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Long-term effect of childhood trauma: Role of inflammation and white matter in mood disorders

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ABSTRACT

Bipolar disorder (BD) and major depressive disorder (MDD) are severe psychiatric illnesses that share among their environmental risk factors the exposure to adverse childhood experiences (ACE). Exposure to ACE has been associated with long-term changes in brain structure and the immune response. In the lasts decades, brain abnormalities including alterations of white matter (WM) microstructure and higher levels of peripheral immune/inflammatory markers have been reported in BD and MDD and an association between inflammation and WM microstructure has been shown. However, differences in these measures have been reported by comparing the two diagnostic groups. The aim of the present study was to investigate the interplay between ACE, inflammation, and WM in BD and MDD. We hypothesize that inflammation will mediate the association between ACE and WM and that this will be different in the two groups. A sample of 200 patients (100 BD, 100 MDD) underwent 3T MRI scan and ACE assessment through Childhood Trauma Questionnaire. A subgroup of 130 patients (75 MDD and 55 BD) underwent blood sampling for the assessment of immune/inflammatory markers. We observed that ACE associated with higher peripheral levels of IL-2, IL-17, bFGF, IFN-γ, TNF-α, CCL3, CCL4, CCL5, and PDGF-BB only in the BD group. Further, higher levels of CCL3 and IL-2 associated with lower FA in BD. ACE were found to differently affect WM microstructure in the two diagnostic groups and to be negatively associated with FA and AD in BD patients. Mediation analyses showed a significant indirect effect of ACE on WM microstructure mediated by IL-2. Our findings suggest that inflammation may mediate the detrimental effect of early experiences on brain structure and different mechanisms underlying brain alterations in BD and MDD.

1. Introduction

Adverse childhood experiences (ACE), encompass a wide range of detrimental early life events such as physical, psychological, and sexual abuse, neglect and other environmental stressors (i.e. parental substance/alcohol abuse, domestic violence, parental separation and other forms of parental loss). The connection between ACE and the onset of psychopathology has long been established and ACE are regarded as a transdiagnostic risk factor for the development of a wide variety of psychopathological conditions (Curran et al., 2018; McLaughlin et al., 2020). Concerning major depressive disorder (MDD), ACE have been shown to increase the lifetime risk of developing depression (Wiersma, 2015), accelerate MDD onset, increase suicide rate and symptoms severity, and decrease treatment response (Hayashi et al., 2015; Nemeroff, 2016). These effects could be linked to brain structural and functional alterations due to ACE exposure (Teicher and Samson, 2013) which, indeed, preferentially affects brain circuitry associated with emotion regulation, sleep/wake regulation, threat detection, and executive functions (Teicher et al., 2016). As for Bipolar Disorder (BD), a highly hereditable condition, ACE are one of the very few established environmental risk factors for the development of the disease (Bortolato et al., 2017); ACE have also been associated with unfavorable clinical features such as rapid cycling BD, higher severity of episodes and more frequent suicide attempts (Agnew-Blais and Danese, 2016).

Early experiences have been shown to physiologically affect the development of both the brain and the immune system in order to

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maximize their adaptation to the individual's unique environment (Bateson et al., 2004; Greenough et al., 1987). On the other hand, ACE have been found to be often linked with long lasting alterations in brain integrity and the immune response. Animal studies show a reduction in fractional anisotropy (FA) and an increase in radial diffusivity (RD) in several white matter (WM) clusters in maltreated rhesus monkeys, suggesting a detrimental effect of ACE on WM maturation from childhood to adolescence (Howell et al., 2013). In humans, tract-based spatial statistics (TBSS) and tractographic studies show a general reduction of FA in the inferior longitudinal fasciculus, arcuate fasciculus, cingulum bundle, and fornix in subjects exposed to childhood abuse (Choi et al., 2009, 2012). In mood disorders, ACE have been found to have a detrimental effect on WM integrity in several fiber tracts involved in mood, cognitive functioning, and emotions both in MDD (Meinert et al., 2019; Poletti et al., 2018) and BD (Benedetti et al., 2014; Stevelink et al., 2018).

ACE have also been shown to affect the immune/inflammatory status in adulthood; childhood trauma has been shown to be linked to altered peripheral inflammatory markers later in life both in the general population and in psychiatric samples (Baumeister et al., 2016); furthermore, subjects exposed to ACE appear to be more likely to develop rheumatic and autoimmune disorders (Salihoglu et al., 2019). Therefore, considering the role of ACE as risk factors for the development of both conditions, the alteration of adulthood inflammatory status induced by ACE has been proposed to mediate, at least partially, the connection between childhood trauma and future development of psychopathology (Miller and Raison, 2016). Immune and inflammatory alterations have long been reported in both MDD and BD and are hypothesized to play a major role in their pathophysiology (Miller and Raison, 2016; Rowland et al., 2018) although distinct immune activation profiles seem to characterize the two disorders (Poletti et al., 2020b). Further, differences in the pathophysiology of the two disorders are suggested by other studies showing that distinct brain alterations may predict BD and MDD diagnosis (Vai et al., 2020) and that immune markers associate to WM microstructure in BD but not in MDD(Comai et al., 2022).

