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Research paper

White matter integrity in bipolar disorder investigated with diffusion tensor magnetic resonance imaging and fractal geometry

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ABSTRACT

Background: Growing evidence suggests the presence of white matter (WM) alterations in bipolar disorder (BD). In this study we aimed to investigate the state of WM structures, in terms of tissue integrity and morphological complexity, in BD patients compared to healthy controls (HC), in an attempt to better elucidate the micro-structural changes associated with BD.

Methods: We collected a dataset of 399 Diffusion Tensor Magnetic Resonance Imaging (167 BD and 232 healthy controls) images, acquired at five different sites, which was processed with Tract-Based Spatial Statistics (TBSS) and fractal analysis.

Results: The TBSS analysis demonstrated significantly lower FA values in the BD group. Diffusion abnormalities were primarily located in the temporo-parietal network. The Fractal Dimension (FD) analysis did not reveal consistent significant differences in the morphological complexity of WM structures between the groups. When the FD values of patients were considered individually, it is possible to notice some localized significant deviations from the healthy population.

Limitations: DTI sequences have not been harmonized before acquisition, samples' sizes are heterogeneous.

Conclusions: This study, by applying both TBSS and FD analyses, allows to evaluate diffusion and structural alterations of WM at the same time. The evaluation of WM integrity from these two different perspectives could be useful to better understand the pathophysiological and morphological changes underpinning bipolar disorder.

1. Introduction

Bipolar Disorder type 1 (BD I) is an affective disorder, in the spectrum of bipolar disorders, characterized by the occurrence of at least a manic episode, identified< by excessively elevated or irritable mood, possibly accompanied by delusions or psychotic feature. Individuals with BD I may also experience depressive episodes (American Psychiatric Association, 2013). According to a 2007 study (Merikangas et al., 2007), the lifetime prevalence of BD I in the United States, calculated in a probability sample, is 1 %. Despite being among the most common psychiatric disorders, the underlying pathophysiological processes are still largely unclear and the treatment options often unsatisfactory (Harrison et al., 2018). Unsuccessful treatment of BD not only leads to the deterioration of symptoms, poor quality of life and worsening cognitive and functional impairments, but also to significant risk for suicide; in fact, 9–15 % of affected individuals are estimated to commit suicide (Medici et al., 2015), and of those, around 80 % are affected by BD I (Novick et al., 2010). For this reason, it is fundamental to improve our understanding of the biological underpinnings of BD I and develop more effective and tolerated pharmacologic treatments.

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Growing evidence suggests the presence of cerebral structural alterations, involving both the gray matter (GM) and white matter (WM), in subjects diagnosed with BD. Structural MRI studies conducted on BD I patients have displayed very heterogeneous findings, likely due to different inclusion criteria and study designs; moreover, the confounding effects of psychotropic medications could hinder the morphological characterization of the bipolar patients' brain. However, the most involved areas appear to be the prefrontal cortex (PFC), anterior cingulate cortex (ACC) and amygdala (Haldane and Frangou, 2004). Specifically, the PFC (López-Larson et al., 2002; Strakowski et al., 1999; Vita et al., 2010) and ACC (Phillips and Swartz, 2014; Haldane and Frangou, 2004) were demonstrated to be smaller and the amygdala larger (Strakowski et al., 1999; Phillips and Swartz, 2014; Altshuler et al., 1998) in BD compared to HC. Furthermore, BD was found to be associated to larger volumes of the lateral and third ventricles (Abramovic et al., 2016; Strakowski et al., 1999; Vita et al., 2010), as well as to widespread cortical thinning (Abramovic et al., 2016; Hibar et al., 2018; Scaini et al., 2020) and smaller total brain volumes (Abramovic et al., 2016; Yucel et al., 2008). Findings regarding the hippocampus are controversial, but recent volumetric studies suggest it could be smaller in lithium-untreated bipolar subjects (Hajek et al., 2012; Sani et al., 2018; Simonetti et al., 2016) and larger (López-Jaramillo et al., 2017) or comparable (T. Hajek et al., 2012; Sani et al., 2018; Simonetti et al., 2016) to HC in those on long-term lithium treatment, likely due to the neuroprotective effects of this medication. Studies demonstrated greater structural abnormalities in BD I compared to BD II (Toma et al., 2019), but the influence of the subtype is not always clear: for example, Hibar et al. (2016) found bigger ventricles and smaller hippocampus and amygdala in BD patients. However, when stratifying for subtype, they found no significant differences between BD II and BD I, and no significant differences between BD II and healthy controls.

