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White matter hyperintensities, inflammation and cognitive impairments in drug-naïve first episode schizophrenia patients: a cross-sectional study

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Abstract

Background Studies have reported that white matter hyperintensities (WMHs) are associated with disturbances in immune function, and the relationship between WMHs and cognitive impairments have been documented in various clinical populations. The present study was to examine the relationship between WMHs, immune function, and cognitive impairments in patients with schizophrenia (SCH) remains unknown.

Methods A sample of 127 drug-naïve first episode SCH and 72 healthy controls (HCs) were included in this study. Serum levels of cytokines and oxidative stress indices were measured using enzyme-linked immunosorbent assay and microtiter plate method. WMHs were assessed using T2-weighted magnetic resonance imaging scanning, and cognitive performance was evaluated using the MATRICS Consensus Cognitive Battery.

Results We found patients with SCH are more likely to present with WMHs compared with HCs (OR = 2.076, 95%CI 1.007–4.277, $p = 0.048$). SCH with WMHs displayed more pronounced cognitive deficits in domains including speed of processing, working memory, verbal learning, visual learning, reasoning, and problem-solving compared with patients without WMHs ($p < 0.05$). Correlation analysis showed that the volume of WMHs was negative correlated with the problem-solving score (r=-0.331, $p = 0.042$) in patients with SCH. Within the SCH group, patients with WMHs exhibited elevated levels of interleukin-2 (IL-2), reactive oxygen species (ROS), and superoxide dismutase (SOD), along with lower levels of serum interleukin-4 (IL-4) and interferon-γ (IFN-γ) compared with those without WMHs ($p < 0.05$). The mediation analyses demonstrated that serum levels of IFN-γ in SCH had fully indirect effects on cognitive function, mediated by the WMHs.

Conclusions This study suggests that WMHs may play a vital mediating role in the relationship between inflammation, oxidative stress, and cognitive impairments in SCH. Future studies exploring the potential clinical utility of WMHs as biomarkers for early detection and intervention of SCH are warranted.

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Keywords Schizophrenia, Cognitive impairments, White matter hyperintensities, Inflammation, Oxidative stress indices

Introduction

Schizophrenia (SCH) is a complex and debilitating mental disorder characterized by a combination of positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., social withdrawal, anhedonia), and cognitive impairments. While antipsychotic medications can help alleviate positive symptoms, they demonstrate limited efficacy in addressing negative symptoms and cognitive impairments [1, 2], which are closely associated with real life function and the ability to reintegrate into society [3].

Researchers have proposed that changes in brain microstructure, such as extensive reductions in white matter and gray matter volume [4], decreased white matter integrity [5], and altered myelin content [6], may underlie the cognitive deficits observed in SCH patients. One such structural abnormality is white matter hyperintensities (WMHs), which are bright white areas on T2-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). WMHs are associated with gliosis, axonal loss, and ischemic demyelination. Cognitive impairments in patients with cerebral small vessel disease are associated with the development of WMHs [7]. Furthermore, the volume of WMHs has been shown to affect white matter connectivity, leading to specific cognitive deficits in adults with cardiometabolic risk factors [8].

The existing literature has reported inconsistent prevalences of WMHs in SCH patients. Oxidative stress indices and inflammation are involved in the pathophysiology of SCH [9, 10]. Specific cytokines, including interleukin-2 (IL-2), interleukin-4 (IL-4) and interleukin-6 (IL-6) have been associated with cognitive impairments in SCH patients [11–13]. Evidence suggests that inflammation is connected to the occurrence of WMHs [14–16]. Longitudinal studies have demonstrated that elevated levels of systemic inflammatory markers at baseline predicted subsequent progression and severity of WMHs [17]. In addition, an abnormal distribution of pro-oxidative and antioxidant factors, which plays acritical role for the progression of cerebral white matter lesions, has been found in SCH [18, 19].

Studies on the relationship between cytokines, oxidative stress indices, and WMHs have been more focused in the middle-aged and elderly populations [20, 21]. Similarly, research examining the association between the volume of WMHs and cognitive impairments have largely been conducted in middle-aged and elderly cohorts [22, 23]. Studies in healthy populations have demonstrated a significant increase in the incidence of WMHs after the age of 30 [24]. Studies in the younger populations to investigate the relationship between cytokines, oxidative stress markers, WMHs, and cognitive impairments are lacking. To minimize the confounding effects of antipsychotic medications, disease duration, and other potential factors, we focused specifically on drug-naïve first episode SCH patients.