Following this line of reasoning, we hypothesize, that ACE could lead to an altered immune response with increased levels of immune/inflammatory markers, which, in turn, would affect WM microstructure. Our study had therefore several aims: 1 – to investigate the effect of ACE on peripheral inflammatory/immune markers; 2 – to investigate the effect of ACE on WM microstructure in depressed patients with a diagnosis of either MDD or BD; 3 – to investigate the effect of immune/inflammatory markers found to be affected by ACE on WM and whether the associations between ACE and WM is mediated by inflammation; 4 – to investigate if the association between ACE, inflammation, and WM microstructure is the same in MDD and BD.

2. Materials and methods

2.1. Participants and data collection

The sample was composed of 200 depressed inpatients (100 MDD and 100 BD) consecutively admitted (age 18–65) to our hospital. Among bipolar patients, 44 were taking lithium for at least 6 months, other treatments included antidepressants, atypical antipsychotics, and antiepileptic drugs. Twenty percent of MDD and 23% of BD patients were smokers. Exclusion criteria were current diagnosis of any additional psychiatric disorder, including alcohol and/or substance dependence or abuse in the last 6 months, intellectual disability, pregnancy, major medical and neurological disorders, medical conditions affecting the immune system (i.e. ongoing inflammatory diseases, autoimmune diseases, cancer) and ongoing treatment with drugs known to affect the immune system (i.e. anti-inflammatory agents, corticosteroids, immunosoppresants). All patients underwent Magnetic Resonance (MR) scanning. A subsample of 130 patients (75 MDD and 55 BD) underwent fasting blood sampling in the morning (between 7:00 to 9:00 a.m.). After a complete description of the study, written informed consent was obtained. All research activities have been approved by the local Ethical Committee.

2.2. Assessment of stress

ACE were measured using the 28 items Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The CTQ is widely used in clinical research and general population samples (Janiri et al., 2015) and has good psychometric properties (Bernstein et al., 2003). The questions refer to the period before 17 years of age. CTQ subscales emotional, physical and sexual abuse were added up to form a composite "Abuse" score, whereas from emotional and physical neglect scores was obtained a total "Neglect" score.

2.3. Laboratory determinants

Plasma concentrations of the following immune analytes were determined using the Bio-Plex Pro Human Cytokine 27-plex using the bead-based Luminex system based on xMAP technology (Bio-Rad Laboratory, Hercules, CA, USA): Cytokines: Interleukin (IL)-1β, IL-1rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Interferon (IFN)γ, Tumor Necrosis Factor (TNF)α; Chemokines: C–C motif ligand 1 (CCL2), CCL3, CCL4, CCL5, CCL11,; C-X-C motif chemokine (CXCL)10; Growth factors: fibroblast growth factor (FGF) basic, Granulocyte Colony Stimulating Factor (G-CSF), Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), Platelet-Derived Growth Factor Beta (PDGF-B), Vascular Endothelial Growth Factor (VEGF). Lower limits of quantification (LLOQ) and coefficients of variations (CVs) are shown in Table 1_suppl. Assays were performed on Luminex 200 system. Samples were analyzed according to manufacturer's instructions. The intra-assay CV was 2.3–4.8%, inter-assay CV was 4.9–28.2%.

2.4. Image acquisition

All MRI acquisition were performed at C.E.R.M.A.C. (Centro d'Eccellenza di Risonanza Magnetica ad Alto Campo) in San Raffaele hospital in Milan on two 3.0 T Philips scanners with a standard quadrature head coil. DTI was executed using SE Eco-planar imaging (EPI) and the following parameters for the first scanner TR/TE = 8753.89/58 ms, FoV (mm) 231.43 (ap), 126.50 (fh), 240.00 (rl); acquisition matrix 2.14 × 2.71 × 2.31; 55 contiguous, 2.3 mm thick axial slices reconstructed with in-plane pixel size 1.88 × 1.87 mm; SENSE acceleration factor = 2; 1 b0 and 35 non-collinear directions of the diffusion gradients; b value = 900 s/mm^2; and the following for the second Philips scanner TR/TE = 5900/78 ms, FoV (mm) 240 (ap), 129 (fh), 232 (rl); acquisition matrix 2.14 × 2.73 × 2.30; 56 contiguous, 2.3 mm thick axial slices reconstructed with in-plane pixel size 1.88 × 1.88 × 2.30 mm; SENSE acceleration factor = 2; 1 b0 and 40 non-collinear directions of the diffusion gradients; b value = 1000 s/mm^2. Fat saturation was performed to avoid chemical shift artifacts.

