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A frontotemporal free water signature associated to interleukin-8 and cognitive impairment in schizophrenia with comorbidity of metabolic syndrome

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ABSTRACT

Neuroimmune hypothesis posits that inflammation plays a key role in shared neurobiological substrate responsible for the comorbidity between schizophrenia and metabolic syndrome (MS). However, the specific neural mechanisms by which inflammation contributes to this comorbidity remain elusive. This study investigated whether inflammation-related brain microstructural alterations were associated with this comorbidity and its concomitant cognitive deficits. We utilized multi-site data from independent centers. Applying the two-factor experimental design, a total of 398 participants were included and categorized into four groups based on diagnoses of schizophrenia and MS: schizophrenia patients with/without metabolic syndrome (SZ-wMS and SZ-nMS), and healthy controls with/without metabolic syndrome (HC-wMS and HC-nMS). By leveraging diffusion and structural magnetic resonance imaging, free water (FW) was estimated to quantify the microstructure in cerebral gray matter. Clinical assessments included peripheral inflammatory cytokines and cognitive function tests. Interaction effects of schizophrenia and MS on brain microstructural FW were revealed, with SZ-wMS exhibiting exacerbated microstructural alterations in frontotemporal lobes compared with SZ-nMS, HC-wMS and HC-nMS groups. More pronounced cognitive deficits in multiple cognitive domains were also observed in SZ-wMS group. In SZ-wMS group, correlations between elevated FW within frontotemporal lobes and both peripheral level of interleukin-8 and scores of multiple cognitive functions were revealed. In addition, an indirect effect of interleukin-8 on delayed recall via FW of right middle frontal gyrus was revealed. Several findings were validated within each independent dataset. These results suggest that inflammation-related microstructural FW alterations within frontotemporal lobes may be associated with the comorbidity of schizophrenia and MS and the associated long-term memory decline.

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1. Introduction

Metabolic syndrome (MS), one of the most frequent comorbidities in schizophrenia, shows a markedly higher prevalence in patients with schizophrenia than in the general population (Mitchell et al., 2013a, 2013b). The prevailing consensus agrees that antipsychotics do not fully explain the high prevalence of comorbid MS in schizophrenia (Enez Darcin et al., 2015). Neuroimmune hypothesis posits that inflammation contributes to the shared neurobiological substrate underlying the comorbidity between schizophrenia and MS (Nusslock and Miller, 2016). In schizophrenia, overactivated inflammation can disrupt synaptic function and promote neuronal apoptosis, thereby contributing to its pathophysiology (Forsyth and Lewis, 2017; Inta et al., 2016). Concurrently, inflammation is also implicated in the underlying pathogenesis of several somatic diseases, including atherosclerosis, insulin resistance, obesity, type 2 diabetes and MS (de Melo et al., 2017; Maes et al., 2011). The findings from mendelian randomization study support the inflammation as a common mechanisms for schizophrenia and insulin resistance (Minelli et al., 2021). Peripherally elevated broad-scale inflammatory cytokines have been identified as a stable feature of both psychiatric and cardiometabolic diseases (Esser et al., 2014; Khandaker et al., 2014). Despite this converging evidence, the specific neural mechanisms through which inflammation contributes to the comorbidity of schizophrenia and MS remain unclear.

Alterations of cerebral microstructure represent a well-documented feature of both schizophrenia and MS (Stauffer et al., 2021; Drakesmith et al., 2016). In schizophrenia, magnetic resonance imaging (MRI) studies have linked cognitive impairments to deficits in fractional anisotropy and neurite density within white matter tracts (Stauffer et al., 2021; Kochunov et al., 2017). Recent studies have increasingly highlighted microstructural abnormalities in the gray matter of schizophrenia patients (Wei et al., 2020, 2022; Nazeri et al., 2017), characterized by altered intracortical myelination and markedly elevated levels of extracellular free water (FW) (Cho et al., 2024; Lesh et al., 2021). In addition, two micro-structural MRI metrics in prefrontal and temporal cortices are associated with obesity (Kitzbichler et al., 2023). Clinical manifestations of MS may aggravate the microstructural abnormalities in individuals with psychiatric disorders, including schizophrenia and bipolar disorder (Hidese et al., 2021; Spangaro et al., 2018; Blasco et al., 2025). Elevated extracellular FW, reflecting microstructural alterations in gray matter, has been proposed as a potential proxy for activated neuroinflammatory state. Associations between FW and peripheral pro-inflammatory cytokines, as well as the antioxidant glutathione, provide converging support for this interpretation (Lesh et al., 2021; Di Biase et al., 2021). However, it remains to be elucidated whether the inflammation-related FW alterations constitute the neural basis underlying the comorbidity of schizophrenia and MS.

More severe cognitive impairment is a clinical feature of schizophrenia patients with comorbidity of MS (Hagi et al., 2021; Kolenič et al., 2025), particularly in memory performance (Friedman et al., 2010). Chronic inflammation has been identified as a potential risk factor for the cognitive impairments (Fillman et al., 2015). According to the cytokine model of cognitive function, cytokines play an intimate role in the molecular and cellular mechanisms subserving learning, memory and cognition (McAfoose and Baune, 2009). The proposed inflammation-sensitive emotion-cognitive circuit may reflect a specific role of inflammatory processes in the emotional and cognitive symptoms characteristic of schizophrenia (Goldsmith et al., 2023). The subgroup of individuals with schizophrenia characterized by elevated inflammatory cytokines tends to exhibit poorer cognitive performance (Fillman et al., 2015). Nevertheless, the potential mechanisms underlying the influence of inflammation on cognitive impairments in schizophrenia patients with comorbidity of MS remain to be investigated to develop the novel therapeutic interventions.