The purpose of the present study was to investigate the relationship among inflammation, oxidative stress indices, WMHs and cognitive function in young patients with drug-naïve, first episode SCH.

Methods and materials

The Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Approval No. 2019-KY-0271) provided full ethical approval for this study, and written informed consent was obtained from all study participants before investigation.

The study samples

SCH patients

A sample of 127 drug-naïve first episode SCH patients were recruited from April 2020 to July 2023 in outpatient clinics and wards in the Psychiatry Department at the First Affiliated Hospital of Zhengzhou University. The inclusion criteria for the patient group were as follows:

(1) Diagnosis of first-episode SCH based on the Diagnostic and Statistical Manual of Mental Disorders(5th edition, DSM-V) criteria, and confirmed by the Mini International Neuropsychiatric Interview for DSM-V;
(2) Age < 30 years old;
(3) No prior use of antipsychotics or other psychotropic medications;
(4) The Positive and Negative Syndrome Scale (PANSS) total score ≥ 60;
(5) Duration of illness < 5 years.

The study excluded individuals with diabetes, autoimmune diseases, neurological disorders, heart diseases, blood diseases, endocrine system diseases, and other organic diseases. Individuals with a history of head injury, substance abuse, as well as pregnant women and those undergoing treatment with folate supplements or antioxidants, were also excluded. Individuals with incidental brain findings such as arachnoid cysts, ventricular asymmetry, enlargement of perivascular spaces on image reports were excluded.

Healthy controls

A sample of 72 healthy controls (HCs) were recruited from people who underwent health screening at the physical examination department between April 2020 and July 2023. The inclusion and exclusion criteria for HCs were the same as those used for SCH patients except without being diagnosed with SCH.

Assessments

Nine subtests are administered to evaluate 7 key cognitive domains, including speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition. All raw scores for subtests are standardized to T scores (Mean = 50, SD = 10) based on a community sample. The MCCB does not have minimum and maximum scores due to the use of T scores. T scores are summed to calculate domain scores and an overall composite score for global cognition.

MRI acquisition and processing

MRI data were obtained using a 3.0 Tesla Scanner (GE, Siemens, Philips) at the First Affiliated Hospital of Zhengzhou University. High-resolution T-2 flair images were acquired using the following parameters: repetition time (TR) = 8400.0ms, echo time (TE) = 155.7ms, flip angle = 11°, matrix size = 512 × 512, slice thickness = 5 mm, slice number = 27. During the scanning process, all subjects were instructed to relax, remain still, and close their eyes. To ensure image quality, all images were visually inspected to eliminate any with motion or metal artifacts. We invited two experienced image physicians to identify the occurrence of WMHs by visual assessment method. The criteria for WMHs include high signal intensity on T2-weighted or FLAIR images and either equal or low signal intensity on T1-weighted MRI sequences. The volume of WMHs was assessed by automatic labelling based on the Lesion Prediction (LPA) algorithm using the Lesion Segmentation Tool for statistical parametric mapping (SPM) based on SPM12.

Table 1 Characteristics of the study participants

Variable	HC (*n* = 72)	SCH (*n* = 127)	t/χ^2	*P*
Age (yeas)	25.53 ± 3.29	23.93 ± 7.55	1.706	0.090
BMI (kg/m^2)	21.63 ± 3.54	21.16 ± 3.19	0.930	0.354
Sex				
Male	30 (41.67%)	60 (47.24%)	0.976	0.325
Female	42 (58.33%)	67 (52.76%)		
PANSS-P	-	19.91 ± 4.61	-	-
PANSS-N	-	23.34 ± 8.61	-	-
PANSS-G	-	29.71 ± 8.62	-	-
PANSS-T	-	82.95 ± 17.37	-	-

Blood biomarker measurements

The levels of serum IL-2, IL-4, IL-6, interferon-gamma (IFN-γ) and reactive oxygen species (ROS) were measured using enzyme-linked immunosorbent assay (ELISA) (Guangdong Andy Gene Biotechnology Co., Ltd); the sample concentration was calculated from the standard curve. The level of malondialdehyde (MDA), superoxide dismutase (SOD) and reduced glutathione (GSH) were measured using the microtiter plate method (Jiangsu Meimian industrial Co., Ltd).

