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Research paper

T-cell immunophenotype correlations with cortical thickness and white matter microstructure in bipolar disorder

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A B S T R A C T

Background: Inflammation and immunological alterations, such as T-cell and cytokine changes, are implicated in bipolar disorder (BD), with some evidence linking them to brain structural changes (e.g., cortical thickness (CT), gray matter (GM) volume and white matter (WM) microstructure). However, the connection between specific peripheral cell types, such as T-cells, and neuroimaging in BD remains scarcely investigated.
Aims of the study: This study aims to explore the link between T-cell immunophenotype and neuroradiological findings in BD.
Methods: Our study investigated 43 type I BD subjects (22 depressive, 21 manic) and 26 healthy controls (HC), analyzing T lymphocyte immunophenotype and employing neuroimaging to assess CT for GM and fractional anisotropy (FA) for WM.
Results: In lymphocyte populations, BD patients exhibited elevated CD4+ and CD4+ central memory (T_{CM}) cells frequencies, but lower CD8+ effector memory (T_{EM}) and terminal effector memory (T_{TEM}) cells. Neuroimaging analysis revealed reduced CT in multiple brain regions in BD patients; and significant negative correlations between CD4 + T_{CM} levels and CT of precuneus and fusiform gyrus. Tract-based spatial statistics (TBSS) analysis showed widespread alteration in WM microstructure in BD patients, with negative and positive correlations respectively between FA and radial diffusivity (RD) and CD4 + T_{CM}. Additionally, positive and negative correlations were found respectively between FA and RD and the CD8 + T_{EM} and CD8 + T_{TEM} subsets.
Conclusions: Our research revealed distinct T lymphocyte changes and brain structure alterations in BD, underscoring possible immune-brain interactions, warranting further study and therapeutic exploration.

1. Introduction

1.1. Bipolar disorder

Bipolar disorder (BD) is a chronic and disabling condition that profoundly affects emotions, energy levels, and cognitive processes. It is characterized by episodes of mania or hypomania, as well as depression, often accompanied by mixed features. BD affects over 1 % of the general population and has a significant hereditary component, although its genetic basis is complex (Vieta et al., 2018).

1.2. Immune dysfunction in BD

While the exact underlying mechanisms of BD remain unclear, there is growing support for the involvement of neuroinflammation as a hypothesis. In recent years, the field of immuno-neuropsychiatry has gained increasing interest in the study of the etiopathogenesis of psychiatric disorders and numerous studies, supported by investigations of

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biomarkers in plasma, cerebrospinal fluid, and postmortem brain tissue, have provided evidence of the involvement of neuroimmune mechanisms in the pathophysiology of BD (Isgren et al., 2017). Additionally, there is emerging evidence suggesting the potential effectiveness of anti-inflammatory treatments in the management of BD (Fitton et al., 2022). The role of the immune system in bipolar disorder has been supported by population-based studies, which indirectly confirm the connection between mood disorders and immune system dysfunctions. Multiple studies consistently reported the presence of chronic low-grade inflammation in individuals with BD, indicating innate immune system dysfunctions. Abnormal expression of immune-related genes and elevated levels of pro-inflammatory cytokines, such as IL-1β, TNF-α, and CRP, have been observed in the serum and cerebrospinal fluid of individuals with BD, as well as evidence of microglial activation. These inflammatory markers have the potential to disrupt the activity of neuroendocrine axes and neurotransmitter systems, contributing to mood, cognitive, and behavioral abnormalities associated with the disorder (Bauer and Teixeira, 2019; Rosenblat, 2019). More limited research on adaptive immunity alterations in BD suggest the presence of autoreactive T lymphocytes, together with increased levels of pro-inflammatory cytokines, macrophage/monocyte inflammatory activation, and alterations in blood-brain barrier permeability (Benedetti et al., 2020; Furlan et al., 2019). Altered circulating lymphocyte frequencies and subpopulations, crucial for cell-mediated immune response, are observed in BD. Differentiating from lymphoid stem cells are natural killer (NK) cells, CD4 and CD8 subsets of T-cells, and B cells. CD4 cells secrete cytokines, aiding immune response, while CD8 cells mediate cytotoxic responses. Their dysregulation might have a potential involvement in BD pathophysiology (Z. Chen et al., 2023). Remarkably, alterations in the circulating frequencies of T lymphocytes and their subpopulations, have been observed in BD and its various phases (Barbosa et al., 2014a; Barbosa et al., 2014b; Becking et al., 2018; Brambilla et al., 2014; Breunis et al., 2003; Çakır et al., 2015; Counotte et al., 2018; Do Prado et al., 2013; Drexhage et al., 2011; Foiselle et al., 2023; Lu et al., 2019; Maes et al., 2021; Magioncalda et al., 2018; Pietruczuk et al., 2019; Poletti et al., 2017; Snijders et al., 2019; Su et al., 2022; Vogels et al., 2017; Wieck et al., 2013; Wilson et al., 1991; T. N. Wu et al., 2019; W. Wu et al., 2017). In peripheral blood of individuals with bipolar disorder (BD), there is a decrease in the percentage of CD8+ T-cells observed during both the onset of the disease and periods of euthymia. Furthermore, the CD4 + T-cell lineage exhibits a shift towards Th2 and Th17 cells, characterized by an upregulation of these subpopulations, along with a downregulation of Th1 and Tregs, suggesting a co-activation of both pro-inflammatory and anti-inflammatory pathways in BD (Z. Chen et al., 2023).

1.3. Neuroimaging studies correlated with immune dysfunction in BD

The literature on the correlation between immunological and brain structural alterations in BD includes studies investigating whole brain and/or regional gray matter volumes (Andreou et al., 2021; Bai et al., 2020; Bond et al., 2020; M. H. Chen et al., 2019, Chen et al., 2020a; Chung et al., 2013; Hoseth et al., 2016; Lesh et al., 2018; Lizano et al., 2021; Mohite et al., 2022; Papiol et al., 2008; Poletti et al., 2019b; Quidé et al., 2021; Savitz et al., 2015; Shonibare et al., 2020; Strenn et al., 2021; Tsai et al., 2022), as well as white matter volumes (Chung et al., 2013; Mohite et al., 2022; Papiol et al., 2008), cortical thickness (Lesh et al., 2018; Poletti et al., 2019a; Tu et al., 2017), and white matter microstructure alterations (Benedetti et al., 2016; Comai et al., 2022; Dalby et al., 2013; Furlan et al., 2019; Paola et al., n.d.; Poletti et al., 2016, 2017; Poletti et al., 2019b). While many of these studies focus on assessing inflammation markers, such as cytokines, only a few studies have reported evidence regarding the correlation between peripheral cell subpopulations, such as T-cells (Magioncalda et al., 2018; Poletti et al., 2017) or NK cells (Furlan et al., 2019).