2.5. DT-MRI data preprocessing

DTI analysis and tensor calculations were carried out using the "Oxford Center for Functional Magnetic Resonance Imaging of the Brain Software Library" (FSL 6.0; www.fmrib.ox.ac.uk/fsl/index.html) (Smith et al., 2004; Woolrich et al., 2009). First, each DTI volumes was affine registered to the T2-weighted b = 0 vol using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson and Smith, 2001). Then, correction for motion between scans and residual eddy-current distortions present in the diffusion-weighted images was performed. After removal of non-brain tissue (Smith, 2002), least-square fits were performed to estimate the fractional anisotropy (FA), eigenvector, and eigenvalue maps. Mean diffusivity (MD) was defined as the mean of all three eigenvalues

$(\lambda_1 + \lambda_2 + \lambda_3)/3$, axial diffusivity (AD) as the principal diffusion eigenvalue (λ_1), and radial diffusivity (RD) as the mean of the second and third eigenvalues $(\lambda_2 + \lambda_3)/2$ (Stone et al., 2009).

Next, all individuals' volumes were skeletonized and transformed into a common space as used in Tract-Based Spatial Statistics (Smith et al., 2006, 2007). Briefly, all volumes were nonlinearly warped to the FMRIB58_FA template supplied with FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/FMRIB58_FA.html) and normalized to the Montreal Neurological Institute (MNI) space, by use of local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT) (Rueckert et al., 1999; Westlye et al., 2010). Next, a mean FA volume of all subjects was generated and thinned to create a mean FA skeleton representing the centers of all common tracts. We thresholded and binarized the mean skeleton at FA > 0.20 to reduce the likelihood of partial voluming in the borders between tissue classes. Individual FA values were warped onto this mean skeleton mask. The resulting tract invariant skeletons for each participant were fed into voxelwise permutation-based cross-subject statistics. Similar warping and analyses were used on MD, AD, and RD data.

Voxelwise DTI analyses were performed using nonparametric permutation-based testing (Nichols and Holmes, 2002b) as implemented in Randomise in functional MRI of the brain software library. We tested for linear effects ACE and inflammation on FA, MD, AD, and RD across the WM skeleton using general linear models. We accounted for the effects of nuisance covariates which could influence WM structure such as: age (Kochunov et al., 2007), gender (Herting et al., 2012), duration of illness (Poletti et al., 2015), lithium treatment (Benedetti et al., 2013), BMI (Mazza et al., 2017) and equivalents of imipramine. Threshold-free cluster enhancement (TFCE)(Smith and Nichols, 2009) was used to avoid defining arbitrary cluster-forming thresholds and smoothing levels. TFCE is particularly useful when the spatial correlation length of signal exceeds that of noise, as it is expected when studying WM tracts. It can be seen as a generalization of the cluster mass statistics (Bullmore et al., 1999), using spatial neighborhood information in a nonlinear image processing to increase sensitivity and boost the height of spatially distributed signals, without changing the location of their maxima. Voxelwise levels of significance, corrected for multiple comparisons, were then calculated with a standard permutation testing by building up the null distribution (across permutation of the input data) of the maximum (across voxels) TFCE scores, and then using the 95th percentile of the null distribution to threshold signals at a corrected $p < 0.05$. The data were tested against an empirical null distribution generated by 5000 permutations for each contrast, thus providing statistical maps fully corrected for multiple comparisons across space. Corrected $p < 0.05$ in a minimum cluster size of $k = 100$ was considered significant.

To overcome possible biases related to the use of two different scanners we utilized the ComBat approach(Johnson et al., 2007) for harmonization of the DTI data. Harmonization tries to control for "batch effects" of data taken using different equipment or at different locations and times and this specific method works by utilizing the Empirical Bayes method to better estimate parameters of location and scale (Eshaghzadeh Torbati et al., 2021; Horng et al., 2022; Johnson et al., 2007). The ComBat model was reconfigured for DTI analysis and has proved to be the most efficient approach for adjusting for inter-scanner and site variability in DTI scans compared to other harmonization techniques (Fortin et al., 2017).

2.6. Statistical analyses

Statistical analyses were performed using STATISTICA (StatSoft Statistica 11, Tulsa, OK, USA). Similar to previous studies, only cytokines with non-detected (missing) values $< 20\%$ were included in the analyses (Wolf et al., 1998).

Baseline clinic-demographic differences between BD and MDD groups were performed using *t*-test analyses and chi-square analyses for dichotomous variables with $p < 0.05$. In analyses comparing variables associated with an inflammatory response we employed non parametric Mann-Whitney test to account for the distributional characteristics of the data and the heterogeneity of variance. In order to control for multiple comparisons p-values were corrected through False Discovery Rate procedure (obtaining q values) (Benjamini and Hochberg, 1995).

All analyses were performed accounting for the effects of nuisance covariates that could influence peripheral levels of immune/inflammatory markers: age, sex, duration of illness, BMI, imipramine equivalents and lithium treatment.