This study utilized cross-sectional diffusion and structural MRI data from two independent datasets and applies the two-factor experimental design to categorize the cross-sectional sample into four groups according to the diagnoses of schizophrenia and MS. Ten peripheral inflammatory markers were selected on the basis of previously described relationships with schizophrenia (Lizano et al., 2021). Cognitive function was evaluated using both the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), as the frequently used instruments for assessing the cognitive impairments in schizophrenia (Daderwal et al., 2022; Gredicak et al., 2024). We hypothesized an interaction effect between schizophrenia and MS on brain microstructural FW, potentially indicating a comorbidity-related neural mechanism. Recent meta-analyses have proposed an inflammation-sensitive emotion-cognitive regions, including prefrontal, temporal, insular and limbic cortices (Goldsmith et al., 2023; Kraynak et al., 2018). Therefore, we conducted an exploratory whole-brain–level analysis and hypothesized that schizophrenia patients with comorbidity of MS exhibit exacerbated microstructural alterations in this inflammation-sensitive emotion-cognitive regions, and these exacerbated microstructural changes are associated with peripheral inflammatory cytokines and cognitive performance. Finally, mediation analyses were performed to test the potential mechanistic pathways by which peripheral inflammation may influence cognitive deficits via microstructural changes.

2. Methods

2.1. Participants

This study included a cross-sectional sample collected from two independent datasets. A total of 398 participants were categorized into four groups according to the diagnoses of schizophrenia and MS, comprising 85 schizophrenia patients with comorbidity of MS (SZ-wMS; mean age = 43.42 ± 11.13 years; 25 females), 139 schizophrenia patients without comorbidity of MS (SZ-nMS; mean age = 41.34 ± 11.52 years; 59 females), 36 healthy controls with MS (HC-wMS; mean age = 44.56 ± 9.84 years; 9 females), and 138 healthy controls without MS (HC-nMS; mean age = 39.68 ± 12.21 years; 71 females). Demographic and clinical characteristics of the sample are summarized in Table 1. All schizophrenia patients were recruited from the Clinical Hospital of Chengdu Brain Science Institute and The Third People's Hospital of Wenjiang District, Chengdu, and were diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (SCID-I-CV). Healthy controls (HC) were recruited from the local community through advertisements. Individuals in the HC group were excluded if they met criteria for any current or past Axis I psychiatric disorder, as assessed using the Structured Clinical Interview for DSM-IV. Detailed inclusion and exclusion criteria for patients with schizophrenia and healthy controls are provided in the Supplemental Materials.

Metabolic syndrome was diagnosed for all participants using a slightly modified criteria based on that proposed by the International Diabetes Federation in 2005 (Zhou et al., 2025). Briefly, the participants were diagnosed with metabolic syndrome if they displayed random three of the following criteria defined by International Diabetes Federation: (1) central obesity (body mass index (BMI) $\geq$27 kg/m^2); (2) fasting blood glucose (FBG) $\geq$5.6 mmol/L or treatment for diabetes mellitus; (3) blood pressure (BP) $\geq$130/85 mmHg or on anti-hypertensives; (4) triglycerides (TG) $\geq$1.695 mmol/L or on lipid lowering agent; (5) high-density lipoprotein (HDL) $<$ 1.036 mmol/L for men, $<$1.295 mmol/L for women or treatment for dyslipidemia with lipid-lowering agent (Supplemental Materials).

After a complete description of the study was given to all participants and/or their guardians, written informed consent was obtained. The Ethics Committee of the Clinical Hospital of Chengdu Brain Science Institute in accordance with the Helsinki Declaration approved this study.

Table 1
Demographic information and clinical characteristics in two Datasets (n = 398).

Site	Dataset 1					Dataset 2			
Characteristic	SZ-wMS (n = 49)	SZ-nMS (n = 65)	HC-wMS (n = 36)	HC-nMS (n = 37)	P-value	SZ-wMS (n = 36)	SZ-nMS (n = 74)	HC-nMS (n = 101)	P-value
Sex (male/female)	42/7	48/17	27/9	31/6	0.35	18/18	32/42	36/65	0.3
Age (years)	44.96 (9.1)	43.26 (11.29)	44.56 (9.84)	42.78 (9.89)	0.71	41.33 (13.25)	39.83 (11.55)	38.54 (12.81)	0.49
Education (years)	10.31 (3.7)	11.01 (3.06)	11.28 (3.89)	11.83 (3.65)	0.25	10.31 (3.7)	12.72 (3.4)	12.79 (4.32)	0.33
Disease duration (years)	18.92 (8.56)	16.91 (9.88)	-	-	0.26	14.79 (10.04)	11.43 (8.67)	-	0.1
Current antipsychotic dosage	269.7 (162.2)	308.4 (141.7)	-	-	0.18	357.3 (160)	344.1 (156.4)	-	0.7
PANSS total score	61.59 (14.73)	62.17 (15.29)	-	-	0.85	75.43 (16.53)	74.16 (16.12)	-	0.71
PANSS positive symptoms score	12.3 (5.22)	14.8 (5.85)	-	-	0.03*	19.28 (6.53)	19.85 (5.82)	-	0.64
PANSS negative symptoms score	19.86 (6.66)	18.98 (5.94)	-	-	0.49	21.83 (8.39)	21.53 (8.19)	-	0.86
PANSS general symptoms score	29.43 (6.52)	28.37 (6.53)	-	-	0.42	34.31 (5.56)	32.78 (6.14)	-	0.21

Note: *$p < 0.05$; SZ: schizophrenia; MS: metabolic syndrome.