1.4. Aim of the study

The literature on bipolar disorder regarding alterations in T lymphocyte subpopulations and their correlations with white matter is particularly scarce. To the best of our knowledge, there are no studies that specifically investigate the correlations between T-cell alterations and gray matter in bipolar disorder. Given these premises, the aim of this study is to investigate alterations in T lymphocyte subpopulations and their correlations with cortical thickness and white matter integrity in bipolar disorder.

2. Methods

2.1. Subjects

A cohort of 43 patients diagnosed with bipolar disorder type I were recruited for our study from the Psychiatry Section of Ospedale Policlinico San Martino, affiliated with the University of Genova, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Maternal-Infant Science (DINOGMI). Inclusion criteria involved patients aged 18 to 65 years with a diagnosis of BD according to the criteria outlined in the Diagnostic and Statistical Manual for Mental Disorders-Fifth Edition (DSM-5). The Ethical Committee of IRCCS Ospedale Policlinico San Martino approved the study and patients were required to express willingness and provide their written consent to participate in the study. Diagnosis of the manic phase was established for a Young Mania Rating Scale (YMRS) score of ≥13, while diagnosis of the depressive phase was established for a 17-items Hamilton Depression Scale (HAM—D) score of ≥18. Exclusion criteria encompassed the following: 1) current substance use, 2) history of drug and alcohol abuse, 3) past or present use of pharmaceutical opioids or cannabinoids, 4) diagnoses of schizophrenia spectrum or other major psychiatric disorders, 5) clinical history of acute brain damage, neurodegenerative disease, intellectual disability, or loss of consciousness linked to serious neurological conditions, 6) presence of physically disabling diseases, 7) previous treatment with electroconvulsive therapy (ECT), chemotherapy, or cerebral radiotherapy, 8) pregnancy or breastfeeding, 9) left-handedness, and 10) contraindications to magnetic resonance (MR) imaging (such as claustrophobia or metallic implants). Additionally, we recruited 26 healthy controls (HC) (14 males and 12 females, mean age 41.5) who were selected through a clinical interview to ensure the absence of lifetime or current psychiatric disorders. This was further confirmed by a HAM-D score lower than 8 and a YMRS score lower than 7. The same exclusion criteria applied to the bipolar disorder group were applied to the HC group. Demographic and clinical information was collected from both the BD and HC groups. Clinical evaluations were conducted by expert clinicians and confirmed by trained psychiatrists. The recruitment interview included several assessment tools such as the Mini International Neuropsychiatric Interview (MINI), Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II), Structured Interview for Mood Disorder - Revised (SIMD-R), HAM—D, and YMRS. Sociodemographic and clinical features were investigated through psychiatric clinical history and a psychological examination. Information such as age, sex, age of onset, duration of illness was gathered. Informed consent was obtained from each patient prior to their participation in the study. The participants' data are summarized in Table 1.

2.2. Data acquisition and processing

2.2.1. MRI data

2.2.1.1. MRI data acquisition. We used a 1.5-T GE scanner with a standard head coil for MRI recording. To reduce head motion and scanner noise foam pads were employed. Through a 3D-SPGR sequence

Table 1
Demographic and clinical characteristics of patients with bipolar disorder and healthy controls.

	BD	HC
Sample size	43	26
Female n	25	12
Age Mean ± SD	45.2 ± 8.05	41.5 ± 13.6
Illness duration mean ± SD	15.7 ± 12.3	
Depression	22	
Mania	21	
Tobacco Smokers, N	26	7
Years of education, years	14.2 ± 4.1	16.8 ± 3.2
Family status (married), N	27	14

(TR/TE = 11.5/5 ms, IR = 500 ms, flip angle = 8 degree, FOV = 25.6 cm) with a resolution in-plane of 256 × 256 and slice thickness of 1 mm we were able to acquire three-dimensional T1-weighted anatomical images in a sagittal orientation. DTI was acquired with a pure axial single-shot echo-planar imaging sequence. The diffusion sensitizing gradients were applied along 60 non-collinear directions (b = 1000 s/mm^2), 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 a gap. The acquisition parameters were as follows: TR/TE = 13,750/93 ms; image matrix = 128 × 128; FOV = 24 cm; NEX = 1.

2.2.1.2. MRI data processing

2.2.1.2.1. Cortical thickness (CT) analyses. 3D T1-weighted MRI scans were converted to NIFTI format and resliced from sagittal to axial orientation. They were visually inspected, and their origin was set in correspondence of the anterior commissure. The following processes were carried out with the Computational Analysis Toolbox (CAT, version 12.6) within SPM12 using MATLAB (version 2017b). All images were normalized using an affine followed by non-linear registration, corrected for bias field inhomogeneity, and then segmented into GM, WM, and CSF components (Ashburner and Friston, 2005). The Diffeomorphic Anatomic Registration Through Exponentiated Lie (DARTEL) algebra algorithm was used to normalize the segmented scans into a standard MNI space (Klein et al., 2009) using 6 iterations. Compared to the conventional algorithm, the DARTEL approach can provide more precise spatial normalization to the template (Matsuda et al., 2012). As part of the modulation step, we performed a non-linear deformation on the normalized segmented images with the CAT12 toolbox. This modulation provides a comparison of the absolute amounts of tissue corrected for individual differences in brain size (Cousijn et al., 2012). All segmented, modulated, and normalized GM and WM images were smoothed using 8-mm full-width-half-maximum (FWHM) Gaussian smoothing. Cortical thickness (CT) was evaluated according to the projection-based thickness (PBT) method (Dahnke et al., 2013). The surface extraction pipeline used topology correction (Yotter et al., 2011a), spherical mapping (Yotter et al., 2011b), estimation of local surface complexity and local gyrification (Luders et al., 2006). Finally, cortex surfaces were smoothed (FWHM = 15 mm) and resampled to a 32 k mesh compatible with the Human Connectome Project (HCP). For each participant, we thus obtained a CT surface composed of the values of its 32,000 vertexes. Additionally, the subjects' mean CT (mCT) and Total Intracranial Volume (TIV) values were calculated.

2.2.1.3. Diffusion data analysis

2.2.1.3.1. Individual pre-processing. The diffusion-weighted data were skull-stripped using the Brain Extraction Tool implemented in FSLv6.0 (*http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/*) and then corrected for distortions caused by eddy currents and movements. The diffusion tensor (DT) was estimated on a voxel-by-voxel basis using the DTIfit toolbox, part of the FMRIB Diffusion Toolbox within FSL, to obtain fractional anisotropy (FA), mean (MD), axial (AD), and radial (RD) diffusivities maps, the latter obtained by averaging L2 and L3 images. A bedpostX processing was done on eddy-current corrected images to allow probabilistic tractography analysis later.

