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Research paper

Patterns of microstructural white matter abnormalities and their impact on cognitive dysfunction in the various phases of type I bipolar disorder

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ABSTRACT

Background: In recent years, diffusion tensor imaging (DTI) studies have detected subtle microstructural abnormalities of white matter (WM) in type I bipolar disorder (BD). However, WM alterations in the different phases of BD remain to be explored. The aims of this study is to investigate the WM alterations in the various phases of illness and their correlations with clinical and neurocognitive features.
Methods: We investigated the DTI-derived fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) in patients with type I BD ($n=61$) subdivided in manic ($n=21$), depressive ($n=20$) and euthymic phases ($n=20$) vs. healthy controls ($n=42$), using a tract-based spatial statistics (TBSS) approach. Then, we investigated whether the subgroups of patients in the various phases of illness present different patterns of WM abnormalities. Finally we studied the correlations between WM alterations and clinical-cognitive parameters.
Results: We found a widespread alteration in WM microstructure (decrease in FA and increase in MD and RD) in BD when compared to controls. The various subgroups of BD showed different spatial patterns of WM alterations. A gradient of increasing WM abnormalities from the euthymic (low degree and localized WM alterations mainly in the midline structures) to the manic (more diffuse WM alterations affecting both midline and lateral structures) and, finally, to the depressive phase (high degree and widespread WM alterations), was found. Furthermore, the WM diffuse alterations correlated with cognitive deficits in BD, such as decreased fluency prompted by letter and decreased hits and increased omission errors at the continuous performance test.
Limitations: Patients under treatment.
Conclusions: The WM alterations in type I BD showed different spatial patterns in the various phases of illness, mainly affecting the active phases, and correlated with some cognitive deficits. This suggests a complex trait- and state-dependent pathogenesis of WM abnormalities in BD.

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1. Introduction

Bipolar disorder (BD) type I is a chronic mental disease (1–2% in general population) associated with high rates of non-recovery, psychiatric and medical comorbidity, and progressive cognitive deterioration (especially in attention and executive functioning) (A.P.A., 1994; Akiskal, 1996; Quraishi and Frangou, 2002). Since a growing number of neurobiological abnormalities have been recently reported in patients affected by BD (Frangou, 2014; Savitz et al., 2013; Soares and Mann, 1997), magnetic resonance imaging (MRI) has become a relevant non-invasive tool to investigate *in-vivo* the pathophysiology of the disease (Heng et al., 2010).

Diffusion tensor imaging (DTI) is a MRI technique particularly suited for the study of white matter (WM) microstructure and provides relevant information about fiber integrity and orientation (Heng et al., 2010). Previous DTI studies have reported subtle microstructural abnormalities of WM in BD, characterized by a loss of WM network connectivity involving not only prefrontal regions but also projection, associative and commissural fiber tracts (Heng et al., 2010; Nortje et al., 2013; Vederine et al., 2011; Wise et al., 2015). Owing to the widespread nature of WM abnormalities, a few of these DTI studies of patients with BD employed a tract-based spatial statistics (TBSS) approach that allows a whole brain analysis in an automated and reliable fashion, thus providing a global perspective of WM alterations (Heng et al., 2010). The previous TBSS studies in BD confirmed that all major classes of tracts are implicated, but included only adult patients in euthymic/remitted or depressed phase (Bauer et al., 2015; Benedetti et al., 2011a; 2011b; Chan et al., 2010; Emsell et al., 2013; Heng et al., 2010; Kumar et al., 2015; Lagopoulos et al., 2013; Mahon et al., 2012; Nortje et al., 2013; Oertel-Knochel et al., 2014; Poletti et al., 2015; Sprooten et al., 2013; Vederine et al., 2011; Versace et al., 2008; 2010; Wessa et al., 2009; Wise et al., 2015; Yip et al., 2013).

Since none of these studies included and directly compared the various phases of type I BD, it is still not clear whether WM abnormalities are prevalent in the active states or whether they are present in all the phases of BD (i.e. trait- and/or state-dependent). Since type I BD presents a cyclic pattern with dramatic changes in clinical states across the different phases, showing acute phases characterized by full blown and opposite psychopathological states (mania and depression), as well as subclinical states similar to healthy (euthymia), the investigation of state-dependent brain changes assumes particular relevance in this illness. Some functional and metabolic data suggest state dependent changes across the different phases of BD (Brady et al., 2012; Fountoulakis et al., 2008; Magioncalda et al., 2015; Pomarol-Clotet et al., 2015). Beyond functional changes, recent evidences in DTI studies suggest that dynamic changes also occur in the WM microstructure, both in healthy after learning-induced plasticity (Imfeld et al., 2009; Oechslin et al., 2009; Scholz et al., 2009) and in depressed patients when compared to those in remission (Bracht et al., 2015; Zanetti et al., 2009). However, to date, WM alterations in all the various phases of type I BD – i.e., including at the same time mania, depression and euthymia – have yet to be investigated.

Moreover, WM abnormalities may play a role at a clinical level. BD is associated with various cognitive deficits, whose profile changes across the different phases of illness (Quraishi and Frangou, 2002). The different impairment of some cognitive domains among the different phases of BD, especially between active phases and euthymia, could depend on several factors, including potential dynamic changes of WM microstructure across the phases of illness. Although a few DTI studies in depressed and euthymic patients showed that WM abnormalities are associated with cognitive deficits (Bauer et al., 2015; Oertel-Knochel et al., 2014; Poletti et al., 2015), the impact of WM abnormalities on cognitive dysfunctions in patients in all the various phases of type I BD remains still unclear.

Therefore, the aims of our study were to: (i) investigate the presence and extent of WM abnormalities as measured by DTI-derived fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) in patients with type I BD in any phase of illness (i.e. depressive, manic and euthymic phases); (ii) determine whether the subgroups of patients in the various phases of illness present different patterns of WM abnormalities; and (iii) explore the relationship of WM alterations with cognitive and clinical parameters.

2. Methods

2.1. Subjects and clinical assessment

Subjects were admitted to the in-patients and out-patients service of the Psychiatric Clinic at the University of Genoa (IRCCS AOU San Martino – IST, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health), from 2013 to 2015. The study was conducted on 61 type I bipolar patients (43 females, 18–60 years old, 21 in manic phase, 20 in depressive phase and 20 in euthymic phase) and 42 healthy participants (Table 1). The Ethical Committee of San Martino Hospital approved the study, and written informed consent was obtained from all the participants.

Each participant was evaluated using the following standardized structured and/or semi-structured clinical instruments to obtain information on clinical and diagnostic features, course of illness, family history, and actual and past pharmacotherapy: Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998); Structured Clinical Interview for Axis-I Disorders/Patient edition (SCID-I/P) (Ventura et al., 1998); Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (First et al., 1994); Structured Interview for Mood Disorder – Revised (SIMD-R) (Cassano et al., 1989); Hamilton Depression Scale (HAM-D) with 17 items (Hamilton, 1960); Young Mania Rating Scale (YMRS) (Young et al., 1978). General, physiologic, pathologic and psychopathologic history was also investigated.