Statistical analysis

Data were analyzed using IBM SPSS Statistics 26.0 software (IBM Corp, Armonk, NY, USA). Independent samples t-test was used for normally distributed continuous variables, such as age and MCCB scores; Mann–Whitney U test was used for non-normally distributed continuous variables, such as cytokines and oxidative stress indices. The incidence of WMHs was quantified based on imaging reports. Binary logistic regression was used to calculate the odds ratio of developing WMHs between SCH patients and HCs. SCH patients were categorized into groups with and without WMHs based on imaging reports. The levels of serum cytokine, oxidative stress index and cognitive impairments were compared between the two groups. Appropriate statistical tests were employed on the basis of the distribution of the variables, including independent samples t-tests for normally distributed continuous variables, such as age and MCCB scores; Mann–Whitney U tests for non-normally distributed continuous variables, such as cytokines and oxidative stress indices. The mediation effect was examined using the bootstrap method with 5,000 iterations in the Mplus 8.7 software. A significant mediation effect was indicated by a confidence interval that did not include 0.

Results

Characteristics of the study participants

A total of 127 SCH patients (SCHs) and 72 healthy controls (HCs) were recruited in the present research. There were no significant differences in age, sex and body mass index (BMI) between the SCH patients and HCs ($p > 0.05$) (Table 1).

HCs: Healthy controls; PANSS-P: Positive symptom scores of PANSS; PANSS-N: Negative symptom scores of PANSS; PANSS-G: General pathological symptom scores of PANSS; PANSS-T: Total scores of PANSS.

Associations between groups (SCHs and HCs) and WMHs

Findings from the logistic regressions are shown in Table 2. We found a significant effect of group, controlling for sex and age. Specifically, SCH patients were

Table 2 Associations between groups (SCHs and HCs) and WMHs

	Odds Ratio	95% CI	*P*
SCH	2.076	1.007–4.277	0.048
Sex	0.833	0.438–1.587	0.579
Age	0.939	0.891–0.991	0.021

more likely to present WMHs than healthy controls (OR = 2.076, $p = 0.048$).

Cognitive function in SCH patients

Thirty-eight patients with WMHs and thirty-five patients without WMHs who completed both the cognitive assessment and MRI were included in the analysis. There were no significant differences in age, sex, education level, family history of SCH, and smoking status between the two groups. ($p > 0.05$). Importantly, SCH patients with WMHs exhibited severe cognitive deficits in domains including speed of processing, (t = 2.185, $p = 0.032$), working memory, (t = 2.733, $p = 0.008$), verbal learning (t = 2.127, $p = 0.037$), visual learning (t = 3.284, $p = 0.002$), and problem-solving (t = 3.042, $p = 0.003$), compared to SCH patients without WMHs (Table 3).

Values were expressed as (mean ± SD) or N(%). PANSS-P: Positive symptom scores of PANSS; PANSS-N: Negative symptom scores of PANSS; PANSS-G: General pathological symptom scores of PANSS; PANSS-T: Total scores of PANSS; SOP: Speed of Processing; AV: Attention and Vigilance; WM: Working Memory; Vrbl. Lrng: Verbal Learning; Vis. Lrng: Visual Learning; RPS: Problem-solving; SC: Social Cognition.

Relationship between the volume of WMHs and cognitive performance in patients with SCH

A significant correlation exists between the volume of WMHs and cognitive performance. Correlation analysis showed that the volume of WMHs was negative correlated with the problem-solving score (r=-0.331, $p = 0.042$) in patients with SCH (Fig. 1).