2.2.1.3.2. Exploratory TBSS analysis. An exploratory tract-based spatial statistics (TBSS) was performed on the whole group. Individual FA images of all subjects were non-linearly registered to a standard fractional anisotropy template (*http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FMRIB58_FA*). We did not create a study-specific skeleton template, but we non-linearly reported each subject's fractional anisotropy map to the FMRIB58 skeleton (parameter –T in the tbss_3_postreg script). This was done to better segment our results with the xTRACT atlas, as described later. The same operations were subsequently applied to the individual mean, axial, and radial diffusivity images using the previously calculated transformation. Voxelwise cross-subject statistics were then applied to these data.

2.2.1.3.3. TBSS Results segmentation. To understand which tracts the TBSS significant voxels belonged to and which tract percentage extent they covered, significant maps resulting from TBSS analysis were clustered according to the tracts defined in the xTRACT atlas. To do this, we first created a skeletonized version of each xTRACT's tract in the standard space by masking the FMRIB58 skeleton with each volume of the xtract-tract-atlases-maxprob5-1 mm image. The number of voxels composing each skeletonized xTRACT atlas tracts was calculated. Then, we masked TBSS results with each of these skeletonized tracts, and we calculated the number of significant voxels belonging to each of these tracts and their coverage percentage (the number of voxels divided by the number of voxels composing each tract *100). Mean FA, AD, RD, MD values of the significant skeleton voxels within each subject tract were correlated to T-cells population parameters to exclude any outlier subject. The CC region, not present in the xTRACT atlas, was obtained from the "Atlas of Human Brain Connections" (*http://bcblab.com/BCB/Atlas_of_Human_Brain_Connections.html*).

2.2.1.3.4. Immunological analyses. Blood samples were collected at hours between 8 and 10 a.m. on the same day that each participant underwent clinical evaluation and MRI scanning. This ensured consistency in the timeline for all procedures and data collection for every subject. Analysis of cell expression of membrane antigens was performed by immunofluorescence and flow cytometry. In particular, analyses were performed to achieve information on frequency in the peripheral blood of the following ten cells population: total CD4+ and

Table 2
T-cell subsets showing altered circulating frequency in BD patients with respect to HC. Age and gender corrected significant group differences in the cells' population investigated. *P*-values were corrected for multiple comparison according to the FDR criterion.

Nomenclature	Membrane antigens	BD	HC	*p*-Value
CD4	CD4+	65.6 ± 11.9	60.0 ± 8.14	*0.047*
CD4 + T_{CM}	CD4+ CD28+ CD45-	36.3 ± 10.1	29.4 ± 7.09	*0.023*
CD8 + T_{TEM}	CD8+ CD28-CD45RA+	6.94 + 7.79	8.89 ± 4.75	*0.025*
CD8 + T_{EM}	CD8+ CD28-CD45RA-	1.66 ± 1.57	3.31 ± 2.76	*0.023*

Table 3
T-cell subsets showing altered circulating frequency in DEP and MAN patients with respect to HC. Age and gender corrected significant group differences in the cells' population investigated. P-values were corrected for multiple comparison according to the FDR criterion.

Nomenclature	Group effect	DEP vs HC	MAN vs HC
CD4	*0.12*	*n.s.*	*n.s.*
CD4 + T_{CM}	*0.048*	*0.0054*	*0.051*
CD8 + T_{TEM}	*0.048*	*0.265*	*0.013*
CD8 + T_{EM}	*0.048*	*0.044*	*0.0054*

CD8+ T-cells as well as their subpopulations CD28 + CD45RA+ (naïve), CD28 + CD45RA- (central memory), CD28-CD45RA- (effector memory), CD28-CD45RA+ (terminal effector memory) (Fenoglio et al., 2011; Larbi and Fulop, 2014). Data were expressed as percentages of total CD3+ T-cell population (See supplementary methods).

2.3. Statistical analysis

2.3.1. Demographic and Immunology

Non-parametric *t*-test and Fisher Chi-square were run to compare continuous (e.g., age) and categorical (e.g., gender) variables between groups. The effect of group on the ten T-cells population concentration were evaluated with an Ordinal Regression Model (ORM), using age and gender as covariate, implemented in the rms package of R software (R Core Team, 2021). This approach fits ordinal cumulative probability models on continuous response variables (Liu et al., 2017) allowing to run factorial analysis also on data that does not fulfill the requirements of parametric approaches like Analysis of Variance (Anova). First, we explored BD vs HC differences, then we divided patients according to their phases (DEP, MAN, HC). Pairwise comparisons with the three groups were done with nonparametric Wilcoxon rank sum tests. The ten *p*-values were corrected for multiple comparison with false discovery rate (FDR) criteria.

2.3.2. Whole brain imaging data

Concerning whole brain imaging data, regardless of the specific implementation of either FSL (for TBSS) or SPM (for CT) software, the same General Linear Models were tested. We run three different GLM models. First, we explored the age and gender corrected *group* (DEP, MAN, HC) effect. Investigating the six canonical pairwise comparisons (HC > DEP, DEP > HC, HC > MAN, MAN > HC, MAN > DEP, DEP > MAN) and also the differences between HC and all BD (HC > BD and BD > HC). Second, only for each cells' population whose frequency resulted altered in BD with respect to HC, we investigated *group* (DEP, MAN, HC) x *cells* interactions, correcting for subjects' age and gender. Third, since in healthy controls no relation between MRI metrics and cells' frequency could be observed while disease duration may have instead modulated such relation in patients, a *group* (DEP vs MAN) x *cells* interaction, correcting for subjects' age, gender and disease duration was run. In the latter two *group x cells* analyses, each cell frequency was inserted as a regressor and contrasts evaluating their positive and negative correlation were set up for each group. In such a context, where each regressor competed with each other to explain data variance, multiple comparison correction was done in each specific MRI analysis package using family wise error (FWE) for CT analyses in SPM and threshold-free cluster enhancement (TFCE) correction for TBSS analyses in FSL. Significance threshold was set to $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

There were no significant differences in age and gender.

3.2. Immunological group differences

First, the frequencies of total CD4+ and CD8+ T-cells as well as their naïve, central memory, effector memory and terminally effector memory cell subsets were compared between BD patients and HC. A significant reduction of CD8 + T_{TEM} and CD8 + T_{EM} and an increment of total CD4 and CD4 + T_{CM}, after correcting for age and gender, was found between BD and HC. Results were summarized in Table 2.

Second, we repeated the analysis comparing HC with BP patients divided in two groups (DEP and MAN), The group effect disappeared for CD4+ and was confirmed for the other three cells population (Table 3).

Posthoc analysis showed that, compared to HC, CD4 + T_{CM} increment and CD8 + T_{EM} decrement were present in both groups while CD8 + T_{TEM} reduction only in MAN.