Inclusion criteria were: (a) diagnosis of type I BD according to the Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM-IV) criteria (A.P.A., 1994) assessed by the SCID-I/P (Ventura et al., 1998) (for manic, depressed and euthymic patients); (b) score ≥ 18 at HAM-D with 17 items (Hamilton, 1960) and/or score ≥ 13 at YMRS (Young et al., 1978) (for manic and depressed patients); HAM-D score < 8 (Hamilton, 1960) and YMRS score < 8 (Young et al., 1978) for euthymic patients; (c) age between 18 and 60; (d) ability to provide written informed consent. Exclusion criteria were: (a) diagnoses of schizophrenia, mental retardation, dementia and other cognitive disorders; (b) history of severe or decompensated somatic diseases, neurological diseases (e.g. former stroke, cerebral vascular malformations, or epilepsy), previous head injury with loss of consciousness (for 5 or more minutes); (c) current alcohol and substance abuse (during the previous 3 months); history of alcohol or substance dependence; history of synthetic and new drugs abuse; (d) pregnancy and lactation; (e) left-handed; (f) the inability to undergo an MR examination (claustrophobia, metal implants, etc); (g) previous treatment with electroconvulsive therapy, chemotherapy or brain radiotherapy. Healthy participants did not meet the DSM-IV criteria for psychiatric disorders, either currently or in the past; they had a score at HAM-D < 8 and at YMRS < 8; they also met the same exclusion criteria indicated for patients.

A brief cognitive assessment was carried out on all participants. We chose to focus on the assessment of attention and executive functions not only because they are the most affected cognitive

Table 1
Subject demographic and clinical information.

	BD TOT	MANIC	DEPRESSED	EUTHYMIC	**HC**	**ANOVA** F (p)
Sample Size *n* (%)	61 (100%)	21 (34.4%)	20 (32.8%)	20 (32.8%)	42 (100%)	–
Age *mean* (SD)	44.6 (11.1)	45.6 (11.8)	44.9 (10.9)	43.1 (11)	44.3 (12.7)	0.258 (0.773)
Female *n* (%)	43 (70.5%)	18 (85.7%)	13 (65%)	12 (60%)	27 (64.3%)	1.321 (0.272)
HAM-D *mean* (SD)	–	6.9 (5.3)	21.5 (4)	3.6 (2.8)	1.0 (1.4)	103.460 (0.000)
YMRS *mean* (SD)	–	18.8 (5.6)	4.2 (2.8)	3.9 (2.7)	0.5 (1.0)	93.146 (0.000)
Age of Onset *mean* (SD)	25.1 (10.8)	25.4 (12.1)	25.3 (9.8)	24.6 (10.9)	–	0.009 (0.991)
Duration of Illness *mean* (SD)	19.6 (11.6)	20.9 (14.6)	19.5 (10.8)	18.2 (9)	–	0.257 (0.774)
Number of previous total episodes *mean* (SD)	8.6 (8.3)	10.0 (9.5)	8.8 (9.3)	6.9 (5.8)	–	0.713 (0.494)
Number of previous manic episodes *mean* (SD)	4.7 (4.8)	6.1 (5.6)	4.1 (4.9)	3.8 (3.9)	–	1.463 (0.240)
Number of previous depressive episodes *mean* (SD)	3.5 (4.3)	3.6 (4.8)	4.2 (4.6)	2.7 (3.2)	–	0.632 (0.535)
Mood Stabilizers *n* (%)	52 (85.2%)	16 (76.1%)	18 (90%)	18 (90%)	–	0.478 (0.622)
Antidepressants *n* (%)	22 (36.1%)	2 (9.5%)	11 (55%)	9 (45%)	–	5.835 (0.005)
Antipsychotics *n* (%)	35 (57.4%)	14 (66.7%)	12 (60%)	9 (45%)	–	1.009 (0.371)
Benzodiazepines *n* (%)	21 (33.4%)	6 (28.6%)	7 (35%)	8 (40%)	–	0.287 (0.752)
Unmedicated *n* (%)	2 (3.3%)	1 (4.8%)	0 (0%)	1 (5%)	–	0.488 (0.616)

Demographic and clinical information of the samples. In the last column the ANOVAs of the comparisons between BD subgroups are shown.
Abbreviations: BD, bipolar disorder; HC, healthy controls; HAM-D, Hamilton Depression Scale; YMRS, Young Mania Rating Scale.

domains especially in the active phases of BD with respect to euthymia (Malhi et al., 2007; Quraishi and Frangou, 2002), but also because these domains show differences in some parameters across the active phases (e.g., more commission errors during mania while more omission errors during depression) (Quraishi and Frangou, 2002). Thus, in order to assess the cognitive impairment in BD across the different phases of illness - with a particular focus on active phases and their potential relationship with WM abnormalities - all participants were administered the continuous performance test (CPT), a computerized test used to evaluate distractibility and impulsivity in the study of attention functions (Conners et al., 2003), and the fluency test, a verbal test (prompted by letter and by category) used to evaluate the integrity of executive functions (fronto-temporal functions) (Strauss et al., 2006).

Almost all the bipolar patients were under medications with mood stabilizers (lithium: $n=17$; valproate: $n=26$; other antiepileptic drugs: $n=28$), antipsychotics (atypical antipsychotics: $n=31$; typical antipsychotics: $n=7$), antidepressants (serotonin reuptake inhibitors: $n=10$; tricyclic antidepressants: n=6; duals and others antidepressants: $n=10$) and benzodiazepines ($n=21$). Therefore, for each patient, we generated a psychotropic medication load, reflecting the number and dose of different medications, as a measure of drug therapy which was entered into correlation analyses (Phillips et al., 2008). This was done by converting antipsychotics into chlorpromazine dose equivalents (Baldessarini, 2013), mood stabilizers into lithium dose equivalents (Baldessarini, 2013), antidepressants into imipramine dose equivalents (Baldessarini, 2013), and benzodiazepines into diazepam dose equivalents (Arana and Rosenbaum, 2000). Then we used the codes 0, 1, 2 or 3, respectively for: no medication, and dose equivalents below, equal or above the mean effective daily dose (Davis and Chen, 2004). We generated a composite measure of medication load by summing all individual medication codes for each category for each individual BD patient (Zanetti et al., 2009).

2.2. MRI data acquisition

A 1.5-T GE scanner with a standard head coil was used to acquire all the images. Foam pads were used to reduce head motion and scanner noise. Diffusion tensor imaging was acquired with pure axial single-shot echo planar imaging sequence. The diffusion sensitizing gradients was applied along 60 non-collinear directions ($b=1000$ s/mm2), together with 5 acquisitions without diffusion weighting ($b=0$). Fifty-five contiguous axial slices were acquired with a slice thickness of 2.5 mm without gap. The acquisition parameters were as follows: TR/TE=13750/93 ms; image matrix=128 × 128; FOV=24 cm; NEX=1.

In addition, the following images were acquired for all participants: three-dimensional T1-weighted anatomical images, which were acquired in a sagittal orientation employing a 3D-SPGR sequence (TR/TE=11.5/5 ms, IR=500 ms, flip angle=8°, FOV=25.6 cm) with a resolution in-plane of 256 × 256 and slice thickness of 1 mm; fluid-attenuated inversion recovery (FLAIR) images (TR/TE=8000/120 ms, inversion time 2000 ms, FOV=24 cm, matrix 256 × 192, 5 mm slice thickness without gap).

2.3. DTI imaging analysis

All image post-processing was performed off-line on a PC workstation. T1-weighted and FLAIR images from all participants were reviewed by a board-certified neuro-radiologist. None of them showed structural visible lesions (except for one patient, who had a millimeter colloid cyst at the level of the interventricular foramen).

Diffusion data were preprocessed and analyzed using tools from the Oxford University Centre for FMRIB software library (FSL 5.0, http://www.fmrib.ox.ac.uk/fsl/) (Woolrich et al., 2009). First, the b0 image of each subject was skull-stripped using the brain extraction tool. Since head motion can affect the DTI data and may be phase specific – manic patients could move more than depressed patients – we checked this issue in various ways. Each participant's motion was assessed by means of translation/rotation, and an exclusion criterion (translation >3 mm and rotation $>3°$ in each direction) was set. All participants selected for this study showed head motion of less than 1 mm. Head motion parameters themselves were entered into an analysis of variance (ANOVA) in order to detect differences between the various subgroups, which revealed no significant differences among them ($F=0.909$; $p=0.440$). Then, the data was corrected for subject motion and eddy-current induced geometrical distortions, and the diffusion sensitizing gradients ("bvecs") were rotated to correct for motion. Subsequently, using the FMRIB's Diffusion Toolbox (FDT), the diffusion tensor (DT) was estimated in each voxel using a linear regression and FA, MD, RD and AD maps were derived.

