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Different effect of adverse childhood experiences on white matter microstructure in major depression and bipolar disorder: moderating role of genetic liability

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ABSTRACT

Adverse childhood experiences (ACEs) are risk factors for both major depressive (MDD) and bipolar disorder. ACEs have been associated with white matter (WM) alterations, but whether they have different effects in MDD and BD remains unclear. Polygenic risk scores (PRS) allow for an individual estimation of genetic liabilities for most psychiatric conditions. The aim of the present study was to characterize the effect of ACEs on WM microstructure in MDD and BD, testing a possible differential effect between the two diagnoses and investigating whether genetic liabilities might modulate this relation. 260 depressed inpatients (140 MDD and 120 BD, mean age 49.29 ± 10.60, $F = 161$) underwent 3T MRI scan and ACEs evaluation. MDD and BD PRS were calculated in a subset of patients. Significant ACEs x diagnosis interactions were found for several DTI metrics. Single group analyses showed widespread detrimental effects of ACEs on WM integrity in BD, and less pronounced effects in MDD. Significant moderating effect of BD PRS in the whole sample and in MDD specifically were found for the relation between ACEs, fractional anisotropy and radial diffusivity, with bipolar-like relations for higher values of BD PRS. The differential effect of ACEs on WM microstructure in the two diagnostic groups points towards putative differential pathophysiological routes through which childhood maltreatment affects the two conditions, while the identification of a BD PRS moderation on the whole sample and in MDD specifically sheds light on the causal relation between ACEs, diagnostic phenotype and DTI metrics, and provides a possible tool to disentangle MDD heterogeneity.

1. Introduction

Adverse childhood experiences (ACEs), including childhood maltreatment and dysfunctional family environments, are risk factors for the development of both major depressive (MDD) and bipolar disorder (BD) (Bortolato et al., 2017; Li et al., 2022).

Childhood maltreatment has been associated with the subsequent development of depressive symptomatology in childhood, adolescence,

Written informed consent was obtained for all participants to the study. All the research activities were approved by the local ethical committee.
Data available upon request.

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and adulthood (Li et al., 2022), with several possible mechanisms implicated (Kuzminskaite et al., 2021).

Environmental risk factors might have a smaller impact on the development of BD compared to MDD, with a stronger contribution of genetic liability (Pettersson et al., 2019), but childhood maltreatment is among the few robust and replicated environmental determinants of the disease (Bortolato et al., 2017), being associated also to unfavorable clinical features and clinical course (Agnew-Blais et al., 2016).

In general population samples, ACEs have been associated to reduced brain volumes particularly in frontal and parietal lobes and in subcortical structures (Madden et al., 2023); fronto-parietal structural abnormalities associated to ACEs are also paralleled by alterations in functional connectivity (Heany et al. 2018). Concerning psychiatric patients, a recent meta-analysis investigated structural and functional brain differences between MDD patients with or without a positive history of ACEs, identifying significant clusters in several cortical and sub-cortical regions (Antoniou et al., 2023). Similar results were also identified for BD patients, with childhood maltreatment associated to prefrontal, hippocampal and thalamic volumetric reductions and altered fronto-parietal functional connectivity (Zovetti et al., 2022), and in first-episode psychosis, with adverse childhood experiences associated with reduced cortical thickness (Fares-Otero et al., 2024).

Fewer studies on the other hand investigated the effect of ACEs on white matter (WM) microstructure: a meta-analysis (Lim et al., 2020) performed on 14 tract based spatial statistic (TBSS) studies identified six clusters of reduced fractional anisotropy (FA) in individuals exposed to childhood maltreatment, relative to non-maltreated controls. However, studies included in the analysis were performed both on healthy subjects and on psychiatric patients (Lim et al., 2020): while in studies including exclusively healthy individuals childhood maltreatment was associated to lower values of FA, the only study performed entirely on MDD patients (Tatham et al., 2016) found high depression severity and experiences of childhood physical or emotional neglect to predict *higher* FA; this was confirmed by a subsequent study performed on 186 individuals suffering from MDD, which identified higher FA in participants with a self-reported history of bullying (Graziano et al., 2019).

Only two studies included in the meta-analysis had samples exceeding 100 participants: one was performed on 240 veterans with or without a history of childhood abuse, and found no difference between the two groups (Corbo et al., 2016); the other investigated 251 patients with BD and 163 healthy controls (Stevelink et al., 2018): while again the authors found no differences between healthy individuals with and without abuse, BD patients with childhood abuse had widespread reductions of FA relative to patients without (Lim et al., 2020; Stevelink et al., 2018). A subsequent study by our group performed on 100 MDD and 100 BD patients identified a significant diagnosis interaction in the effect of childhood maltreatment on WM microstructure, with widespread reductions of FA associated with trauma apparent only in BD and not MDD patients (Poletti et al., 2022).

Taken together, these findings seem to point to a diagnosis-specific impact of ACEs on WM integrity; childhood maltreatment seems to have strong and widespread detrimental effects on FA in BD (Poletti et al., 2022; Stevelink et al., 2018), with a less clear effect in MDD and control samples (Graziano et al., 2019; Tatham et al., 2016). Interestingly, the negative association between childhood maltreatment and FA seems to extend beyond BD also to patients with psychotic or schizophrenia-spectrum disorders (Asmal et al., 2019), suggesting a specific effect in patients with serious mental illness. However, whether this differential effect might have a role in the pathophysiology of BD and MDD, or rather be a consequence of the distinct clinical presentation of the two disorders, remains to be determined.

Furthermore, while BD appears to be a relatively robust clinical entity, MDD is probably a more heterogeneous condition (Lynall et al., 2023), partially because of its challenging distinction from BD itself. A retrospective 8 years study showed that 7.6–12.1 % of MDD patients had their diagnosis changed to BD (Li et al., 2012); further, the current nosological dichotomy of mood disorders has been widely criticized, with some authors proposing a widening of BD current diagnostic criteria (Ghaemi, 2013).

