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Association between peripheral inflammation and body mass index on white matter integrity and free water in bipolar II depression

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ABSTRACT

Immuno-metabolic dysregulation is implicated in mood disorders and elucidating non-invasive brain correlates may aid clinical translation of pathomechanism. This study aims to investigate the interrelationship between peripheral inflammation and body mass index (BMI) and their effects on white matter (WM) microstructure and free water (FW) in bipolar II depression (BDII-D). Voxel-wise FW and FW-corrected fractional anisotropy (FAt) were compared between 146 BDII-D and 151 healthy controls (HCs) using FSL Randomise. Partial correlations were used to explore associations between BMI, peripheral inflammation, FW measures, and psychiatric symptoms. Moderation analysis examined the interrelationships among BMI, peripheral inflammation, and FW measures. BDII-D showed lower FAt in the genu of the corpus callosum (CC) and bilateral anterior corona radiata, and higher FW in the body of the CC compared with HCs. Higher BMI was linked to lower global FAt ($q < 0.001$), while higher peripheral inflammation was associated with higher global FW ($q \leq 0.01$) in BDII-D. Lower FAt in the genu of the CC and higher FW in the body of CC were significantly related to higher BMI, inflammation, and greater depressive symptoms ($q < 0.05$). Low-grade Inflammation moderated the relationship between higher BMI and lower FAt in the genu of the CC in BDII-D ($B = -3.094e{-}05$, $p < 0.001$). We found evidence for a mechanistic link between immune-metabolic dysregulation and altered connection in BDII-D. Next

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to mediating BMI effects on WM integrity, there seems to exist specific relationships between inflammation and BMI with different MR-based tract markers that need further investigation.

1. Introduction

Approximately 68 % of individuals with bipolar disorder (BD) are at heightened risk for being overweight or obese (McElroy et al., 2004), and it is associated with poorer clinical outcomes, higher morbidity and mortality rates, and heightened illness burden in bipolar depression (Fagiolini et al., 2002; Fagiolini et al., 2003). Heightened peripheral inflammation, insulin resistance, and obesity have been observed in unipolar and bipolar depression (Milaneschi et al., 2020; Sen et al., 2021). The relationship between depressive symptoms and obesity has been largely confined to unipolar or bipolar depression individuals whose symptom profile is often characterized as atypical (Pistis et al., 2021). Increased prevalence of atypical features has been observed in bipolar II depression (BDII-D) with nearly 32.5 % of individuals having atypical depression (Perugi et al., 1998). Additionally, the incidence of depression with atypical features is twice as high in BDII-D compared to unipolar depression (Benazzi, 2000). While studies imply that immune-metabolic dysregulation occurs more frequently in individuals with unipolar or bipolar depression with atypical features, the immune-metabolic interactions are still under debate (Lamers et al., 2018). The underlying biological underpinnings between overweight/obesity and inflammation in BDII-D remains poorly understood and warrant further exploration.

Recently, low-grade inflammation has been implicated in the progression of neuropsychiatric disorders including psychosis (Parksepp et al., 2022), unipolar and BDII-D (Cao et al., 2023; Osimo et al., 2019). Furthermore, being overweight or obesity is recognized as a low-grade chronic inflammation state, which may be involved in the pathophysiology of psychiatric disorders (Gialluisi et al., 2020). One study suggested that the effects of inflammation on depression are attenuated when body mass index (BMI) is controlled (Fried et al., 2020). Further, a Mendelian Randomization study indicated that both C-reactive protein (CRP) and BMI were found to be genetically correlated with depressive symptoms and metabolic dysregulation, suggesting a causal association with specific depressive symptoms (Kappelmann et al., 2021). Additionally, immuno-metabolic relationships were also observed in BD populations, showing that peripheral inflammation levels could predict depressive relapse of BD, whereas elevated BMI contributed to inflammation (Bond et al., 2016). These studies provide evidence that immune and metabolic changes are indeed inextricably linked to depression to some extent. However, no study to date has investigated immuno-metabolic associations in BDII-D.

Recent studies have shown that higher BMI, aldosterone/cortisol ratio, and CRP levels were correlated with lower volumes in the mid anterior and central part of corpus callosum in depression (Cyprien et al., 2019; Murck et al., 2021). Additionally, Murck et al. observed that lower volumes in these regions were associated with higher axial diffusivity, but not fractional anisotropy (Murck et al., 2024). These findings suggested a potential link between metabolic dysregulation, systemic inflammation, and white matter (WM) integrity in depression. Furthermore, the interplay between immuno-metabolic dysregulation and brain microstructural alterations may also help explain the contribution of elevated BMI and inflammation in bipolar depression (Aronica et al., 2022). Studies have shown that increased BMI is related to lower fractional anisotropy (FA) in the corpus callosum in bipolar depression and healthy individuals (Mazza et al., 2017; Stanek et al., 2011), especially in the genu part. Meanwhile, elevated peripheral inflammatory cytokines in depressed individuals are related to lower FA in fronto-cingulate-limbic tracts, especially the genu of the corpus callosum (Ho et al., 2022; Sugimoto et al., 2018). Our subsequent finding on the WM subgroup of BDII-D suggested that the subgroup with greater disruption of WM integrity in the genu and anterior midbody of corpus callosum showed not only associated with significantly higher levels of interleukin-(IL)-6, IL-1β, and CRP, but also significantly correlated with higher BMI and greater depressive and psychotic symptoms (paper in review at Nature Mental Health). However, whether BMI effects WM integrity and the volume in the corpus callosum and how it relates to inflammatory cytokines in BDII-D is still unclear.

Neuroinflammation has been observed in several psychiatric disorders, including schizophrenia (Pasternak et al., 2012), bipolar disorder (Tuozzo et al., 2018), and depression (Bergamino et al., 2016). Free water (FW) imaging is used to reduce the partial volume effect of freely diffusing extracellular water in the WM, thus providing a more accurate estimate of the microstructure of the WM (Pasternak et al., 2009). Meanwhile, the accumulation of extracellular water can be reflected by increased FW in the WM, which may be closely related to neuroinflammation. Lower free water corrected FA (FAt) may indicate the presence of compromised white matter or axonal damage in neuropsychiatric disorders. While higher levels of FW may be related to peripheral inflammation in schizophrenia (Di Biase et al., 2021; Wu et al., 2024b). Specifically, Biase et al. observed that higher IL-6 and tumor necrosis factor (TNF)-α levels were specifically related to higher FW but not FA in schizophrenia (Di Biase et al., 2021). These studies may help to bridge the gap between neuroinflammation and peripheral inflammation and provide preliminary evidence for the pathophysiological mechanisms underlying neuroinflammatory and peripheral inflammatory alterations in psychiatric disorders. Even though current findings have demonstrated inflammatory associations with WM integrity in psychiatric disorders, the focus has been primarily on peripheral inflammation. However, the association between neuroinflammation and peripheral inflammation has not been clarified in BDII-D.

The current study aims to investigate the WM (including FAt and FW) differences between BDII-D and HCs, explore the effects of BMI and peripheral inflammation on both global and regional altered FW measures, and examine the potential interactive associations among BMI, peripheral inflammation, and FW parameters. Additionally, in exploratory analyses, we examined differences in corpus callosum segment volumes between BDII-D and HCs and examined their relationship with BMI, global and regional altered FW measures, and peripheral inflammation in BDII-D. Based on existing evidence suggesting a relationship between BMI and impaired WM integrity, as well as a relationship between peripheral inflammation and neuroinflammation, we expect to find BMI to have a greater impact on the WM integrity, whereas peripheral inflammation is more likely to associate with FW in BDII-D. Specifically, we hypothesize that individuals with BDII-D will show lower FAt and higher FW in the corpus callosum compared with HCs, and that these differences will be linked to higher peripheral inflammation, BMI, and depressive symptoms. Since evidence suggests that higher BMI affects the integrity of the genu of the corpus callosum, and that low-grade inflammation impacts both of BMI and WM integrity of the corpus callosum (Cyprien et al., 2019; Khanna et al., 2022), we suspected that low-grade inflammation may moderate the relationships between higher BMI and disruption of WM integrity in the genu of corpus callosum in individuals with BDII-D.

2. Methods

2.1. Participants

This study was approved by the Medical Research Ethics Committee of West China Hospital (approval number: 2021511) and complied with the ethical standards of the relevant national and institutional

committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 (Ashcroft, 2008). All enrolled individuals signed the written informed consent before participating this study.