TBSS analysis was used to perform a whole-brain analysis of the WM DT MRI measures (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html) (Woolrich et al., 2009). Briefly, the individual FA images were non-linearly registered to the FMRIB58_FA standard space, provided within FSL, and averaged to create a mean FA image. The

resulting mean FA image was then thinned to create a WM tract 'skeleton', which was thresholded at a FA=0.2 to include only WM voxels. Each subject's aligned FA data were then projected onto this skeleton and the resulting alignment-invariant representation of the central trajectory of WM pathways was used for whole-brain statistical analyses. Similar processes were applied to non-FA data – MD, RD and AD maps – by using the individual registration and projection vectors obtained in the FA non-linear registration and skeletonization stages.

Whole-brain differences in FA, MD, RD and AD values between BD patients and controls were tested using a permutation-based inference for non-parametric statistical thresholding ('randomize' program within FSL) (Nichols and Holmes, 2002) and two-sample *t*-test. The number of permutations was set to 5000. Age and gender were entered into this analysis as confound regressors to ensure that any observed effect of group on FA, MD, RD and AD was independent of age- and gender-related changes. A p value < 0.01, corrected for family-wise error (FWE) using the threshold-free cluster enhancement (TFCE) option in the 'randomize' tool (Smith and Nichols, 2009), was set for between-group comparisons. The WM tracts were identified using the JHU White Matter Tractography Atlas provided within FSL (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007). Those voxels of the skeleton that resulted significantly different between patients and controls were transformed back to the native space, and the values of DT-MRI measures averaged within each cluster at tracts and skeleton level were extracted to perform the analysis of subgroup comparisons and correlation analyses.

The mean FA values of all the tracts were entered into an ANOVA followed by post-hoc Games-Howell test to detect differences between the various subgroups, i.e. depressed, manic and euthymic patients, and HC. Subsequently, the FA value of each tract was entered into an ANOVA followed by post-hoc Games-Howell test to explore differences between the various subgroups at the single tracts level. The same procedure was performed for the MD, RD and AD values. All results were thresholded at a corrected p value of 0.01.

Then, the whole-brain differences in FA, MD, RD and AD values between the various subgroups of patients and HC were also tested using 'randomize' program within FSL (Nichols and Holmes, 2002) and two-sample *t*-test, with age and gender as coregressors. A p value < 0.01, corrected for FWE using the TFCE (Smith and Nichols, 2009), was set for between-group comparisons. We also performed the same analyses at a p value < 0.05 and < 0.005, in order to investigate various thresholding in the differences between subgroups. Finally we extracted the total cluster size from each significant contrast, with the purpose of evaluate the overall alterations load in each subgroup.

2.4. Cognitive and clinical correlation analyses

A two-sample *t*-test was performed to detect differences between BD and HC and between the various subgroups in terms of cognitive variables – i.e. CPT parameters such as total hits, total omission errors and total commission errors, as well as fluency prompted by letter and by category.

Correlation analyses were performed to investigate the relationship of the cognitive measures – i.e. CPT and fluency - and clinical scales - i.e. YMRS and HAM-D scores - with the DTI parameters - i.e. the overall mean FA, mean MD, mean RD and mean AD values of all the tracts, as well as the FA, MD, RD and AD values of the single tracts - in the BD sample (and, separately, in the HC sample, when appropriate). In particular, partial correlation analyses were conducted between the cognitive variables and DTI parameters, adjusted for subgroups, YMRS and HAM-D scores, as well as between the clinical scales and the same DTI parameters, adjusted for subgroups.

Finally, we controlled for potential relationships between DTI parameters and various confounders. Kruskal–Wallis test was used to determine differences between patients and controls in terms of age and between the various subgroups of patients in terms of age, duration of illness and medication load. Correlation analyses were performed between the same DTI variables and duration of illness (partial correlation analysis, adjusted for subgroups) as well as between DTI parameters and medication load (Spearman correlation analysis, since the Shapiro–Wilks test showed a non-normal distribution for medication load, $p < 0.05$). All the results were thresholded at a corrected $p < 0.05$ (Bonferroni correction was carried out for multiple comparisons and Bootstrap correction was carried out to detect outliers).

T-tests and correlation analyses were performed using IBM SPSS Statistics® Version 19 for Windows® (Chicago Inc., USA)®.

3. Results

3.1. Comparison of DTI metrics between BD and HC

A widespread decrease in FA values and increase in MD and RD values was found in BD compared to controls in clusters belonging to various tracts, including the bilateral anterior thalamic radiation (ATR L/ATR R), cingulate gyrus (CG L/CG R), corticospinal tract (CST L/CST R), forceps major (Fmaj), forceps minor (Fmin), inferior fronto-occipital fasciculus (IFOF L/IFOF R), inferior longitudinal fasciculus (ILF L/ILF R), superior longitudinal fasciculus (SLF L/SLF R) and uncinate fasciculus (UF L/UF R), at $p < 0.01$ TFCE corrected (Fig. 1). No significant differences in AD values were found between groups. A combined FA decrease and MD/RD increase was found in clusters belonging to all these tracts - especially in Fmin, ILF, IFOF and SLF, especially on the left side (Supplementary Fig. 1 and Supplementary Table 1).

3.2. Comparison of DTI metrics among subgroups

We carried out comparisons between the subgroups – i.e. depressed, manic and euthymic patients, and HC. Firstly, the ANOVA showed a significant difference between subgroups: in the mean FA values of all the tracts ($F=10.332$; $p=0.000$), with decreased values in depressed ($p=0.002$) and manic ($p=0.000$) patients compared to HC; in the mean MD values ($F=9.437$; $p=0.000$), with only depressed patients showing increased values compared to HC ($p=0.001$); and in the mean RD values ($F=9.715$; $p=0.000$), with increased values in depressed ($p=0.002$) and manic ($p=0.001$) patients compared to HC. Then, at the single tracts level, the ANOVA showed a significant difference between subgroups in FA, MD and RD values in all the investigated tracts, at a corrected p value < 0.01. Specifically, among subgroups, FA value was decreased in: ATR R and Fmaj only in depressed patients when compared to HC; Fmin, CG L/R, SLF L/R and CST L/R only in manic patients when compared to HC; ATR L, IFOF L/R, ILF L/R and UF L/R in both depressed and manic patients when compared to HC. MD values were increased in all the tracts except for CG R in depressed patients when compared to HC and in CG R, IFOF L and IFL L also in manic patients when compared to HC. Finally, RD values were increased in: ATR L/R, CG R, Fmaj and ILF R only in depressed patients when compared to HC; SLF L/R and CST L/R only in manic patients when compared to HC; CG L, IFOF L/R, ILF L and UF L/R in both depressed and manic patients when compared to HC (Table 2). No significant differences were found in euthymic patients when compared to HC at a corrected p value < 0.01. Lowering the threshold at a $p < 0.05$, a decrease in FA values mainly in Fmin, as well as a more widespread increase in RD