3.3. Whole brain group differences

The whole-brain analysis of cortical thickness (CT) group differences revealed a significant (cluster level correction, extent threshold $k > 120$) reduction in several brain clusters in both BD phases with respect to healthy controls (Fig. 1). No differences between MAN and DEP were found.

Since cortical thinning with respect to HC occurred in almost the same areas equally in both BD subgroups, for simplicity we reported and results of the contrast HC > BD, displayed in Fig. 2 and summarized in Table 4.

3.4. Relation between immunological alterations and cortical thickness in BD patients

To search for a potential relation between immunological and MRI data we proceeded as follows. First, we run a single factorial design testing the interaction between the four significanT-cell populations and the group factor, correcting for age and gender. This model evaluated whether a correlation existed between CT and the frequency of each cell population and whether the slopes of those regression lines were different between the three groups. Since we did not find any relation between cells population and CT in HC, we moved to the third model that investigated the same *group x cells* interaction but considering only DEP and MAN and controlling result also for their disease duration. No relations were found considering each separately group while, considering BD patients together, CT in two clusters of vertices resulted negatively related with

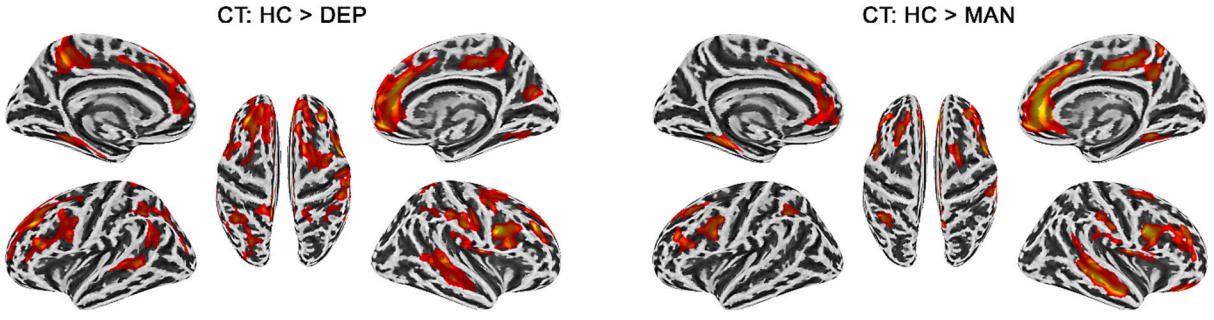

Fig. 1. CT differences between HC and BD patients divided by their phases (cluster correction with extent threshold of k > 120).

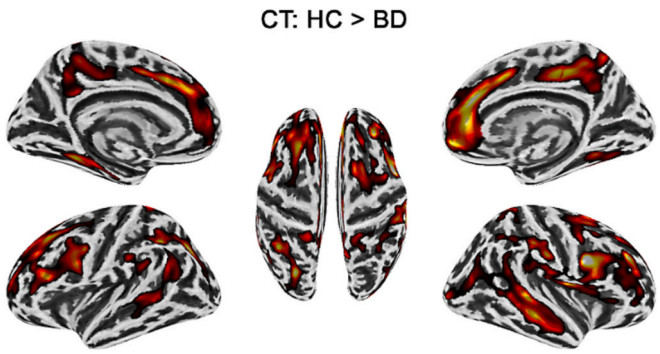

Fig. 2. CT differences between HC and all BD patients (cluster correction with extent threshold of k > 111).

CD4 + T_{CM} cells: in right precuneus cortex and left fusiform area. Results were displayed in Fig. 3 and summarized in Table 5.

3.5. Tract-Based spatial statistics (TBSS analysis)

TBSS analyses adopted exactly the same schema used for CT ones. Whole-brain TBSS analysis identified a huge number of voxels where FA and RD resulted respectively decreased and increased in both patients' subgroups compared to HC (Fig. 4).

3.6. Correlation between immunological alterations and white matter integrity in BD patients

We then explored the correlations between frequencies of group-affected T-cell subpopulations and DTI metrics. Again, no relation between DTI metrics and cells' frequencies were found and we moved to the third model investigating the two patients' subgroups and including disease duration as a further covariate. Considering both depressive and maniac patients together, we found that FA negatively correlates with the frequency of CD4 + T_{CM} cells and positively correlates with CD8 + T_{EM} and CD8 + T_{TEM} while RD did the opposite. These results are presented in Fig. 5.

Considering the two phases separately, correlation between CD8 + T_{EM} and DTI metrics could not be confirmed while that of CD8+ T_{EM} was confirmed only in DEP patients. Regarding the correlation of CD4 + T_{CM} with white matter integrity, the positive correlation with RD was present in both phases, while the positive one with FA only in DEP one (Fig. 6).

3.7. Clusterization of TBSS results in known tracts

To associate TBSS resulting voxels to known tracts and thus ease results discussion, a logical intersection between each significant TBSS map of Fig. 5 and each xTract's tract was run to calculate to which percentage the latter were involved in each correlation with cells populations. The result of this analysis is shown in Table 6.

4. Discussion

Significant differences in four cell populations were observed between groups after controlling for age and gender in our study. Specifically, individuals with BD exhibited lower levels of CD8 + T_{TEM} cells ($p = 0.025$) and CD8 + T_{EM} cells ($p = 0.023$) compared to HC. Conversely, BD patients showed higher levels of CD4+ cells ($p = 0.047$) and CD4 + T_{CM} cells ($p = 0.023$). Several studies have shed light on alterations in T lymphocytes in bipolar disorder (BD). CD8 + T_{EM} and CD8 + T_{TEM} cells play a role in immune responses to chronic antigens or persistent viral infections and are implicated in immune-mediated diseases. These cells are particularly cytolytic and express integrins and chemokine receptors facilitating their migration to inflamed tissues (Martin and Badovinac, 2018). The CD4 + T_{CM} cells refer to a specific subset of memory CD4+ T-cells. These cells play a crucial role in immune responses by providing long-term immunity and coordinating the activities of other immune cells, are characterized by their capacity to synthesize IL-2, proliferative capacity, and the ability to migrate and to recirculate through the blood, lymphatics, and secondary lymphoid organs (Künzli and Masopust, 2023). Upon re-exposure to antigens, these cells can quickly differentiate into effector cells and contribute to the immune response. The CD4 + T_{CM} have been implicated in various immune-mediated diseases and are of great interest in vaccine development and immunotherapy strategies (Raphael et al., 2020; Samat et al., 2021). The whole-brain analysis revealed reduced CT in BD patients compared to HC in multiple bilateral brain clusters extending from frontal up to occipital regions. These findings are consistent with the existing literature (Hibar et al., 2018). When considering immunological parameters, only in the BD group (corrected for disease duration) a negative correlation was found between CD4 + T_{CM} cell frequency and cortical thickness in the right precuneus, located in the posterior-medial part of the superior parietal lobule, and the left fusiform area, which is part of the inferior temporal gyrus. The precuneus is primarily involved in visual processing and serves as a central hub of the default mode network (DMN) (Cavanna and Trimble, 2006). The DMN has been associated with self-related processing, internal mental states, and emotions (Conio et al., 2019), and studies have consistently reported decreased resting-state functional activity in individuals with BD (G. Chen et al., 2022). The left fusiform gyrus, part of the ventral visual stream, plays a pivotal role in high-level visual processes such as face perception, object recognition, and reading (Weiner and Zilles, 2016). Among the fronto-parieto-temporal brain regions investigated for cortical thickness differences associated with BD in adults, the left fusiform gyrus emerged among the most pronounced and highly significant findings ($d = -0.288$; $P = 8.25 \times 10^{-21}$), according to a large-scale study by the ENIGMA Consortium. Additionally, the right precuneus was identified as another significant area ($d = -0.188$; $P = 1.00 \times 10^{-7}$) within the same study (Hibar et al., 2018). Few