The dramatic advances made by psychiatric genetic research in the last decade could prove to be crucial in disentangling MDD heterogeneity: polygenic risk scores (PRS) now allow for an individual estimation of the genetic liability for a given disorder, providing data directly related to the biological underpinnings of psychiatric conditions (Murray et al., 2021). In this regard, Wiste and colleagues investigated the effect of BD PRS on the clinical features of the STAR*D major depression sample (Wiste et al., 2014), identifying higher BD PRS to be associated with earlier age of onset, history of suicide attempt and presence of sub-clinical manic symptoms, all features classically regarded to reflect bipolar vulnerability (Frankland et al., 2018). Further, significant interactions between history of childhood maltreatment and psychiatric PRSs in affecting the development of psychiatric phenotypes were identified in a large population study (Yao et al., 2023).

Our hypothesis in the present study was therefore that adverse childhood experiences (ACEs) could have a different effect on white matter microstructure in patients with major depressive disorder (MDD) or bipolar disorder (BD), and that genetic liability might underlie at least part of this differential effect. We aimed to: (1) replicate, in a larger clinical sample, our previous finding that childhood maltreatment differentially affects DTI metrics in MDD versus BD patients (Poletti et al., 2022), further characterizing the contribution of specific CM subtypes and also testing the effect of dysfunctional family environment; (2) examine whether genetic liability might underlie this differential effect, testing its interaction with environmental stressors (i.e. ACEs) through moderation models; (3) investigate whether the interaction between CM and polygenic risk helps explain clinical heterogeneity within mood disorders.

2. Experimental procedures

2.1. Participants and study design

Our sample was composed of 260 inpatients (140 MDD and 120 BD) consecutively admitted to San Raffaele hospital psychiatric ward (age 21–69) during an ongoing depressive episode. Each patient diagnosis was made by a staff psychiatrist according to DSM-5 criteria. 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. All patients underwent 3 T Magnetic Resonance scanning. A subsample of 162 patients (90 MDD and 72 BD) underwent venous blood sampling for genotyping. All patients were receiving psychotropic drug treatment at the time of the MRI scan: antidepressant drug treatment was recorded and converted into the equivalent dose of Imipramine; lithium treatment was also recorded. 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 adverse childhood experiences

We examined two key dimensions of ACEs: childhood maltreatment and dysfunctional family environment. Childhood maltreatment, defined as any physical or emotional ill-treatment or neglect that compromises health or development before age 18 (World Health Organisation, 2022), was assessed using the 28-item Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), a psychometric scale with good internal reliability (Cronbach's $\alpha = 0.93$ - 0.99; Innamorati et al., 2016). The CTQ includes five subscales (physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect), that we summed to also obtain a total score. Standard Error of Measurements (SEM) for the present sample were: physical abuse 0.616, emotional abuse 0.865, sexual abuse 0.246, physical neglect 0.751, emotional

neglect 1.084.

Both total score and subscales were used in the statistical and neuroimaging analyses as continuous variables to test their effects on DTI measures. Furthermore, for group comparisons, patients were classified as having a positive history of abuse or neglect using established CTQ cutoff scores: ≥8 for Physical Abuse and Physical Neglect, ≥9 for Emotional Abuse, ≥6 for Sexual Abuse, and ≥ 10 for Emotional Neglect (Bernstein et al., 2003). All the neuroimaging and statistical analyses were corrected for a minimization score, which was computed as in Bernstein et al., 2003. Higher scores indicate a greater tendency to minimize or deny experiences of childhood maltreatment, suggesting possible underreporting of adversity.

The family environment was retrospectively assessed using the 13-item Risky Families Questionnaire (Taylor et al., 2004), an instrument that rates the degree of conflict, deficient nurturing, harsh parenting, perceived parental affection and care, household organization, and exposure to substance abuse in the family environment during childhood. The total score can range from 13 (low dysfunctional family environment) to 65 (very high dysfunctional family environment). Internal consistency was previously shown to be acceptable (Cronbach's α = 0.89; Crosswell et al., 2014). RFQ scores were treated exclusively as continuous variables, as no cut-off scores are available for this instrument. SEM for the present sample was 4.136.

2.3. Genotyping and polygenic risk scores calculation

Genotyping, quality control (QC), and imputation of genetic data were performed in a larger cohort including 192 patients with MDD and 265 BD patients, of which the present sample represents a subset. Genotyping was performed using the Infinium PsychArray 24 BeadChip (Illumina, Inc., San Diego), which is a cost-effective, high-density microarray developed in collaboration with the Psychiatric Genomics Consortium and containing 595,427 genetic markers associated with psychiatric disorders (https://www.illumina.com/products/by-type/microarray-kits/infinium-psycharray.html). QC was conducted with PLINK1.9 (Purcell et al., 2007). Individuals with discrepant sex information, genotype rate < 95 %, or outlying autosomal heterozygosity (Fhet > ±0.2) were removed. Markers with minor allele frequency (MAF) < 1 %, call rate < 95 %, or deviant from Hardy-Weinberg equilibrium at $p < 10^{-6}$ were excluded. Relatedness of participants was checked by excluding individuals with a degree of recent shared ancestry (i.e., identity by descendent, IBD) > 0.1875, which is the threshold corresponding to the halfway between third- and second-degree relatives (Anderson et al., 2010). Finally, population principal component analyses (PCA) was used to identify and remove population outliers (those outside mean± 5 standard deviations for the first two population principal components). After QC, the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html) was used for genotype imputation and PRS calculation. The post-QC dataset was imputed (Minimac3) using the 1000 Genomes Project V5 as reference panel, with Eagle V2.3 for genotype phasing. Finally, MDD PRS and BD PRS were calculated by the Michigan Imputation Server using the SNPs weights calculated in a previous study (BD and MDD weights used) (Gui et al., 2022). Briefly, the study used GWAS summary statistics from the Psychiatric Genomics Consortium and each minor allele was given a risk score using SDPR (Zhou et al., 2021).