Levels of cytokines and oxidative stress indices in SCH patients

Serum levels of cytokines and oxidative stress indices were assessed in SCH patients. The levels of IL-2 were higher in patients with WMHs than in those without WMHs (Z = -2.219, $p = 0.026$). In contrast, the levels of IL-4 and IFN-γ were lower in patients with WMHs than in those without WMHs (Z = -2.175, $p = 0.029$; Z = -2.937, $p = 0.003$ respectively). Serum levels of ROS were higher in patients with WMHs than in those without WMHs (Z = -2.089, $p = 0.036$). Serum levels of SOD were significantly higher in patients with WMHs than in those

Table 3 Comparison of demographics, clinical characteristics, and cognitive performance between SCH patients with and without WMHs (mean ± SD)

Variable	SCH with WMHs($n = 38$)	SCH without WMHs($n = 35$)	t/χ^2	*P*
Age (years)	19.58 ± 4.48	19.49 ± 4.80	0.086	0.932
Education (years)	11.43 ± 2.47	11.29 ± 2.54	0.249	0.804
BMI (kg/m^2)	20.10 ± 2.42	21.51 ± 3.67	-1.800	0.077
PANSS-P	19.71 ± 5.00	19.03 ± 5.14	0.566	0.573
PANSS-N	21.23 ± 6.54	20.57 ± 6.68	0.416	0.679
PANSS-G	39.77 ± 7.80	40.86 ± 9.31	-0.529	0.599
PANSS-T	80.71 ± 16.18	80.46 ± 17.67	0.064	0.950
Sex				
Male	16(42.11%)	19(54.29%)	1.083	0.298
Female	22(57.89%)	16(45.71%)		
Smoking status				
Yes	2(5.26%)	2(5.71%)	0.007	0.933
No	36(94.74%)	33(94.28%)		
Family history				
Yes	4(10.53%)	3(8.57%)	0.080	0.778
No	34(89.47%)	32(91.43%)		
Cognitive Function				
SOP	26.38 ± 13.42	33.15 ± 12.03	2.185	0.032
AV	28.56 ± 14.76	35.33 ± 12.98	1.993	0.050
WM	36.80 ± 11.54	44.03 ± 10.18	2.733	0.008
Vrbl. Lrng	36.00 ± 9.49	41.33 ± 11.58	2.127	0.037
Vis. Lrng	33.31 ± 18.05	45.19 ± 10.05	3.284	0.002
RPS	31.17 ± 10.20	39.06 ± 11.19	3.042	0.003
SC	36.94 ± 12.25	36.09 ± 12.62	-0.280	0.780

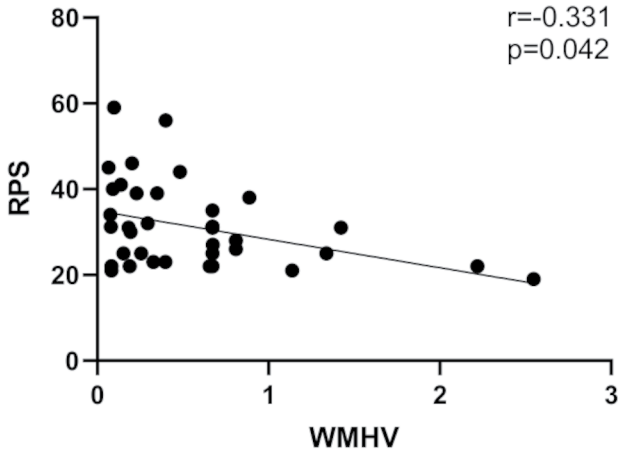

Fig. 1 Relationship between the volume of WMHs and Cognitive performance in SCH Patients
RPS: Problem-Solving; WMHV: the Volume of WMHs

without WMHs (Z = -2.021, $p = 0.043$). No significant differences were observed in MDA and GSH (Fig. 2).

Relationship between cytokines, oxidative stress indices, and cognitive performance in SCH patients with WMHs

Previous studies have indicated that cytokine levels and oxidative stress indices are correlated with the progression of WMHs [25]. The burden of WMHs can exacerbate cognitive impairment. Therefore, we selected cytokines and oxidative stress indices that differed in SCH patients with and without WMHs as independent variables, the presence or absence of WMHs as the mediating variable. Cognitive domain scores were designated as dependent variables. A mediation model was constructed to examine the potential links that may exist between them. Mediation analyses showed that the effect of serum levels of IFN-γ on working memory, (95% CI = 0.028 to 1.029), visual learning (95% CI = 0.108 to 1.499), problem-solving (95% CI = 0.009 to 0.992) in SCH patients was fully mediated by the WMHs. Figure 3 presents detailed results.

Discussion

This study demonstrates a mediation model linking cytokines, oxidative stress indices, and cognitive impairments via WMHs in drug-naïve, first-episode SCH patients. Our findings provide evidence that cytokines and oxidative stress indices contribute to cognitive deficits possibly by affecting the development of WMHs in this patient population.