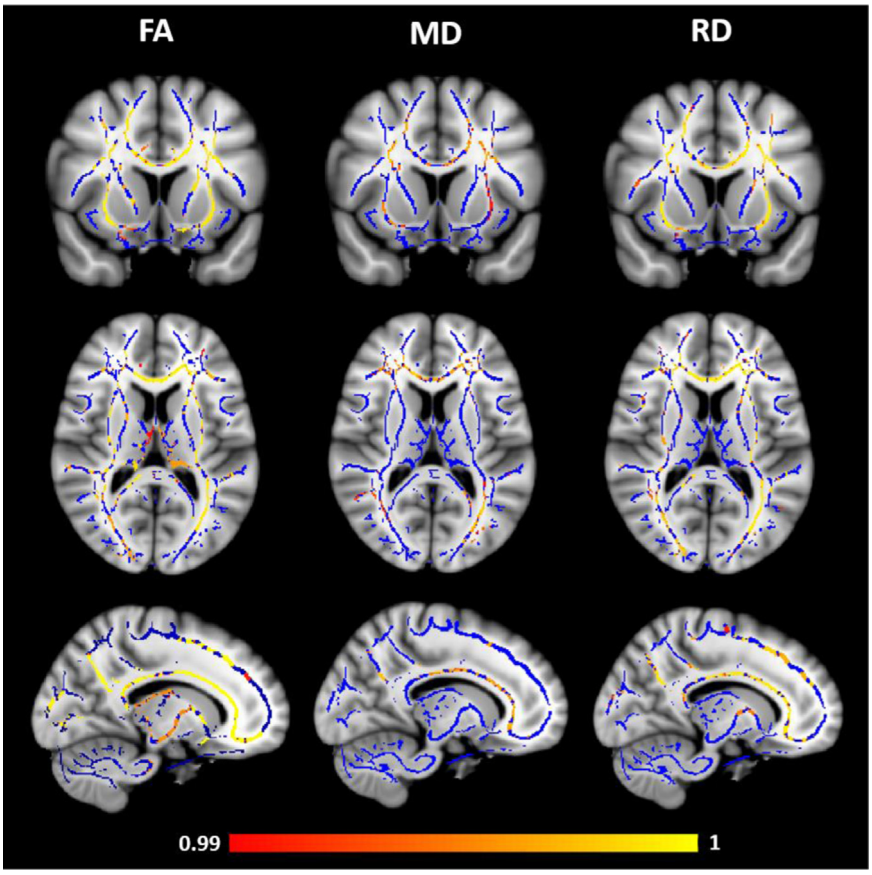

Fig. 1. DTI parameters in BD vs HC: FA, MD and RD values. Results obtained from between-group comparison showing in *red–yellow* the clusters of voxels with significantly decreased fractional anisotropy values (FA column), increased mean diffusivity values (MD column) and increased radial diffusivity values (RD column) in patients with bipolar disorder when compared with healthy controls ($p < 0.01$, FWE corrected). For display purposes the statistically significant clusters are displayed as 1-p values. The white matter skeleton, thresholded at FA > 0.2, is represented in *blue*. Group differences are mapped onto standard T1 Montreal Neurological Institute (MNI) template. Images are in radiological convention. Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; BD, bipolar disorder; HC, healthy controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
FA, MD and RD differences between the various subgroups.

	FA			**MD**			**RD**		
WM Tracts	**ANOVA** F (p)	**M vs. HC** p	**D vs. HC** p	**ANOVA** F (p)	**M vs. HC** p	**D vs. HC** p	**ANOVA** F (p)	**M vs. HC** p	**D vs. HC** p
ATR L	8.869 (.000)	.006	.001	5.647 (.001)		.007	5.984 (.001)		.008
ATR R	8.309 (.000)		.001	4.913 (.003)		.004	5.447 (.002)		.005
CG L	5.105 (.003)	.008		6.810 (.000)		.005	7.603 (.000)	.005	.003
CG R	6.229 (.001)	.005					6.018 (.001)		.005
CST L	5.735 (.001)	.000		7.658 (.000)		.004	6.352 (.001)	.001	
CST R	5.064 (.003)	.001		6.144 (.001)		.005	5.359 (.002)	.003	
Fmaj	5.739 (.001)		.008	6.810 (.000)		.004	6.714 (.000)		.007
Fmin	4.742 (.004)	.006		6.400 (.001)		.004	5.976 (.001)		
IFOF L	8.801 (.000)	.002	.003	9.710 (.000)	.007	.001	9.422 (.000)	.004	.002
IFOF R	8.562 (.000)	.000	.004	7.055 (.000)		.003	7.880 (.000)	.008	.004
ILF L	8.136 (.000)	.002	.003	1.178 (.000)	.002	.001	9.608 (.000)	.002	.002
ILF R	8.253 (.000)	.009	.002	5.781 (.001)		.006	7.891 (.000)		.002
SLF L	7.530 (.000)	.000		7.674 (.000)		.004	8.691 (.000)	.000	
SLF R	7.215 (.000)	.000		6.650 (.000)		.003	7.414 (.000)	.001	
UF L	8.250 (.000)	.004	.001	10.676 (.000)		.000	9.941 (.000)	.002	.001
UF R	7.943 (.000)	.004	.002	8.070 (.000)		.005	7.734 (.000)	.007	.003

ANOVA and Games-Howell post hoc test of FA, MD and RD values of each tract to detect differences between the various subgroups, i.e. depressed, manic and euthymic patients and HC. All results were thresholded at a corrected p value of 0.01.
Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; WM, white matter; M, manic patients; D, depressed patients; HC, healthy controls; ATR L, anterior thalamic radiation left; ATR R, anterior thalamic radiation right; CG L, cingulate gyrus left; CST L, corticospinal tract left; CST R, corticospinal tract right; Fmaj, forceps major; Fmin, forceps minor; IFOF L, inferior fronto-occipital fasciculus left; IFOF R, inferior fronto-occipital fasciculus right; ILF L, inferior longitudinal fasciculus left; ILF R, inferior longitudinal fasciculus right; SLF L, superior longitudinal fasciculus left; SLF R, superior longitudinal fasciculus right; UF L, uncinate fasciculus left; UF R, uncinate fasciculus right.

values with the largest cluster in Fmin, was found in euthymic patients when compared to HC.

Then, the whole-brain comparisons at a corrected p value < 0.01 confirmed: a diffuse decrease in FA values and a diffuse increase in MD and RD values in WM belonging to various tracts in the depressed subgroup when compared to HC (Fig. 2a); a decrease in FA values and an increase in RD values but no differences in MD values in the manic subgroup when compared to HC (Fig. 2b); no differences in FA, MD and RD values in the euthymic subgroup when compared to HC (but a localized decrease in FA and an increase in RD values was found at a $p < 0.05$). Regarding to the global load of WM alterations in the various subgroups, depressed patients showed the largest overall cluster size of WM alterations, that survived at a more stringent thresholding in the between-groups comparisons ($p < 0.005$); manic patients showed an intermediate overall cluster size of WM alterations (approximately half of the cluster size that was observed in depression), that survived at an intermediate thresholding ($p < 0.01$); euthymic patients showed the smaller overall cluster size of WM alterations, that survived only at the less stringent thresholding ($p < 0.05$) (Table 3).