2.4. Image acquisition and preprocessing

All patients underwent 3 tesla MRI acquisition on two Philips MRI scanners. All MRI acquisitions were performed at C.E.R.M.A.C. (Centro d'Eccellenza di Risonanza Magnetica ad Alto Campo) in San Raffaele Hospital in Milan. 64 patients were scanned with Gyroscan Intera; 196 patients were scanned with Ingenia CX scanner.

DWI was executed using SE Eco-planar imaging and the following parameters for the first scanner TR/TE=8753.89/58 ms, FoV (mm) 231.43 (ap), 126.50 (Negele et al., 2015), 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/mm2; and the following for the second Philips scanner TR/TE=5900/78 ms, FoV (mm) 240 (ap), 129 (5), 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/mm2. Fat saturation was performed to avoid chemical shift artefacts.

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., 2006). First, removal of nonbrain tissue was performed with brain extraction tool (BET) provided by FSL, supplying a brain mask for each subject. Then FSL eddy tool was used, which handles a Gaussian process to predict undistorted data, to which the actual volumes can be aligned. (Andersson et al., 2015). It can estimate and correct for volume-to-volume movement and off-resonance fields, signal dropout due to movement during the diffusion encoding, intra-volume movement (Andersson et al., 2018). After, 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 (λ1 + λ2 + λ3)/3, axial diffusivity (AD) as the principal diffusion eigenvalue (λ1), and radial diffusivity (RD) as the mean of the second and third eigenvalues (λ2 + λ3)/2.

Next, all individuals' volumes were skeletonized and transformed into a common space as used in Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006). 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 space, by use of local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT). 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 > 0.2 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 voxel-wise permutation-based cross-subject statistics. Similar warping and analyses were used on MD, AD, and RD data.

2.5. Neuroimaging analysis

To investigate the effect of ACEs on WM microstructure we performed voxelwise DTI analyses using nonparametric permutation-based testing as implemented in Randomise in FSL. All analyses were carried out in the context of general linear models (GLM) entering age, sex, level of education, duration of illness, BMI, lithium treatment, imipramine equivalents and CTQ minimization subscale as nuisance covariates. To account for the two different MRI scanners, a "scan" nuisance covariate was also added to all analyses. In the analyses testing the effect of RFQ, CTQ minimization subscale was not used as a covariate.

The primary aim of the present study was to test whether the effects of ACEs on WM differed between the two diagnostic groups. To this end, continuous covariate interaction models were implemented (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/GLM), entering RFQ and CTQ total scores, as well as CTQ subscale scores (physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse), separately as continuous independent variables. Where a significant diagnosis interaction was identified, the effect of the significant indices within each diagnostic group was further investigated through regression models.

Further, within each diagnostic group, we examined whether patients with a positive history of childhood maltreatment showed differences in WM integrity compared with those without such history. For

this purpose, patients were divided according to CTQ subscale cut-off scores (emotional abuse ≥9; physical abuse ≥8; sexual abuse ≥6; emotional neglect ≥10; physical neglect ≥8) (Bernstein et al., 2003), and group differences in DTI metrics were tested using two-sample *t*-tests.

Threshold-free cluster enhancement (TFCE) was used to avoid defining arbitrary cluster-forming thresholds and smoothing levels. 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 $p < 0.05$ was considered significant.

2.6. Statistical analysis

In order to investigate whether the relationship between childhood maltreatment and WM microstructure is moderated by genetic liability to major psychiatric disorders, average values of FA, RD and MD of the WM tracts found to be differently affected by ACEs between the two diagnoses were extracted for each of the 162 subjects with genetic data available. This was achieved by creating binary masks from the voxels where a significant ACEs × diagnosis effect on DTI metrics was identified, and then applying such masks to the FA, RD and MD skeletonized data.

Moderation analyses were performed using the SPSS "Process" Macro (version 4.0) in IBM SPSS Statistics for Windows, Version 26.0. CTQ scores that exhibited a significant differential effect between the two diagnoses (total, emotional abuse, physical abuse, physical neglect) were entered as continuous independent variables; values of the DTI metrics of the respective voxels in which such differential effects occurred were entered as dependent variables; BD and MDD polygenic risk scores (with higher PRS values indicating greater genetic risk) were entered as moderators. The same nuisance covariates used in the TBSS analysis were included in the model. Furthermore, to exclude the possible confounding effect of the diagnostic category, "diagnosis" was also entered as a nuisance covariate. Moderation analyses were then repeated separately in MDD and BD groups. For each moderation, Johnson-Neyman outputs were obtained.

3. Results

Clinical and demographic characteristics of the sample are shown in Table 1. The sample included 260 patients (140 MDD, 120 BD). BD patients (72 F, mean age = 49) had an earlier age of onset and longer illness duration than MDD patients (28.28 vs 33.99 years, $p < 0.001$; 20.57 vs 15.69 years, $p < 0.001$ respectively), as well as higher BMI (26.38 vs 24.70, $p = 0.004$) and more frequent lithium treatment (42 % vs 2 %, $p < 0.001$). No significant group differences were observed in RFQ scores or in CTQ total and subscale scores. A genetic subsample of 162 participants (90 MDD, 72 BD) showed comparable demographic and clinical characteristics. Correlation coefficients between CTQ and its subscales and RFQ are reported in sup. Table 19.

3.1. Effects of adversity on white matter

Childhood maltreatment was found to differently affect WM microstructure in MDD and BD patients. Significant childhood maltreatment x diagnosis interactions were found for CTQ total score, physical abuse, physical neglect, and emotional abuse on FA, RD and MD (Table 2a, Figs. 1a and 2a, sup. Figures 1–11, sup. Tables 5–8). No significant results were found for emotional neglect.

In BD patients, higher CTQ total scores, as well as physical abuse, physical neglect, and emotional abuse, were associated with lower FA. MD showed a positive association with CTQ total and physical abuse, while RD was positively associated with CTQ total, physical abuse, physical neglect, and emotional abuse (Table 2b, Fig. 1b, Supplementary Figures 12–26, Supplementary Tables 9–13).