WM microstructural characteristics have been primarily investigated by mean of Diffusion Tensor Imaging (DTI). The four main diffusion indexes, namely fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) allow the investigation of WM microstructural abnormalities (Alger, 2012; Shizukuishi et al., 2013). The most replicated finding in DTI studies comparing BD I to HC is that of lower FA in the patient groups. Although these findings appear to be widespread (Abramovic et al., 2018; Favre et al., 2019) rather than localized in specific areas of the brain, some tracts have shown more consistent and marked diffusivity alterations than others. Among these, we find the corpus callosum (Abramovic et al., 2018; Bellani et al., 2016; Duarte et al., 2016; Favre et al., 2019; Squarcina et al., 2017) and cingulum (Bellani et al., 2016; Duarte et al., 2016; Favre et al., 2019). Other commonly involved fiber tracts are the corona radiata (Barysheva et al., 2013; Abramovic et al., 2018; Bellani et al., 2016; Favre et al., 2019; Squarcina et al., 2017)), longitudinal fasciculi (Barysheva et al., 2013; Vederine et al., 2011; Bellani et al., 2016; Squarcina et al., 2017; Nortje et al., 2013), posterior thalamic radiation (Abramovic et al., 2018; Barysheva et al., 2013; Favre et al., 2019; Nortje et al., 2013; Vederine et al., 2011), uncinate fasciculus (Bellani et al., 2016; Favre et al., 2019; Nortje et al., 2013), internal capsule (Bellani et al., 2016; Favre et al., 2019; Squarcina et al., 2017) and external capsule (Abramovic et al., 2018; Favre et al., 2019). These WM tracts are part of the limbic, frontal and temporo-parietal circuits, which all play a role in emotional regulation and cognitive functioning. Results in BD I are generally more robust (Bellani et al., 2016; Nortje et al., 2013).

In this context, tract-based spatial statistics (TBSS) gained popularity in the evaluation of WM tracts' integrity due to the high sensitivity and suitability for comparisons across groups. Moreover, it allows partially overcoming the issues of misalignment and smoothing, typical of voxel-based morphometry (VBM) analyses (Smith et al., 2006). On the other hand, the fractal analysis of the brain is a way to estimate the morphological complexity of cerebral structures by measuring the fractal dimension (FD) (Squarcina et al., 2017; Di Ieva et al., 2014), an index of self-similarity and space-filling properties measured by mean of the box-counting method (Di Ieva et al., 2015). Lower values of FD in white and gray matter, as found in BD patients (Squarcina et al., 2017) could be an early sign of apoptosis which leads to microstructural alterations (Losa, 2014).

With this study, we investigated the tissue integrity of white matter in bipolar disorder, using TBSS and fractal geometry, with the aim of elucidating the WM microstructural changes happening in BD I, both from a morphological and functional point of view.

2. Methods

2.1. Participants

The present study includes a total of 374 participants (227 HC, 147 BD I patients, details in Table 1) recruited at five different research centers, i.e., the University of Verona (n = 130), Verona, Italy, the Institut für Neuropsychologie in Mannheim (n = 75), Germany, Centre Hospitalier Universitaire de Grenoble (n = 19), France, University of Pittsburgh, (n = 82) PA, USA, and Neurospin in Paris (n = 68), France. 20 subjects were non medicated at the time of the scan. The diagnosis of BD I was confirmed by means of the fourth edition of the Structured Clinical Interview for DSM Disorders (SCID-IV). All the procedures were in accordance with the Helsinki Declaration of 1975. All subjects signed a written informed consent to the protocol. Demographics of the subjects are reported in Table 1.

2.2. Data acquisition and analysis

DTI acquisition parameters for each site are reported in Table 2. In order to evaluate both the characteristics of water diffusion and the structural integrity of the WM tracts, the original DTI data were analyzed using two different techniques, namely TBSS and FD analysis.

