253)=13.34, p<0.001; F(1,253)=16.06, p<0.001). Mean FA did not differ significantly between patients on and off AP (F(1,236)=3.33, p=0.07), but mean MD was significantly higher in AP+ patients than in AP− patients (F(1,236)=5.94, p=0.02).

Local—BD patients had significantly lower FA than controls in the corpus callosum, fornix, external capsule, cerebral peduncle, sagital stratum, superior corona radiata and posterior thalamic radiation (see Figure 2a). There were no areas where controls showed lower FA than patients with BD.

Patients showed significantly higher MD than controls in the corpus callosum, anterior and superior corona radiate, posterior thalamic radiation, and superior longitudinal fasiculus. The local pattern of higher MD largely overlapped with the tracts that had lower FA in patients (see Figure 2b). There were no areas where patients showed lower MD than controls.

Lithium: Li− patients showed significant lower FA values than Li+ patients in the corpus callosum, fornix, and the major and minor forceps. There were no areas of lower FA in patient on versus off lithium (see Figure 2c). MD showed an opposite, although less pronounced effect in similar areas, where MD was higher in Li− than in Li+ patients. There were no areas where MD was higher in Li+ than in Li− patients (see Figure 2d).

Antipsychotics: There were no significant differences in FA between patients on and off antipsychotic medication. There were a few significant voxels spread throughout the brain where AP+ patients showed significantly higher MD than AP− patients (see Figure 2e). There were no areas with higher MD in AP− than AP+ patients.

See supplemental data for a comparison between both medication based patient groups and controls.

Association between IQ and white matter microstructure

There was a significant positive correlation between IQ and mean FA (t(360)=0.21, p<0.001) and a significant negative correlation between IQ and mean MD (r(360)=−0.14, p<0.01) in the combined group of patients and controls. Also, voxelwise, there were significant positive correlations between IQ and FA and negative correlations between IQ and MD (see Figure 3 and suppl. 3). Positive correlations between FA and IQ were found in the cingulum, fornix, external capsule, posterior thalamic radiation and uncinate fasiculus. Negative correlations between MD and IQ were found in the corpus callosum, superior and posterior corona radiate, left sagittal striatum, bilateral posterior limb of the internal capsule and superior longitudinal fasiculus.

There were no significant group-by-IQ interactions for mean and local FA and MD, implicating that the correlations of FA and MD with IQ did not differ significantly between BD patients and controls.

4. Discussion

In the largest single-site sample of patients with BD type I and controls we investigated the association of white matter microstructure with IQ and psychotropic medication.

In addition to the confirmation of substantial white matter differences in bipolar disorder two findings stand out. First, we found association of FA and MD within BD patients consistent with a 'normalizing' or 'protective' effect of lithium on white matter microstructure in BD patients, similar to what has been reported for brain volume (Hafeman *et al.*, 2012; Abramovic *et al.*, 2016). In contrast, patients on antipsychotics showed slightly higher MD as compared to those without, while FA showed no differences between groups, implicating that the effects of antipsychotics are subtle relative to those of lithium. A second finding of note is the small positive correlations between IQ and mean and local FA and negative correlations with mean and local MD in the total sample, which did not differ significantly between patients and controls.

In a review of the literature, Bellani and colleagues (2009) summarized the evidence for white matter disruptions (estimated from diffusion tensor imaging [DTI]) in patients with BD, and provided suggestive evidence for a link with cognitive and emotional deficits. More recently, a meta-analysis showed a significant decrease in FA in the genu of the corpus callosum, left cingulum, and right anterior superior longitudinal fasiculus as compared with controls (Wise *et al.*, 2016). In addition, MD is shown to increase in the anterior part and the corpus of the CC in patients (Bruno *et al.*, 2008; Bellani *et al.*, 2009, 2016). Based on these

findings, abnormalities in FA and MD in BD appear widespread, affecting many white matter tracts.

The differences we report between BD patients and controls are most pronounced in the corpus callosum and in clusters widespread across the brain. Findings in the corpsus callosum are in line with current literature of evidence for altered white matter microstructure in fibers connecting the two hemispheres (Wise et al, 2016; Bellani *et al.*, 2009, 2016). The widespread deviations suggest deficits of neural connectivity in multiple networks. Recently, a study on the brains' network architecture in this same cohort, showed reduced global efficiency in association with disruptions in interhemispheric connectivity, while the central brain hubs were not affected (Collins *et al.*, 2016). Consequently, simple correlations between regions of interest and specific clinical variables may be less informative than linking these variables to networks of brain measures.