A total of 146 BDII-D individuals and 151 HCs with complete clinical data and diffusion magnetic resonance imaging (dMRI) scanning were included this study, and the details of recruitment were described in previous studies. The BDII-D individuals were diagnosed according to the Structured Clinical Interview for The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (SCID-5) (First et al., 2015). All the BDII-D individuals completed the 17-item Hamilton Depression Scale (HAMD) (Hamilton, 1960), Hamilton Anxiety Scale (HAMA) (Hamilton, 1959), Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2008), and Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1998), while the HCs were screened using the Structured Clinical Interview (SCID)-non-patient edition and completed the CTQ. Additionally, clinical profiles including hypomanic episode frequency, duration of depressive episodes, illness duration, and age of onset in individuals with BDII-D were also assessed. Inflammatory cytokines, including IL-6, CRP, IL-1β, and TNF-α and a low-grade inflammation score (an average of the standardized z-scores of IL-6, IL-1β, and TNF-α in each sex group and then calculating a composite as previous study suggested) (Bonaccio et al., 2016; Cao et al., 2023; Kim et al., 2020). Routine blood tests were obtained in BDII-D individuals and included the absolute value of the lymphocytes, monocytes, neutrophils, platelet, and white blood cell (WBC) counts. The Neutrophil-to-Lymphocyte (NTL) ratio, Monocyte-to-Lymphocyte (MTL) ratio, and Platelet-to-Lymphocyte (PTL) ratio were calculated to reflect indirect inflammatory levels. For lipid metabolic measures, the serum specimens were extracted, aliquoted and stored at −80 °C. The triglyceride, cholesterol, high density lipoprotein (HDL), and low-density lipoprotein (LDL) measurements were assayed using enzymatic methods on the Cobas 8000 analyzer c702 module (Roche Diagnostics, Mannheim, Germany). Medication effects were assessed by the medication load as Hassel et al suggested (Hassel et al., 2008). Specific details, including inclusion criteria for BDII-D and HCs, testing of inflammatory cytokines and blood cells, and calculation of medication loads, are shown in the Supplementary Method 1–3.

2.2. MRI acquisition and preprocessing

The magnetic resonance imaging (MRI) was performed on a 3.0 T scanner (Siemens Trio Tim, Germany) and 32-channel phased-array head coil in Huaxi MR Research Center, West China Hospital. The 3D T1-weighted images were acquired using a 3D-magnetization prepared rapid acquisition gradient echo sequences (3D-MPRAGE) with the following parameters: repetition time/echo time (TR/TE) = 2400/2.01 ms; inversion time = 1000 ms; flip angle = 8∘; slice thickness = 0.8 mm without gap; matrix = 320 × 320; field of view (FOV) = 256 × 256 mm^2; voxel size = 0.8 × 0.8 × 0.8 mm^3. The dMRI was acquired using a spin-echo planar imaging (SE-EPI) sequence with the left–right/right-left (L-R/R-L) phase encoding direction with the following parameters: TR/TE = 4200/104 ms; slice gap = 1.8 mm; slice thickness = 1.8 mm; voxel size = 1.8 × 1.8 × 1.8; FOV = 216 × 216 mm2; flip angle = 80°. The 90 gradient directions were acquired at each of the four b-values (5, 995, 1000, and 1005 s/mm2). The MRI preprocessing and details on the calculation of corpus callosum segment volumes using FreeSurfer are shown in Supplementary Method 4.

2.3. Statistical analysis

2.3.1. Demographic and clinical differences between BDII-D and HCs

Independent t-tests were applied to normally distributed variables, Mann-Whitney U tests were employed for variables that did not follow a normal distribution, and chi-square tests were used for categorical variables. All statistical analyses were conducted using R software version 4.0.5 (https://www.rstudio.com).

2.3.2. Free water analysis

The free water (FW) and FW-corrected FA (FAt) maps were calculated by applying the bi-tensor model in each voxel as described by Pasternak et al. (2009). The equation for this model is as follows:

$$A_q(D,f) = f\cdot(exp[-bq^TDq]) + (1-f)\cdot exp[-bD_{water}]$$

In brief, this model comprises of two compartments: one is FA tissue compartment represented by a diffusion tensor D. Another one is an isotropic free water compartment characterized by (1-f), where f denotes the fractional volume. The estimation of the free water model using a conventional dMRI acquisition requires additional mathematical constraints on continuity so that the two compartments can be estimated. The model and continuity constraints constitute a cost function that is fitted using an iterative method while minimizing the function for both the free water parameters and the diffusion tensor representing the tissue partitions.

The voxel-wise statistical analysis of the FAt and FW images was carried out through tract-based spatial statistics (TBSS) in FSL. The FAt and FW image was registered and skeletonized to the DTI atlas generated by the Enhanced Neuroimaging Genetics by Meta-Analysis (ENIGMA) DTI Working Group at the University of Southern California (https://enigma.ini.usc.edu/ongoing/dti-working-group). The FAt and FW images were calculated and projected onto the mean FA skeleton with the FA intensity threshold at −0.049. The "Randomise" was used to perform the general linear models (GLMs) with a *t*-test controlling for the effect of age, sex, education, and medication load at each voxel on the individual FA skeleton. To correct for multiple comparisons, the family-wise error (FWE) correction with a threshold of $p < 0.05$ was performed on the threshold-free cluster enhancement statistic image with 5000 random permutations. In addition, the global FAt values and global FW values were extracted. Subgroup analysis of FW and FAt differences between unmedicated BDII-D individuals and HCs was also tested and showed in the Supplementary Method 5.

2.3.3. Partial correlation analysis

The FAt and FW values were extracted from each ROI and at the global level, and partial Pearson/Spearman correlations were performed to explore the association between FAt and FW values (including global level and identified significant WM regions between the groups) and peripheral inflammatory cytokines (including IL6, IL-1β, TNF-α, and CRP), indirect inflammatory factors (including NTL ratio, MTL ratio, and PTL), lipid measures (including triglyceride, cholesterol, HDL, and LDL), psychiatric symptoms (including HAMD, HAMA, and PANSS), severity of suicide ideation (C-SSRS), clinical profiles (hypomanic episode frequency, duration of depressive episodes, illness duration, and age of onset) in BDII-D group, while the association of FAt and FW values with BMI and childhood maltreatment (CTQ) were tested in both BDII-D and HCs, respectively. Moreover, the relationships between BMI and inflammation were also explored in BDII-D. The age, sex, education level, and medication load, which were selected by a priori knowledge and were imbalanced between BDII-D and HCs, were controlled for as covariates in the partial correlation analyses. To control the impact of multiple comparisons, the *p*-values were corrected with false discovery rate correction through the Benjamin-Hochberg method, and subsequently, the q-values were reported (Benjamini and Hochberg, 1995). The partial correlation was performed by "ppcor" R package. The detailed information of determining the degree of freedom and the number of independent tests was shown in the Supplementary Method 6.1.

2.3.4. Moderation analysis

A moderation analysis was performed to explore whether low-grade

Table 1
Demographic and Clinical Characteristics of Participants.