2.3. Preprocessing

First of all, the DTI images were corrected for distortions using FSL eddy correction tool (Jenkinson et al., 2012). Secondly, the images were skull-stripped and the data were fit to the tensor model using the function FDT of FSL. This allowed us to and create an FA map for each participant. To minimize the effect of the acquisition scanner on the FA maps, we applied a method developed specifically to harmonize DTI data after their collection (ComBat, Johnson et al., 2007). Briefly, with this method, introduced first in the context of gene expression analysis, location and scale are adjusted according to a Bayesian framework, with the aim of minimizing site effects while keeping the biological variability (e.g., due to age, sex, disease). ComBat has been shown to

Table 1
Demographics of the subjects participating to the study (n = 374,110+).

	HC Age (years, mean (SD))	BD Age (years, mean (SD))
Overall sample (n = 374)	227 (92 males)) 34.50 (11.56)	147 (73 males) 38.31 (11.72)
University of Verona (n = 130)	110 (46 males) 32.10 (11.18)	20 (10 males, 8 depressed, 12 euthymic) 34.76 (13.27))
Institut für Neuropsychologie in Mannheim (n = 75)	35 (14 males) 41.27 (12.13)	40 (17 males, 9 unmedicated) 40.50 (10.68)
Centre Hospitalier Universitaire de Grenoble (n = 19)	9 (4 males) 41.67 (11.03)	10 (6 males, 10 euthymic, 2 unmedicated) 41.50 (7.84))
University of Pittsburgh (n = 82)	27 (11 males) 32.81 (6.42)	55 (12 males, 20 depressed, 34 euthymic, 9 unmedicated) 33.45 (8.54)
Neurospin in Paris (n = 68)	46 (17 males) 34.83 (12.07)	22 (17 males) 34.64 (11.55)

HC = healthy controls; SD = standard deviation; BD = bipolar disorder.

Table 2
Details of DTI acquisition in the different centers.

Centre	Magnetic field (manufacturer)	B0 (mm/s^2)	TR (s)	TE (s)	Flip angle	Directions
University of Verona (Verona)	3 T (Siemens)	1000	5	0.12	90°	35
Institut für Neuropsychologie (Mannheim)	3 T (Siemens)	1000	14	0.09	90°	41
Centre Hospitalier Universitaire de Grenoble (Grenoble)	3 T (Philips)	600; 1000; 1400	10.8	0.10	90°	30
University of Pittsburgh (Pittsburgh)	3 T (Siemens)	1000	14	0.09	90°	41
Neurospin (Paris)	3 T (Siemens)	1000	14	0.09	90°	41

outperform other harmonization methods when used on DTI data (Fortin et al., 2017).

2.4. TBSS, fractal analyses and statistics

The TBSS analysis was conducted using the standard processing pipeline available in FSL (Smith et al., 2006). TBSS was applied to the data harmonized using ComBat. First, we obtained a mean FA map by performing a non-linear registration of all the FA images to the FMBRIB-FA standard space using FSL-FNIRT (Andersson et al., 2010). Subsequently, a "skeleton" was obtained by thinning of the WM tracts, and values for all subjects were obtained by projecting the FA values of the center of each tract to the skeleton.

Voxel-wise cross-subject statistics were applied to the data by using FSL randomize function ($p < 0.05$, 5000 permutations). The results were corrected for multiple comparisons with threshold-free duster enhancement (TFCE, Winkler et al., 2014). Due to the possible biological variability in WM diffusion associated to age and sex, these factors were used as covariates. Moreover, also the scanning site was considered as a covariate, due to the known effects of different scanners and scanning sequences on DTI quality, even if this effect was reduced with ComBat. In a separate analysis, we considered only patients undertaking medication.

The fractal dimension was estimated on the harmonized data, using the box-counting method we applied in a previous study (Squarcina et al., 2015), obtaining an FD value for each slice. Briefly, we modified the standard boxcount algorithm (Mandelbrot) by taking into account the voxels' intensity level, so to avoid the need of a segmentation pre-processing step and exploit the whole information given by the image. We computed the slice-by-slice FD values for the whole brain, and then for each lobe (frontal, parietal, temporal, occipital). We then applied the ANOVA test slice by and obtained the *P* values at each slice, at the whole brain and at the lobe level. The influence of the different variables (diagnosis, age, sex, center) on the model was tested to better understand their contribution to the variability of FD. In an additional analysis, we considered only the medicated patients, similarly to the TBSS analysis.