ACEs exhibited different effects on DTI metrics in MDD patients, with a negative association found only for physical abuse and AD, physical neglect and MD, RFQ scores and AD and MD (Table 2c, sup. figures 27–30, sup Tables 16–18).

In BD, DTI T-test analyses confirmed these results, with lower FA and higher RD and MD in subjects with a positive history of physical abuse and physical neglect (MD significant only for physical abuse) (sup. Tables 1, 14, 15, sup. figures 17, 19, 21, 23, 25), and a similar trend between subject with or without emotional abuse for FA ($p = 0.063$). No statistically significant result was found in the MDD t-test analyses (sup. Table 1).

3.2. Moderation by genetic liability

BD PRS, but not MDD PRS, significantly influenced the relationship between childhood maltreatment and WM integrity.

Significant moderating effect of BD PRS in the whole sample were found for the relation between CTQ total score and FA ($\beta = -0.003$; $p = 0.008$; 95 % CI [–0.005, –0.0008]), emotional abuse and FA ($\beta = -0.011$; $p = 0.004$; 95 % CI [–0.019, –0.0037]), physical abuse and FA

Table 1
Clinical and demographic characteristic of the sample. † *y* = having received lithium drug treatment for at least six months. CTQ, Childhood Trauma Questionnaire; RFQ, Risk Family Questionnaire.

	Whole sample (*n* = 260)			**Genetic subsample** (*n* = 162)		
	Major depression (n = 140)	**Bipolar disorder** (*n* = 120)	χ^2/*t*-test p	**Major depression** (n = 90)	**Bipolar disorder** (*n* = 72)	χ^2/*t*-test p
Age	49.68 ± 9.63	48.85 ± 11.66	0.531	49.89 ± 9.59	49.17 ± 11.27	0.660
Sex (F/M)	89/51	72/48	0.554	53/37	49/23	0.230
Years of education	12.88 ± 3.85	12.80 ± 3.93	0.871	12.57 ± 3.99	12.60 ± 3.98	0.961
Age of onset	33.99 ± 12.24	28.28 ± 10.44	*<0.001*	33.01 ± 12.17	27.90 ± 10.24	*0.005*
Duration of illness	15.69 ± 11.68	20.57 ± 11.58	*<0.001*	16.88 ± 10.86	21.26 ± 11.87	*0.015*
BMI	24.70 ± 4.47	26.38 ± 4.92	*0.004*	24.73 ± 4.13	26.67 ± 5.07	*0.008*
Lithium treatment (y/n)†	4/136	51/69	*<0.001*	3/87	30/42	*<0.001*
Imipramine equivalents	180.59 ± 87.35	118.39 ± 99.64	*<0.001*	147.07 ± 86.88	128.09 ± 100.39	0.199
CTQ total score	39.59 ± 12.05	38.92 ± 10.98	0.643	40.77 ± 13.19	37.12 ± 10.26	0.056
Physical abuse	6.06 ± 2.04	6.22 ± 2.64	0.581	6.28 ± 2.31	5.85 ± 1.72	0.191
Emotional abuse	8.41 ± 3.90	8.47 ± 3.86	0.914	8.53 ± 4.15	8.26 ± 3.71	0.668
Sexual abuse	5.75 ± 2.57	5.67 ± 2.33	0.807	5.92 ± 2.96	5.42 ± 1.73	0.200
Physical neglect	7.21 ± 3.06	6.71 ± 2.54	0.158	7.24 ± 3.28	6.29 ± 2.20	*0.036*
Emotional neglect	12.15 ± 4.74	11.85 ± 4.99	0.620	12.54 ± 4.84	11.30 ± 5.12	0.117
Minimization	9.01 ± 2.89	8.90 ± 3.04	0.756	8.98 ± 2.80	9.04 ± 3.19	0.892
RFQ	27.36 ± 10.71	28.53 ± 10.67	0.380	27.88 ± 11.08	27.55 ± 10.75	0.852

Table 2
Results of the DTI regression analysis. * $p < 0.05$; ** $p < 0.01$; U = Major depression; B = Bipolar disorder. CTQ, Childhood Trauma Questionnaire; RFQ, Risk Family Questionnaire; FA, fractional anisotropy; AD, axial diffusivity; RD, radial diffusivity; MD, mean diffusivity.

	(a) Interaction (n = 260)				(b) Bipolar disorder (*n* = 120)				(c) Major depression (*n* = 140)			
	FA	**AD**	**RD**	**MD**	**FA**	**AD**	**RD**	**MD**	**FA**	**AD**	**RD**	**MD**
CTQ total score	U↑B↓*	-	U↓B↑**	U↓B↑*	↓**	-	↑*	↑*	-	-	-	-
Emotional abuse	U↑B↓*	-	U↓B↑*	U↓B↑*	↓**	-	↑*	-	-	-	-	-
Physical abuse	U↑B↓*	-	U↓B↑**	U↓B↑**	↓*	-	↑*	↑*	-	↓*	-	-
Sexual abuse	-	-	-	-	-	-	-	-	-	-	-	-
Emotional neglect	-	-	-	-	-	-	-	-	-	-	-	-
Physical neglect	U↑B↓**	-	U↓B↑**	U↓B↑**	↓**	-	↑*	-	-	-	-	↓*
RFQ	-	-	-	-	↓*	-	-	-	-	↓*	-	↓*