2.2. Behavior measures

The severity of psychiatric symptoms in patients with schizophrenia was assessed using the Positive and Negative Syndrome Scale (PANSS). Cognitive function was evaluated across all participants using both the MoCA and the MMSE. The MoCA comprises seven cognitive domains: Visuospatial and Executive Function, Naming, Attention and Working Memory, Language, Abstraction, Delayed recall, and Orientation. The MMSE also comprises seven cognitive domains: Orientation to time, Orientation to place, Immediate recall, Attention and calculation, Delayed recall, Language, Visuospatial and Construction.

2.3. Laboratory tests

Fasting blood samples were obtained from participants between 7:00 and 9:00 a.m. following an overnight fast of 12 h. The samples were centrifuged at 3200 rpm for 10 min to separate serum and plasma. First, FBG levels in plasma, as well as serum levels of TG and HDL, were measured using enzymatic photometric assays, which were used in the diagnosis of MS. Second, serum concentrations of cytokines—including interleukin (IL)-1β, IL-2, IL-8, IL-10, IL-4, IL-6, IL-17A, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF)—were quantified using flow cytometry with the Cytometric Bead Array Human Th1/Th2/Th17 Kit (BD Biosciences) to evaluate the peripheral inflammatory status of participants.

2.4. Imaging data acquisition and processing

Diffusion tensor imaging (DTI) data and T1-weighted structural magnetic resonance imaging were acquired. Acquisition parameters were provided in the Supplementary Materials. Image processing procedures are also provided in the Supplementary Materials and briefly described here. First, T1-weighted images were processed by standard voxel-based morphometry analysis implemented in FSL version 6.0 (FSL; https://fsl.fmrib.ox.ac.uk/fsl/) to generate gray matter volume (GMV) maps and cerebrospinal fluid (CSF) maps (Smith et al., 2004). Second, DTI were preprocessed using FSL (version 6.0) (Jenkinson et al., 2012). A bi-tensor FW elimination model (Pasternak et al., 2009) was implemented through the Free Water Elimination DTI toolkit (https://github.com/mvgolub/FW-DTI-Beltrami) (Golub et al., 2020) to compute voxel-wise FW map. FW images were registered into the standard Montreal Neurological Institute (MNI) space using the individual transformation matrix between DTI image and MNI standard space. To specifically isolate FW surrounding gray matter, it was necessary to minimize CSF contamination (Cho et al., 2024). Hence a uniform gray matter mask excluding CSF was generated by subtracting the group-level CSF mask from the group-level gray matter mask (Jiang et al., 2019).

2.5. Harmonization of images

ComBat is a data harmonization method based on an improved generalized linear model, specifically designed to reduce site-related heterogeneity from the effects of variations in MRI scanners and acquisition parameters across different datasets (Radua et al., 2020). In this study, all FW maps, GMV maps and CSF maps were harmonized using the ComBat tool implemented in the DPABI toolbox (http://rfmri.org/dpabi), thereby removing site-related batch effects across the 2 sites (Wang et al., 2024). Within the uniform gray matter mask, region-wise FW values were subsequently extracted from the harmonized FW images based on the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), yielding mean FW values for 116 cortical and subcortical regions for further statistical analyses.

2.6. Statistical analysis

First, the demographics and clinical characteristics were analyzed in Dataset 1, Dataset 2, and harmonized dataset. Differences in age and education level were assessed by one-way analysis of variance (ANOVA). Difference in gender were evaluated with the chi-square test. Comparisons between the SZ-wMS and SZ-nMS groups were performed using two-sample t-tests for disease duration, current antipsychotic dosage (chlorpromazine equivalents), and PANSS scores. Second, in harmonized dataset, a two-way analysis of covariance (ANCOVA) was conducted to examine the main effects and interaction effects of schizophrenia and MS diagnoses on regional FW, with age, sex, education level, and total intracranial volume (TIV) included as covariates. The main effects and the interaction effect were corrected for multiple comparisons using the false discovery rates (FDR) correction. Third, one-way ANCOVA was performed to examine group differences of peripheral inflammatory cytokine levels. Then, a two-way ANCOVA was conducted to examine the main effects and interaction effects of schizophrenia and MS diagnoses on MoCA and MMSE scores. In ANCOVA for inflammatory cytokines and cognitive function scores, age, sex, and education level, were included as covariates. In all analysis of covariance, pairwise post-hoc comparisons were performed using the Least Significant Difference (LSD) test. Finally, in two-way ANCOVA on regional FW, we further conducted supplementary sensitivity analyses on FW post-hoc comparisons utilizing more conservative Tukey's post-hoc test.

2.7. Clinical correlation analysis

To investigate the associations of FW changes with peripheral

inflammatory cytokines and cognitive performance, the values of FW in regions of interest (ROI) were extracted based on the pairwise post-hoc comparisons between the SZ-wMS and SZ-nMS groups. Partial correlation analyses were performed between extracted FW and peripheral inflammatory cytokines that differed between groups. To investigate the relationships between FW and multiple cognitive functions, partial correlation analyses were performed between FW and scores of all cognitive domains in MoCA and MMSE. These analyses controlled for age, sex, and education level as covariates. Multiple comparisons were corrected using FDR correction. Additionally, mediation analyses were conducted to examine the potential mediation effect of FW on the associations between inflammatory cytokines and cognitive function scores using Hayes's PROCESS macro (Model 4) (Hayes, 2013). FDR correction was applied to the p-values of all paths in the mediation model.