In order to compare the FD values of individual BD participants to an FD value assumed to be representative of the healthy population, a template (TMP) was built by averaging the HC data. Furthermore, we computed the standard deviation (SD) of HC values and used it to create a confidence interval of 2SD around the mean value. By doing this, it was possible to assess the deviations of BD individual data from the mean of HC, and detect any value found outside the confidence interval.

3. Results

3.1. TBSS

TBSS results show a widespread reduction of FA in the WM of BD patients, with the most significant differences ($p = 0.05$, TFCE corrected) located in the CC, anterior and posterior CR, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), IC, EC, CR, thalamus and inferior fronto-occipital fasciculus (IFOF) (Fig. 1). Overall, FA appears to be reduced in a bilateral fashion. Very similar results were obtained considering only patients taking medication (Fig. 2).

3.2. Fractal analysis

ANOVA results for the whole brain are reported in Table 3. We obtained a main effect of diagnosis only in slices 12, 14 and 21. Also a main effect of age, center and sex could be detected. Similar results were obtained considering only medicated patients, with a main effect of diagnosis in slices 12 and 14, and effects of center, age and sex (Table 4).

Similar results for frontal, parietal, temporal, occipital lobes were obtained and are reported in Tables S1-S4 for all patients together, and Tables S5-S8 considering only medicated patients. We also found some interaction effects in some isolated slices, regarding primarily age and sex and sex and age. In all, our results highlight some sparse differences between HC and BD. Results were similar when we considered the lobes

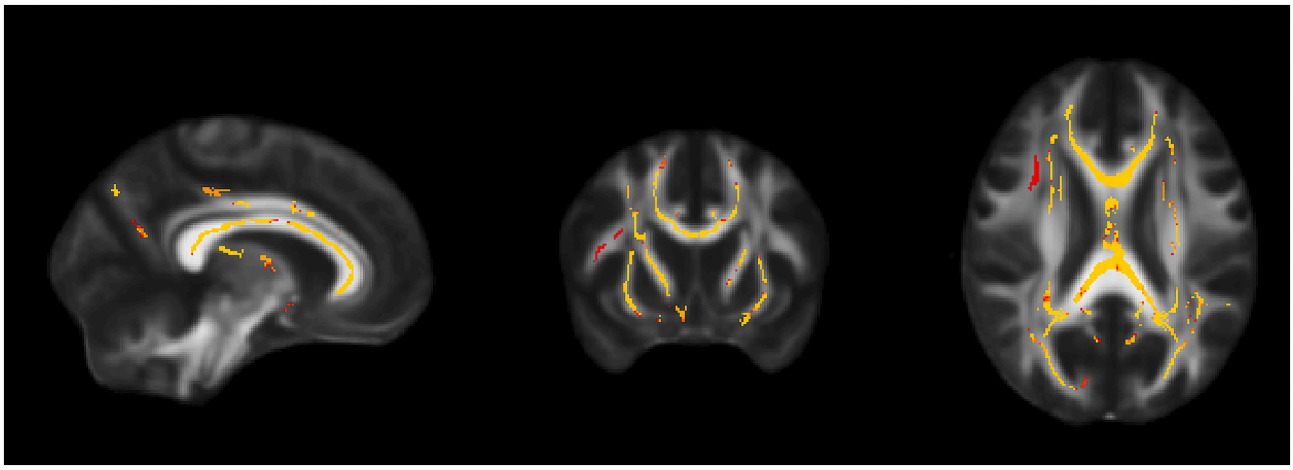

Fig. 1. Results of TBSS analysis for BD I patients compared to HC ($p = 0.01$ (yellow) to 0.05 (red), TFCE corrected). Age, sex and center were considered as covariates. In these slices the most affected structures (yellow) are the corpus callosum, internal capsule, external capsule and superior longitudinal fasciculus, which are visible in the middle and right images. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