To analyze the interplay between ACE and inflammation on WM microstructure we performed the following analyses:

1) To investigate the effect of ACE on peripheral levels of immune/inflammatory markers we performed two separate MANCOVAs in MDD and BD, adding all immune/inflammatory markers as dependent variables and ACE as the independent factor.
2) To investigate the effect of ACE and inflammation on WM microstructure we performed voxelwise DTI analyses using nonparametric permutation-based testing (Nichols and Holmes, 2002a) as implemented in Randomise in FSL. We tested for linear effects of stress on FA, MD, AD, and RD across the WM skeleton with general linear models (GLM) separately in MDD and BD patients. The difference in DTI parameters between the two groups was assessed through a *t*-test, and a separate slopes analysis was performed to investigate the different relationships between ACE and WM in the two diagnostic groups. First, analyses have been performed for CTQ total score and only if these were significant CTQ subscales have been analyzed. Finally, we tested for linear effects of immune/inflammatory markers associated with ACE on WM microstructure.
3) We investigated whether immune/inflammatory markers mediated the association between ACE and WM microstructure. To test the hypothesis of inflammation mediating the effect of ACE on FA, we extracted mean FA values and we then performed a multiple regression mediation analysis with the PROCESS macro for SPSS, version 3.0 (Hayes, 2013), with 10.000 bootstrap resamples to generate 95% confidence percentile intervals.

3. Results

The clinical and demographic characteristics of the participants are shown in Table 1. Bipolar patients had an earlier onset ($t = 3.08$; $p = 0.004$) and a longer duration of illness ($t = 4.65$; $p < 0.001$) compared to MDD patients and a lower dosage of imipramine equivalents ($t = 3.53$; $p = 0.001$). Median values of immune/inflammatory markers are shown in Table 2_suppl. Immune/inflammatory markers with >20% of imputation values were excluded from the analyses thus leaving 21 markers.

3.1. Stress and inflammation

The investigation of the effect of ACE on immune/inflammatory markers showed a main effect of ACE ($\lambda = 0.333$, $F = 2.472$, $p = 0.014$) only in the BD group. Analyses of coefficients showed that higher levels of ACE associated with higher peripheral levels of IL-2 ($\beta = 0.387$, $p = 0.003$), IL-17 ($\beta = 0.298$, $p = 0.027$), bFGF ($\beta = 0.313$, $p = 0.026$), IFN-γ ($\beta = 0.392$, $p = 0.002$), TNF-α ($\beta = 0.263$, $p = 0.049$), CCL3 ($\beta = 0.270$, $p = 0.046$), CCL4 ($\beta = 0.340$, $p = 0.014$), and CCL5 ($\beta = 0.294$, $p = 0.029$), PDGF-BB ($\beta = 0.265$, $p = 0.044$).

3.2. White matter microstructure

MDD patients showed higher AD compared to BD patients (Fig. 1_suppl and Tab 3_suppl) in two clusters including, projection, association, and commissural fibers; a separate slope model, performed on the whole sample showed the linear relationship between FA and CTQ total scores to be different between the two diagnostic groups.

Table 1
Clinical and demographic characteristics of the sample. HDRS, Hamilton depression rating scale; BMI, body mass index; CTQ, childhood trauma questionnaire.

	Whole sample			Patients with immune/inflammatory markers		
	MDD (n = 100)	BD (n = 100)	χ/t q	MDD (n = 75)	BD (n = 55)	χ/t q
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age	49.90 ± 9.81	49.18 ± 11.23	0.48 0.440	50.47 ± 9.01	47.29 ± 11.75	1.74 0.105
Sex	M = 37 F = 63	M = 35 F = 65	0.08 0.768	M = 23 F = 52	M = 16 F = 39	0.03 0.846
Onset (yrs)	33.72 ± 12.21	28.59 ± 10.90	3.08 **0.004**	32.80 ± 11.91	26.36 ± 10.38	3.17 **0.002**
Duration of illness (yrs)	15.99 ± 12.04	23.61 ± 11.09	4.65 **< 0.001**	17.37 ± 12.08	23.80 ± 10.21	3.19 **0.002**
N. Depressive episodes	3.96 ± 5.60	5.52 ± 4.43	1.77 0.082	4.48 ± 6.29	5.64 ± 4.62	1.01 0.217
Imipramine equivalents	181.23 ± 115.12	111.08 ± 107.17	3.53 **0.001**	181.23 ± 115.12	111.08 ± 107.18	3.53 **0.001**
BMI	24.77 ± 4.54	26.36 ± 5.12	2.28 0.036	24.97 ± 4.87	26.31 ± 4.94	1.54 0.129
HDRS	21.55 ± 6.48	19.69 ± 6.46	1.91 0.071	20.52 ± 6.54	19.24 ± 6.36	1.10 0.214
CTQ	40.38 ± 13.53	39.13 ± 11.37	0.70 0.378	41.39 ± 13.94	27.23 ± 6.37	1.33 0.164

Simple regressions showed that CTQ total scores were negatively associated with FA and AD in BD patients in several WM tracts encompassing anterior and posterior thalamic radiation, posterior and superior corona radiata, inferior and superior longitudinal fasciculus, superior and inferior fronto-occipital fasciuculus, internal and external capsule, cingulum bundle, uncinate fasciculus, forceps minor and major, and of corpus callosum (Fig. 1, Table 4_suppl; Fig. 2_suppl and Fig. 3_suppl). CTQ scores on the other hand had no effect on DTI parameters in MDD patients.