2.8. Validation analysis

We performed three additional analyses to validate the robustness of the findings from the present study. First, to evaluate potential confounding effects of medication, we examined the associations between FW values within ROI and current antipsychotic dosage using partial correlation analysis, with age, sex, and education level included as covariates. Furthermore, current medication dosage was incorporated as an additional covariate in subsequent clinical correlation analyses involving FW. Second, we investigated the potential confounding effects of duration of illness and symptom severity. Duration of illness and total scores of PANSS were incorporated as an additional covariate in post-hoc analyses comparing the SZ-wMS and SZ-nMS group, respectively. Third, using analytical procedures identical to those applied in the multi-site dataset, we validated the key findings separately within each independent dataset.

3. Results

3.1. Demographics and clinical characteristics

First, no significant differences in gender, age, or education level were observed in either Dataset 1 or Dataset 2. In addition, no significant differences in disease duration or current antipsychotic dosage were observed between the SZ-wMS and SZ-nMS groups. No differences were observed in negative symptoms and general symptoms (Table 1). However, we found that the SZ-wMS group had lower positive symptom scores than the SZ-nMS group in Dataset 1 (Table 1, $t = -2.35, p < 0.05$). Second, in harmonized dataset, there were differences in gender, age and education level (Table S1). The differences in disease duration and positive symptom scores were observed between the SZ-wMS and SZ-nMS groups. No significant differences in current antipsychotic dosage, negative symptoms or general symptoms scores were observed (Table S1).

3.2. Interaction effects of FW

The main effects of schizophrenia on FW were observed (Fig. S1a, $p < 1 \times 10^{-3}$, FDR. However, no significant main effect of MS was detected after FDR correction (Fig. S1b, $p < 1 \times 10^{-3}$, FDR). Importantly, the interaction effects between schizophrenia and MS on FW were found across widespread cortical regions and several subcortical regions, including the thalamus and hippocampus (Fig. 1a, $p < 1 \times 10^{-3}$, FDR). Compared with healthy controls (including HC-wMS and HC-nMS groups), both SZ-wMS and SZ-nMS groups showed elevated FW in cortical areas, including bilateral middle frontal gyrus, bilateral medial superior frontal gyrus, bilateral dorsolateral superior frontal gyrus, right superior temporal pole, and left Heschl gyrus (Table S2; Fig. 1b–i). In addition, SZ-wMS group exhibited further increases of FW within these regions compared with SZ-nMS group (Fig. 1b–i). However, in sensitivity analyses, only the increased FW in right medial superior frontal gyrus (Fig. S2) remained significant after Tukey's post-hoc test. No significant difference of FW was found between the HC-wMS and HC-nMS groups.

3.3. Altered serum cytokine profiles

Peripheral inflammatory cytokines were measured in 48 participants from the SZ-wMS group, 81 participants from the SZ-nMS group, and 90 participants from the HC-nMS group. No inflammatory cytokines data was collected in HC-wMS group. In the comparisons of inflammatory cytokines, group differences of IL-8 (Table S3, $F = 11.84$, $p = 1 \times 10^{-5}$) and IL-2 ($F = 3.11$, $p = 0.04$) were revealed.

Compared with HC-nMS group, SZ-wMS showed higher levels of IL-8 (Fig. S3). SZ-nMS showed higher level of IL-8 and lower level of IL-2. However, no significant difference of inflammatory cytokines was observed between SZ-wMS and SZ-nMS group.

3.4. Cognitive test on MoCA and MMSE

Main effects of schizophrenia were observed across nearly all cognitive domains except Naming and Abstraction. Particularly pronounced differences were found in Delayed recall (Table 2; Score in MoCA: $F = 19.84$, $p = 1 \times 10^{-5}$, $\eta^2 = 0.1$; Score in MMSE: $F = 43.94$, $p = 1 \times 10^{-10}$, $\eta^2 = 0.12$), Orientation to time ($F = 79.8$, $p = 3 \times 10^{-17}$, $\eta^2 = 0.2$), Orientation to place ($F = 35.29$, $p = 7 \times 10^{-9}$, $\eta^2 = 0.1$), Attention and calculation ($F = 22.06$, $p = 4 \times 10^{-6}$, $\eta^2 = 0.06$). The main effect of MS was only observed in Orientation to time ($F = 4.14$, $p = 0.04$, $\eta^2 = 0.01$). No significant interaction effect was detected.

Compared with healthy controls (including HC-wMS and HC-nMS groups), both SZ-wMS and SZ-nMS groups had lower score in four cognitive domains, including Delayed recall, Orientation to time, Orientation to place, and Attention and calculation (Fig. S4). Compared with healthy controls, SZ-wMS group showed lower score in Visuospatial and Construction, while SZ-nMS group did not exhibit significant difference. Importantly, compared with SZ-nMS, SZ-wMS group exhibited further reductions cognitive scores in three domains, including Delayed recall, Orientation to time and Attention and calculation (Fig. S4).

3.5. Clinical relevance of FW

The values of FW from eight ROI, two inflammatory cytokines, including IL-2 and IL-8, and fourteen cognitive function scores were included in partial correlation analyses. In the SZ-wMS group, positive correlations were revealed between IL-8 and FW in the right middle frontal gyrus ($r = 0.3$, $p = 0.04$), left medial superior frontal gyrus ($r = 0.34$, $p = 0.02$), and right superior temporal pole ($r = 0.32$, $p = 0.03$) (Table S4). Additionally, FW in prefrontal regions, including bilateral middle frontal gyrus, right medial superior frontal gyrus, and bilateral dorsolateral superior frontal gyrus, showed negative correlations with scores of multiple cognitive domains, including Naming, Attention and Working Memory, Abstraction, Orientation, Immediate Recall, and Delayed Recall (Fig. 2a, $p < 0.05$). However, these observed correlations did not remain significant after FDR correction. No corresponding associations were found in SZ-nMS, HC-wMS or HC-nMS groups (Fig. S5).