3.3. Correlations between DTI metrics, cognitive and clinical parameters

With regard to the neuropsychological evaluation, bipolar patients showed significant deficits in CPT measures – i.e. reduced total hits ($t = -4.716$; $p = 0.000$) as well as increased omission errors ($t = 4.820$; $p = 0.000$) and commission errors ($t = 2.694$; $p = 0.008$) – and in fluency prompted by letter ($t = -3.633$; $p = 0.000$), when compared to HC. In particular, depressed patients showed deficits in CPT measures – i.e. increased omission errors ($t = 3.397$; $p = 0.001$) – as well as in fluency prompted by letter ($t = -3.758$; $p = 0.000$) and by category ($t = -2.772$; $p = 0.007$), when compared to HC. Manic patients showed deficits in CPT measures – i.e. reduced total hits ($t = -4.291$; $p = 0.000$) as well as increased omission errors ($t = 4.622$; $p = 0.000$) and commission errors ($t = -3.182$; $p = 0.002$) – when compared to HC. No significant deficits in CPT and fluency measures were detected in euthymic patients. Significant correlations were found in the BD sample between some of the cognitive variables and the mean FA value, mean MD value and mean RD value, by using partial correlation analyses adjusted for subgroups, HAM-D and YMRS total scores (with bootstrapping and correction for multiple comparisons). CPT total hits showed a direct correlation with the mean FA value ($r = 0.564$; $p = 0.000$; CI:0.287∼0.740) as well as an inverse correlation with the mean MD ($r = -0.489$; $p = 0.000$; CI: −0.663∼−0.255) and RD values ($r = -0.555$; $p = 0.000$; CI: −0.732∼−0.306). CPT total omission errors showed an inverse correlation with the mean FA value ($r = -0.548$; $p = 0.000$; CI: −0.699∼−0.328) as well as a direct correlation with the mean MD ($r = 0.519$; $p = 0.000$; CI:0.312∼0.672) and RD values ($r = 0.566$; $p = 0.000$; CI:0.357∼0.705). Fluency prompted by letter showed a direct correlation with the mean FA value ($r = 0.411$; $p = 0.001$; CI:0.132∼0.612) as well as an inverse correlation with the mean MD ($r = -0.444$; $p = 0.000$; CI: −0.619∼−0.215) and RD values

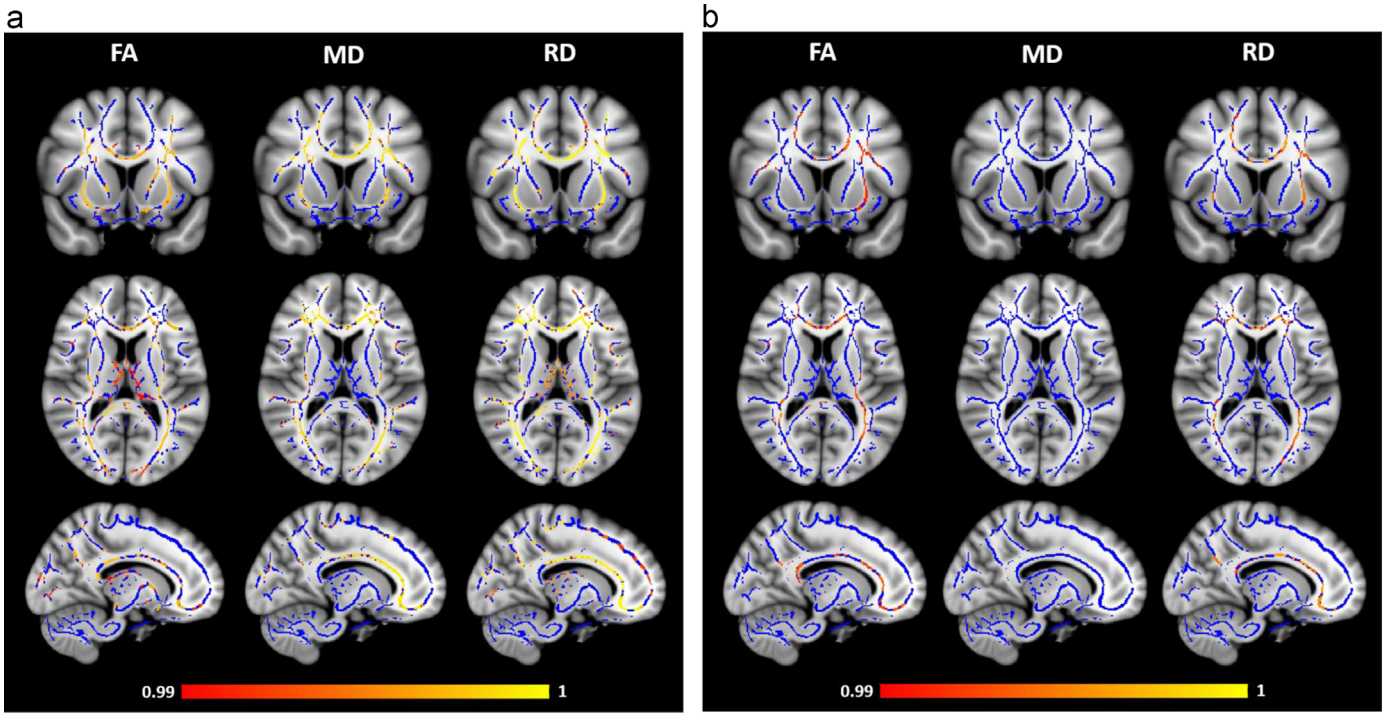

Fig. 2. a. DTI parameters in D vs HC: FA, MD and RD values. Results obtained from between-group comparison showing in *red–yellow* the clusters of voxels with significantly decreased fractional anisotropy values (FA column), increased mean diffusivity values (MD column) and increased radial diffusivity values (RD column) in patients in depressive phase when compared with healthy controls ($p < 0.01$, FWE corrected). For display purposes the statistically significant clusters are displayed as 1-p values. The white matter skeleton, thresholded at FA > 0.2, is represented in *blue*. Group differences are mapped onto standard T1 Montreal Neurological Institute (MNI) template. Images are in radiological convention. Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; D, depressed patients; HC, healthy controls. b. DTI parameters in M vs HC: FA, MD and RD values. Results obtained from between-group comparison showing in *red–yellow* the clusters of voxels with significantly decreased fractional anisotropy values (FA column), increased mean diffusivity values (MD column) and increased radial diffusivity values (RD column) in patients in manic phase when compared with healthy controls ($p < 0.01$, FWE corrected). For display purposes the statistically significant clusters are displayed as 1-p values. The white matter skeleton, thresholded at FA > 0.2, is represented in *blue*. Group differences are mapped onto standard T1 Montreal Neurological Institute (MNI) template. Images are in radiological convention. Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; M, manic patients; HC, healthy controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Overall cluster size of FA, MD and RD differences in the various subgroups.

	FA			MD			RD		
	CS ($p=0.05$)	CS ($p=0.01$)	CS ($p=0.005$)	CS ($p=0.05$)	CS ($p=0.01$)	CS ($p=0.005$)	CS ($p=0.05$)	CS ($p=0.01$)	CS ($p=0.005$)
D vs. HC	64,808	42,915	28,316	62,383	44,138	37,731	78,114	54,548	47,593
M vs. HC	42,253	20,023		21,740			34,531	19,378	10,112
E vs. HC	2937						10,811		

Overall cluster size of FA, MD and RD differences between the various subgroups at different thresholding.
Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; CS, cluster size (number of voxels); D, depressed patients; M, manic patients; E, euthymic patients; HC, healthy controls.