Characteristic	BD II-D (N = 146)	Healthy controls (N = 151)	t/χ^2	*p*
Sociodemographic				
Age, mean ± SD	22.68 ± 7.31	25.52 ± 7.19	−3.37	<0.001
Sex (male/female)	38/108	35/116	0.32	0.569
Total education, mean ± SD, yrs	13.89 ± 2.51	16.88 ± 3.11	−9.09	<0.001
Smoke (yes/no)	34/112	22/128	3.85	0.05
Marriage status (yes/no)	16/130	16/135	0.01	0.920
Childbearing (yes/no)	13/133	9/142	0.94	0.333
Clinical, mean ± SD				
No. of hypomanic episodes, mean (SD)	2.43 ± 2.11	–	–	–
The duration of depressive episode, mean (SD) (days)	99.16 ± 143.5	–	–	–
Duration of illness, mean (SD) (yrs)	4.056 ± 3.86	–	–	–
Age at onset, mean (SD)	20.28 ± 6.41	–	–	–
Questionnaires, mean ± SD				
HAMD score	15.58 ± 5.43	–	–	–
HAMA score	12.82 ± 6.61	–	–	–
PANSS_P score	8.28 ± 1.97	–	–	–
PANSS_N score	8.05 ± 2.19	–	–	–
PANSS_G score	22.89 ± 3.76	–	–	–
PANSS_T score	39.23 ± 5.80	–	–	–
C-SSRS intensity of suicide ideation	2.36 ± 1.99	–	–	–
Childhood adversity, mean ± SD				
Emotional Abuse	10.5 ± 5.38	5.68 ± 1.42	10.50	<0.001
Physical Abuse	7.35 ± 3.16	5.29 ± 0.91	7.59	<0.001
Sexual Abuse	6.16 ± 2.60	5.12 ± 0.42	4.79	<0.001
Emotional Neglect	13.66 ± 6.20	7.04 ± 2.88	11.74	<0.001
Physical Neglect	9.27 ± 4.12	5.46 ± 1.32	10.67	<0.001
CTQ total	46.96 ± 17.08	28.59 ± 5.56	12.37	<0.001
Blood Cells, mean ± SD				
IL-1beta	3.97 ± 3.68	–	–	–
IL-6	2.42 ± 1.97	–	–	–
TNF-alpha	6.18 ± 3.56	–	–	–
CRP	2.71 ± 3.47	–	–	–
WBC	6.26 ± 1.89	–	–	–
Neutrophil to Lymphocyte ratio	1.60 ± 0.89	–	–	–
Monocyte to Lymphocyte ratio	0.24 ± 0.12	–	–	–
Platelet to Lymphocyte ratio	113.6 ± 40.64	–	–	–
Lipid metabolic measures, mean ± SD				
Triglyceride	1.19 ± 0.66	–	–	–
Cholesterol	4.03 ± 0.72	–	–	–
HDL	1.26 ± 0.32	–	–	–
LDL	2.28 ± 0.61	–	–	–
Medical characteristics				
Medication load index, mean ± SD	1.48 ± 1.76	–	–	–
Antidepressants, No.of. patients	52	–	–	–
SNRI	11	–	–	–
SSRI	21	–	–	–
Agomelantine	19	–	–	–
Mood stabilizer, No.of patients	57	–	–	–
Antipsychotics, No.of patients	48	–	–	–
Benzodiazepines, No.of patients	23	–	–	–
No medication, No.of patients	74	–	–	–

Abbreviations: BD-bipolar type II depression; HAMD-17-item Hamilton Depression Scale; HAMA-Hamilton Anxiety Scale; PANSS-Positive and Negative Syndrome Scale; P-positive; N-negative; G-general; T-Total; C-SSRS- Columbia-Suicide Severity Rating Scale; CTQ-Childhood Trauma Questionnaire; IL-Interleukin; CRP- C-reactive protein; TNF-Tumor Necrosis Factor; WBC-white blood cell; SNRIs-serotonin and norepinephrine reuptake inhibitors; SSRIs-selective serotonin reuptake inhibitors; HDL-high density lipoprotein, LDL-low-density lipoprotein.

inflammation (moderator) interacted with BMI (independent variable) to affect the WM integrity of genu of corpus callosum (dependent variable). The bootstrap method with 5000 repetitive times was used to estimated 95 % confidence interval (CI). The moderation analysis was performed by using the R package "interactions".

The outlier detection and assumption of multi-collinearity, auto-correlation, normality, and homoscedasticity of the model was tested in both mediation model and moderation model by using the Bonferroni outlier test, variance inflation factor (VIF), Durbin-Watson statistics, Shapiro–Wilk test, and Breusch-Pagan test, respectively, through "car" and "stats" R packages.

2.3.5. *Exploratory analyses*

Based on the evidence provided by previous studies (Murck et al., 2024; Murck et al., 2021), we extracted the volumes of five corpus callosum segments and compared them between BDII-D and HCs. Furthermore, for corpus callosum segments that showed significant differences between BDII-D and HCs, we conducted partial correlation analyses to explore their associations with BMI, inflammation, as well as global and regional altered FW measures. The age, sex, education level, medication load, and total intracranial volume (TIV) were controlled for in the partial correlation analyses and the p-values were corrected with the false discovery rate, Benjamin-Hochberg method described above. The detailed information for determining the degrees of freedom and the number of independent tests are shown in Supplementary Method 6.2.

Table 2
Free water corrected FA and free water differences between BDII-D and HCs.

Cluster Index	WM region	Voxels	*p*-FWE	MNI coordinates		
				x	y	z
FAt						
1	Anterior corona radiata L	27	0.045	−24	29	7
2	Genu of corpus callosum	120	0.031	−15	33	4
3	Anterior corona radiata R	326	0.013	23	31	−4
Free water						
1	Body of corpus callosum	715	0.008	9	11	27

Abbreviations: FAt-fractional anisotropy tissue (Free water corrected FA); BDII-D-bipolar II depression; HCs-health controls; WM-white matter; MNI-Montreal Neurologic Institute.

3. Results

3.1. Demographic and clinical profiles in BDII-D and HCs

Table 1 illustrates the demographic and clinical information of 146 BDII-D individuals and 151 HCs. Briefly, compared with HCs, BDII-D individuals showed differences in age (Cohen's d = −0.39, $p < 0.001$), education level (d = −1.05, $p < 0.001$), and childhood adversity (d = 1.45, $p < 0.001$). No significant differences were found for sex, marital status, smoking, or childbearing status between groups.

3.2. Group difference for FAt and FW between BDII-D and HCs

Whole brain TBSS analyses indicated that compared to HCs, BDII-D individuals showed lower FAt in the genu of the corpus callosum (cluster size = 120; *p*-FWE corrected = 0.031; MNI = −15, 33, 4) and the bilateral anterior corona radiata (ACR) (left: cluster size = 27; *p*-FWE corrected = 0.045; MNI = −24, 29, 7; right cluster size = 326; *p*-FWE corrected = 0.013; MNI = 23, 31, −4), and higher FW in the body of the corpus callosum (cluster size = 715; *p*-FWE corrected = 0.008; MNI = 9, 11, 27) (Table 2). The BDII-D showed lower global FAt values (0.294 ± 0.006 v.s. 0.296 ± 0.006; Cohen's d = −0.33, $p = 0.001$) and higher global FW values (0.291 ± 0.021 v.s. 0.279 ± 0.016; Cohen's d = 0.64, $p = 0.001$) compared with HCs. The FAt and FW results and the summary of underlying relationships among FW parameters, peripheral inflammation, BMI, and depressed mood are depicted in Fig. 1. The subgroup differences between unmedicated BDII-D and HCs are shown in the Supplementary Table 1 and Supplementary Fig. 1.