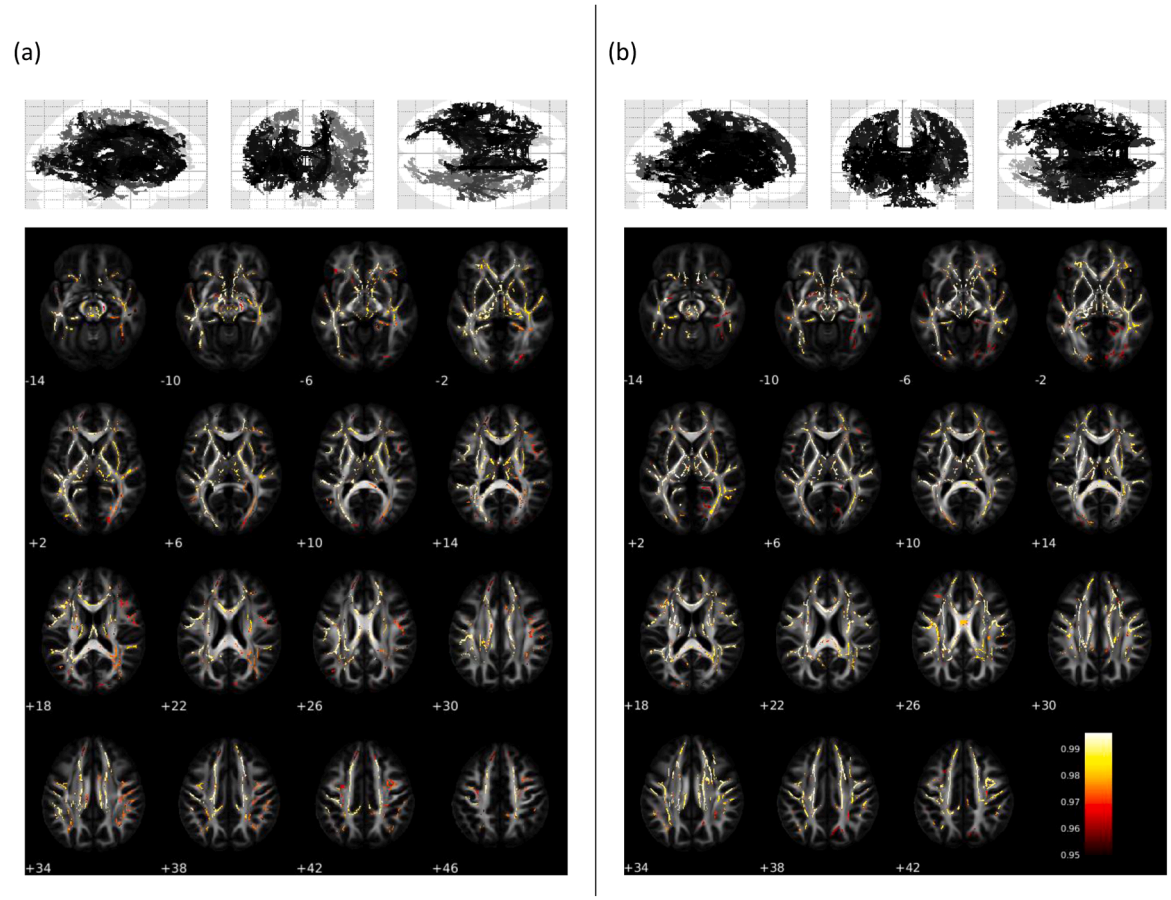

Fig. 1. (a): white matter tracts where FA is differently affected by CTQ total score in MDD and BD. (b): white matter tracts where CTQ total score is negatively associated with FA in BD. FA: fractional anisotropy. CTQ: childhood trauma questionnaire. MDD: major depressive disorder. BD: bipolar disorder.

(β=−0.01; p = 0.007; 95 % CI [–0.039, –0.0062]) and RD (β=0.000008; p = 0.032; 95 % CI [–0.00004, –0.00001]), physical neglect and FA (β=−0.013; p = 0.015; 95 % CI [–0.024, –0.0027]) and RD (β=0.00001; p = 0.046; 95 % CI [–0.0000002, –0.00002]) (Fig. 2b, Table 3 and sup. Table 2). In the Johnson-Neyman output of the moderation, significant negative correlation between childhood maltreatment and FA were observed for highest BD PRS values, while significant positive associations were observed for lowest BD PRS; the opposite effect was observed for the relation between PA and PN and RD (positive association for high BD PRS, negative for low BD PRS) (Fig. 2b, sup. Table 3).

Performing the analysis separately in the two diagnostic groups, no significant PRS moderation was found in BD (Fig. 2d, Table 3 and sup. Table 2). In MDD on the other hand, BD PRS significantly moderated the relation of CTQ total score with FA (β=−0.004; p = 0.008; 95 % CI [–0.007, –0.001]) and RD (β=0.00005; p = 0.013; 95 % CI [0.000001, 0.000008]); emotional abuse with FA (β=−0.016; p = 0.001; 95 % CI [–0.0026, –0.0065]) and RD (β=0.00001; p = 0.016; 95 % CI [0.0000026, 0.00002]); physical abuse with FA (β=−0.028; p = 0.004; 95 % CI [–0.048, –0.009]), MD (β=0.00002; p = 0.019; 95 % CI [0.000004, 0.00004]) and RD (β=0.00003; p = 0.005; 95 % CI [0.000009, 0.00005]); physical neglect with FA (β= −0.017; p = 0.019; 95 % CI [−0.031, −0.0029]) and RD (β=0.00001; p = 0.031; 95 % CI [0.000001, 0.00003]) (Fig. 2c, Table 3 and sup. Table 2). The Johnson-Neyman output resembled the analyses performed on the whole sample, with trends towards negative associations between childhood maltreatment and FA for higher values of BD PRS (significant only for EA) and opposite significant relations at lower BD PRS values (Fig. 2c, sup. Table 4).

No significant moderating effect of MDD PRS was found either in the whole sample or in MDD or BD separately.