The relevance of the findings in the corpus callosum are supported by previous reports that the white matter microstructure in the corpus callosum is associated with cognitive performance (Poletti et al., 2015; Ajilore et al., 2015). The pattern of significant correlations of IQ with FA and MD in the corpus callosum that we here report is also in line with the study from Navas-Sanchez and colleagues (2014), who reported a positive correlation between IQ and FA in the CC in healthy subjects. Of note is that across the whole sample, global and local FA and MD were, respectively positively and negatively correlated to level of IQ. This may not be surprising as data from healthy twins and their siblings suggest a common genetic origin between callosal white matter connectivity and intelligence (Hulshoff Pol *et al.*, 2006).

An important finding is the evidence that lithium possibly attenuates decreases in FA, which suggests that lithium masks illness-related FA decreases. Higher MD in patients without lithium versus those on lithium could result from a direct effect of lithium on water diffusion, as MD measures the restriction of water diffusion and lithium is an important electrolyte. Lithium is also known to affect neurotransmission via several second messenger systems, thereby modifying gene transcription within the cells. It inhibits Glycogen Synthase Kinase 3 Beta (GSK-3β), which is shown to be overactive in BD patients (Muneer, 2017; Luykx *et al.*, 2010). GSK-3β plays a role in gene transcription, synaptic plasticity and cell structure (Mahli *et al.*, 2013). Interestingly rodent studies have shown re-myelinisation after GSK-3β inhibition (Azim and Butt, 2011; Chen et al., 2016), suggesting that lithium may affect white matter microstructure via inhibiting GSK-3β (Hunsberger *et al.*, 2009).

In contrast to the large differences in white matter microstructure related to lithium, the differences related to antipsychotic medication were limited. Bipolar disorder patients on antipsychotics showed higher MD, and no differences on FA, in several small areas scattered across the white matter. In a review of the literature, Hafeman and colleagues (2012) reported that most studies show no significant effect of antipsychotic medication status on brain measures. However, the current study is about 5 times larger than the largest study to date, implicating that the effect of AP on white matter microstructure is subtle, and less pronounced than the effect of lithium.

In addition to the cross-sectional design of the study several limitations should be considered. First, it was not possible to take duration of medication use and medication dosages into account, nor was it feasible to include medication naïve patients. Second, patients on lithium have a slightly lower IQ than patients off lithium. However, because we did not find a significant group-by-IQ interaction it is unlikely that IQ explains the higher FA and lower MD in patients on lithium. In addition, it might be that patients who were lithium free at time of study inclusion used lithium in the past. However, in that event this would not lead to type I error as we would underestimate the effect of lithium in FA and MD, as animal studies have shown that lithium effects on the brain are not reversible (Vernon *et al.*, 2013).