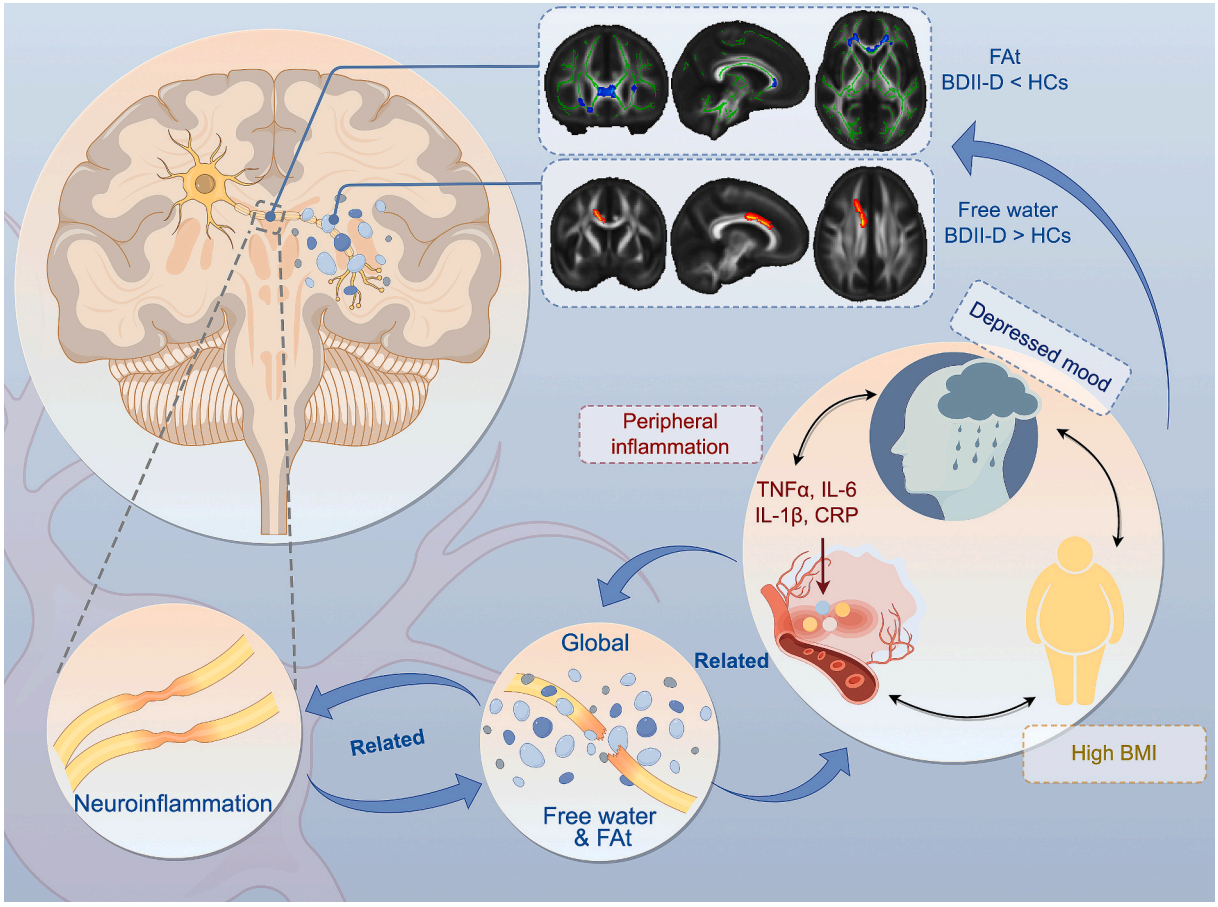

Fig. 1. Summary of underlying relationships among FW parameters, peripheral inflammation, BMI, and depressive symptoms and TBSS results. This figure illustrates the complex interplay between white matter microstructural alterations, neuroinflammation, peripheral inflammation, and clinical factors in BDII-D. Disruptions in white matter microstructure contribute to neuroinflammation. Neuroinflammation, in turn, exhibits a bidirectional relationship with both free water increases and white matter integrity deficits, creating a cycle of progressive changes. Meanwhile, increased FW and white matter damage are correlated with elevated peripheral inflammatory markers, suggesting a connection between neuroinflammatory processes and peripheral inflammation. Peripheral inflammation is further associated with higher BMI (obesity) and depressive symptoms, and these factors that are also closely related to in white matter integrity and FW alterations in specific regions. This highlights a potential pathophysiological bridge between metabolic dysregulation, mood disturbances, and neuroinflammation in BDII-D. The TBSS results shows that lower FW corrected fractional anisotropy in the genu of corpus callosum and bilateral anterior corona radiata and higher FW in the body of the corpus callosum were observed in BDII-D individuals compared to HCs. Abbreviations: BDII-D-bipolar II depression; HCs-healthy controls; TBSS- tract-based spatial statistics; BMI-body mass index; FW-free water.

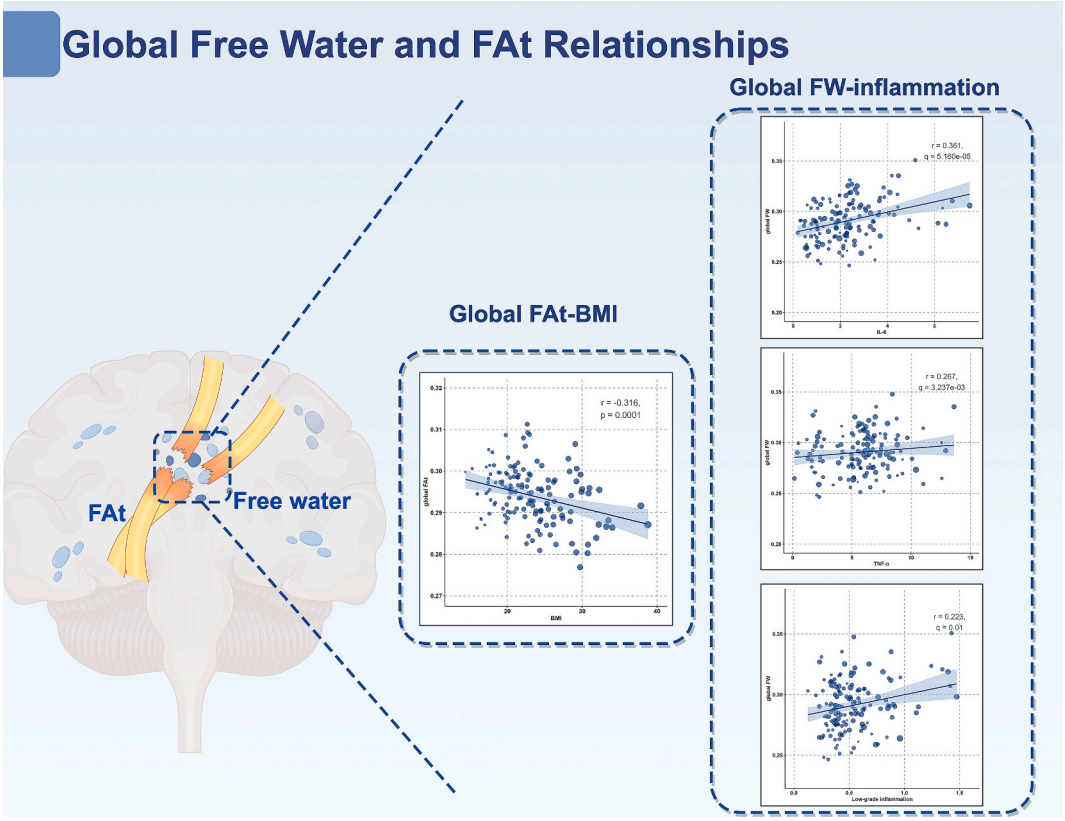

Fig. 2. Relationships of global FAt and FW with BMI and peripheral inflammation in BDII-D. Lower global FAt was significantly correlated higher BMI (left), while higher global FW was significantly correlated with higher IL-6, higher TNF-α, and higher low-grade inflammation (right). Abbreviations: BDII-D-bipolar II depression; BMI-body mass index; FAt-free water corrected fractional anisotropy; FW-free water; IL-interleukin; TNF- tumor necrosis factor.

3.3. Partial correlation analyses

Global FW correlated with peripheral inflammation, while global FA correlated with BMI in BDII-D. Specifically, an association was observed between higher global FW and higher IL-6 ($r = 0.361$, $q < 0.001$), higher TNF-α ($r = 0.267$, $q = 0.003$), and higher low-grade inflammation ($r = 0.223$, $q = 0.01$), while lower global FAt was significantly correlated with higher BMI ($r = -0.316$, $q < 0.001$) in BDII-D (Fig. 2).

At the ROI level, FAt and FW values were extracted from WM regions that significantly differed between BDII-D and HCs. Particularly, higher FW in the body of the corpus callosum was significantly related to higher BMI ($r = 0.31$, $q < 0.001$), higher WBC level ($r = 0.221$, $q = 0.033$), and higher HAMD score ($r = 0.247$, $q = 0.003$) in BDII-D. For FAt relationships, only lower FAt in the genu of the corpus callosum was found to be related to higher inflammation including IL-1β ($r = -0.230$, $q = 0.029$), CRP ($r = -0.398$, $q < 0.001$), and low-grade inflammation ($r = -0.412$, $q < 0.001$), as well as higher BMI ($r = -0.25$, $q = 0.008$) and HAMD score ($r = -0.273$, $q = 0.003$) in BDII-D (Fig. 3).

For relationships between BMI and inflammatory cytokines, higher BMI was correlated with higher IL-1β ($r = 0.233$, $q = 0.013$), low-grade inflammation ($r = 0.236$, $q = 0.013$), and WBC ($r = 0.251$, $q = 0.011$) (Fig. 3). The preliminary correlation findings in BDII-D and HCs are shown in Supplementary Tables 2–11.

3.4. Moderation analysis

The moderation model indicated that low-grade inflammation moderated the association between higher BMI and lower FA value of the genu of the corpus callosum ($B = -3.094e{-}05$, 95 % CI [$-5.888e{-}05$, $-3.010e{-}06$], $p < 0.001$) (Fig. 4). The detailed results of the moderation model and the model assumptions are shown in Table 3.