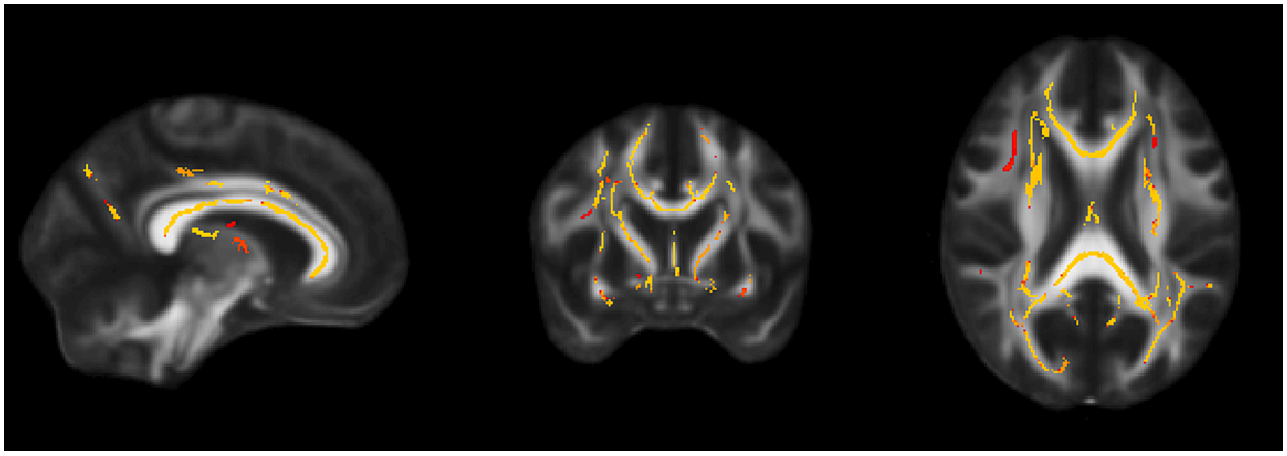

Fig. 2. Results of TBSS analysis for medicated BD I patients compared to HC ($p = 0.01$ (yellow) to 0.05 (red), TFCE corrected). Age, sex and center were considered as covariates. In these slices the most affected structures (yellow) are the corpus callosum, internal capsule, external capsule and superior longitudinal fasciculus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

separately (Tables S1-S8), with sparse differences between groups.

4. Discussion

In this work, we investigated WM changes in BD I from a microstructural and a morphological point of view. We evaluated microstructural alterations in the major WM tracts using TBSS, and morphological differences between BD patients and HC using fractal geometry. We found widespread reduced FA in patients in respect to HC with TBSS. The fractal analysis could not identify consistent differences between groups, but could give interesting insights at the individual level.

Morphological, functional and structural alteration in the brains of BD I patients have been consistently demonstrated with a variety of MRI methodologies. In particular, loss of volume in frontal, temporal and parietal areas has been demonstrated with structural imaging, while microstructural alterations in the major WM tracts, both intra- and interhemispheric, have been shown thanks to diffusion imaging. The CC, SLF, ILF, and thalamic radiations have all been demonstrated to be altered in terms of diffusion (Favre et al., 2019). These alterations, namely lower values of FA in patients, and higher values of MD and RD, hint to a loss of organization in brain connections, leading to defective brain connectivity. Our results are in line with previous literature: we found widespread reductions of FA in all major WM fibers. This points at a general alteration in brain connectivity: mood symptoms have in fact been linked with fronto-limbic and interhemispheric dysconnectivity (Favre et al., 2019).

In particular, the CC plays a fundamental role in inter-hemispheric connectivity, and has been consistently found to be altered in BD I from a microstructural point of view (Bellani et al., 2016; Brambilla et al., 2003). Notably, the fibers specifically stemming from the genu of CC interconnect frontal areas (Prunas et al., 2018), known to be heavily involved in BD. A lower FA in the genu of CC might mirror axonal disorganization, gliosis or deterioration of the axonal myelin sheaths (Beaulieu and Allen, 1994). Our results are in line with previous literature reporting disrupted callosal microstructure (Bellani et al., 2016; Brambilla et al., 2003).

We also found lower FA in the cingulum of BD I patients: the cingulum is one of the main pathways in the limbic system, thus its impairment is in line with dysconnectivity models of BD involving this particular network (Mahon et al., 2010), involved with emotion regulation and processing. The role of the limbic system in BD has been extensively investigated, given its possible role in the pathophysiology of the disease (Vai et al., 2019), and its involvement with BD has also been confirmed by imaging genetic studies (Li et al., 2022) exploring the relationship between BD genetic risk and neuroimaging signatures.