Based on the results of the partial correlation analyses, mediation analyses were conducted using FW values from three regions (right middle frontal gyrus, left medial superior frontal gyrus, and right superior temporal pole) as mediators, peripheral IL-8 levels as the independent variable, and cognitive performance across six domains (Naming, Attention and Working Memory, Abstraction, Orientation, Immediate Recall, and Delayed Recall) as dependent variables. In total, eighteen mediation models were tested. Although the significant mediation effects were not revealed, an indirect effect of IL-8 on Delayed recall via FW of right middle frontal gyrus was revealed in SZ-wMS

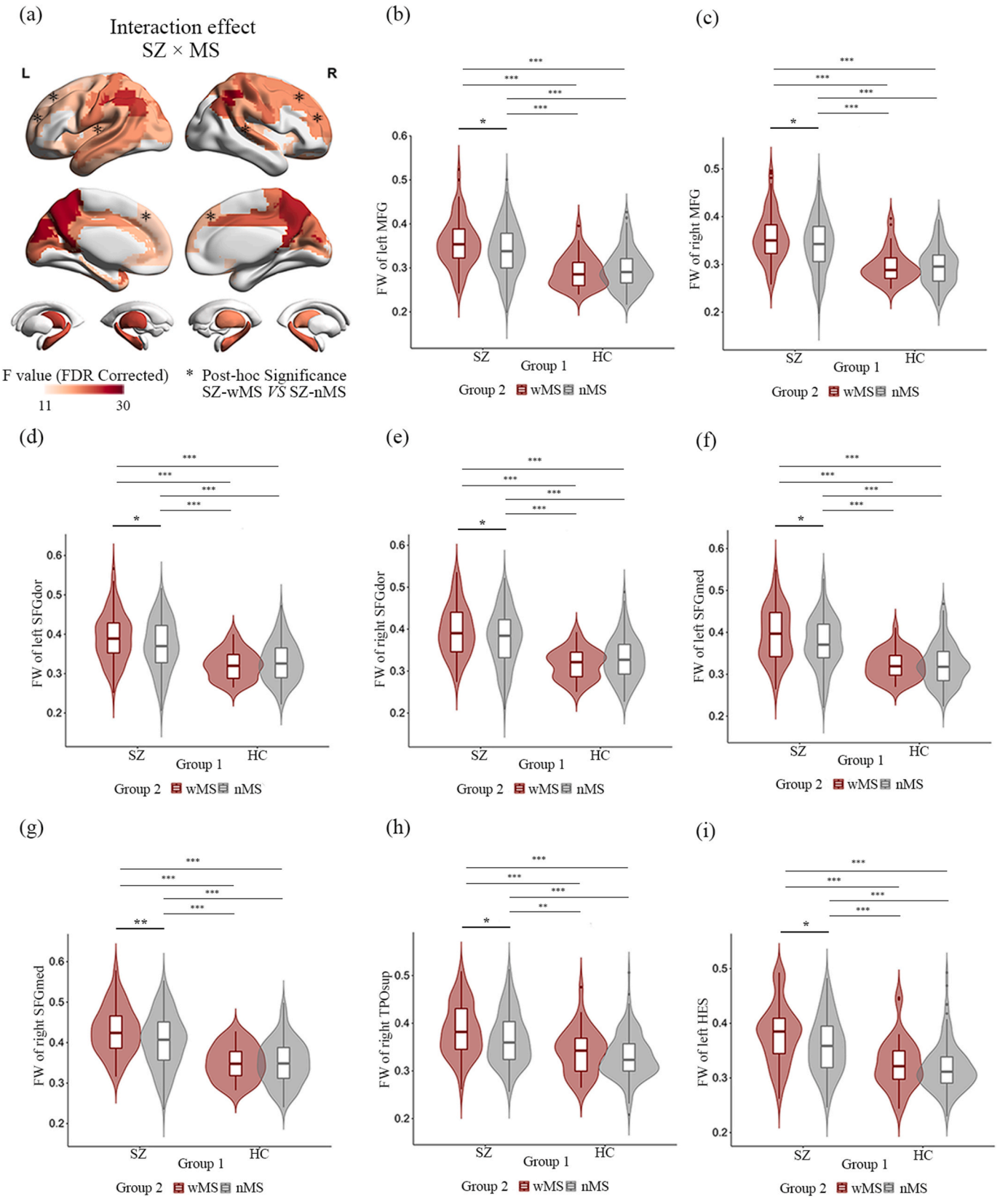

Fig. 1. The interaction effects of FW. (a) F-statistic map illustrating interaction effects of FW ($P < 1 \times 10^{-3}$, FDR correction); * indicate the post-hoc significance between SZ-wMS and SC-nMS group (LSD post-hoc test). (b) Violin plot illustrating the post-hoc comparisons of FW in left middle frontal gyrus. (c) Post-hoc comparisons of FW in right middle frontal gyrus. (d) Post-hoc comparisons of FW in left dorsolateral superior frontal gyrus. (e) Post-hoc comparisons of FW in right dorsolateral superior frontal gyrus. (f) Post-hoc comparisons of FW in left medial superior frontal gyrus. (g) Post-hoc comparisons of FW in right medial superior frontal gyrus. (h) Post-hoc comparisons of FW in right superior temporal pole. (i) Post-hoc comparisons of FW in left Heschl gyrus. MFG, middle frontal gyrus; SFGdor, dorsolateral superior frontal gyrus; SFGmed, medial superior frontal gyrus; TPOsup: superior temporal pole; HES: Heschl gyrus.

Table 2
Simple main effect and interaction effect on scores of cognitive scales.