3.5. Exploratory analyses

The volume differences of corpus callosum segments were compared between BDII-D and HCs (Supplementary Table 12). Specifically, the volume of the corpus callosum central region was significantly lower in BDII-D compared to HC (Cohen's $d = -0.25$, $p = 0.02$), while the volume of the corpus callosum mid anterior region showed a trend toward significance (Cohen's $d = -0.22$, $p = 0.06$) (Supplementary Fig. 2). Other corpus callosum segments did not show significant volume differences between BDII-D and HCs.

For partial correlational analysis, smaller volume of the corpus callosum in the posterior ($r = 0.287$, $q = 0.003$) and mid posterior region ($r = 0.242$, $q = 0.010$) were significantly correlated with lower global FAt value (Supplementary Fig. 3), while smaller volume of the corpus callosum in the mid posterior ($r = -0.282$, $q = 0.003$), anterior ($r = -0.228$, $q = 0.011$), and mid anterior region ($r = -0.263$, $q = 0.004$) were significantly correlated with higher global FW value in BDII-D (Supplementary Fig. 4).

The preliminary correlation results between the volume of corpus callosum segments and inflammation cytokines, BMI, and lipid indicators in BDII-D are shown in Supplementary Tables 13–16.

4. Discussion

To the best of our knowledge, this is the first study to investigate FW alterations and explore the associations of BMI and peripheral inflammation with both global and altered FW and FAt in BDII-D individuals. At the global level, higher global FW was associated with higher IL-6, TNF-α, and low-grade inflammation, while lower global FAt was related to higher BMI in BDII-D. At the ROI level, lower FAt in the genu of the corpus callosum and higher FW in the body of the corpus callosum

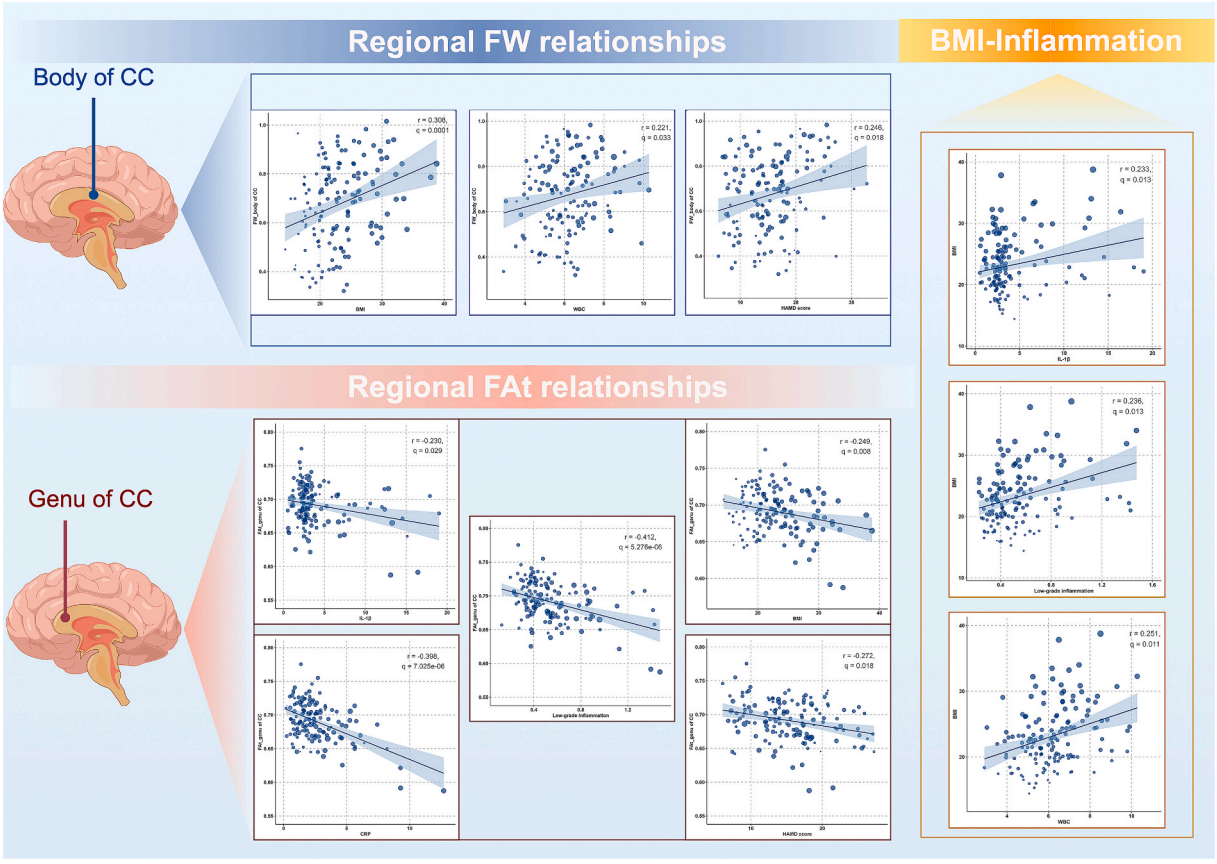

Fig. 3. Relationships among regional FAt and FW, BMI, peripheral inflammation, and depressive symptoms. Higher FW in the body of corpus callosum was significantly related to higher BMI, higher WBC level, and higher HAMD score (regional FW relationships). Lower FAt in genu of corpus callosum was significantly related to higher IL-1β, CRP, and low-grade inflammation, higher BMI, and HAMD score (regional FAt relationships). Higher BMI was significantly correlated with higher IL-1β, low-grade inflammation, and WBC (BMI-inflammation). Abbreviations: BDII-D-bipolar II depression; BMI-body mass index; FAt-free water corrected fractional anisotropy; FW-free water; IL-interleukin; WBC-white blood cell; HAMD-17-item Hamilton Depression Scale.

were significantly associated with higher BMI, higher peripheral inflammation, and greater depressive symptoms in BDII-D. A relationship was also established between higher BMI and lower FAt in the genu of the corpus callosum, which was moderated by low-grade inflammation, and this effect was primarily observed when low-grade inflammation levels were at a high level in BDII-D individuals. These findings were consistent with our hypothesis that BMI and peripheral inflammation acted separately on global FAt and global FW but intertwined to affect the integrity of the corpus callosum.

Accumulating evidence indicates that neural-immune interactions are one pathophysiological factor contributing to psychiatric disorders (Meyer et al., 2020; Miller et al., 2009). The current understanding of this neural-immune interaction suggests that chronic stress triggers microglial activation, which on the one hand leads to an upsurge in the production of pro-inflammatory cytokines within the brain, but on the other hand promotes the transition from serotonin synthesis to the generation of neurotoxic metabolites along the kynurenine pathway, ultimately fostering glutamate-mediated excitotoxicity in neurons. The specific brain regions where microglia are activated are thought to potentially render depression-associated brain neural connection more susceptible to inflammation-induced deficits (Torres-Platas et al., 2014). The current view is that neuroinflammation and peripheral inflammation have some complex interrelationships, but the sequence in which they occur, and their mechanisms of interaction are not clear. In addition, seeking noninvasive approaches reflect neuroinflammation could help characterize the tissue inflammatory state, thus may provide disease specific biomarkers (Garcia-Hernandez et al., 2022). FW allows the measurements of freely diffusing water molecules in extracellular space, while enlarged extracellular volume is considered an alternative biomarker of neuroinflammation (Pasternak et al., 2012). Recent studies have observed higher free water in several WM regions including corpus callosum, corona radiata, superior and inferior longitudinal fasciculus, and cingulum in schizophrenia individuals (Carreira Figueiredo et al., 2022). Our study found that the distribution of elevated FW in BDII-D was not as extensive as in schizophrenia but was only concentrated in the body of the corpus callosum. Additionally, the associations between higher FW and higher peripheral inflammation were also demonstrated in individuals with schizophrenia, which further confirms the links between neuroinflammation and peripheral inflammation (Wu et al., 2024a). Consistent with this, the current study found positive associations between higher global FW and higher peripheral inflammation (IL-6, TNF-a, and low-grade inflammation) in BDII-D individuals.