Our results demonstrated a reduction in FA bilaterally in the superior and inferior longitudinal fasciculi: these WM tracts are implied in memory, language, attention and emotional functions (El Nagar et al., 2021), which are all heavily involved in BD I symptomatology. Disruptions of WM microstructure in these regions have been found both in BD and in schizophrenia (El Nagar et al., 2021), and have been related with psychotic symptoms. Moreover, lesions in the longitudinal fasciculi in BD have been associated with deficits in executive tasks (Biesbroek et al., 2013), working memory and processing speed (McKenna et al., 2015). Interestingly, when we considered only patients taking medication, accounting for around 10 % of the patient population, we did not notice any difference at a group level, indicating that the presence of patients not taking medication did not influence the results in terms of brain tissue integrity.

With this work, we aimed to evaluate WM morphology, jointly with microstructure. In a previous work of ours (Squarcina et al., 2017) we demonstrated that BD I patients show lower FD than controls in structural MRI images, mirroring a decrease in complexity of cerebral structures. Deviations of brain FD values in patients have been demonstrated also in schizophrenia (Squarcina et al., 2017; Narr et al., 2004; Sandu et al., 2008; Nenadic et al., 2017), attention deficit disorder (Li et al., 2007) and obsessive-compulsive disorder (Ha et al., 2005). A local increase of FD in patients with BD (Nenadic et al., 2017) has been linked to early neurodevelopmental pathologies which, possibly mediated by genetics, might contribute to BD etiology.

Our results demonstrate a deviation of FD values in BD I patients, taken individually, in respect to average values obtained from HC images. Fig. 3 illustrates how the FD of some specific subjects affected by bipolar disorder deviates from the mean value of HC. The trend of the patients FD can be easily compared to the TMP HC FD. The selected patients were found to have significantly abnormal FD values when considering the entire brain or just a region (i.e., frontal, temporal, parietal, occipital) at specific slices. While the effect of BD on FD is not consistently visible at a group level, it is significant when considering FD data at a subject level.

Fractal properties measured from structural MRI data have been demonstrated to be altered in psychiatric conditions: higher FD was found in schizophrenia (Narr et al., 2004; Sandu et al., 2008). Differently from other approaches, we compute a FD value for each MRI slice, so to evaluate the geometric properties of the tissue more locally. This was done with the aim of avoiding possible underestimation of the modifications induced by the pathology, which may happen when considering the whole brain or multiple regions at once. As in our previous work (Squarcina et al., 2017) our technique does not need a hard

Table 3
Fractal analysis ANOVA results (p-values) for each slice, for the whole brain. Significant results ($p < 0.05$) are reported in bold.

	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DiAGNOSIS	0.89	0.57	0.54	0.19	0.75	0.99	0.78	0.28	**0.01**	0.58	**0.00**	0.31	0.24	0.20	0.60	0.25	0.53	**0.04**	0.75	0.08
Centre	0.05	0.91	0.85	0.38	**0.04**	0.08	0.50	0.59	0.12	0.93	0.07	0.94	0.10	0.34	0.56	**0.00**	**0.00**	0.36	0.38	0.27
Age	0.22	0.43	0.23	0.94	0.05	0.48	**0.00**	**0.02**	0.10	0.15	0.24	0.06	0.25	0.08	0.10	0.10	0.97	0.15	**0.02**	0.10
SEX	0.71	0.50	0.48	0.27	0.65	0.71	0.76	0.33	0.90	0.31	0.55	0.81	0.20	0.94	0.99	**0.03**	0.68	0.25	0.76	**0.01**
diagnosis X centre	0.13	0.94	0.77	0.22	0.66	0.65	0.13	0.81	0.98	0.97	0.08	**0.01**	0.81	0.26	0.33	0.84	0.64	0.40	0.42	0.51
diagnosis X age	0.65	0.77	0.62	0.11	0.77	0.45	0.80	0.22	**0.00**	0.33	**0.00**	0.09	**0.04**	**0.03**	0.47	0.06	0.52	0.09	0.45	0.07
diagnosisX SEX	0.69	0.69	0.59	0.87	0.35	0.32	0.84	0.96	0.86	0.09	0.68	0.20	0.58	0.32	0.84	0.10	0.07	**0.01**	0.89	0.37
Centre X age	**0.04**	0.56	0.93	0.61	**0.02**	0.37	0.69	0.43	0.32	0.92	**0.03**	0.49	**0.04**	0.16	0.61	0.18	0.09	0.60	0.47	0.37
Centre X SEX	0.78	0.01	0.04	0.28	0.93	0.54	0.23	0.21	0.80	0.12	0.45	0.31	**0.03**	0.58	0.38	0.92	0.89	0.90	0.07	0.86
SEX X age	0.49	0.08	0.22	0.25	0.42	0.95	0.70	0.07	0.76	0.12	0.10	0.14	**0.03**	0.69	0.47	**0.00**	0.22	0.11	0.18	0.06