Studies in a variety of clinical populations have found that the larger the WMHs volume, the more severe the cognitive deficits [22, 26]. Some studies suggest that detrimental effect of the frontal/occipital WMHs on executive function was partly mediated by the decreased differentiation of the connectivity pattern between the primary and transmodal areas [27]. Du et al. reported that WMHs disrupt the structural connectivity of large-scale brain networks, thereby impairing the ability of

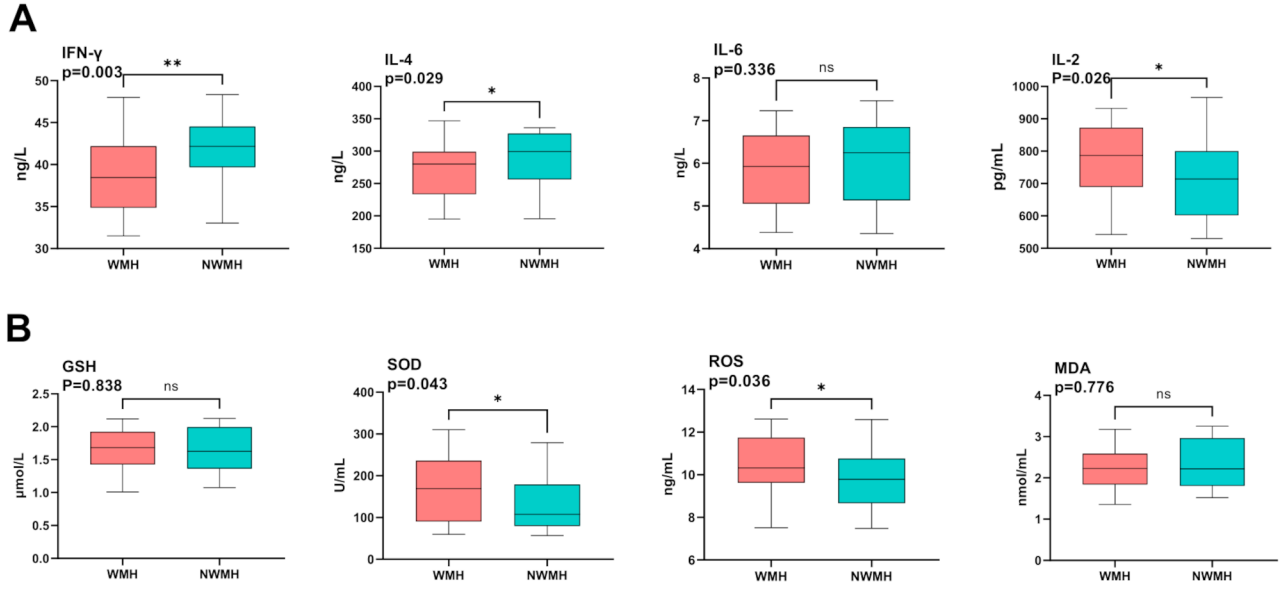

Fig. 2 Comparison of cytokines and Oxidative Stress Indices in SCH patients with and without WMHs
A box-plot is a statistical graph for describing the discrete degree of a group of data. Box plot shows minimum (lower whiskers), maximum (upper whiskers), median (central line) and interquartile range (box margins). A: Serum levels of cytokines; IFN-γ: interferon-gamma; IL-4: Interleukin-4; IL-6: Interleukin-6; IL-2: Interleukin-2; B: oxidative stress indices; GSH: Reduced glutathione; SOD: Superoxide Dismutase; ROS: Reactive Oxygen Species; MDA: Malondialdehyde
$^{*}p < 0.05$; $^{**}p < 0.01$