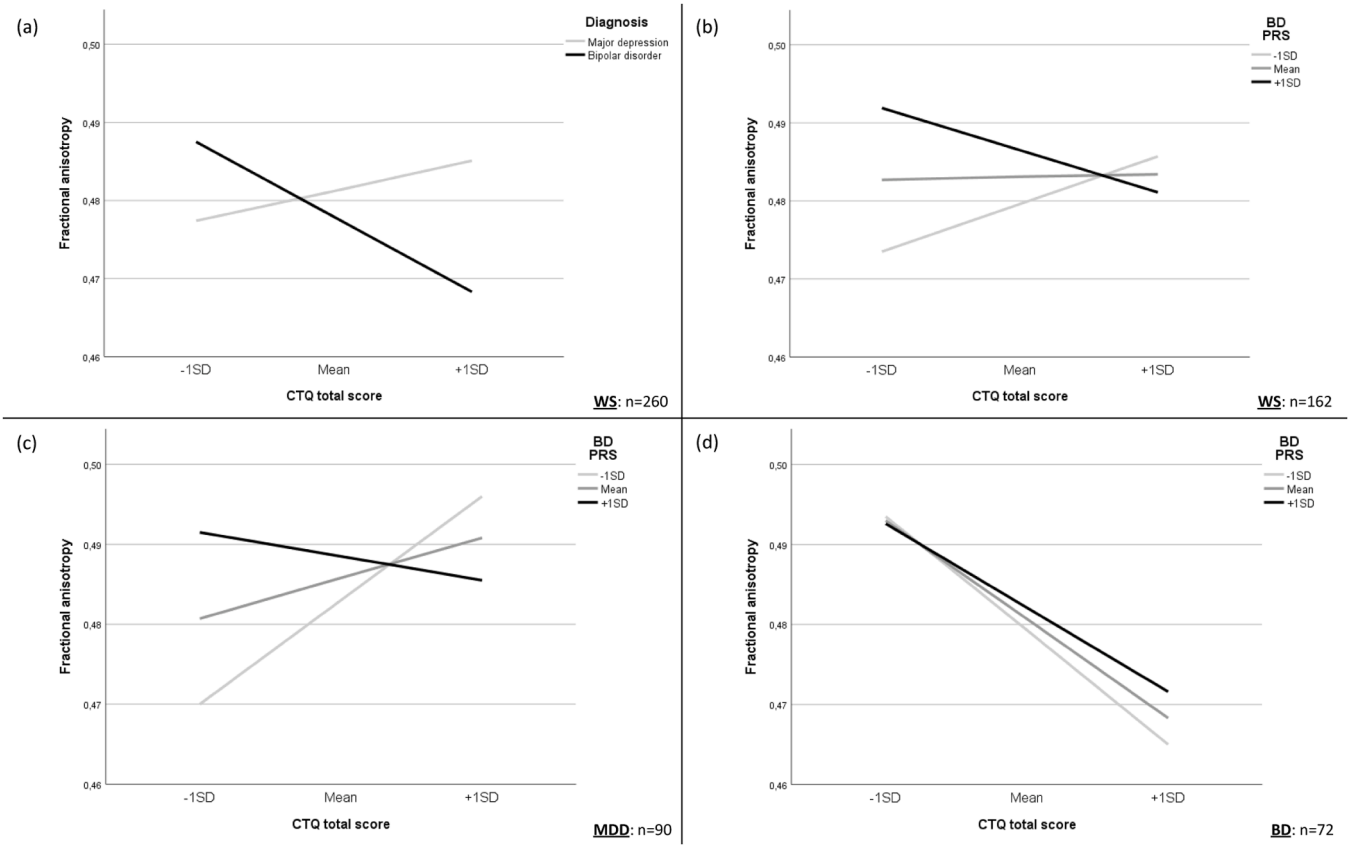

Fig. 2. (a): association between CTQ total score and FA in MDD and BD. (b): association between CTQ total score and FA at various BD PRS levels in the whole sample. (c): association between CTQ total score and FA at various BD PRS levels in MDD. (d): association between CTQ total score and FA at various BD PRS levels in BD. CTQ: childhood trauma questionnaire. WS: whole sample. MDD: major depressive disorder. BD: bipolar disorder. BD PRS: bipolar disorder polygenic risk score. SD: standard deviation.

Table 3
Results of the CT x BD PRS moderation. Statistical significance reported (p). CTQ, Childhood Trauma Questionnaire; FA, fractional anisotropy; AD, axial diffusivity; RD, radial diffusivity; MD, mean diffusivity.

	Whole sample (n = 162)			Bipolar disorder (n = 72)			Major depression (n = 90)		
	FA	**RD**	**MD**	**FA**	**RD**	**MD**	**FA**	**RD**	**MD**
CTQ total score	**0.008****	0.052	0.199	0.549	0.249	0.161	**0.008****	**0.013***	0.061
Emotional abuse	**0.004****	0.071	0.358	0.947	0.527	0.335	**0.001****	**0.016***	0.145
Physical abuse	**0.007****	**0.032***	0.099	0.617	0.280	0.248	**0.004****	**0.005****	**0.019***
Physical neglect	**0.015***	**0.046***	0.125	0.874	0.875	0.688	**0.019***	**0.031***	0.078

4. Discussion

In our study we observed a differential effect of ACEs on WM microstructure between depressed patients with a diagnosis of MDD or BD, specifically for childhood emotional abuse, physical abuse and physical neglect. This different effect appeared evident also performing the analysis in the two groups separately, with emotional abuse influencing WM microstructure only in BD, and physical neglect, physical abuse and dysfunctional family environment affecting different DTI metrics in the two groups.

As hypothesized, childhood maltreatment showed diagnosis-dependent effects on WM microstructure, with a stronger impact in BD than in MDD. In line with this, only the BD group displayed a robust association between total CTQ scores and DTI alterations. Childhood maltreatment dimensions also tended to affect WM predominantly in BD, suggesting heightened neurobiological vulnerability to early adversity in BD. Although no significant interaction emerged for dysfunctional family environment, the RFQ similarly showed stronger associations with WM measures in BD, pointing to a broader pattern of sensitivity to adverse early environment in this group.