Table 4
Fractal analysis ANOVA results (p-values) for each slice, for the whole brain, only considering patients taking medication. Significant results ($p < 0.05$) are reported in bold.

	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DiAGNOSIS	0.87	0.77	0.46	0.27	0.56	0.69	0.97	0.20	**0.01**	0.71	**0.00**	0.55	0.52	0.19	0.86	0.28	0.58	0.09	0.59	0.10
Centre	0.20	1.00	0.71	0.40	**0.04**	0.09	0.41	0.76	0.15	0.85	0.13	1.00	0.10	0.36	0.43	**0.00**	**0.00**	0.38	0.36	0.47
Age	0.09	0.18	0.14	0.76	**0.04**	0.29	**0.01**	**0.04**	0.18	0.23	0.38	0.17	0.51	0.09	0.25	0.19	0.99	0.14	**0.03**	0.16
SEX	0.28	0.32	0.39	0.38	0.68	0.59	0.66	0.79	0.52	0.43	0.72	0.99	0.29	0.81	0.83	0.08	0.65	0.35	0.93	**0.01**
diagnosis X centre	0.28	0.91	0.76	0.37	0.66	0.52	0.17	0.66	0.99	0.98	0.15	**0.02**	0.76	0.26	0.38	0.90	0.75	0.52	0.28	0.47
diagnosis X age	0.78	0.89	0.62	0.15	0.62	0.70	0.99	0.15	**0.00**	0.41	**0.00**	0.18	0.13	**0.03**	0.66	0.07	0.49	0.18	0.35	0.07
diagnosisX SEX	0.42	0.71	0.41	0.80	0.23	0.36	0.86	0.90	0.59	0.09	0.61	0.27	0.49	0.33	0.94	0.09	0.08	**0.01**	0.79	0.30
Centre X age	0.10	0.75	0.80	0.65	**0.02**	0.43	0.50	0.56	0.33	0.82	0.06	0.53	**0.03**	0.17	0.46	0.18	0.10	0.62	0.51	0.58
Centre X SEX	0.62	**0.01**	**0.01**	0.34	0.79	0.50	0.28	0.20	0.62	0.14	0.44	0.18	**0.02**	0.64	0.32	0.89	0.79	0.89	0.07	0.75
SEX X age	0.21	0.07	0.14	0.29	0.48	0.80	0.60	0.26	0.96	0.16	0.18	0.18	0.05	0.98	0.50	0.**00**	0.18	0.17	0.35	0.08