Cognitive scales	Main effect of SZ (SZ *vs* HC)			Main effect of MS (wMS *vs* nMS)			Interaction effect (SZ × MS)		
	F	P	Partial η^2	F	P	Partial η^2	F	P	Partial η^2
MoCA Scale									
Visuospatial and Executive Function	3.47	0.04*	0.02	0.14	0.71	1×10^{-3}	1.38	0.24	7×10^{-3}
Naming	2.56	0.11	0.01	0.6	0.44	3×10^{-3}	0.06	0.8	3×10^{-4}
Attention and Working Memory	7.57	7×10^{-3}*	0.04	0.07	0.78	3×10^{-3}	1.34	0.25	7×10^{-3}
Language	5.95	0.01*	0.03	0.51	0.47	3×10^{-3}	1.07	0.3	6×10^{-3}
Abstraction	1.97	0.16	0.01	0.14	0.71	1×10^{-3}	0.05	0.82	2×10^{-4}
Delayed recall	19.84	1×10^{-5}*	0.1	0.69	0.41	4×10^{-3}	0.04	0.84	1×10^{-4}
Orientation	20.81	9×10^{-6}*	0.1	0.01	0.95	1×10^{-4}	0.35	0.56	2×10^{-3}
MMSE Scale									
Orientation to time	79.8	3×10^{-17}*	0.2	4.14	0.04*	0.01	2.5	0.11	8×10^{-3}
Orientation to place	35.29	7×10^{-9}*	0.1	0.75	0.39	2×10^{-3}	0.39	0.53	1×10^{-3}
Immediate recall	6.53	0.01*	0.02	0.3	0.58	1×10^{-3}	1.1	0.29	4×10^{-3}
Attention and calculation	22.06	4×10^{-6}*	0.06	1.58	0.21	5×10^{-3}	0.85	0.36	3×10^{-3}
Delayed recall	43.94	1×10^{-10}*	0.12	3.17	0.07	0.01	1.78	0.18	6×10^{-3}
Language	0.05	0.82	1×10^{-4}	2.1	0.18	7×10^{-3}	0.74	0.39	2×10^{-3}
Visuospatial and Construction	5.63	0.01*	0.02	1.93	0.16	2×10^{-3}	2.96	0.08	0.01

Note: *$p < 0.05$; Partial η^2 indicates the effect size. SZ: schizophrenia; MS: metabolic syndrome.

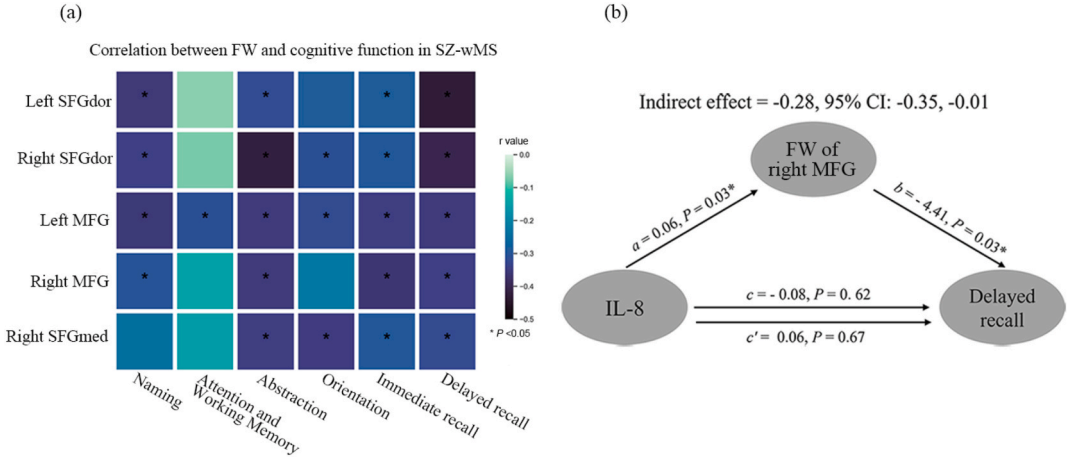

Fig. 2. Relationships between FW and cognitive functions, and inflammatory cytokines. (a) Heat map shows correlations between FW and scores of cognitive functions in SZ-wMS group. (b) Indirect effect of IL-8 on delayed recall via FW of right middle frontal gyrus in SZ-wMS group (indirect effect = −0.28, 95% CI −0.35 to −0.01). SFGdor, dorsolateral superior frontal gyrus; MFG, middle frontal gyrus; SFGmed, medial superior frontal gyrus; *$p < 0.05$.

group (Fig. 2b, indirect effect = −0.28, 95% CI −0.35 to −0.01), which was not observed in either the SZ-nMS or HC-nMS groups. The indirect effect did not remain significant after FDR correction.

3.6. Results from validation analysis

First, no significant associations between FW within ROI and current antipsychotic dosage were observed (Table S5). After controlling for current medication dosage effects, the correlations between FW and IL-8 remained significant (Table S6), as did most FW correlations with multiple cognitive domain scores (Fig. S6). However, the correlations of FW in left dorsolateral superior frontal gyrus and right medial superior frontal gyrus with scores of Immediate Recall were no longer significant following adjustment (Fig. S6).

Second, the differences of FW within ROI between the SZ-wMS and SZ-nMS groups were attenuated after controlling the duration of illness (Fig. S7a). Only the difference of FW within right medial superior frontal gyrus remained significant. After adjusting for total PANSS scores, the differences in FW between the SZ-wMS and SZ-nMS groups were partially attenuated (Fig. S7b). FW differences in the right middle frontal gyrus and the left Heschl's gyrus did not remain significant, while those in the other regions persisted.