In conclusion, this study presents evidence for widespread abnormalities in patients with bipolar disorder, suggesting affected neural connectivity in multiple networks. The reported white matter abnormalities may be attenuated by lithium use, while antipsychotic medication showed a more subtle effect. It is unlikely that these abnormalities white matter microstructure explain the lower IQ reported in bipolar disorder patients.To disentangle the underlying mechanisms of BD it is of relevance to further study the clinical and functional relevance of white matter abnormalities, and particularly longitudinal studies are of value to evaluate the effects of different treatments over time and inform of the underlying causality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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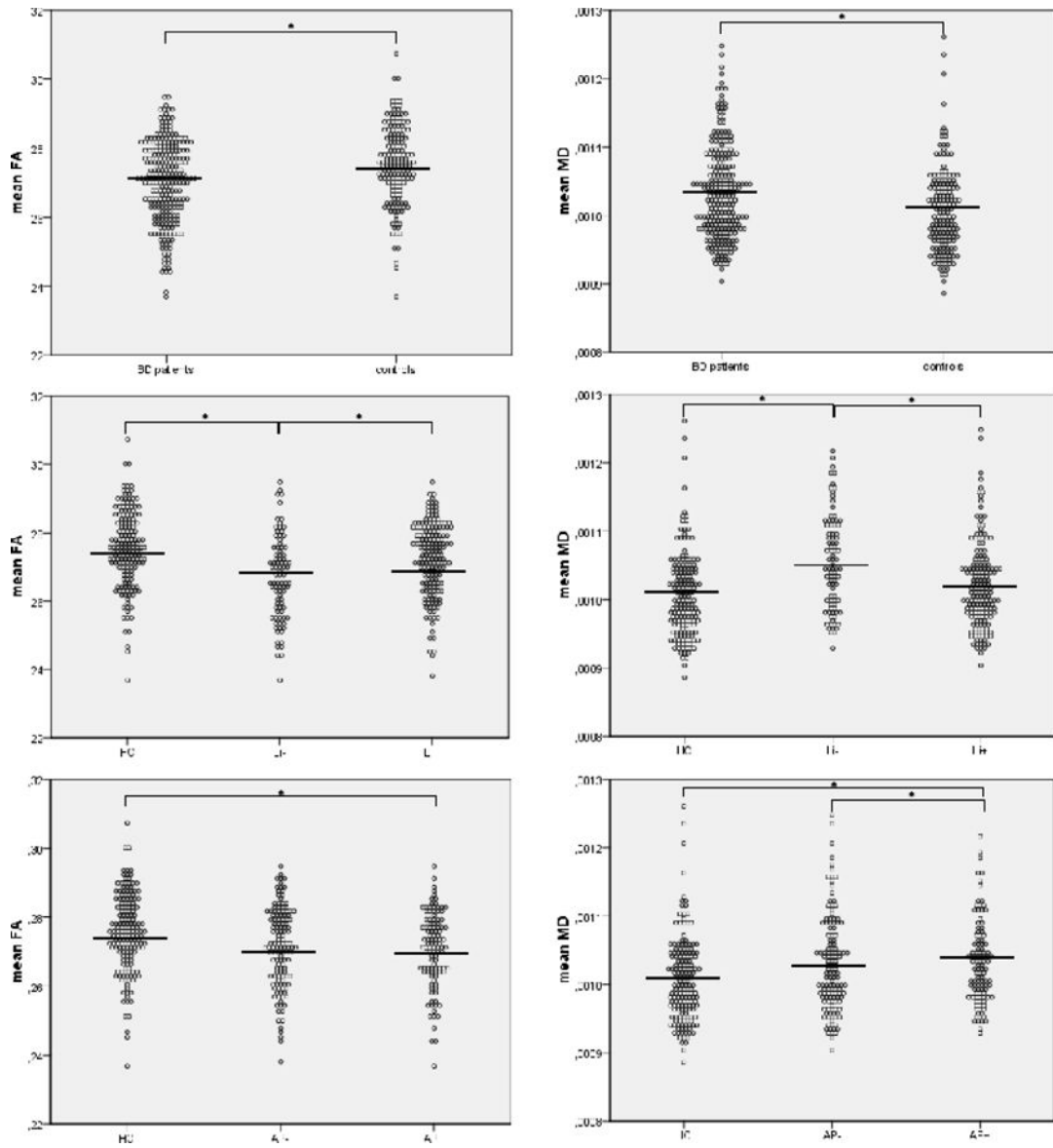
Figure 1.
Comparison of mean FA and mean MD in Li- (N=88) and Li+ (N=169) patients with bipolar disorder versus controls (N=107). and AP− (N=132) and AP+ (N=108) patients with bipolar disorder versus controls. Corrected means are shown.
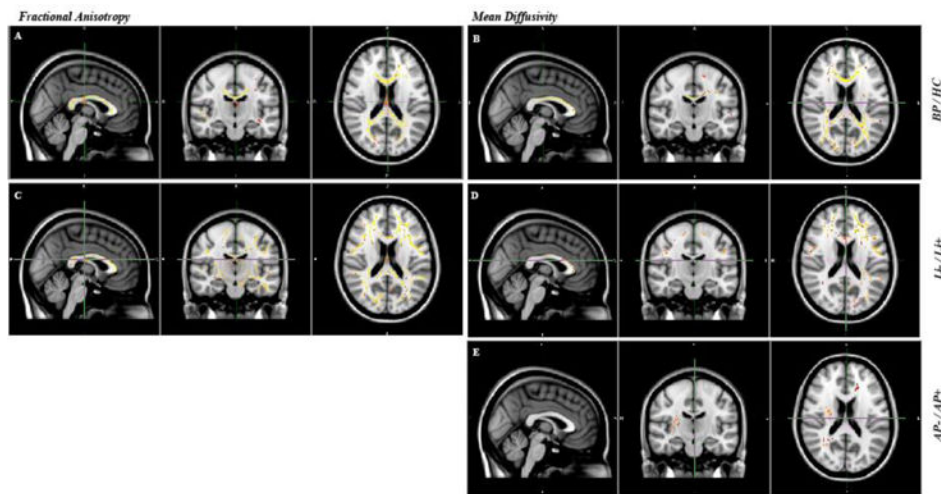
Figure 2.
A) Lower FA in patients with BP (N=257) compared with controls (N=167). B) Lower MD in controls than in patients with BP. Age and gender have been added to the analyses as covariates. C) Lower FA in Li– patients compared with Li+ patients. D) Lower MD in Li+ patients compared with Li- patients. E) Higher MD in AP+ patients compared with AP– patients.