Regarding trauma types, our data suggest that emotional neglect does not exert a detectable effect on WM integrity, in contrast to physical abuse, physical neglect, and emotional abuse. This pattern may indicate that being emotionally ignored or unsupported during childhood has a comparatively weaker biological impact on WM development than exposure to physical violence, inadequate physical care (e.g., nutrition and hygiene), or systematic emotional devaluation and verbal aggression. Interestingly, we did not observe a significant effect of sexual abuse. A possible explanation is that sexual abuse may be underreported in self-report measures, as suggested by several previous works (Widom and Morris, 1997; Finkelhor et al., 2014), leading to reduced statistical power to detect its effects.

These results largely confirmed our previous work (Poletti et al., 2022), further defining the subtypes of childhood maltreatment associating with WM. Further, the effect of ACEs in BD is in line with other studies in which widespread reductions of FA were found in exposed

patients compared to ones with no history of trauma (Stevelink et al., 2018).

The association between ACEs, reduction of FA and increase of RD and MD in BD may reflect dysmyelination or demyelination (Song et al., 2005). ACEs have been shown to affect BD onset and its course, but also cognitive performances (Agnew-Blais et al., 2016; Jiménez et al., 2017). Both cognitive impairment (Masuda et al., 2020) and earlier age of onset (Favre et al., 2019) have been associated with lower FA in BD: it seems therefore reasonable to hypothesize that ACEs might influence such clinical features at least partially via its effect on WM integrity. It is still unclear whether ACEs might affect BD WM microstructure impacting adolescence and early adulthood brain myelination, or rather enhancing and accelerating loss of myelin integrity in later stages of the disease; however the notion that both DTI alterations (Favre et al., 2019) and cognitive impairments (Miskowiak et al., 2020) appear to be relatively stable features of BD, apparent even in the early phases of the disease, might support the first hypothesis.

We identified different effects of childhood maltreatment and family environment on WM microstructure in MDD patients, with negative correlations with AD (the only DTI metric unaffected in BD) and MD and no effect on FA and RD (for which strong effects were found in BD). While FA and RD are usually thought to reflect myelin integrity, AD is classically regarded as an index of axonal damage (Song et al., 2005). Neuroaxonal injury has been implicated in MDD pathophysiology, with increased levels of plasma neurofilament light protein reported (Spanier et al., 2019). Interestingly in MDD axonal damage has been associated to treatment resistance (Spanier et al., 2019), a reported consequence of ACEs as well (Williams et al., 2016). However, strong caution is warranted in interpreting this result, as the in vivo biological meaning of AD changes is very much a matter of debate (Wheeler-Kingshott et al., 2009).

The biological underpinnings of this divergent effect are a matter of speculation, but immune alterations may partially explain this difference: ACEs have a strong impact on the inflammatory/immune system, having been robustly associated to elevated inflammatory markers in adulthood (Baumeister et al., 2016). Inflammatory status and peripheral markers have been in turn repeatedly associated with detrimental effects on WM microstructure (Benedetti et al., 2016; O'Donovan et al., 2021). Immune-inflammatory alterations are implicated both in MDD (Ruiz et al., 2022) and BD (Rosenblat et al., 2017) pathophysiology; however distinct immunological signatures between the two disorders are beginning to emerge (Martinuzzi et al., 2021; Poletti et al., 2021). Whether these distinct immunological profiles between the two disorders might contribute to the different relation between ACEs and WM microstructure remains to be determined.

It appears unlikely, however, that immune/inflammatory mechanisms might fully explain the divergent effect observed: far from completely understood, it is reasonable to assume that distinct, albeit partially overlapping, pathophysiological mechanisms underlie the development of the two disorders (including, among others, alterations of synaptic plasticity and neurogenesis, neurotransmission, insulin signaling, circadian rhythms, mitochondrial malfunction and oxidative stress, HPA axis dysfunction) (McIntyre et al., 2020). ACE itself is a risk factor for the development of both conditions, as well as for numerous other psychiatric phenotypes (Teicher et al., 2013, 2016). ACEs have profound effects on brain development, structure and function, albeit it is still unclear whether and to what extent such changes represent detrimental consequences or rather adaptive biological processes (Teicher et al., 2016). Maltreated individuals with a wide array of psychiatric diagnosis are nonetheless characterized by some common features, such as earlier age at onset, greater symptom severity and poorer treatment response, and childhood maltreatment positive subtypes can be likely identified for most psychiatric conditions (Teicher et al., 2013). Still, how a common environmental risk factor (ACEs) could influence the development of so many distinct psychiatric phenotypes remains an open research question. Under this framework, the distinct effect on DTI metrics we identified could be reflective, either as a pathological or compensatory mechanism, of two different pathophysiological routes leading from a common risk factor to two distinct phenotypes.

Furthermore, given the position of ACEs in the natural history of the disease (long before symptom onset) a candidate for the role of modulator of its effect on disease development is genetic liability. In line with our hypothesis, in our study, BD PRS significantly moderated the relation among childhood maltreatment and DTI metrics, with negative associations between childhood maltreatment and FA for higher values of BD PRS and positive for lower PRS, and an opposite effect for RD; it is worth noting that for high values of BD PRS, the relation between childhood maltreatment and DTI metrics mimics the one observed in BD subjects, even after controlling for the effect of the diagnosis.

Performing the moderation analysis separately in the two diagnostic groups, significant interactions with BD PRS were found in MDD and not in BD, suggesting that a negative association between childhood maltreatment and FA is present in BD irrespective of PRS, whereas in MDD bipolar vulnerability modulates the relation between childhood maltreatment and DTI metrics.

This finding has several implications: first, it confirms the existence of divergent effects of childhood maltreatment across mood disorders, linked at least partially to genetic liability rather than to the diagnostic category per se. Second, it sheds further light on the relation between childhood maltreatment, diagnosis and WM microstructure, allowing us to partially discard the hypothesis that the divergent effect we identified could be related to the different clinical course of the two disorders. Furthermore, it highlights the heterogeneous nature of the MDD conceptualization.