Further, similar differential effects between the two diagnostic groups were observed for neglect (on FA) and abuse scores (on FA, RD, and MD) in fiber tracts overlapping with those observed for CTQ total score. Simple regressions showed that neglect scores were negatively associated with AD in BD (Fig. 4_suppl and Table 5_suppl), whereas abuse scores had a negative association with FA and a positive one with RD in BD subjects (Fig. 5_suppl, Fig. 6_suppl and Table 6_suppl).

Finally, among the immune-inflammatory markers associated with ACE, we observed a negative association between CCL3 (Fig. 2) and IL-2 (Fig. 3) and FA in several WM tracts. CCL3 associated with lower FA in the anterior thalamic radiation, anterior corona radiata, inferior fronto-occipital fasciuculus, uncinate fasciculus, and forceps minor (Table 7_suppl), whereas IL-2 associated with lower FA in the corpus callosum, corona radiata, corticospinal tract, forceps minor, and superior longitudinal fasciculus (Table 8_suppl).

Mediation analyses showed a significant indirect effect ([−0,326, −0,032]; p = 0,005) of ACE on WM microstructure mediated by IL-2 (p < 0.05, Fig. 4). We observed an initial negative relationship between ACE and FA (Total effect: b = −0,0011, 95% CI [−0,0020, −0,0002]) which was no longer significant after controlling for IL-2 (Direct effect: b = −0,005, 95% CI [0,6158, 0,7564]), in turn, IL-2 was significantly increased by ACE exposure (b = 0.2487, 95% CI [0.0593, 0.4380]) and significantly decreased FA (b = −0.0014, 95% CI [−0.0027, −0.0001]). The analysis suggests then a total mediation of IL-2 on the effect of ACE on FA.

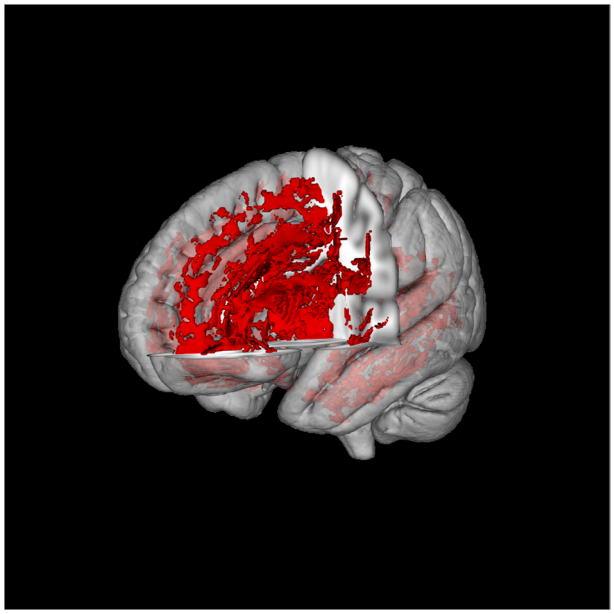

Fig. 1. WM tracts where ACE negatively associated with FA.

4. Discussion

Our study provided several significant results suggesting a complex interplay between ACE, inflammation, and WM integrity. A continuous covariate interaction model identified differential effects of total CTQ scores and of the Abuse and Neglect subscales separately, on WM microstructure in MDD compared to BD patients. A detrimental effect of ACE, measured via the CTQ, on WM microstructure was observed only in bipolar patients with widespread effects across the brain, encompassing large tracts of the WM skeleton. A detrimental effect of ACE on WM integrity in bipolar patients is in agreement with previous studies (Benedetti et al., 2014; Stevelink et al., 2018). No effect of CTQ scores on WM microstructure was observed in MDD subjects, despite ACE being a risk factor for the development of the disorder.

To the best of our knowledge, this is the first study to investigate the differential effects of ACE on WM microstructure in subjects suffering from MDD and BD. These results seem to point to a divergent effect of ACE on WM in the two conditions and are in line with previous studies showing different patterns of WM alterations in the two diagnostic groups (Comai et al., 2022). Despite the partially shared clinical presentation, numerous elements distinguish the two disorders and point to a different pathophysiology: BD is also characterized by the presence of manic or hypomanic symptomatology, is highly heritable (heritability estimates of approximately 70–80%), tends to have an earlier age of onset, and has a higher recurrence risk (McIntyre et al., 2020). Lithium, the mainstay of BD treatment, is considered to be a second line add-on drug in MDD while antidepressants, the first line treatment of MDD, have dubious clinical efficacy in BD and might have deleterious effects (Taylor et al., 2021). Considering that WM changes in both MDD and BD have been associated with neuroprogression and that the clinical characteristics of the illness have been shown to affect the changes observed in the brain of patients with mood disorders (Moylan et al., 2013; Serafini et al., 2021), clinical differences between the two disorders could partially explain our results. Our finding that BD patients have lower AD (an index of axonal intergity) compared to MDD ones further support this suggestion. Indeed, given the likely different pathophysiology of the two disorders, it seems reasonable to assume that childhood trauma may affect their development through different routes, and the divergent effect on WM in the two diagnostic categories might be seen in light of this hypothesis.