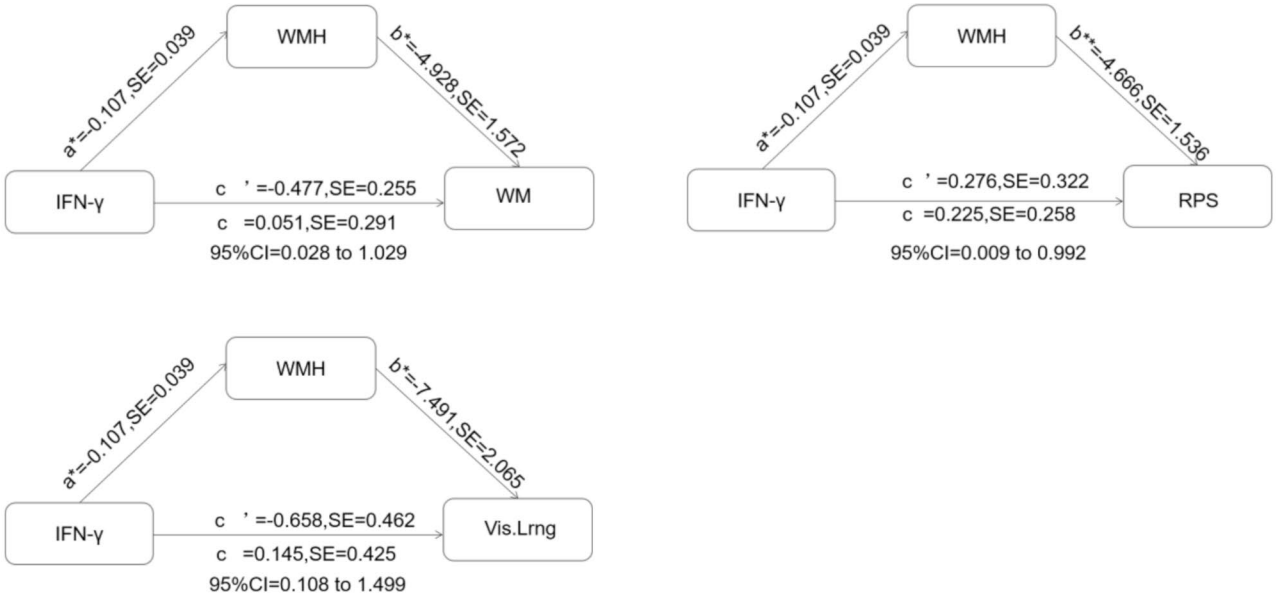

Fig. 3 Mediation model of the interrelationships among serum levels of IFN-γ, presence of WMHs and Cognitive performance
WM: Working Memory; Vis. Lrng: Visual Learning; RPS: Problem-solving
$^{*}p < 0.05$, $^{**}p < 0.01$

the brain to integrate neural processes [28]. The location of WMHs appears to be an important risk factor; prior studies have linked WMHs in the anterior thalamic radiations and pons to poor executive function, and memory [29, 30]. Consistent with the previous findings from the literature, our study found poor performance across various cognitive domains including speed of processing, working memory, verbal learning, visual learning, and reasoning/problem-solving in SCH patients with WMHs. Correlation analysis revealed a negative correlation between the volume of WMHs and the problem-solving scores. The lesion sites of the subjects in our study were predominantly located in the parietal and frontal lobes. However, owing to the limited sample size, the impact of lesion distribution on cognitive function could not be further investigated. Further, our study identified that these cognitive effects occurred in a relatively young patient population under 30 years old, suggesting the negative impact of WMHs on cognition could happen at a young age and in the early-stage of illness. To mitigate potential confounding effects of vascular dysfunction and associated risk factors on WMHs, individuals with a history of hypertension, diabetes mellitus, or hyperlipidemia were excluded from the study population.

The study also sheds light on the role of cytokines in cognitive dysfunction among SCH patients. Specifically, we found that serum levels of IL-2 are higher in SCH patients with WMHs, while serum levels of IL-2 are lower compared to those without WMHs. IL-2 is a pleiotropic cytokine that exhibits immunostimulatory or immunoinhibitory activities depending on the target cell type [31]. It can regulate the homeostasis between Treg and effector T (Teff) cells. High doses of IL-2 inevitably activate Teff cells, thereby exacerbating autoimmune diseases. IL-2 has also been reported that plays a role in the molecular cascade leading to white matter damage during periventricular leukomalacia [32]. Conversely, IL-4 has been shown to shift the microglial response towards an anti-inflammatory, pro-recovery phenotype [33]. An animal experiment demonstrated that IL-4 activates microglial PPAR-γ and arginase 1, significantly shifting the microglial response towards an inflammatory abatement and pro-neurological recovery phenotype [33]. While prior research has associated serum IL-6 levels with WMHs [34, 35], our findings suggest no difference between potentially due to the young age and/or the early stage of illness. Satizabal et al. studied 1841 participants aged 65–80 years from the Three City-Dijon cohort and showed that higher levels of IL-6 were associated with higher volumes of WMHs, independent of age, sex, and vascular risk factors [36]. Myriam et al. observed significant and graded associations between plasma IL-6 levels and WMHs among those aged 65 and older [37]. These findings indicate that the characteristics of WMHs in younger individuals may differ from those observed in middle-aged and older adults.