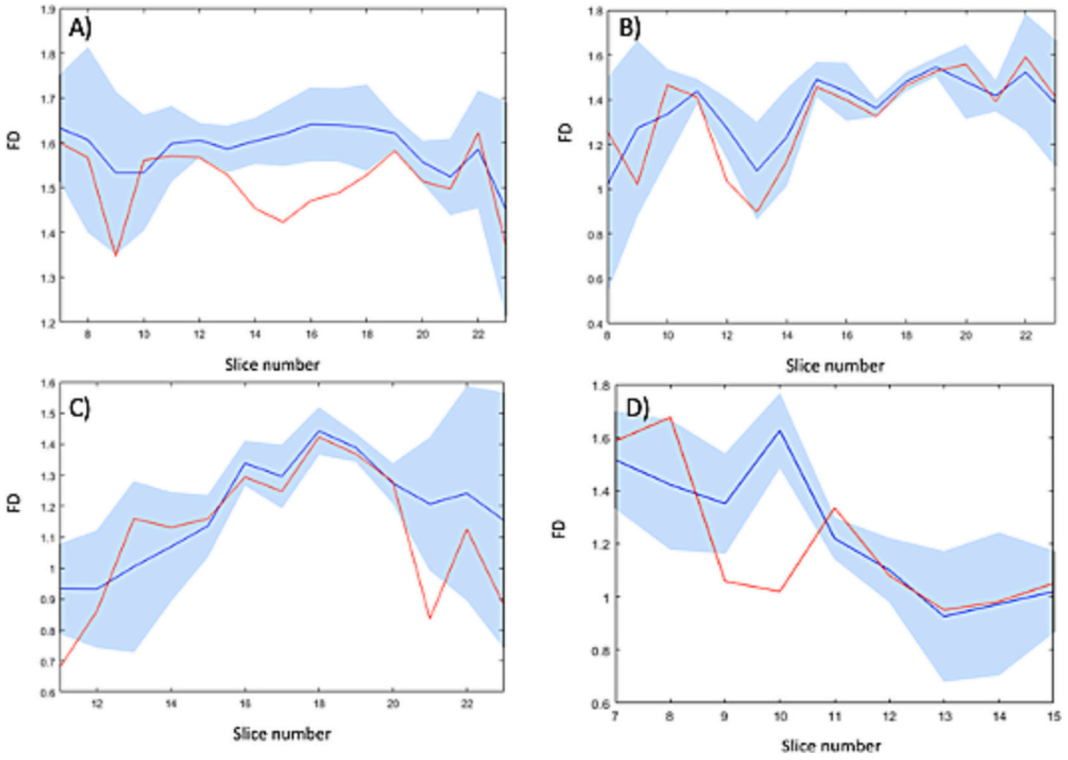

Fig. 3. Graphs comparing patients' FD (red line) to the template HC values (blue line) and confidence interval (average ± 2SD, comprising 95 % of HC values, light blue area) in the whole brain (A), frontal lobe (B), parietal lobe (C), temporal lobe (D). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

segmentation before the application of the boxcount algorithm for the estimation of FD. We applied the FD estimation algorithm directly on the FA images, since the intensity of these images is linked with the microstructural tissue integrity: in this way, we took into account the variations of FA caused by tissue alterations.

4.1. Limitations

A limitation of this study is the fact that the DTI sequences have not been harmonized before acquisition: we minimized the effect of inter-scanner variability applying a harmonization procedure, but it has to be taken into account that the site effect was not completely removed from the data. In fact, at some slices it is still possible to notice how the center played an important role in causing the differences between the two groups. Moreover, the size of samples across different site is different, which may partially influence results. Another source of heterogeneity is the co-presence of euthymic and depressed patients: this heterogeneity is mitigated by the fact that the patients' phase is not correlated with the specific site. Finally, given the multicentric nature of this study, patients were treated following local clinical practice, which limited the possibility to control the analyses for medications. This aspect should be taken into account by future studies, as some drugs, such as Lithium, may have neuroprotective effects, ultimately impacting on brain tissue characteristics.

5. Conclusions

In this work, we aimed at elucidating the impact of BD in the patient population, as well as unveiling particular, individual changes induced by the pathology on a specific subject. Importantly, our method allows an individual evaluation of the brain complexity, which is not possible with group-level analyses, as TBSS, which are inherently limited to comparing groups. These techniques indeed grant the study of the etiology of the diseases, but the individual contribution of single patients becomes somewhat lost. We believe that with our approach, the possibility of identifying changes in a particular patient, guided by modifications in microstructure happening in the whole BD population, becomes predominant and may be of great help in the diagnostic process and towards a personalized evaluation of brain changes in BD I.

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CRediT authorship contribution statement

All authors: conceptualization, writing – reviewing and editing.

Letizia Squarcina: literature search curation, statistical analyses, writing – original draft.

Susanna Lucini Paioni: literature search curation, statistical analyses writing – original draft.

Maria Gloria Rossetti: data curation.

Paolo Brambilla: supervision.

Declaration of competing interest

None.

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