Age and gender have been added to the analyses as covariates. Results are FWE-corrected and projected on a red-yellow color scale for which the range is shown for (red) p<0.05.
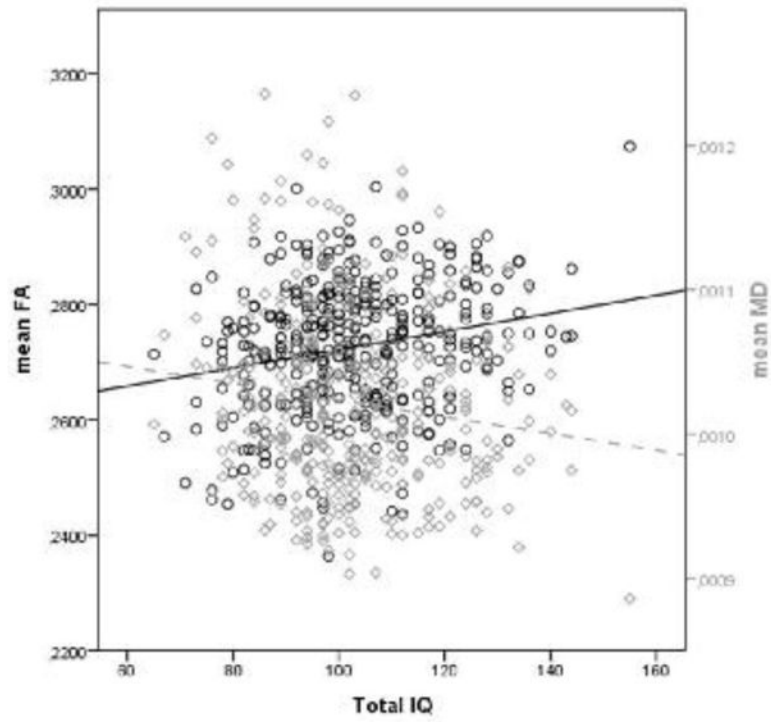
Figure 3.
The correlation between mean FA and mean MD, and IQ in the combined group of patients
and controls.

Table 1

Demographical and clinical information of patients with bipolar disorder (N=257) and controls (N=167).

Demographics	Bipolar patients (N = 257)	Control subjects (N = 167)	t-test/χ^2 (p-value)
Age in years, mean (s.d.)	48.2 (12.3)	45.1 (14.9)	**0.03**
Sex, M/F (% male)	125/132 (48.6%)	84/83 (50.3%)	0.77
Handedness, R/L/B (% right) [a]	224/24/8 (87.5%)	140/21/5 (84.3%)	0.57
Premorbid IQ, mean (s.d.)	107.5 (9.2)	107.5 (9.2)	0.89
Current IQ, mean (s.d.)	99.3 (14.0)	107.9 (16.6)	**<0.001**
Number of episodes, median			
Mania	4		
Depression	5		
Mood status at inclusion			
Manic symptoms (ASRM), mean (s.d.)	2.6 (2.9)		
Depressive symptoms (IDS-SR$_{30}$), mean (s.d.)	16.6 (11.4)		
Medication[b], N (% on):			
Lithium	169 (65.8%)		
Antipsychotic medication	108 (42.0%)		
Typical antipsychotic medication[c]	9		
Atypical antipsychotic medication[c]	100		

[a] Handedness was missing for 1 patient and 1 control

[b] at time of scanning

[c] one subject used typical and atypical antipsychotic medication

Table 2

Demographical and clinical information of patients with bipolar disorder using lithium (Li+) and lithium-free (Li−) and patients using antipsychotic medication (AP+) versus patients not using antipsychotics (AP−). Significant differences were depicted in bold.

Demographics	Li− (N = 88)	Li+ (N = 169)	p-value	AP+ (N = 108)	AP− (N = 132)	p-value
Age in years (s.d.) [range]	49.7 (11.98)	47.4 (12.5)	0.15	45.8 (11.2)	49.8 (12.9)	**0.01**
Sex, M/F (% male)	42/46 (47.3%)	83/86 [20–79]	0.83	50/58 [21–67][b]	68/64 [20–79][b]	0.42
Handedness, R/L/B (% right)	76/9/3 (86.8%)	148/15/5 (49.7%)	0.92	(46.5%) 91/12/4	(52.2%) 117/12/3	0.68
Premorbid IQ, mean (s.d.)	107.5 (8.4)	107.7 (9.3) (86.3%)[a]	0.80	(85.8%) 106.6 (9.6)	108.3 (8.5)	0.19
Current IQ, mean (s.d.)	102.4 (13.1)	98.4 (13.6)	**0.04**	99.6 (13.9)	99.6 (12.7)	0.98
Medication, N (% on):						
Lithium	–	–		68 (63.0%)	95 (72.0%)	0.14
Antipsychotic medication	40 (51.9%)	68 (41.7%)	0.14	–	–	–