Growing evidence suggests that there is a connection between obesity and the impairment of WM integrity observed in both neurotypical individuals and those with psychiatric disorders. Studies have observed that higher body mass was associated with lower FA in the genu and the splenium of the corpus callosum, fornix, posterior thalamic radiation, internal capsule and external capsule, middle cerebellar peduncle, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus in neurotypical populations (Kullmann et al., 2016; Repple et al., 2018; Stanek et al., 2011). Although studies have found slight variations in the association between BMI and WM integrity, these studies were conducted in populations free from psychiatric disorders and medications, which may suggest that WM integrity is impacted by weight-related processes even before the occurrence of any known mental disorders. Mazza et al. (2017) first demonstrated in BDI-D

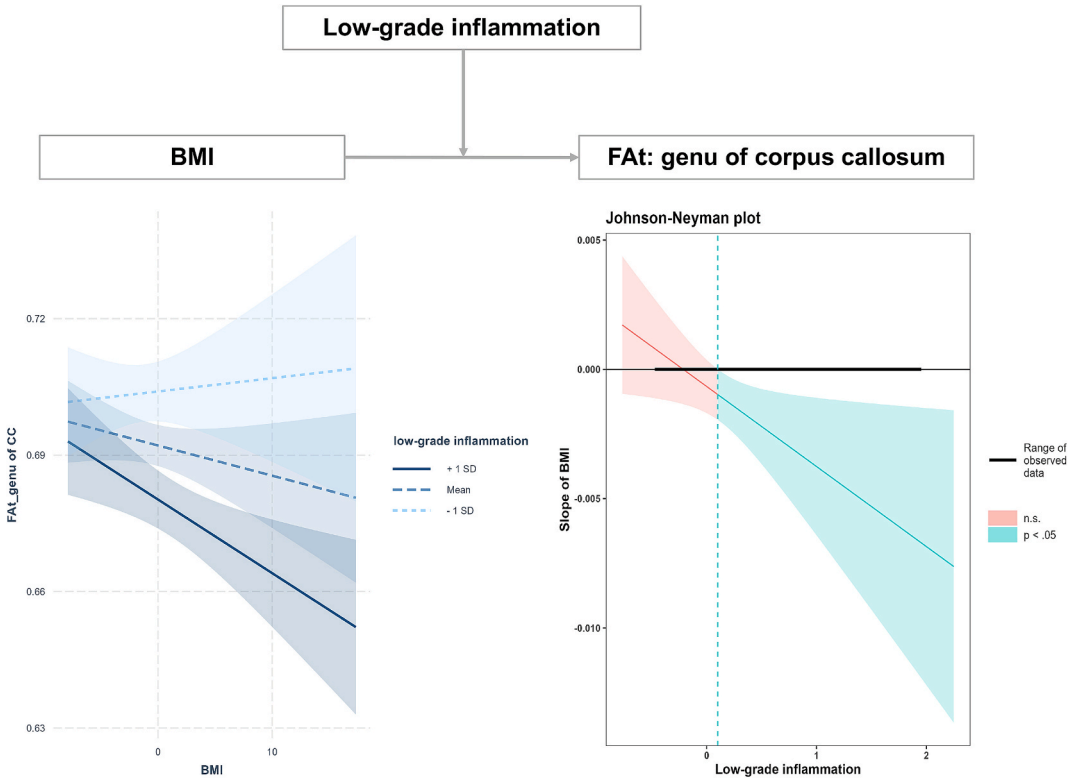

Fig. 4. Moderation analysis between BMI, low-grade inflammation, and FAt in the genu of the corpus callosum in BDII-D. The left-panel shows how the relationship between BMI and FAt in the genu of the corpus callosum depending on different levels of low-grade inflammation. When low-grade inflammation was at average or high levels, higher BMI was associated with lower FAt values in the genu of the corpus callosum, whereas when low-grade inflammation was at a low level, higher BMI was associated with higher FAt values in this region. The right-panel illustrates the significant moderating effect of low-grade inflammation on the relationship between BMI and FAt in the genu of the corpus callosum. When low-grade inflammation was at average or low levels, this relationship was not significant. When low-grade inflammation was high, a significant association emerges, where higher BMI was linked to lower FAt in the genu of the corpus callosum. Abbreviations: BDII-D-bipolar II depression; BMI-body mass index; FAt-free water corrected fractional anisotropy.

Table 3
Ordinary Least Squares regression and moderation analysis for FA_genu of CC (Y), BMI (X), and low grade inflammation (W).

	Estimate	SE	t-value	p-value	95 % CI for Beta		VIF	R^2	Adjusted R^2	F
					Lower	Upper				
Ordinary Least Squares regression										
Intercept	0.706	0.013	52.880	0.00**	0.679	7.323E−01		0.220	0.190	F(6,139) =
BMI	−0.001	4.993E−04	−2.050	0.04*	−0.002	−3.636E−05	1.10			6.64,
Low grade inflammation Z value	−0.036	0.007	−4.772	0.00**	−0.001	−2.127E−04	1.07			$p = 0.00$**
Education	−2.11E−04	9.624E−04	−0.219	0.83	−0.002	1.692E−03	1.13			
Age	−5.69E−04	3.364E−04	−1.692	0.09	−0.001	9.586E−05	1.17			
Sex	0.003	0.005	0.699	0.49	−0.006	1.418E−02	1.06			
Medication load	−3.235E−05	0.001	−0.025	0.98	−0.002	2.529E−03	1.02			
Moderate model										
Intercept	7.073E−01	1.318E−02	53.640	0.00**	0.6812	0.7334		0.250	0.210	F(7,138) =
BMI	−6.627E−04	5.194E−04	−1.280	0.20	−1.69E + 03	3.642E−04	1.22			6.53,
Low grade inflammation Z value	−3.855E−04	7.578E−05	−5.090	0.00**	−5.354E−04	−2.356E−04	1.09			$p = 0.00$**
Education	−2.102E−04	9.495E−04	−0.220	0.83	−2.087E03	1.667E−03	1.14			
Age	−6.048E−04	3.322E−04	−1.820	0.07	−1.261E−03	5.212E−05	1.17			
Sex	3.120E−03	5.236E−03	0.600	0.55	−7.233E−03	1.347E−02	1.06			
Medication load	4.123E−04	1.294E−03	0.320	0.75	−2.147E−03	2.971E−03	1.05			
BMI:Low grade inflammation Z value	−3.094E−05	1.413E−05	−2.19	0.03*	−5.888E−05	−3.010E−06	1.14			

OLS: D-W = 1.85; p-value = 0.38; Moderate model: D-W = 1.89; p-value = 0.54.
*$p < 0.05$; **$p < 0.01$.

individuals that the higher BMI was significantly associated with altered WM integrity measures in the anterior corona radiata, anterior thalamic radiation, inferior fronto-occipital fasciculus, and the body and the genu of the corpus callosum. The range of BMI-related WM damage was greater in BDI-D compared to our findings in BDII-D. However, it is worth noting that both the genu and the body of corpus callosum were observed to be associated with BMI in both BD depression type I and type II or healthy individuals (Daoust et al., 2021). This finding suggests

that the genu and the body of the corpus callosum may be key to the pathophysiologic mechanisms involved in BMI-related WM disruptions.

Higher weight or obesity is a source of chronic stress, impacting intracellular pathways by providing excess macronutrients in adipose tissue that subsequently stimulate the release of TNF-α and IL-6, leading to inflammation and oxidative stress (Rodríguez-Hernández et al., 2013). Further, higher IL-6 levels stimulate hepatic synthesis and secretion of CRP. Obesity-induced neuroinflammation occurs because the high-calorie diet-induced weight gain or obesity could increase the permeability of the blood–brain barrier (BBB), allowing pro-inflammatory cytokines to enter the CNS and promoting infiltration of peripheral macrophages into the brain (Guillemot-Legris et al., 2016; Stranahan et al., 2016). A previous study has suggested that the associations between higher BMI and lower FA of the body and the splenium of the corpus callosum and fornix were affected by peripheral inflammatory cytokines (IL-6 and CRP) and vascular factors, while the relationships between higher BMI and lower FA of the genu of the corpus callosum were not (Bettcher et al., 2013). There has also been a Diffusion Basis Spectrum Imaging (DBSI) study suggesting that the increased neuroinflammation-associated cells and decreased apparent axonal density in several WM tracts were associated with obesity in individuals without psychiatric disorders (Samara et al., 2020). Although BMI-related inflammation and WM integrity impairments have been examined separately in several psychiatric disorders, the interactional relationships among BMI, inflammation, and WM integrity are still largely unknown. Our study simultaneously provides insights into BMI-related neuroinflammation (reflected by FW), peripheral inflammation, and WM integrity in BDII-D individuals. More importantly, our study further explored and determined that higher BMI was significantly associated with lower FAt in the genu of the corpus callosum, and that this relationship was regulated by low-grade inflammation (IL-6, IL-1β, and TNF-α).