In our analyses, we found CTQ scores to be associated with increased

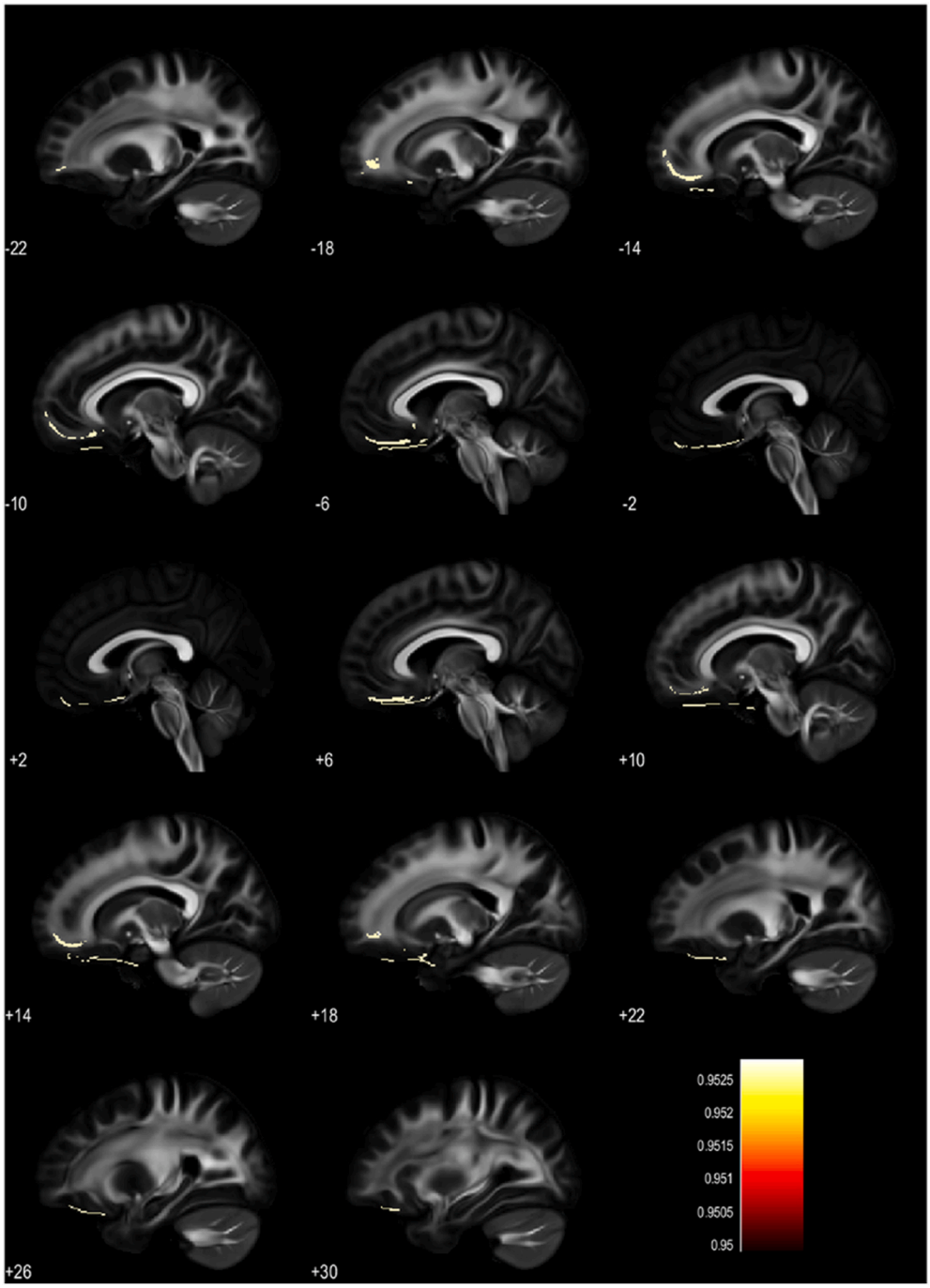

Fig. 2. WM areas where CCL3 peripheral levels significantly correlated with lower fractional anisotropy in BD. Voxels of significant negative correlation are mapped on the mean FA template of the studied sample, and are shown in glass-brain images. The colorbar refers to 1-p values for the observed differences. Numbers are z coordinates in the standard Montreal Neurological Institute (MNI) space.

immune/inflammatory markers only in patients suffering from BD and not in MDD patients. ACE have repeatedly been shown to alter immune/inflammatory markers in adulthood in psychiatric samples and healthy controls: a recent meta-analysis reported higher levels of CRP, IL-6, and TNF-α in adults with a history of childhood trauma (Baumeister et al., 2016). Despite being more extensively studied in MDD, alterations of inflammatory pathways have also been reported in BD and implicated in its pathophysiology (Vieta et al., 2018). Increased peripheral immune/inflammatory markers compared to healthy controls have been reported both in MDD (Beurel et al., 2020) and BD (Pereira et al., 2021). Some markers appear to be linked to the specific phase of the disease, with CRP and IL-6 levels found to be elevated during euthymic and manic phases and TNF-α during depressive and manic ones (Rowland et al., 2018). However, recent studies comparing MDD and BD (Bai et al., 2015; Brunoni et al., 2020; Chen et al., 2019; Kim et al., 2002; Mota et al., 2013) suggest differences in the immune activation in the two disorders with different immune/inflammatory profiles characterizing and distinguishing MDD and BD (Poletti et al., 2020a).