Table 4
Brain vertices found thicker in HC compared to BD. Results underwent cluster correction with extent threshold of k > 111. K = cluster extension, T-score value and position [mm] within MNI atlas. Areas legenda: OFC = orbito-frontal cortex, SMG = supramarginal gyrus, SFG = superior frontal gyrus, pSTG = posterior superior temporal gyrus, preCG/postCG = pre and post central gyrus, SPL = superior parietal lobule, G. = gyrus, Cx. = cortex.

Area	*k*	*T*	x	y	z	Area	*k*	*T*	x	y	z
r. OFC	138	*4.58*	22	31	-18	l. postCG/SPL	168	*4.49*	-18	-42	74
r. Para Cingulate G.	1248	*6.03*	14	35	23	l. SMG	242	*4.47*	-51	-43	29
l. Para Cingulate G.	2838	*5.5*	-10	16	39	l. postCG	614	*4.8*	-16	-45	53
r. SFG	633	*4.98*	22	7	51	l. Temp. Occipital Fus	335	*5.59*	-32	-47	-7
r. preCG	3011	*6.91*	39	4	29	r. Temp. Occipital Fus	332	*4.95*	31	-52	-7
l. Centr. Operculum	132	*3.73*	-40	-8	15	l. Angular G.	716	*4.62*	-45	-54	21
r. postCG	124	*4.12*	42	-13	31	l. Temp. Occipital Fus	120	*3.75*	-41	-60	-21
l. SMG	111	*4.07*	-47	-28	34	l. Lateral Occipital Cx.	821	*5.93*	-26	-64	31
r. pSTG	1710	*5.46*	54	-31	0	r. Lateral Occipital Cx.	227	*4.16*	32	-66	37
r. SFG	910	*5.63*	17	-34	41	l. Lateral Occipital Cx.	156	*3.72*	-10	-67	60
r. postCG/SPL	287	*4.56*	20	-42	63	r. Cuneal Cx	111	*4.29*	20	-72	21

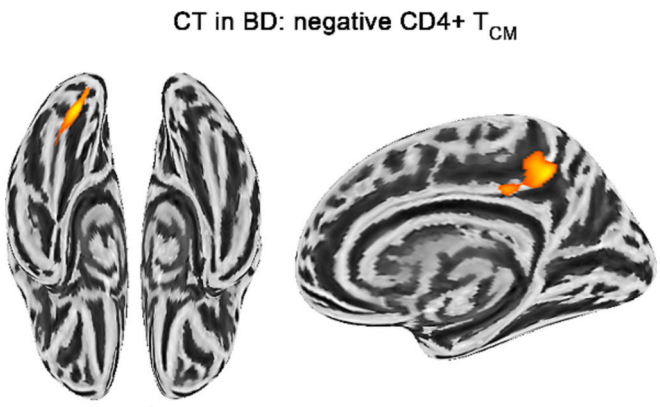

Fig. 3. Negative relation between CT and CD4 + T_{CM} in bipolar disorder.

Table 5
Brain vertices found whose thickness was negatively related with CD4 + T_{CM} cell frequency in BD. Results underwent cluster correction with extent threshold of k > 104. K = cluster extension, T-score value and position [mm] within MNI atlas.

Area	*k*	*T*	x	y	z
Right precuneus cx	217	*6.03*	8	-48	42
Left Fusiform gyrus	138	*4.02*	-23	-82	-9

studies have explored the correlation between structural MRI and inflammatory markers in bipolar disorder. Notably, a recent systematic review suggested that volumetric reductions are associated with increased pro-inflammatory markers in several brain regions, including the temporal cortex, fusiform gyrus, precuneus, frontal cortex, cingulate cortex, putamen, cerebellum, amygdala, and hippocampus (Saccaro et al., 2023). According to Chen et al., reduced gray matter volumes in the orbitofrontal, middle frontal, and inferior frontal cortices, as well as in occipitotemporal regions such as the lingual gyrus and planum polare, were negatively correlated with levels of sIL-6R (M. H. Chen et al., 2019). Notably, the same research group reported that specific regions exhibiting structural changes linked to inflammation also show related alterations in functional connectivity (P. Chen et al., 2020b; Gong et al., 2022; Tang et al., 2021). Poletti et al. found a significant negative association between tryptophan/kynurenine ratio (an indicator of pro-inflammatory state) and volumes of the left fusiform gyrus and right precuneus in depressed individuals with BD (Poletti et al., 2019a). In a study by Tsai et al., involving 31 young individuals with bipolar disorder, it was found that elevated plasma levels of YKL-40, MCP-1, and IL-1β were linked to decreased volumes of the left inferior temporal lobe. These findings suggest that these peripheral inflammatory markers may play a role in neuroinflammation, cell migration, and reactive gliosis (Tsai et al., 2022). Knowledge regarding the correlations between inflammatory parameters and CT in bipolar disorder is scarce. Tu and colleagues conducted a study involving 74 euthymic BD subjects, in which they found a correlation between higher sIL-6R levels and cortical thinning specifically in the left middle temporal gyrus ($p = 0.02$) (Tu et al., 2017). More recently, in a sample of clinically stable subjects with psychosis, including those with psychotic bipolar ($n = 61$) and schizophrenia spectrum ($n = 79$) disorders, it was found that higher CRP levels were associated with thinner cortical thickness in the right cuneus and precuneus, and left transverse temporal, postcentral, and supramarginal regions (Lizano et al., 2021). Poletti et al. found significant negative correlations between both ICAM1 and CCL4 levels and cortical thickness in the inferior temporal gyrus, as well as between sCD25 levels and cortical thickness in the parahippocampal gyrus in bipolar patients. The authors highlight that ICAM-1 is involved in T-cell activation and migration, sCD25 is crucial for regulatory T-cell maturation, and CCL4 plays a role in regulatory T-cell recruitment (Poletti et al., 2019a). Using whole-brain TBSS analysis, we found widespread reduction and increment in FA and RD values respectively in BD patients compared to HC subjects. As observed for CT analyses, significant correlations between cell populations and DTI data (namely FA and RD) were found only in BD patients, after controlling also for disease duration. Specifically, our findings indicate a negative correlation between FA and the CD4 + T_{CM} and a positive correlation between RD and the same subset. Additionally, a positive correlation was observed between FA and the CD8 + T_{EM} and CD8 + T_{TEM}, while a negative correlation was found between RD and these subsets. When examining the sample divided by disease phases, as opposed to the full sample, results show that the correlation between CD8 + T_{TEM} and DTI metrics was inconclusive, while a significant correlation with CD8 + T_{TEM} was observed only in depressed patients. In terms of the relationship between CD4 + T_{CM} and white matter integrity, the positive correlation with RD was consistent across both phases, whereas the positive correlation with FA was confirmed exclusively in the depressive phase. Nonetheless, it is important to note that these findings are based on relatively small sample sizes.