There are some limitations that need to be considered in this study. First, we did not test inflammatory cytokines, routine blood test, and lipid metabolic measures in HCs, so we cannot compare their differences between BDII-D individuals and HCs, nor explore their relationships with BMI, FAt, or FW in HCs. Secondly, due to the cross-sectional nature of this study, we cannot conduct a mediation analysis among BMI, FA in the genu of the corpus callosum, and low-grade inflammation to explore causal relationships. These limitations highlight the caution of drawing definitive conclusions from our findings and suggest the need for further longitudinal exploration.

5. Conclusions

The findings described herein expand our understanding of the relevance of neuroinflammation to peripheral inflammation in the BDII-D population while identifying the differential effects of BMI and peripheral inflammation on global FAt and FW, i.e., the contribution of BMI to the disruption of global WM integrity, while peripheral inflammation is associated with elevated global FW. Additionally, damage to the corpus callosum, both in terms of WM integrity and FW, needs to be attended to, as its impairment was simultaneously related to BMI, peripheral inflammation, and depressive symptoms in BDII-D. Furthermore, the low-grade inflammation moderated the relationship between greater BMI and impaired WM integrity in the genu of the corpus callosum, which implies that inflammation may play a role in the neurological effects associated with obesity, and changes in white matter integrity. Longitudinal studies are imperative to unveil the causal links among these factors.

Declaration of generative AI in scientific writing

No AI and AI-assisted technologies were used in the writing process.

CRediT authorship contribution statement

Yuan Cao: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paulo Lizano:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Meng Li:** Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Nils Opel:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Zümrüt Duygu Sen:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Lejla Colic:** Writing – review & editing, Funding acquisition. **Huan Sun:** Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xiaoqin Zhou:** Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Merita Aruci:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Tara Chand:** Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Xipeng Long:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gaoju Deng:** Validation, Investigation, Formal analysis, Data curation. **Jingshi Mu:** Validation, Methodology, Investigation, Data curation, Conceptualization. **Shuo Guo:** Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Huaiqiang Sun:** Validation, Project administration, Investigation, Data curation, Conceptualization. **Qiyong Gong:** Funding acquisition. **Changjian Qiu:** Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Martin Walter:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Zhiyun Jia:** Supervision, Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MW is a member of the advisory boards and gave presentations for the following companies: Boehringer Ingelheim, Germany; Bayer AG, Germany; and Biologische Heilmittel Heel GmbH, Germany. MW has further conducted studies with institutional research support from HEEL and from Janssen Pharmaceutical Research for a clinical trial (IIT) on ketamine in patients with major depression unrelated to this investigation. All other authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.04.005.

Data availability

Data will be made available on request.

References

Aronica, R., Enrico, P., Squarcina, L., Brambilla, P., Delvecchio, G., 2022. Association between diffusion tensor imaging, inflammation and immunological alterations in unipolar and bipolar depression: a review. Neurosci. Biobehav. Rev., 104922

Ashcroft, R.E., 2008. The declaration of Helsinki. The Oxford Textbook of Clinical Research Ethics 141–148.

Benazzi, F., 2000. Depression with DSM-IV atypical features: a marker for bipolar II disorder. Eur. Arch. Psychiatry Clin. Neurosci. 250, 53–55.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc.: Ser. B (Methodol.) 57, 289–300.

Bergamino, M., Pasternak, O., Farmer, M., Shenton, M.E., Hamilton, J.P., 2016. Applying a free-water correction to diffusion imaging data uncovers stress-related neural pathology in depression. NeuroImage: Clin. 10, 336–342.

Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., 1998. Childhood trauma questionnaire. Assessment of family violence: a handbook for researchers and practitioners.

Bettcher, B.M., Walsh, C.M., Watson, C., Miller, J.W., Green, R., Patel, N., Miller, B.L., Neuhaus, J., Yaffe, K., Kramer, J.H., 2013. Body mass and white matter integrity: the influence of vascular and inflammatory markers. PLoS One 8, e77741.

Bonaccio, M., Di Castelnuovo, A., Pounis, G., De Curtis, A., Costanzo, S., Persichillo, M., Cerletti, C., Donati, M.B., de Gaetano, G., Iacoviello, L., 2016. A score of low-grade inflammation and risk of mortality: prospective findings from the Moli-sani study. Haematologica 101, 1434.

Bond, D.J., Andreazza, A.C., Hughes, J., Dhanoa, T., Torres, I.J., Kozicky, J.-M., Young, L.T., Lam, R.W., Yatham, L.N., 2016. Association of peripheral inflammation with body mass index and depressive relapse in bipolar disorder. Psychoneuroendocrinology 65, 76–83.

Cao, Y., Lizano, P., Deng, G., Sun, H., Zhou, X., Xie, H., Zhan, Y., Mu, J., Long, X., Xiao, H., 2023. Brain-derived subgroups of bipolar II depression associate with inflammation and choroid plexus morphology. Psychiatry Clin. Neurosci. 77, 613–621.

Carreira Figueiredo, I., Borgan, F., Pasternak, O., Turkheimer, F.E., Howes, O.D., 2022. White-matter free-water diffusion MRI in schizophrenia: a systematic review and meta-analysis. Neuropsychopharmacology 47, 1413–1420.

Cyprien, F., Courtet, P., Maller, J., Meslin, C., Ritchie, K., Ancelin, M.-L., Artero, S., 2019. Increased serum C-reactive protein and corpus callosum alterations in older adults. Aging Dis. 10, 463.

Daoust, J., Schaffer, J., Zeighami, Y., Dagher, A., Garcia-Garcia, I., Michaud, A., 2021. White matter integrity differences in obesity: a meta-analysis of diffusion tensor imaging studies. Neurosci. Biobehav. Rev. 129, 133–141.

Di Biase, M.A., Zalesky, A., Cetin-Karayumak, S., Rathi, Y., Lv, J., Boerrigter, D., North, H., Tooney, P., Pantelis, C., Pasternak, O., 2021. Large-scale evidence for an association between peripheral inflammation and white matter free water in schizophrenia and healthy individuals. Schizophr. Bull. 47, 542–551.

Fagiolini, A., Frank, E., Houck, P.R., Mallinger, A.G., Swartz, H.A., Buysse, D.J., Ombao, H., Kupfer, D.J., 2002. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J. Clin. Psychiatry 63, 528–533.

Fagiolini, A., Kupfer, D.J., Houck, P.R., Novick, D.M., Frank, E., 2003. Obesity as a correlate of outcome in patients with bipolar I disorder. Am. J. Psychiatry 160, 112–117.

First, M., Williams, J., Karg, R., Association, S.R.A.P., 2015. Arlington. VA, American Psychiatric Association.

Fried, E.I., Von Stockert, S., Haslbeck, J., Lamers, F., Schoevers, R., Penninx, B., 2020. Using network analysis to examine links between individual depressive symptoms, inflammatory markers, and covariates. Psychol. Med. 50, 2682–2690.

Garcia-Hernandez, R., Cerdán Cerdá, A., Trouve Carpena, A., Drakesmith, M., Koller, K., Jones, D.K., Canals, S., De Santis, S., 2022. Mapping microglia and astrocyte activation in vivo using diffusion MRI. Sci. Adv. 8, eabq2923.

Gialluisi, A., Bonaccio, M., Di Castelnuovo, A., Costanzo, S., De Curtis, A., Sarchiapone, M., Cerletti, C., Donati, M., de Gaetano, G., Iacoviello, L., 2020. Lifestyle and biological factors influence the relationship between mental health and low-grade inflammation. Brain Behav. Immun. 85, 4–13.

Guillemot-Legris, O., Masquelier, J., Everard, A., Cani, P.D., Alhouayek, M., Muccioli, G. G., 2016. High-fat diet feeding differentially affects the development of inflammation in the central nervous system. J. Neuroinflamm. 13, 1–11.

Hamilton, M., 1959. Hamilton anxiety rating scale. Brit. J. Med. Psychol. 32, 50–55.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56.