In agreement with the literature on both animals and humans (Danese and S, 2017), we observed an association between ACE and peripheral immune/inflammatory markers. Several of the immune/inflammatory markers we found to be associated with higher CTQ values (such as CCL3, CCL4, CCL5, and TNF-α) are hallmark of the classical proinflammatory monocyte activation (Mantovani et al., 2004) and

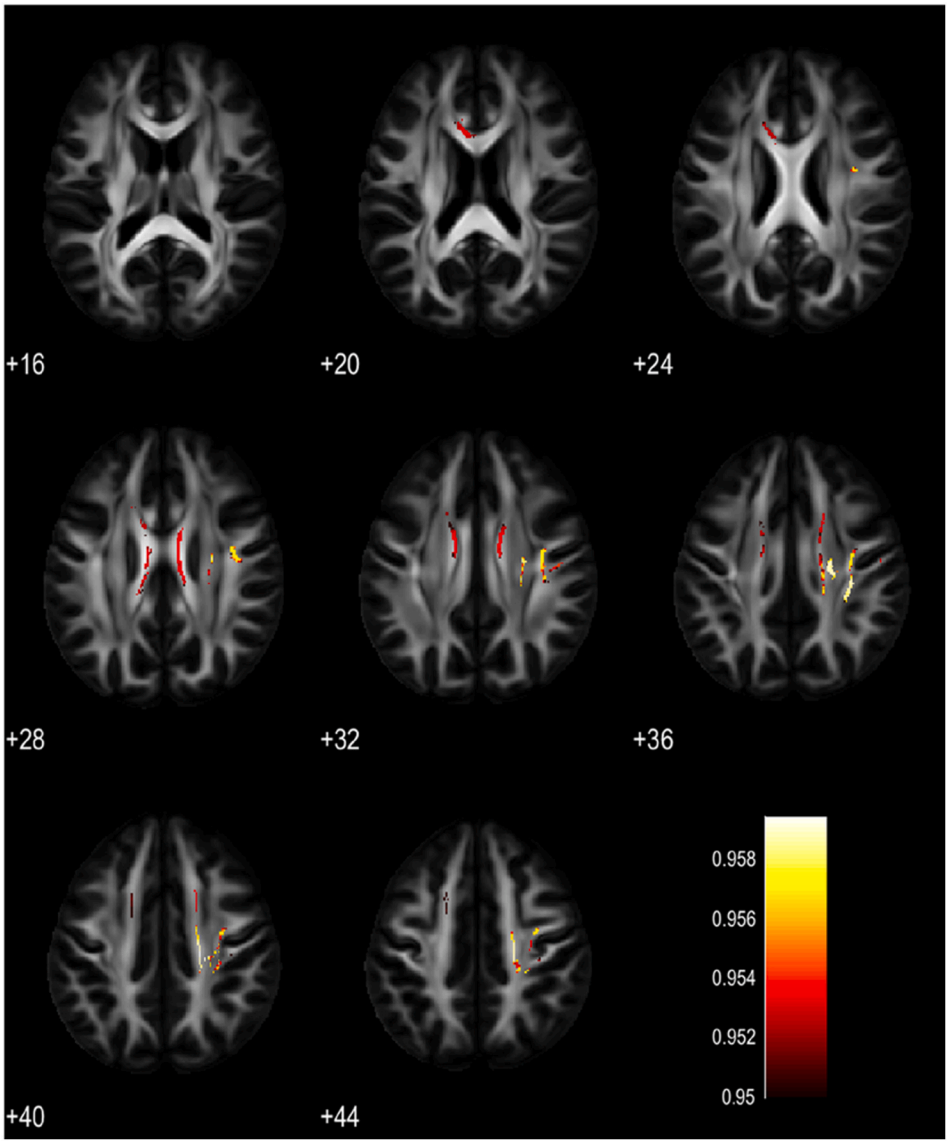

Fig. 3. WM areas where IL-2 peripheral levels significantly correlated with lower fractional anisotropy in BD. Voxels of significant negative correlation are mapped on the mean FA template of the studied sample, and are shown in glass-brain images. The colorbar refers to 1-p values for the observed differences. Numbers are z coordinates in the standard Montreal Neurological Institute (MNI) space.