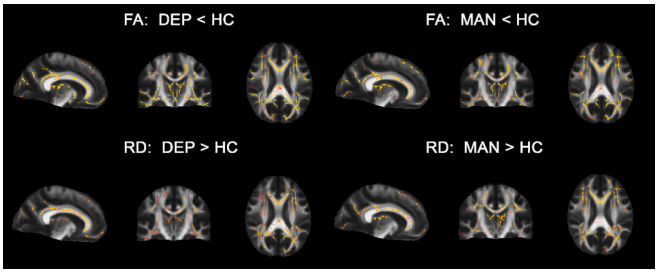

Fig. 4. Whole-brain TBSS analysis: altered white matter micro-structure between. Healthy controls and bipolar patients divided by their phases.

DTI metrics, particularly FA value, serve as an important indicator of anisotropy in white matter voxels. Higher anisotropy suggests well-formed fiber bundles that facilitate directional diffusion of water molecules. This anisotropy is observed not only in myelinated axons (Beaulieu and Allen, 1994; Kasprian et al., 2008) but also in unmyelinated axons and axonal structures (Lebel et al., 2019). Fibers' integrity is better investigated when also AD and RD, respectively axial and radial diffusivity, information is available. Since the latter reflects the diffusivity of water molecules across the myelinated fiber's membrane, the pattern of reduced FA and increased RD here observed suggests a possible myelin damage (Song et al., 2002) compatible with an inflammation process as suggested in diverse neurological disorders such as multiple sclerosis (Jones et al., 2013; Schiavi et al., 2021; Song et al., 2002). Individuals with BD exhibited extensive abnormalities of WM, characterized by significantly lower FA in regions such as the corpus callosum and cingulum. These FA reductions were correlated with the use of antipsychotic and antiepileptic therapies, while an increase in FA was associated with lithium treatment (Favre et al., 2019). The white matter tracts significantly more correlated with T lymphocyte subpopulations were found to be the corpus callosum (CC), the cingulum bundle (CB), the superior longitudinal fasciculus in its subdivisions (SLFI, II, and III), the uncinate fasciculus (UF), and the corticospinal tract (CST). The CC, essential for interhemispheric communication and coordinating sensory-motor, affective, and cognitive functions, shows plasticity linked to stress resilience (Fenlon and Richards, 2015; Galinowski et al., 2015). The CB, connecting subcortical and cortical regions, plays a crucial role in affective and neurocognitive functions (Bubb et al., 2018). The ATR is involved in executive functions and complex behavior planning (Mamah et al., 2010), as well as affective regulation and emotion processing (Coenen et al., 2012; Denier et al., 2020). SLF I and SLF II integrate sensory information and motor planning, subserving visuospatial attention and complex motor functions (Vergani et al., 2021). The SLF II, and SLF III, primarily belonging to the frontoparietal network (Kamali et al., 2014), are involved in auditory and language processing in the dominant hemisphere and spatial

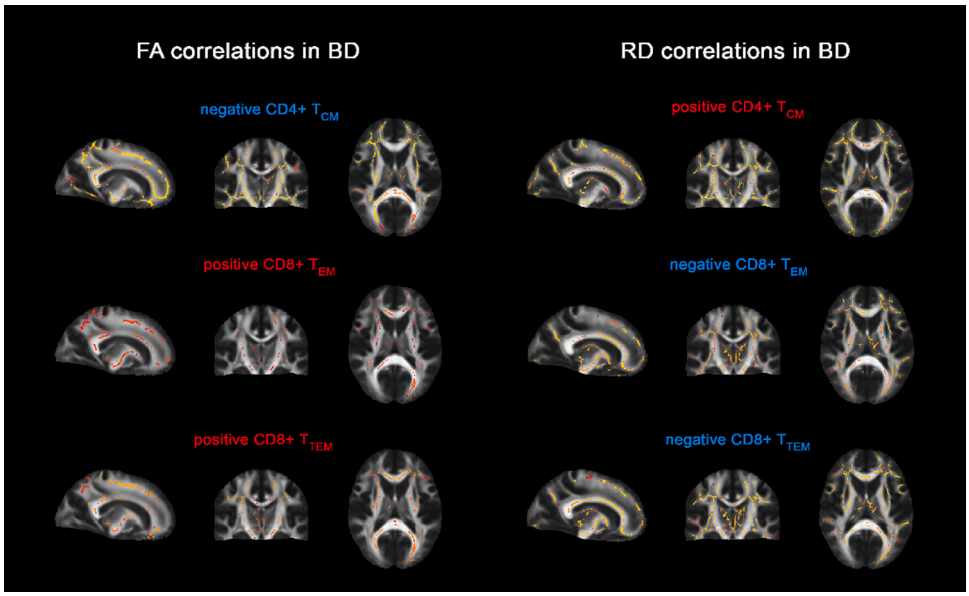

Fig. 5. Correlations between T-cell subpopulations and fractional anisotropy and radial diffusivity in bipolar disorder.