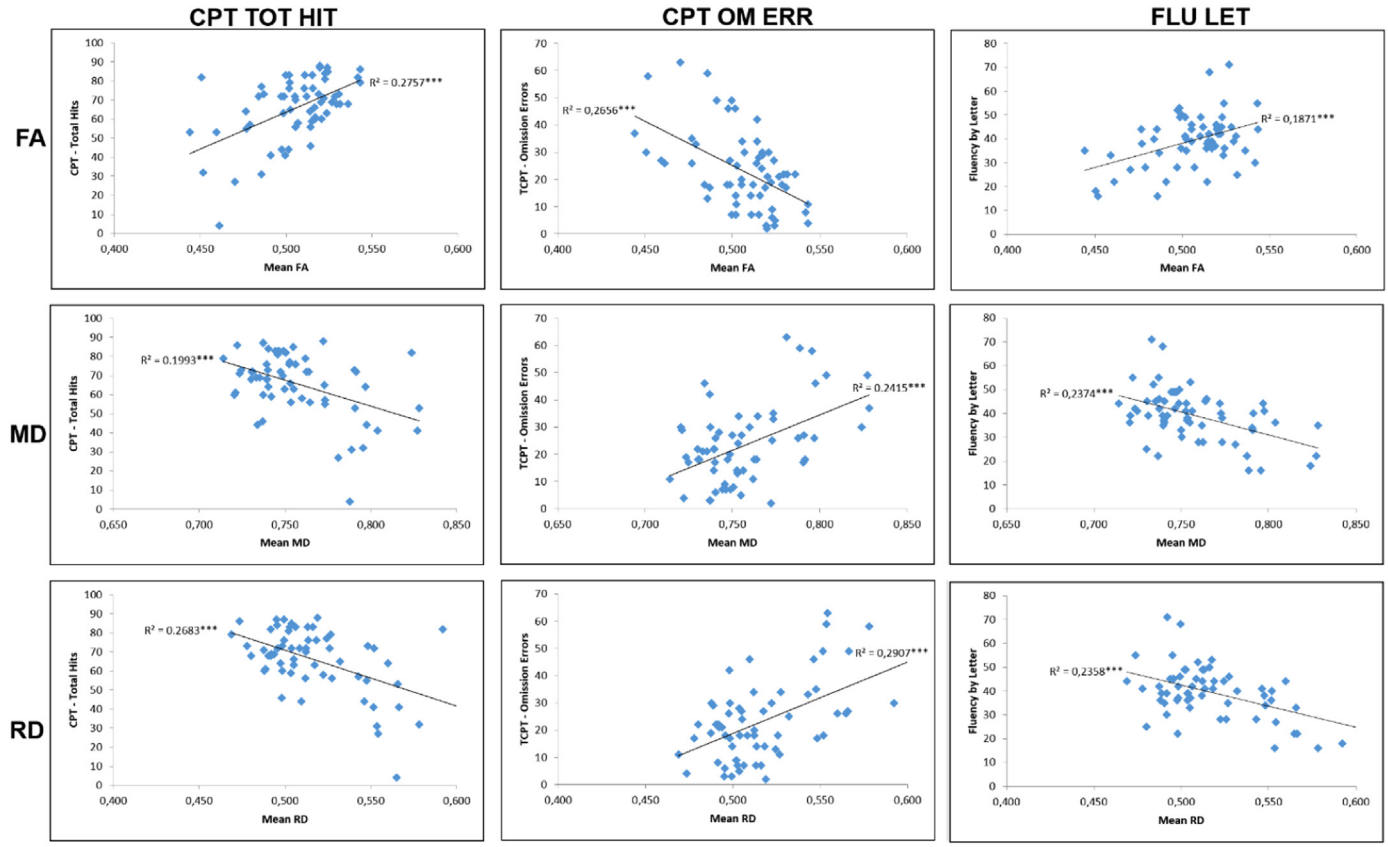

Fig. 3. Correlations between neurocognitive and DTI parameters. Partial correlations (after bootstrapping) of mean FA, mean MD and mean RD values with neurocognitive variables, adjusted for subgroups and YMRS and HAM-D scores, in patients affected by bipolar disorder. The mean FA value was obtained from FA values of all the tracts, i.e. the average of the FA values which were extracted from clusters in all the tracts that showed a significant change between BD and HC at $p < 0.01$ (FWE corrected). The mean MD and RD values were obtained in the same way as FA for the correspondent values. CPT TOT HITS show a direct correlation with mean FA and an inverse correlation with mean MD and mean RD. CPT OM ERR show an inverse correlation with mean FA and a direct correlation with mean MD and mean RD. FLU LET shows a direct correlation with mean FA and an inverse correlation with mean MD and mean RD. $p < 0.001^{***}$. Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; CPT TOT HITS, continuous performance test – total hits; CPT OM ERR, continuous performance test-total omission errors; FLU LET, fluency prompted by letter; HAM-D, Hamilton Depression Scale; YMRS, Young Mania Rating Scale. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

($r=-0.448$; $p=0.000$; CI: $-0.637 \sim -0.197$) (Fig. 3). At the single tracts level, we also found significant correlations between the same cognitive variables and FA, MD and RD values in almost all the tracts (Supplementary Table 2). No additional correlations between the DTI parameters and cognitive measures were found (including fluency prompted by category and CPT total commission errors). No significant correlations were found in the HC group.

With regard to the clinical correlations, HAM-D and YMRS total scores did not show any significant correlation with FA, MD and RD values (Supplementary Fig. 2). No significant differences were detected in age, illness duration and medication load between the various subgroups of patients. Medication load showed: an inverse correlation with FA values in ATR L ($\rho=-0.376$; $p=0.004$) and Fmaj ($\rho=-0.373$; $p=0.004$); a direct correlation with MD values in ILF R ($\rho=0.340$; $p=0.009$); a direct correlation with RD values in ATR L ($\rho=0.343$; $p=0.008$), ATR R ($\rho=0.349$; $p=0.007$), Fmaj ($\rho=0.381$; $p=0.003$) and Fmin ($\rho=0.347$; $p=0.008$). However, only the correlation between medication load and RD values in Fmaj survived after correction for multiple comparisons. Illness duration showed an inverse correlation with FA values in Fmin ($r=-0.266$; $p=0.040$), that did not survived after correction for multiple comparisons. No other correlations between DTI parameters and clinical parameters were found.

4. Discussion

4.1. Main findings

In the present study we found a widespread alteration in WM microstructure (decrease in FA and increase in MD and RD) in type I BD patients when compared to HC. In addition, the subgroups of BD patients showed different spatial patterns of WM alterations and the global load of WM abnormalities was larger in depression, intermediate in mania and smaller in euthymia (Fig. 4). Finally, the WM alterations were associated with cognitive deficits.