In dataset 1, the interaction effect of FW was validated (Fig. S8a, $p < 0.05$, FDR). Compared with the SZ-nMS group, the SZ-wMS group showed further increases of FW within bilateral middle frontal gyrus, bilateral medial superior frontal gyrus, right dorsolateral superior frontal gyrus and bilateral postcentral gyrus (Fig. S8b–h). In dataset 2, although the further increase of FW in the prefrontal regions of the SZ-wMS group was not replicated, a progressive increase in prefrontal FW across groups—from HC-nMS to SZ-nMS and then to SZ-wMS was revealed (Fig. S9). In dataset 1 and dataset 2, correlations were validated between FW within left middle frontal gyrus and Attention and Working Memory scores in the SZ-wMS group (Table S7, Table S8). However, the indirect effect of IL-8 on cognitive functions via FW was not replicated.

4. Discussion

In the present study, in accordance with our hypothesis, interaction effects of schizophrenia and MS on microstructural FW within frontotemporal cortical regions were revealed, with the SZ-wMS group showing further increases of FW in frontotemporal regions compared with the SZ-nMS group. The SZ-wMS group also demonstrated more pronounced cognitive deficits than SZ-nMS group in multiple cognitive domains, including Delayed recall, Orientation to time, and Attention

and calculation. In the SZ-wMS group, elevated FW in frontotemporal regions was positively correlated with peripheral IL-8 levels and negatively associated with performance across multiple cognitive domains. In addition, an indirect effect of IL-8 on Delayed recall via FW of right middle frontal gyrus was revealed in the SZ-wMS group. These results highlight that inflammation-related microstructural FW elevation in frontotemporal cortices may be associated with the comorbidity between schizophrenia and MS. In the SZ-wMS group, prefrontal FW alterations may account for the association between peripheral IL-8 levels and decline of long-term memory, although causal interpretations are limited by the cross-sectional design.

Accumulating evidence indicates that microstructural deficits of the frontal and temporal lobes are implicated in the pathophysiology of both schizophrenia and MS. However, whether the alterations in the brain microstructure underlie the comorbidity between schizophrenia and MS remains unclear. The recently developed FW metric, reflecting interstitial fluid accumulation in cerebral gray matter, has been found elevated in individuals at clinical high risk for psychosis and patients with first-episode schizophrenia (Cho et al., 2024; Lesh et al., 2021). Concurrently, MS is also characterized by brain microstructural changes, including increased gray matter mean diffusivity linked to increased triglyceride and central obesity (Sala et al., 2014; Yau et al., 2014). The large-scale studies from the ENIGMA consortium and UK Biobank support that central obesity may exacerbate microstructural alterations in frontotemporal regions in individuals with severe mental illnesses, including schizophrenia and bipolar disorder (Dietze et al., 2025; Dekkers et al., 2019). Our study applied the two-factor experimental design and identified the synergistic interaction effects between schizophrenia and MS on frontotemporal FW. Compared with the SZ-nMS group, the SZ-wMS group showed further increases of FW within frontotemporal cortical regions, while no such difference was observed between the HC-wMS and HC-nMS groups. This synergistic interaction effects support that frontotemporal microstructural FW elevation is associated with the comorbidity of schizophrenia and MS. Shared pathophysiological mechanisms between schizophrenia and MS—such as inflammation—may heighten the vulnerability of individuals with schizophrenia to the impact of metabolic risk factors on brain microstructure (Minelli et al., 2021).

It should be noted that although findings from validation analysis support the potential confounding effects of duration of illness and symptom severity on differences of FW between the SZ-wMS and SZ-nMS groups, duration of illness and symptom severity does not fully account for the observed differences in FW. Accumulating evidence suggests that duration of illness is also closely related to metabolic dysfunction in schizophrenia, such that a longer illness course often reflects prolonged exposure to metabolic abnormalities and chronic inflammation (Mitchell et al., 2013b). In addition, metabolic dysfunction is associated with the severity and improvement of psychiatric symptoms (Luckhoff et al., 2019; Zhou et al., 2023). Thus, regressing out duration of illness and symptom severity may remove not only nuisance variance but also variance that is intrinsically linked to the pathophysiology underlying the comorbidity between schizophrenia and MS. Given the potential confounding effects of illness duration and symptom severity on FW alterations in schizophrenia patients comorbid with MS, our findings should be further validated in more homogeneous schizophrenia samples.

Inflammation represents a central pathological mechanism shared by schizophrenia and MS. However, the neural mechanisms through which inflammation contributes to the comorbidity of schizophrenia and MS remain to be elucidated. Alterations in FW likely reflect complex biological mechanisms involving different cellular-level changes in the brain, such as reduced somal size, decreased spine density, and altered dendritic arborization (Cho et al., 2024). In addition, previous studies have proposed elevation of microstructural FW as a proxy for activated neuroinflammatory state (Pasternak et al., 2012). The associations between FW and peripheral pro-inflammatory cytokines IL-6 and TNF-α support this hypothesis (Lesh et al., 2021; Di Biase et al., 2021). Schizophrenia and MS are characterized by chronic low-grade inflammation, which may trigger local neuroinflammation by neural and humoral pathways (Milaneschi et al., 2019). Our study identified that FW elevations in frontotemporal lobe were associated with IL-8 in SZ-wMS group, which were not observed in either the SZ-nMS or HC-nMS groups. Although the correlation may suggest that inflammatory processes involving the IL-8 underlie the exacerbated microstructural damage observed in the SZ-wMS group, the absence of differences in IL-8 levels between the SZ-wMS and SZ-nMS groups may limit the interpretation. Therefore, IL-8 may act as a subtype-specific moderator or vulnerability marker rather than a simple state marker. The altered brain-immune coupling between frontotemporal FW and IL-8 may reflect a subtype-specific pathological process in the SZ-wMS group. Dysfunction of circumventricular organs and blood-brain barrier may explain the altered brain-immune coupling between FW and inflammatory cytokines (Lizano et al., 2019; Pollak et al., 2018). Although the specificity of the brain-immune coupling observed in the SZ-wMS group requires further investigation, it aligns with accumulating evidence suggesting heterogeneous cytokine–microstructure relationships across schizophrenia subtypes (Wu et al., 2024). Consequently, altered brain–immune coupling between frontotemporal FW and IL-8 may represent a potential neurobiological substrate related to the comorbidity between schizophrenia and MS.