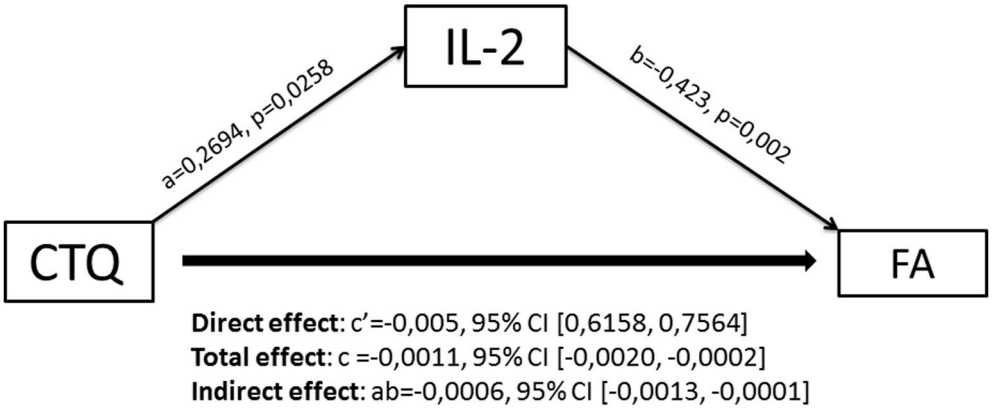

Fig. 4. Mediation model for the effect of ACE through IL-2 for FA measures of WM tracts. a, b, c and c' are path coefficients representing unstandardized regression weights. * Significant confidence intervals at 95%.

have been shown to distinguish BD from MDD patients (Poletti et al., 2020a). However, to the best of our knowledge, this is the first study to link them to the presence of ACE in BD. Increased M1 polarization has also been proposed as a possible pathophysiological contributor to BD, leading to increased BBB permeability and chronic microglial activation (Ascoli et al., 2016). On the other hand, IL-2 and IFN-γ are involved in T cells differentiation and the balance between different T cells populations(Tau and Rothman, 1999). Accordingly, a dynamic pattern of partial T cell defect during adolescence, with high levels of Th17 and T regulatory cells in adult life has been reported in BD. Further, T cells activation with higher percentages of circulating CD4, CD8 and T regulatory cells have been reported in individuals exposed to ACE (Elwenspoek et al., 2017). Finally, a positive association between ACE and bFGF and PDGF-bb may underline neuroprotective/reparatory effects. bFGF in the brain, is involved in maintenance and repair throughout adulthood (Terwisscha van Scheltinga et al., 2013) and mediates neuroprotective and antidepressant effects (Wang et al., 2018). Similarly to our results, higher peripheral levels of FGF2 have been reported in depressed patients with childhood trauma exposure compared to healthy controls (Lu et al., 2013). FGF is sensitive to stress and both acute and chronic stress can alter its expression; FGF and the stress system are thought to act synergistically to modulate affective behavior in a context specific manner(Turner et al., 2016). PDFG-bb, has also a neuroprotective role, acting mainly against glutamate-induced neuronal damage(Beazely et al., 2009), and direct hypoxic–ischemic injury both in animal studies (Egawa-Tsuzuki et al., 2004) and in vivo (Kanamoto et al., 2011).

Finally, we tested the effect of the inflammatory/immune markers associated with ACE on WM integrity, and we found higher levels of CCL3 and IL2 to be associated with lower values of FA in WM tracts which partially overlapped with the ones affected by ACE. These effects appeared to be more localized than the ones identified in the ACE analyses, with CCL3 mainly affecting WM microstructure in orbitofrontal areas (bilateral uncinate fasciculus, inferior fronto-occipital fasciculus, anterior thalamic radiation) and IL-2 found to have detrimental effects in fronto-parietal areas (Corona Radiata, Corpus Callosum, right Superior Longitudinal Fasciculus).

Increased levels of immune/inflammatory markers observed during acute mood episodes, have been proposed to be one of the main contributors to BD neuroprogression, both in the progressive neurocognitive decline and neurostructural changes (Jones et al., 2021). Furthermore, albeit non targeted specifically on BD, a framework has been proposed to link ACE, immune changes and psychopathology, according to which childhood psychosocial stressors might affect immune system development, which in turn could alter brain development and long-term functioning. In agreement with this hypothesis, we observed a mediation effect of IL-2 on the association between ACE and WM integrity in BD, suggesting that stress induced alterations of the immune system may contribute to the brain abnormalities observed in patients with BD.

Our study has several limitations: it was performed in a single center and lacked a control group; the lack of information about the exact age at which early stress occurred potentially limits any specific inferences that might be made about the effect of early stress on the developmental pathway of WM tracts. The retrospective reporting of childhood experiences may be associated with difficulties in recalling certain events. However, this likely results in misclassification (classifying persons exposed to early stress as unexposed) that would bias our results toward the null (Della Femina et al., 1990). Additionally, smoking, past substance abuse, and chronic illnesses were not taken into account, however, a previous study showed that although higher in patients exposed to ACE, they were not correlated with immune activation, suggesting that such a state is not secondary to alterations in the stress system or to health behaviors (Elwenspoek et al., 2017). Finally, patients were not drug naïve, and the drug treatments administered during the course of the illness could have negatively influenced DTI measures. For this reason, all the analyses performed in the MDD group were corrected also for the effect of antidepressants and lithium.

In conclusion, these limitations do not bias the main finding of the present study showing a mediating role of inflammation in the association between ACE and WM microstructure in BD patients. Furthermore, these findings suggest that different processes may lead to WM alterations in BD and MDD and that, at least, part of these alteration could be linked to changes in the immune response associated with early experiences.

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Declaration of competing interest

None.

Data availability

Data will be made available on request.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100529.

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