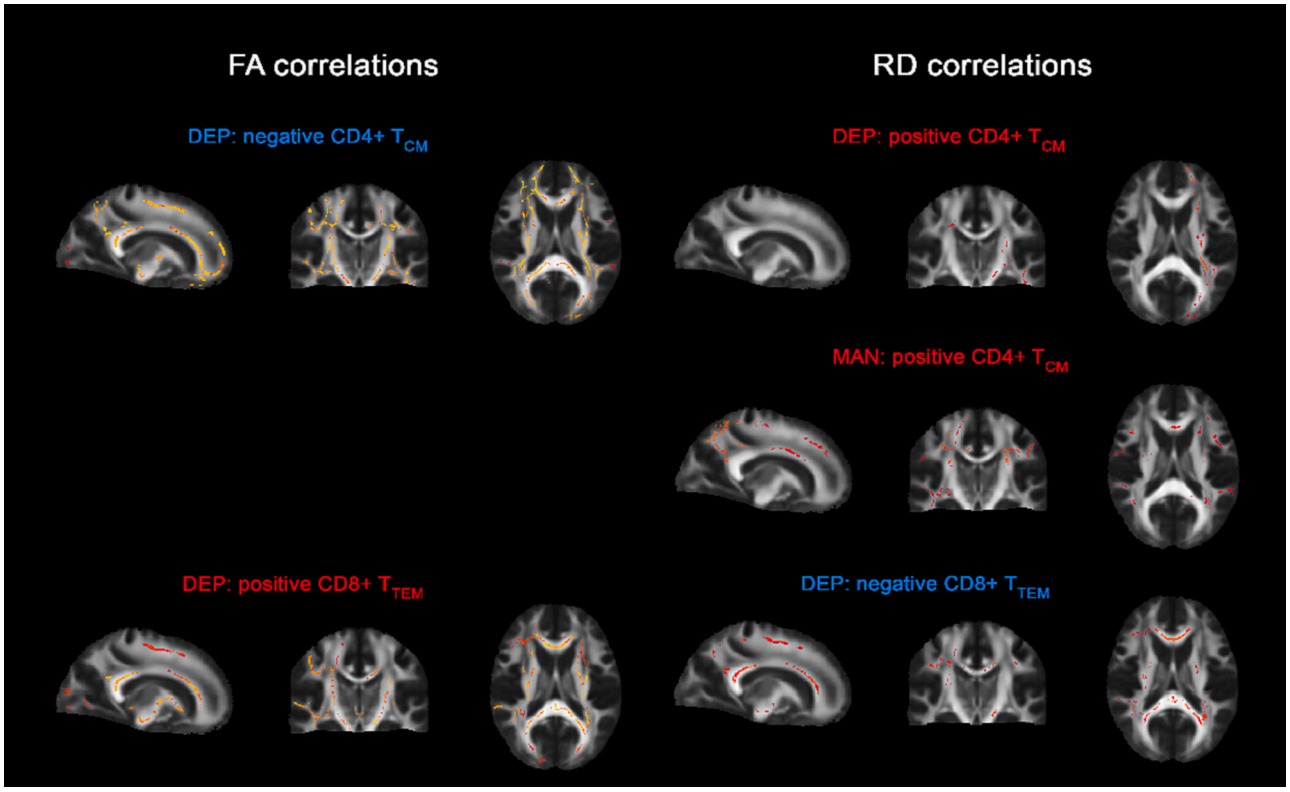

Fig. 6. Correlations between T-cell subpopulations and fractional anisotropy and radial diffusivity in bipolar disorder according to patients' phase.

processing in the right non-dominant hemisphere (Barbeau et al., 2020), as well as in metacognition and empathy (Nakajima et al., 2019). The UF is a major fiber tract that connects the ventromedial prefrontal cortex with the amygdala. It plays a crucial role in mood regulation circuitry, in decoding facial emotional expressions, and social behavior (Li et al., 2021). The CST is a key motor pathway originating from the cerebral cortex, travels through the corona radiata, posterior limb of the internal capsule, and pons (Al Masri Omar, 2011). Abnormalities in these WM tracts are consistently observed not only in bipolar disorder (Bubb et al., 2018; Duarte et al., 2016; Favre et al., 2019; Ji et al., 2019; Linke et al., 2020; Magioncalda et al., 2016; Nagar et al., 2022; Paillère Martinot et al., 2014) but also in other conditions such as schizophrenia (Kelly et al., 2018; Klauser et al., 2017) and major depressive disorder (Nortje et al., 2013; Zhang et al., 2021), as well as in youth at risk for these serious mental illnesses (Shakeel et al., 2021). The literature on the correlation between immune-inflammatory parameters and WM integrity in BD is limited. Immune system activation, including proinflammatory cytokines, CRP, NK cells, and kynurenine pathway metabolites, was associated with reduced WM microstructural integrity in individuals with bipolar depression (Aronica et al., 2022). In their

Table 6
The percentage, for each tract, of voxel significantly related with the indicated cell population. Abbreviations: af, Arcuate Fasciculus; atr, Anterior Thalamic Radiation; cc, Corpus Callosum; cbd, Cingulum subsection: Dorsal; cbp Cingulum subsection: Peri-genual; cst, Corticospinal Tract; fa, Frontal Aslant Tract; fmi, Forceps Minor; l, left; mdlf, Middle Longitudinal Fasciculus; or, Optic Radiation; r, right; slf, Superior Longitudinal Fasciculus; str, Superior Thalamic Radiation; uf, Uncinate Fasciculus.

	FA			RD		
	CD4	CD8 + T_{TEM}	CD8 + TEM	CD4	CD8 + T_{TEM}	CD8 + TEM
af_l	32.52	5.11	7.64	62.02	54.98	49.93
af_r	28.54	15.32	9.45	56.89	47.69	35.31
ar_l	44.35	16.65	10.21	42.77	25.03	26
ar_r	50.32	29.75	17.46	43.98	42.43	23.93
atr_l	51.51	34.33	29.31	53.66	55	55.09
atr_r	50.83	30.49	34.7	44.86	45.03	45.4
cbd_l	56.21	30.99	26.17	55.48	54.68	53.73
cbd_r	52.68	5.24	2.38	49.7	8.82	6.67
cbp_l	26.67	25	16.67	15	11.67	10
cbp_r	45.83	0	0	8.33	50	45.83
cbt_l	34.23	0	0	17.62	0	0
cst_l	51.78	35.75	25.92	46.65	38.51	38.36
cst_r	45.32	38.4	30.25	49.12	46.14	40.77
fa_l	31.36	29.43	34.7	59.55	54.92	54.34
fa_r	32.03	16.21	33.08	60.38	42.53	49.34
fma	35.99	29.61	14.18	47.47	31.11	30.84
fmi	61.44	45.98	41.03	66.39	56.41	57.7
fx_l	13.47	7.03	0	12.74	24.6	24.45
fx_r	13.48	8.15	0.33	17.3	14.31	5.32
ilf_l	11.49	0	0	22.94	25.59	7.29
ilf_r	19.04	10.92	1.63	27.65	18.33	8.29
ifo_l	53.99	17.12	13.61	61.94	50.29	48.63
ifo_r	51.03	30.51	23.77	64.9	42.92	46.66
mdlf_l	53.07	13.2	16.06	59.35	39.96	40.3
mdlf_r	54.11	24.22	8.09	59.14	36	27.03
or_l	44.51	29.36	24.99	66.98	49.43	39.42
or_r	51.76	14.95	11.43	62.32	25.51	32.61
str_l	49.29	38.39	16.97	54.42	60.71	48.05
str_r	37.28	37.33	14.73	50.77	53.47	42.02
slf1_l	46.85	39.7	39.07	60.18	47.65	42.98
slf1_r	50.19	44.55	34.3	61.23	47.09	49.06
slf2_l	35.5	14.5	11.57	60.57	46.63	41.9
slf2_r	46.32	30.49	21.99	64.98	43.13	38.63
slf3_l	34.3	6.22	0.93	66.37	55.85	49.07
slf3_r	44.19	11.09	16.38	54.85	45.42	40.81
ac	27.18	60	2.14	46.21	72.23	66.8
uf_l	31.31	11.76	10.26	35.58	30.04	32.06
uf_r	43.22	25.07	23.79	38.05	28.16	45.61
vof_l	11.23	15.15	4.72	35.74	38.32	25.76
vof_r	10.04	0	0	21.36	0.68	8.45
cc	44.27	38.34	33.57	56.42	49.32	47.82