4.2. Diffuse alteration in WM microstructure in BD, subgroups differences and cognitive correlations

The analysis of WM structural integrity using the TBSS approach showed abnormalities of all major classes of tracts (Bauer et al., 2015; Benedetti et al., 2011a; 2011b; Chan et al., 2010; Heng et al., 2010; Kumar et al., 2015; Lagopoulos et al., 2013; Mahon et al., 2012; Nortje et al., 2013; Oertel-Knochel et al., 2014; Poletti et al., 2015; Sprooten et al., 2013; Vederine et al., 2011; Versace et al., 2008; 2010; Wessa et al., 2009; Wise et al., 2015; Yip et al., 2013). To the best of our knowledge, the previous TBSS studies in BD included only euthymic/remitted (Bauer et al., 2015; Benedetti et al., 2011a; Chan et al., 2010; Emsell et al., 2013; Kumar et al., 2015; Mahon et al., 2012; Oertel-Knochel et al., 2014; Sprooten et al., 2013; Versace et al., 2008; Wessa et al., 2009; Yip et al., 2013) or depressed (Bauer et al., 2015; Benedetti et al., 2011b; Lagopoulos et al., 2013; Poletti et al., 2015; Versace et al., 2008; 2010) adult patients. Our study, including type I bipolar patients in all the phases of illness (i.e. depressed, manic and euthymic phases), confirm the widespread WM alteration reported in previous BD studies and, furthermore, showed a different pattern of WM alterations in the various phases of illness. The subgroup comparisons showed that the diffuse WM abnormalities were more prevalent in the active phases of illness, especially in depression, with respect to euthymia (Fig. 4). Depressed patients showed the largest load of WM alterations (47% of the total number of WM skeleton voxels in all the tracts showed a significant reduction in FA values, with respect to HC, at a $p < 0.05$); manic patients showed an intermediate load of WM alterations (30,7% of the total number of WM skeleton voxels showed a significant reduction in FA values, with respect to HC, at a $p < 0.05$); euthymic patients showed the smaller load of WM alterations (2,1% of the total number of WM skeleton voxels showed a significant reduction in FA values, with respect to HC, at a $p < 0.05$). Moreover, in our sample, depressed, manic and euthymic patients showed a relatively different spatial pattern of WM abnormalities, with a widespread distribution of alterations in the depressive phase; a more constant involvement of midline structures, such as Fmin and CG, as well as some lateral tracts, such as SLF and CST, in the manic phase; and more localized alterations in the midline tract Fmin in the euthymic phase. Thus, our findings confirm widespread WM alterations in the depressive phase of BD (Bauer et al., 2015; Benedetti et al., 2011b; Lagopoulos et al., 2013; Poletti et al., 2015; Versace et al., 2008; Versace et al., 2010). Furthermore, our data suggest a relatively different pattern of WM changes in the manic phase. This seems to show a lower degree of diffuse alterations with a more constant and specific involvement of some tracts that, interestingly, play an important role in interconnecting the regions of different neural networks. Specifically, the Fmin and CG underpin the default mode network which is involved in internal thought and mind wandering, while the SLF underpins the central executive network which is involved in attention focusing on external stimuli (van den Heuvel et al., 2009). Thus, alterations in these tracts suggest dysfunction in information processing at large-scale network level, possibly playing a role in the pathophysiology of acute phases (Magioncalda et al., 2015; Menon, 2011; Ongur et al., 2010). In contrast to the acute phases, in euthymic patients WM alterations were mainly localized in Fmin, near the anterior cingulum, which is key region involved in affective regulation (Fountoulakis et al., 2008). These findings are in accordance with previous evidence showing that most of WM changes in euthymia were found in the left cingulate and right posterior temporo-parietal clusters (Nortje et al., 2013). Since previous DTI studies in euthymia (Bauer et al., 2015; Benedetti et al., 2011a; Chan et al., 2010; Kumar et al., 2015; Mahon et al., 2012; Oertel-Knochel et al., 2014; Sprooten et al., 2013; Versace et al., 2008; Wessa et al., 2009; Yip et al., 2013) included either bipolar patients in remission from depression (Benedetti et al., 2011a) or from mania (Chan et al., 2010), or euthymic and depressed patients together (Versace et al., 2008), or euthymic patients with a psychosis history (Kumar et al., 2015), the reported WM alterations could also be a consequence of the previous active phases or of the concomitant psychosis. However, minor WM abnormalities were also detected in relatives of bipolar patients (Roybal et al., 2015; Sprooten et al., 2013), thus suggesting familiarity of WM abnormalities in BD. In contrast, one DTI study that directly compared depressive patients and remitted patients, showed extensive WM abnormalities in acutely depressed subjects when compared to both remitted and control subjects, but no abnormalities in remitted patients compared to controls (Zanetti et al., 2009). These findings suggest that acute mood state may be associated with acute state-dependent microstructural WM changes. Thus, the different patterns of WM alterations in the various phases of illness could present both trait and state-dependent components, possibly depending on complex and different pathogenetic factors.

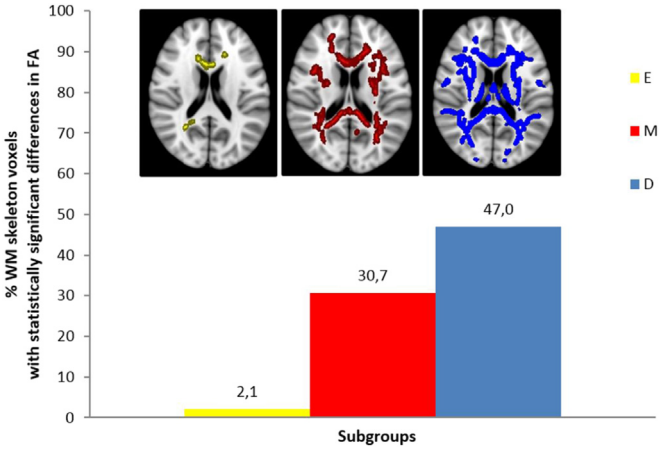

Fig. 4. WM alterations in the euthymic, manic and depressed phases of bipolar disorder. Summary figure that shows the percentage and distribution of WM alterations in the different phases of type I BD. The histograms represent the percentage of the total number of WM skeleton voxels in all the tracts that show statistically significant reduction in FA values, while the brains represent the distribution of the same voxels in euthymia (yellow), mania (red) and depression (blue), with respect to controls (at a corrected $p < 0.05$). A gradient of increasing WM abnormalities from the euthymic (low degree and localized WM alterations mainly in the midline structures) to the manic (more diffuse WM alterations affecting both midline and lateral structures) and, finally, to the depressive phase (high degree and widespread WM alterations), is shown in the figure. Abbreviations: BD, bipolar disorder; WM, white matter; FA, fractional anisotropy; E, euthymic phase; M, manic phase; D, depressive phase. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Overall, the presence of different patterns (size and distribution) of WM alterations in the various phases of BD raises a few intriguing questions. Which are the hypothetical pathophysiologic mechanisms that can mediate the state and/or trait–dependent

WM alterations? Are WM abnormalities cause or consequence of functional alterations of specific neural networks? Are they linked, at least partially, to the bipolar cycle with a progression of severity from mania to depression? Due to cross-sectional nature, our study does allow only speculative interpretations. At the cellular level, the FA reduction is indicative of a generic loss of WM integrity or directionality; however, a concomitant increase in RD suggests a more specific alteration in oligodendroglial and myelin microstructure (Heng et al., 2010). These findings are potentially consistent with the results from postmortem studies in BD patients that showed reductions in glia cell density and abnormalities of gene expression related to the perineuronal and myelinating oligodendroglia (Savitz et al., 2014). However, it is still unclear if these alterations are chronic and stable or acute and partially transitory, as suggested by a study that showed a FA reduction and disruption of integrity of the nerve-sheath in healthy subjects who experienced acute stress and by a preclinical study on acutely stressed mouse brain (Chen et al., 2013; Miller et al., 2009). Since the prolonged activation of the stress system, which could trigger the active phases of BD (Bidzinska, 1984; Hamdani et al., 2012; Proudfoot et al., 2011), induces an increase in pro-inflammatory factors (Elenkov, 2008) and since increased levels of these factors have been associated with a loss of WM integrity (Miralbell et al., 2012), we speculate that the diffuse WM microstructural abnormalities might reflect a stress-related inflammatory/vascular damage. Interestingly, depression seems to be associated with a prolonged stress system activation and with a related increase in pro-inflammatory factors - e.g. Tumor necrosis factor α, Interleukin 1 and C reactive protein - which could contribute to some of the associated behavioral disturbances observed in these patients (Dowlati et al., 2010; Elenkov, 2008; Fornaro et al., 2013; Maes, 1999). For example, an increase in pro-inflammatory factors induces the "sickness behavior syndrome", which includes some of the associated symptoms that are frequently observed in depression, such as sleep disturbances, fatigue, loss of appetite and decreased libido (Elenkov, 2008). Thus, we speculate that the same increase in pro-inflammatory factors might contribute to a state-dependent WM FA decrease (Miralbell et al., 2012) which is found in the depressive phase. However, other pathophysiologic mechanisms can be involved in state-dependent changes of WM microstructures (beyond concomitant trait features). Neuroplasticity and tridimensional re-organization of microstructure can be driven by some antidepressant treatments (Bracht et al., 2015) or by neural activity itself (for example, electrical activity in an axon could regulate its myelination over a time course of days to weeks (Imfeld et al., 2009; Oechslin et al., 2009; Scholz et al., 2009)), also suggesting a potential influence of functional alterations on microstructural changes. Thus, a gradient of increasing WM abnormalities from the euthymic (low degree and localized WM alterations mainly in the midline structures) to the manic (more diffuse WM alterations affecting both midline and lateral structures) and, finally, to the depressive phase (high degree and widespread WM alterations), could be related to different factors. Although mania has a key role in current classification, in which mania is the uniquely defining characteristic of type I BD, mania and depression are often conceived as different entities (A.P.A., 1994). In contrast, according to the classical view, mania and depression are linked in the bipolar cycle, as proposed by the "primacy of mania" hypothesis by Koukopoulos and Ghaemi, where depression (which is seen in a narrow way) is considered a consequence of mania (viewed broadly as a wide range of excitatory processes) (Koukopoulos and Ghaemi, 2009). In accordance with this hypothesis, it is tempting to speculate that the depressive switch occurs when the progressive WM microstructural injury induced by excitotoxic and inflammatory mania-related factors reaches a certain threshold. However, other factors can be involved. For instance, antidepressant treatment, which is prevalent in the depressive phase of BD, can affect WM microstructure (Bracht et al., 2015; Taylor et al., 2011) and, on the other hand, DTI changes in bipolar depression is related to poor antidepressant response (Bollettini et al., 2015). Thus, antidepressant treatment can have a role in the difference of DTI-detected WM abnormalities between mania and depression. Overall, mania (in which antidepressants are not used) and depression, as active states of BD, showed large DTI differences with respect to euthymia, when compared to controls, suggesting complex dynamic changes in the WM microstructures across the various phases of BD that needs to be confirmed in longitudinal studies.