Genome-wide association studies on large samples support partially shared genetic risk factors in patients ranging from MDD to schizoaffective disorders (Coleman et al., 2020). Sub-threshold, single episode and recurrent MDD, BD type 2 and type 1 and schizoaffective disorder exhibit high levels of genetic correlation, with stronger correlations between disorders more clinically alike (Coleman et al., 2020). In other words, many genetic variants associated with psychopathology are shared among disorders, as they exhibit pleiotropy (Richards et al., 2022). On the other hand, some genetic variants appear to be disorder specific, or to be shared selectively only between some psychiatric traits, contributing to the complexity of psychiatric disorders genetic architecture (Richards et al., 2022).

Significant ACEs x BD PRS interactions have previously been shown to affect specific clinical features of BD, such as earlier age of onset and rapid cycling (Aas et al., 2020; Park et al., 2020): we could speculate that also in MDD or mixed samples, ACEs x PRS interactions could translate into specific clinical features at least partially through their effect on WM microstructure.

The identification of a PRS moderation only in MDD, and not in BD, might highlight the heterogeneity of this diagnosis (Lynall et al., 2023), and support the critics of the MDD/BD dichotomous conceptualization of mood disorders, suggesting that a subset of MDD subjects present bipolar-like responses to ACEs. Indeed it has long been suggested that our current definition of BD is too narrow (Ghaemi, 2013), and some authors argue for the reintroduction of the original kraepelinian concept of manic-depressive illness (Kraepelin, 1913), which would include BD and a portion of what today we call MDD. However, it must be noted that, while we observed a general trend towards a negative association between childhood maltreatment and FA at higher BD PRS scores, statistical significance in MDD was reached only for emotional abuse and for a very small percentage of the sample.

In subjects with low BD PRS on the other hand we identified robust opposite effects for the relation between childhood maltreatment and DTI metrics, with high childhood maltreatment associated to higher FA and lower RD. While this is certainly counterintuitive and warranting further investigation, it appears reminiscent of the repeatedly reported positive association between childhood maltreatment and FA in subjects suffering from MDD and their unaffected relatives (Frodl et al., 2012;

Graziano et al., 2019; Tatham et al., 2016). MDD patients appear to have a specific stress response, cortisol and BDNF secretion patterns when compared to both healthy controls and BD patients (Grande et al., 2010; Vinberg et al., 2008), and such distinct stress-response mechanisms may underlie the relation between childhood maltreatment and WM at low BD PRS values (Frodl et al., 2012). Furthermore, if we accept the notion of a broader manic-depressive clinical entity, encompassing beside BD also a portion of MDD patients, and the hypothesis that BD PRS might reflect at least partially its underlying biology, we can speculate that individuals outside this definition – i.e. with lowest BD PRS – might be characterized by a distinct biology in response to ACEs, reflected in the opposite alterations of DTI metrics.

This study has several limitations. The recruitment in a single center and the absence of a healthy control group limits the generalizability of our findings. The cross-sectional nature of our data limits the validity of causal inferences from the associations we identified. As it is often the case, ACEs were assessed retrospectively: this approach is susceptible to each patient sensibility and recollection biases; we tried to partially account for this by including the CTQ minimization subscale as a nuisance covariate. Furthermore, the trauma measures we employed did not identify the specific age when trauma occurred, nor its severity or chronicity over time, all important determinant of CM consequences in adulthood (Teicher et al., 2016). It is also important to note that we did not capture additional dimensions of adversity that are known to influence neurodevelopmental trajectories, such as the developmental timing of exposure and sex- or gender-related differences in vulnerability. Prior work has shown that the timing of adverse experiences may differentially affect brain maturation and psychiatric outcomes, and that neurobiological responses to early stress may vary across sex and gender (Colic et al. 2022; Fares-Otero and Schalinski, 2024). MDD and BD patients significantly differed for duration of illness and BMI, both of which could have an impact on WM integrity: we tried to account for this difference entering BMI and illness duration as covariates in all analyses. Our sample had relatively limited size, particularly for the genetic analyses, partially compensated by deep phenotyping. Patients were prescribed a wide variety of psychopharmacological treatments, which could have an impact on DTI metrics: antidepressant and lithium treatment were used as nuisance covariates, but given the real-world nature of our study we were not able to control for the wide variety of prescribed pharmacotherapies.

Despite these limitations, this study provides novel evidence on the relation between childhood adversity, genetic risk and white-matter microstructure, highlighting the importance of systematically assessing adverse childhood experiences and familial psychiatric risk in clinical settings and underscoring the need for longitudinal, multimodal research to disentangle developmental pathways and inform targeted prevention and intervention strategies.

5. Conclusions

In the present study we identified a differential effect of childhood maltreatment on WM microstructure between patients suffering from Major depression or Bipolar disorder, with more pronounced detrimental effects in BD compared to MDD: this may point to distinct pathophysiological routes through which childhood maltreatment, a shared environmental risk factor, affects the development of the two disorders. Further, we identified a significant interaction between CM and BD genetic liability, suggesting that the different effect in the two diagnosis might be directly related to the distinct genetic architecture of the two disorders. Finally, investigating the two diagnoses separately, the interaction with BD genetic risk was identified only in MDD patients, with bipolar-like relations between CM and DTI metrics at higher BD PRS scores: this finding might stem from MDD clinical and pathophysiological heterogeneity, give credence to the notion of a shared disease biology with bipolar disorder in a portion of MDD patients (Ghaemi, 2013), and possibly provide future tools to disentangle MDD heterogeneity.

Author contributions

M.P., F.B. and S.P. conceptualized the study. C.L. and S.S performed genetic material extraction and genotyping. B.B. performed DTI data preprocessing. L.F.U. and M.P. performed genetic quality check, imputation and PRS calculation. M.P., L.R., V.B., and B.B. performed neuroimaging and genetic analyses. M.P., L.R., V.B. and G.G. wrote the original draft of the paper. C.F., A.S., R.Z., C.C., F.B., and S.P. all contributed to the revised version of the manuscript. F.B. and S.P. supervised all steps of data acquisition, preprocessing, statistical analyses and manuscript drafting.

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Declaration of competing interest

The authors declare no conflicts of interest relevant or related to the work described in this manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2025.11.011.

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