Lipid peroxidation and excessive ROS accumulation are known to contribute to white matter damage. IFN-γ exerts a dual-regulatory function within the neuroinflammation, entailing a complex crosstalk among multiple signaling cascades and diverse cellular responses. Increased IFN-γ has been associated with white matter

damage in the central nervous system in preterm neonates [38]. Masaaki et al. reported that IFN-γ-induced Th1-Treg polarization in inflamed brains limits exacerbation of experimental autoimmune encephalomyelitis [39]. IFN-γproduction in Candida albicans stimulated peripheral blood mononuclear cells was negatively correlated with the progression of WMHs [35]. Its impact on WMHs may be associated with lipid peroxidation. IFN-γ exerts its protective effects by altering the clearance of myelin debris and limiting the substrates for neurotoxic lipid peroxidation products [40]. Our findings of lower IFN-γ levels and higher ROS levels in SCH patients with WMHs compared with those without WMHs are consistent with the reports from previous studies. However, our study showed no significant difference in MDA, a marker of lipid peroxidation, between SCH patients with and without WMHs; this may be due to the relatively mild nature of WMHs in our study participants or the relatively small sample size. The higher SOD levels in SCH patients with WMHs compared with those without WMHs likely reflects the body's compensatory effort to mitigate excessive oxidative stress.

The present study has several strengths: (1) Choosing drug-naïve, first episode SCH patients minimized possible confounding effects of antipsychotic medication treatment and heterogeneity in age and disease duration. (2) Previous studies in WMHs cognitive function primarily focused on middle-age and elderly individuals; our study filled in a gap in the literature by focusing on the young patients. However, given the nature of a cross-sectional study design, we are not able to draw any causal conclusions from our study.

Importantly, our mediation analysis confirmed the fully indirect effects of IFN-γ on cognitive function, mediated through the presence of WMHs. In conclusion, our study suggests that WMHs may play a vital mediating role in the relationship between inflammation, oxidative stress, and cognitive impairments in SCH. Longitudinal studies are needed to further understand the role of WMHs in SCH pathophysiology and to explore the potential clinical utility of WMHs as biomarkers for early detection and intervention of SCH. WMHs may serve as a potential biomarker for early cognitive intervention in patients with SCH.

Abbreviations

FLAIR	Fluid-attenuated inversion recovery
GSH	Reduced glutathione
IFN-γ	Interferon-gamma
IL-2	Interleukin-2
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
MDA	Malondialdehyde
MRI	Magnetic resonance imaging
ROS	Reactive Oxygen Species
SCH	schizophrenia
SOD	Superoxide Dismutase
WMHs	White matter hyperintensities

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Author contributions
Authors Yan Zhang and Xiuxia Yuan designed the study. Author Yan Zhang wrote and revised the manuscript. Authors Yu Zhang, Jingjing Li, Yishao Chen, and Keju Su were in charge of conducting clinical assessment and collecting fasting blood samples. Author Kangkang Xue was in charge of performing the imaging assessment. Authors Suying Ding and Jingfeng Chen were responsible for sample collection from the healthy population. Authors Yan Zhang and Xiuxia Yuan were in charge of statistical analyses and wrote the first draft of the manuscript. Author Xiaoduo Fan reviewed the manuscript. Xueqin Song was responsible for guidance and review. All authors participated and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Approval No. 2019-KY-0271) provided full ethical approval for this study, and written informed consent was obtained from all study participants before investigation. All studies were conducted in accordance with the Declaration of Helsinki, the Data Protection Act and other relevant guidelines and regulations. Written informed consent was obtained from all study participants and their parents or legal guardians.

Consent for publication
The manuscript contains any information/images that the participant agrees to publish.

Competing interests
The authors declare no competing interests.

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