In turn, WM abnormalities might play a role in some clinical aspects. In line with a few previous TBSS studies on euthymic or depressed bipolar patients that detected an association between cognitive deficits and DTI parameters (Bauer et al., 2015; McKenna et al., 2015; Oertel-Knochel et al., 2014; Poletti et al., 2015), we found statistically significant correlations between the widespread WM abnormalities and some of the cognitive scores. Since our analyses were adjusted for subgroups and clinical scores, the correlations between DTI parameters and cognitive deficits were not related to the diagnostic group. Our findings confirm previous data on euthymic and depressed patients and extend the correlations to a whole sample of BD patients in all the various phases of illness. Interestingly, although cognitive deficits were found in the euthymic phase (Bora et al., 2009; Poletti et al., 2014; Quraishi and Frangou, 2002), previous data showed a higher degree of impairment of some cognitive functions, including sustained attention (investigated using CPT), in the active phases with respect to euthymia (Malhi et al., 2007; Quraishi and Frangou, 2002). Accordingly, in our sample, patients in active phases, but not in euthymic phase, showed significant deficits in some CPT and fluency measures. At the same time, in our sample, BD patients showed larger and widespread WM abnormalities in the active phases with respect to euthymia. Thus, WM alterations could underlie some cognitive deficits, becoming structurally and clinically relevant in the acute phases of BD. By contrast, we did not find any significant association between HAM-D and YMRS total scores and the DTI measures. Only few of the previous TBSS studies on BD investigated the relationship between clinical severity scores and WM abnormalities and the findings were controversial; one study found an inverse correlation between FA and depression score, while no correlation was found in another one (Mahon et al., 2012; Oertel-Knochel et al., 2014). The lack of correlation of DTI parameters with YMRS and HAM-D scores can depend on several factors, and non-linear relationships or third factors cannot be excluded. Since mania and depression (which are characterized by opposite clinical features) showed WM changes in the same direction, even if with relative spatial differences, WM alterations may not be directly related with the severity of manic or depressive symptomatology. However, WM alterations, that were mainly found in the active states, showed a significant correlation with some cognitive deficits (mainly present in the active phases as well), that in turn could affect clinical symptomatology. For instance, WM changes could underlie some subtle cognitive deficits, such as omission errors detected in CPT, that can be related to some DSM clinical criteria, such as attention deficit, in depressed patients. Moreover, two longitudinal studies on depressed patients showed that remission after successful antidepressant treatment is associated with FA changes and WM remodeling (Bracht et al., 2015; Taylor et al., 2011). This suggests that WM microstructure alterations may play a role, at least indirectly, in the psychopathology of BD.

4.3. Limitations

The main limitation of the present study is that almost all the bipolar subjects were under different treatments, including mood stabilizers, antipsychotics, antidepressants and benzodiazepines. We examined the potential impact of psychotropic medication load on DTI parameters, by correlating the resulting pharmacological load with FA, MD and RD extracted values. Medication load correlated with FA or MD or RD values in few tracts, including ATR L/R, ILF R, Fmaj and Fmin. Moreover, no significant correlation survived after correction for multiple comparisons (except for Fmaj). Since previous studies showed an association between changes in the DTI parameters and lithium (Benedetti et al., 2011a; Benedetti et al., 2013a; Gildengers et al., 2015) or antidepressant therapy (Benedetti et al., 2013b), we also explored the potential correlation of the DTI variables with lithium and imipramine equivalents, and no significant correlation was found. Furthermore, we compared the DTI values of bipolar patients who were under treatment with lithium with those who were not, and, although there was a difference in FA values of the CG L ($t=-2.223$; $p=0.030$), this result did not survive after correction for multiple comparisons. Nevertheless, we cannot exclude some influence of treatment on our findings, especially for antidepressants, since subgroup differences could be affected in a non-linear way and relationships between these factors may present a degree of complexity that is not captured by linear correlations. Taking together, these results suggest that the DTI changes, even if potentially associated with pharmacotherapy, are not the mere consequence of drug treatment in our sample.

Furthermore, age-related WM changes could represent a confounding factor. Age was found to inversely correlate with FA values (Versace et al., 2008). Although no significant differences in mean age were detected between the various subgroups of our study participants (Table 1), age was entered into between-groups comparison analyses as confound regressor to ensure that WM differences were independent of age-related changes. Likewise age, the duration of illness could affect WM changes. Pediatric and late-life BD are associated with relatively distinct patterns of DTI changes (Gao et al., 2013; Haller et al., 2011), and the pediatric forms are thought to be more aggressive and their evolution over time could lead to accumulation of WM changes. However, the role of illness duration on WM changes is controversial: for example, (Gao et al., 2013) and (Cui et al., 2011) found no correlations of illness duration with DTI parameters, while (Haller et al., 2011) found a trend toward significant correlation between those metrics. In line with other previous DTI studies employing a TBSS approach, we found no significant correlation of the DTI parameters with duration of illness. This suggest a lack of major effects of this clinical factor on the DTI changes in our data. However, a weak inverse correlation of illness duration was detected with FA values in Fmin (at uncorrected $p<0.05$), the main tract which was found to be altered in euthymic patients. Thus, localized WM alterations in this area may also depend on accumulation of microstructural changes over time. By contrast, widespread WM changes could have a more relevant state-dependent component, since they are mostly found in the active phases of illness with no clear correlation with illness duration.

Finally, our study suffers of the typical limits of cross-sectional studies. An ideal study on differences between the various phases of illness would be conducted longitudinally in the same individual going through manic, depressive and euthymic phases. However, such longitudinal studies are extremely difficult to implement, and could be affected by some similar confounders (e.g. ethically it is not possible to keep participants with the same treatment in the different phases). Therefore, the present findings should be regarded as preliminary, but informative and hypothesis generating for future longitudinal studies.

In sum, our findings suggest that WM microstructural abnormalities are mostly present in the acute states, especially depression, possibly underlying an impairment in some cognitive functions in type I BD. However, our findings should be considered as preliminary due to the cross-sectional nature of this study. Future longitudinal investigation on BD patients in the various phases, possibly in addition to inflammatory and immunologic assessment, are needed to confirm the state-dependency of WM changes across the phases and their potential relationship with inflammation/immunity, in order to achieve a better understanding of the pathophysiology of BD.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.12.050.

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