study, Poletti et al. observed reduced levels of kynurenine linked to alterations in WM integrity in several association fibers such as the inferior and superior longitudinal fasciculus, cingulum bundle, corpus callosum, uncus, anterior thalamic radiation, and corona radiata in BD (Poletti et al., 2018). Poletti et al. found positive correlations between Th17 cells and FA in WM tracts, and between Treg cells and RD and MD in patients. They also observed a negative correlation between Th1 cells and white matter integrity in healthy controls, while patients showed a positive correlation between Th1 cells and pro-inflammatory cytokines (Poletti et al., 2017). A previous DTI study by Magioncalda and colleagues investigated the correlation between T-cell subpopulations and WM microstructure in BD. During the manic phase, WM abnormalities were observed in the corpus callosum and corona radiata, along with a depletion of CD8 + T_{TEM} CD4 + T-cells were increased, while CD8 + T_{EM} and CD8 + T_{TEM} subpopulations were decreased. The WM abnormalities correlated with reduced frequencies of CD8 + T_{TEM} and CD8+ IFNγ+ T-cells, suggesting a combined occurrence of WM and immunological alterations in BD during mania (Magioncalda et al., 2018). The authors suggest an acute immune response in mania, sustained by early generated CD4+ T-cell compartment, leading to activation of CD8+ T-cell subpopulations which can migrate in brain areas and actively induce WM alterations (Magioncalda and Martino, 2022). Regarding CD4 + T_{CM}, it has been reported reduced in peripheral blood in different autoimmune disease (Raphael et al., 2020). In multiple sclerosis, the expansion in peripheral blood of CD4 + T_{CM} Th1/Th17 subset has been reported, and correlates with disease severity, predicts the risk of relapse and treatment response. The CD4 + T_{CM}, characterized by its ability to display high autoreactivity, can undergo proliferation, migrates to the central nervous system, recognizes several neuroantigens and produces proinflammatory cytokines. Furthermore, their continuous activation by MHC class II-expressing cells may potentially contribute to the development of chronic inflammation and subsequent damage observed in multiple sclerosis (Paroni et al., 2017). Recent research suggests that lymphocytes and non-microglial myeloid cells may have the capacity to traverse the blood-brain barrier during inflammatory states, potentially playing a role in the emergence of psychiatric symptoms (Pape et al., 2019). In acute psychosis, alterations in peripheral lymphocyte counts, including decreased CD3+ lymphocytes and increased CD4:CD8 ratio, have been reported. Additionally, post-mortem studies have provided evidence of CD3+ and CD20+ lymphocyte infiltration in brain regions relevant to psychosis, such as the hippocampus, temporal lobe, and thalamus (Al-Diwani et al., 2017). A more recent immune-histochemical study revealed lymphocyte infiltration in brain tissue analyses of individuals with schizophrenia, bipolar disorder, and major depressive disorder, indicating compromised blood-brain barrier integrity and neuroinflammation. In bipolar disorder (BD), lymphocyte infiltration has been observed in various brain regions, including the inferior, medial, and superior temporal gyri, hippocampus, paracentral lobe, as well as in the central white matter (Schlaaff et al., 2020). According to our findings, we propose that a peripheral increase of the CD4 + T_{CM} subpopulation may sustain the activation of cytotoxic CD8+ T lymphocytes facilitating their egression from the peripheral blood, where they are found reduced, to infiltrate the brain. Despite their relative increase in peripheral blood, it cannot be excluded that the CD4 + T_{CM} might migrate to brain tissue, where they could potentially exacerbate local inflammation by producing proinflammatory cytokines. This, in conjunction with a general state of neuroinflammation, could potentially contribute to cortical thinning and white matter abnormalities in crucial brain regions associated with the development of the disorder.

4.1. Limitations

This study had several limitations. The main one is the lack of longitudinal evaluations which restricts the generalizability of results, making it difficult to define the association between lymphocyte subpopulation alterations and neuroimaging changes. Nevertheless, such a study has still never been performed. A relatively small sample size was investigated here although, actually, it is similar to those found in the limited studies currently available on immunophenotypic correlates of structural alterations in bipolar disorder. Additionally, information on patients' medication (type and dosage) during the months before examination was not rigorously collected in all patients and thus could not be used to correct for its possible confounding effect. Since we investigated structural and not functional brain properties, correcting our analyses for the medication information limited at the time of the MRI recording date, could have been even more confounding.

5. Conclusions

Our study found that individuals with BD exhibited significant differences in specific cell populations, with increased CD4+ and CD4 + T_{CM} cells, and decreased CD8 + T_{EM} and CD8 + T_{TEM} cells. Reduced cortical thickness was observed in the bilateral fronto-parieto-temporal regions, with a correlation between CD4 + T_{CM} levels and cortical thinning in the left fusiform gyrus and right precuneus. Additionally, we

reported white matter alterations in various tracts, with DTI parameters showing differential correlations with CD4+ and CD8+ cell population levels. Our findings suggest a connection between immune dysregulation and brain changes in bipolar disorder, indicating potential avenues for research into immune-inflammatory treatment strategies.

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No funding source contributed directly to this work.

CRediT authorship contribution statement

Andrea Escelsior: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Alberto Inuggi:** Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **Bruno Sterlini:** Investigation, Methodology. **Anna Bovio:** Investigation, Writing – original draft. **Giacomo Marenco:** Investigation. **Juxhin Bode:** Investigation, Writing – original draft. **Luca Favilla:** Investigation. **Samuele Tardito:** Investigation. **Tiziana Altosole:** Methodology. **Beatriz Pereira da Silva:** Investigation, Resources. **Daniela Fenoglio:** Investigation, Methodology. **Gilberto Filaci:** Investigation, Methodology. **Mario Amore:** Project administration, Writing – review & editing. **Gianluca Serafini:** Conceptualization, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

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