Hassel, S., Almeida, J.R., Kerr, N., Nau, S., Ladouceur, C.D., Fissell, K., Kupfer, D.J., Phillips, M.L., 2008. Elevated striatal and decreased dorsolateral prefrontal cortical activity in response to emotional stimuli in euthymic bipolar disorder: no associations with psychotropic medication load. Bipolar Disord. 10, 916–927.

Ho, T.C., Kulla, A., Teresi, G.I., Sisk, L.M., Rosenberg-Hasson, Y., Maecker, H.T., Gotlib, I. H., 2022. Inflammatory cytokines and callosal white matter microstructure in adolescents. Brain Behav. Immun. 100, 321–331.

Kappelmann, N., Arloth, J., Georgakis, M.K., Czamara, D., Rost, N., Ligthart, S., Khandaker, G.M., Binder, E.B., 2021. Dissecting the association between inflammation, metabolic dysregulation, and specific depressive symptoms: a genetic correlation and 2-sample mendelian randomization study. JAMA Psychiat. 78, 161–170.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Khanna, D., Khanna, S., Khanna, P., Kahar, P., Patel, B.M., 2022. Obesity: a chronic low-grade inflammation and its markers. Cureus 14.

Kim, J., Yoon, S., Lee, S., Hong, H., Ha, E., Joo, Y., Lee, E.H., Lyoo, I.K., 2020. A double-hit of stress and low-grade inflammation on functional brain network mediates posttraumatic stress symptoms. Nat. Commun. 11, 1898.

Kullmann, S., Callaghan, M.F., Heni, M., Weiskopf, N., Scheffler, K., Häring, H.-U., Fritsche, A., Veit, R., Preissl, H., 2016. Specific white matter tissue microstructure changes associated with obesity. Neuroimage 125, 36–44.

Lamers, F., Milaneschi, Y., Penninx, B.W., 2018. Depression subtypes and inflammation: atypical rather than melancholic depression is linked with immunometabolic dysregulations. In: Inflammation and Immunity in Depression. Elsevier, pp. 455–471.

Mazza, E., Poletti, S., Bollettini, I., Locatelli, C., Falini, A., Colombo, C., Benedetti, F., 2017. Body mass index associates with white matter microstructure in bipolar depression. Bipolar Disord. 19, 116–127.

McElroy, S.L., Kotwal, R., Malhotra, S., Nelson, E.B., Keck, P.E., Nemeroff, C.B., 2004. Are mood disorders and obesity related? A review for the mental health professional. J. Clin. Psychiatry 65, 634–651.

Meyer, J.H., Cervenka, S., Kim, M.-J., Kreisl, W.C., Henter, I.D., Innis, R.B., 2020. Neuroinflammation in psychiatric disorders: PET imaging and promising new targets. Lancet Psychiatry 7, 1064–1074.

Milaneschi, Y., Lamers, F., Berk, M., Penninx, B.W., 2020. Depression heterogeneity and its biological underpinnings: toward immunometabolic depression. Biol. Psychiatry 88, 369–380.

Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741.

Murck, H., Fava, M., Cusin, C., Fatt, C.C., Trivedi, M., 2024. Brain ventricle and choroid plexus morphology as predictor of treatment response in major depression: findings from the EMBARC study. Brain Behav. Immun.-Health 35, 100717.

Murck, H., Luerweg, B., Hahn, J., Braunisch, M., Jezova, D., Zavorotnyy, M., Konrad, C., Jansen, A., Kircher, T., 2021. Ventricular volume, white matter alterations and outcome of major depression and their relationship to endocrine parameters – a pilot study. World J. Biol. Psychiatry 22, 104–118.

Osimo, E.F., Baxter, L.J., Lewis, G., Jones, P.B., Khandaker, G.M., 2019. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol. Med. 49, 1958–1970.

Parksepp, M., Haring, L., Kilk, K., Taalberg, E., Kangro, R., Zilmer, M., Vasar, E., 2022. A marked low-grade inflammation and a significant deterioration in metabolic status in first-episode schizophrenia: a five-year follow-up study. Metabolites 12, 983.

Pasternak, O., Sochen, N., Gur, Y., Intrator, N., Assaf, Y., 2009. Free water elimination and mapping from diffusion MRI. Magn. Resonance Med. 62, 717–730.

Pasternak, O., Westin, C.-F., Bouix, S., Seidman, L.J., Goldstein, J.M., Woo, T.-U.-W., Petryshen, T.L., Mesholam-Gately, R.I., McCarley, R.W., Kikinis, R., 2012. Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. J. Neurosci. 32, 17365–17372.

Perugi, G., Akiskal, H., Lattanzi, L., Cecconi, D., Mastrocinque, C., Patronelli, A., Vignoli, S., Bemi, E., 1998. The high prevalence of "soft" bipolar (II) features in atypical depression. Compr. Psychiatry 39, 63–71.

Pistis, G., Milaneschi, Y., Vandeleur, C.L., Lasserre, A.M., Penninx, B.W., Lamers, F., Boomsma, D.I., Hottenga, J.-J., Marques-Vidal, P., Vollenweider, P., 2021. Obesity and atypical depression symptoms: findings from Mendelian randomization in two European cohorts. Transl. Psychiatry 11, 96.

Posner, K., Brent, D., Lucas, C., Gould, M., Stanley, B., Brown, G., Fisher, P., Zelazny, J., Burke, A., Oquendo, M., 2008. Columbia-Suicide Severity Rating Scale (C-SSRS). Columbia University Medical Center, New York, NY.

Repple, J., Opel, N., Meinert, S., Redlich, R., Hahn, T., Winter, N.R., Kaehler, C., Emden, D., Leenings, R., Grotegerd, D., 2018. Elevated body-mass index is associated with reduced white matter integrity in two large independent cohorts. Psychoneuroendocrinology 91, 179–185.

Rodríguez-Hernández, H., Simental-Mendía, L.E., Rodríguez-Ramírez, G., Reyes-Romero, M.A., 2013. Obesity and inflammation: epidemiology, risk factors, and markers of inflammation. Int. J. Endocrinol.

Samara, A., Murphy, T., Strain, J., Rutlin, J., Sun, P., Neyman, O., Sreevalsan, N., Shimony, J.S., Ances, B.M., Song, S.-K., 2020. Neuroinflammation and white matter alterations in obesity assessed by diffusion basis spectrum imaging. Front. Hum. Neurosci. 13, 464.

Sen, Z.D., Danyeli, L.V., Woelfer, M., Lamers, F., Wagner, G., Sobanski, T., Walter, M., 2021. Linking atypical depression and insulin resistance-related disorders via low-grade chronic inflammation: Integrating the phenotypic, molecular and neuroanatomical dimensions. Brain Behav. Immun. 93, 335–352.

Stanek, K.M., Grieve, S.M., Brickman, A.M., Korgaonkar, M.S., Paul, R.H., Cohen, R.A., Gunstad, J.J., 2011. Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesity 19, 500–504.

Stranahan, A.M., Hao, S., Dey, A., Yu, X., Baban, B., 2016. Blood–brain barrier breakdown promotes macrophage infiltration and cognitive impairment in leptin receptor-deficient mice. J. Cereb. Blood Flow Metab. 36, 2108–2121.

Sugimoto, K., Kakeda, S., Watanabe, K., Katsuki, A., Ueda, I., Igata, N., Igata, R., Abe, O., Yoshimura, R., Korogi, Y., 2018. Relationship between white matter integrity and serum inflammatory cytokine levels in drug-naive patients with major depressive disorder: diffusion tensor imaging study using tract-based spatial statistics. Transl. Psychiatry 8, 141.

Torres-Platas, S.G., Cruceanu, C., Chen, G.G., Turecki, G., Mechawar, N., 2014. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. Brain Behav. Immun. 42, 50–59.

Tuozzo, C., Lyall, A.E., Pasternak, O., James, A.C., Crow, T.J., Kubicki, M., 2018. Patients with chronic bipolar disorder exhibit widespread increases in extracellular free water. Bipolar Disord. 20, 523–530.

Wu, D., Wu, Q., Li, F., Wang, Y., Zeng, J., Tang, B., Bishop, J.R., Xiao, L., Lui, S., 2024. Free water alterations in different inflammatory subgroups in schizophrenia. Brain Behav. Immun. 115, 557–564.