MS and its clinical manifestations are potential risk factors for cognitive deficits, particularly memory impairment, in schizophrenia (Hagi et al., 2021; Kolenič et al., 2025; Friedman et al., 2010). Present study revealed more pronounced cognitive deficits across multiple cognitive domains in schizophrenia patients with comorbidity of MS. The cytokine model of cognitive function emphasizes the potential link between inflammation and cognitive functions (McAfoose and Baune, 2009), wherein proinflammatory cytokines released by activated microglia may disrupt memory-related neural circuits (Fourrier et al., 2019). However, the mechanisms through which inflammatory factors affect cognitive function in schizophrenia patients with comorbidity of MS remain to be elucidated. In the present study, correlations were revealed between elevated FW in frontotemporal regions and performance across multiple cognitive domains. In addition, we revealed an indirect effect of IL-8 on Delayed recall via FW of right middle frontal gyrus. Our findings suggest that inflammation-related microstructural alterations in frontotemporal regions may be linked to the amplified cognitive decline observed in schizophrenia patients with comorbid MS. Inflammatory processes involving IL-8 may be associated with memory performance, potentially via microstructural alterations in the prefrontal cortex. However, present observed correlations and indirect effect did not survive more stringent corrections for multiple comparisons. Therefore, these preliminary results require further validation in future studies.

The current study still has several limitations. First, while we hypothsized that inflammation contribute to the comorbidity of schizophrenia and MS, our study did not identify any significant alterations in peripheral inflammatory cytokine levels in SZ-wMS group. Limited sample size may account for the negative results. Another interpretation is that the peripheral immune activation in comorbid patients may not differ from that in those with schizophrenia alone, but rather, the communication between peripheral inflammation and the central nervous system is disrupted. Second, the absence of inflammatory cytokines data in the HC-wMS group precluded investigation of relationships between inflammation and brain microstructure in the context of metabolic abnormalities alone. Third, while differences of FW within frontotemporal lobes were identified between the SZ-wMS and SZ-nMS groups, several regional effects were attenuated in the sensitivity analyses. Additionally, given that the majority of chronic schizophrenia patients included in this study, increases in FW may partially reflect brain atrophy associated with aging process (Cetin-Karayumak et al., 2023). Further studies with larger sample sizes, particularly

including patients at the early stage of schizophrenia, are warranted to confirm the microstructural differences. Fourth, the assessment of cognitive function in the present study was limited by the use of MMSE and MoCA, which are insufficient for a comprehensive characterization of cognitive impairment in schizophrenia. In future studies, comprehensive neuropsychological batteries specifically developed for schizophrenia, such as the MATRICS Consensus Cognitive Battery (MCCB), should be employed to enable a more detailed assessment of cognitive deficits. Fifth, the storage duration of blood samples was not recorded in the laboratory tests. Although all samples were collected and processed within a comparable time window, the potential impact of storage duration cannot be completely ruled out. Sixth, while prior studies have demonstrated that ComBat can effectively reduce inter-site variability in DTI-derived measures and has been widely adopted in multi-site neuroimaging studies (Fortin et al., 2017; Villalón-Reina et al., 2019), it primarily models linear batch effects. Therefore, non-linear DTI harmonization methods should be applied to further validate our findings in more independent datasets (Cetin et al., 2019). Finally, the validation analyses conducted in the separate datasets derived from the harmonized combined dataset have inherent limitations, and true external replication will be needed in future studies.

5. Conclusion

Inflammation-related microstructural FW alterations within frontotemporal lobes may represent a potential neurobiological mechanism associated with the comorbidity between schizophrenia and metabolic syndrome. In schizophrenia patients with comorbidity of metabolic syndrome, the frontotemporal microstructural damages are associated with elevated IL-8 levels and poorer cognitive performance, identifying inflammation-related microstructure as a potential translational target for ameliorating cognitive deficits.

CRediT authorship contribution statement

Jingyu Zhou: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Sisi Jiang:** Writing – review & editing, Supervision, Resources. **Huan Huang:** Methodology. **Xiaoying Sun:** Investigation. **Guofeng Ye:** Investigation. **Yingjie Tang:** Methodology. **Xueguo Wang:** Resources, Investigation. **Hongyuan Deng:** Resources, Investigation. **Hui He:** Supervision, Resources. **Xianmei Luo:** Investigation. **Chao Mu:** Investigation. **Mingjun Duan:** Resources. **María Luisa Bringas Vega:** Supervision, Conceptualization. **Gang Yao:** Resources. **Dezhong Yao:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Cheng Luo:** Writing – review & editing, Supervision, Conceptualization.

Code availability

DTI and T1-weighted structural MRI data preprocessing were performed on the FSL version 6.0 (https://fsl.fmrib.ox.ac.uk/fsl/). Bi-tensor FW elimination model was implemented through the Free Water Elimination DTI toolkit obtained from Department of Bioengineering, Universidade de Lisboa (https://github.com/mvgolub/FW-DTI-Beltrami).

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Declaration of competing interest

The authors declare that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2026.101220.

Data availability

Data will be made available on request.

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