Article

Correlations between Immunoinflammatory Factor Levels and Cognitive Functions and Brain Structural Magnetic Resonance Imaging Features among Patients with Primary Schizophrenia

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Abstract

Background: Schizophrenia is associated with significant cognitive impairment. However, the pathophysiological mechanisms underlying cognitive dysfunction in schizophrenia remain unclear. Based on the latest concept of cognition, immunoinflammatory factors and structural magnetic resonance imaging (sMRI) features of the brain are considered markers of schizophrenia. This study explored the correlations between cognitive function and immunoinflammatory factors and sMRI in primary schizophrenia patients.

Methods: Non-interventional cross-sectional study was conducted, including 21 patients with primary schizophrenia, who were identified based on the Diagnostic and Statistical Manual, Fifth Edition (DSM-V) and grouped under the observation group. Thirty healthy volunteers with age, gender, hand dominance, and education duration matched with those of the primary schizophrenia patients were recruited to the control group. All subjects underwent sMRI examination. MATRICS consensus cognitive battery (MCCB) was employed to assess the cognitive functions among patients with primary schizophrenia. The levels of serum amyloid A (SAA), monocyte chemoattractant protein 1 (MCP-1), and chitinase-3-like protein 1 (YKL-40) were measured by means of enzyme-linked immunosorbent assay (ELISA). Pearson's correlation analysis was carried out to analyze the correlation between immunoinflammatory factor levels and cognitive functions as well as brain sMRI features.

Results: The scores for all MCCB items and the total score for the observation group were apparently lower than those for the control group ($p < 0.001$), while the YKL-40 and SAA levels were notably higher in the observation group ($t = 3.406$, $p < 0.05$; $t = 5.656$, $p < 0.001$). Compared to the control group, the observation group exhibited reduced volumes of left and right insular lobes, left and right anterior cingulate cortexes, left and right hippocampi, right parahippocampal gyrus, right amygdala, left inferior occipital lobe, left superior temporal lobe, left temporal pole, and left middle and inferior temporal lobes ($p < 0.001$). The levels of YKL-40 and SAA were both negatively correlated with MCCB score (r = –0.3668, $p = 0.004$; r = –0.8495, $p < 0.001$). The volumes of right insular lobe, left and right anterior cingulate cortexes, right parahippocampal gyrus, right amygdala, and gray matter in left middle temporal lobe were all negatively correlated with the levels of YKL-40 and SAA ($p < 0.05$).

Conclusion: Cognitive impairment in patients with primary schizophrenia is associated with increased serum SAA and YKL-40 levels and decreased gray matter volume.

Keywords

schizophrenia; magnetic resonance imaging; cognitive function; immunoinflammatory factors

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Introduction

Schizophrenia (SZ) is a chronic, highly disabling mental disease but its etiology remains largely unclear; It is manifested by thought disorder, perception deficit, and behavior disorder, exerting a huge impact on most patients' daily life [1]. Statistics show that the global incidence of SZ stands as high as 1%, with the annual incidence ranging between 0.08% and 0.4%. The incidence is the highest among young and middle-aged people, and by gender and area of residence, it is higher in males residing in urban areas than females in rural areas. It is important to note that the incidence of SZ is negatively correlated with family income [2,3]. Apart from perceptual disorders, SZ patients suffer from cognitive dysfunctions, particularly in concentration, memory, and execution. It has been found that in China, the population with SZ and related mental disorders constitutes the fourth largest group of patients among populations affected by various disabling diseases [4].

Based on our present understanding regarding its pathogenesis, SZ is associated with genetic factors, with environmental factors playing a role in modulating the neurodevelopmental trajectory. The consequent outcome of SZ pathogenesis is impaired cerebral cortex function, causing cognitive dysfunction among the affected individuals. Social psychological factors and subcortical dopamine dysfunction are also reportedly to play a role in the occurrence of SZ [5].

Considerable research findings have established cognitive dysfunction as the primary clinical manifestation of SZ patients. Most patients suffer from varying levels of cognitive dysfunctions at initial stage, with their severity being correlated with the severity of SZ and the prognosis [6]. Cognitive impairment is associated with the reduction of gray matter (GM) volume in brain structural magnetic resonance imaging (sMRI) [7], which is a high-resolution and non-invasive tool for accurate localization of brain areas. sMRI enables the direct visualization of brain tissue changes, providing a vital tool for the diagnosis of brain diseases and the research into their pathogenesis [8]. Therefore, it is widely applied in the diagnosis of brain diseases.

Pro-inflammatory factors are abundantly secreted in SZ patients' brains, diminishing neuronal proliferation and eventually causing loss of brain tissues [9]. In addition, it has been reported that the increase of secreted cerebral pro-inflammatory factors is correlated with cognitive impairment among SZ patients [10]. For instance, serum amyloid A (SAA) is closely associated with acute inflammatory diseases and sequelae [11]. Monocyte chemoattractant protein 1 (MCP-1) is a proinflammatory factor that is mainly synthesized through the mediation by interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), or interferon-7 (IFN-7). The level of MCP-1 rises in chronic inflammation and multiple tumors, where the occurrence of cerebral tissue injury is evident [12]. Chitinase-3-like protein 1 (YKL-40) is a newly discovered inflammatory marker that is abnormally expressed in patients with acute cerebral infarction [13]. Nonetheless, investigations on the levels of SAA, MCP-1, and YKL-40 in SZ patients remain scanty. In addition to the unclear relationship between the levels of these markers and primary SZ, whether their levels are associated with cognitive functions and sMRI features in patients with primary SZ also remains unknown.

Hence, this study aimed to investigate the levels of SAA, MCP-1, and YKL-40 in patients with primary SZ and analyze their correlation with cognitive functions as well as sMRI features. The findings of this research will provide a reliable clinical reference for the diagnosis, treatment, and prognosis of primary SZ and shed light on key clues for the exploration of pathological mechanism underlying primary SZ development.

Materials and Methods

Study Participants

In this non-interventional cross-sectional study, 21 patients with primary SZ who were treated in psychiatric outpatient or inpatient department in Huzhou Third Municipal Hospital. These patients conformed to Diagnostic and Statistical Manual, Fifth Edition (DSM-5) [14] and classified under the observation group. Thirty healthy volunteers with age, gender, hand dominance, and education duration matched with those of the 21 patients were recruited in the control group. The study was conducted in accordance with the principles set out in the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Huzhou Third Municipal Hospital (approval number: 2020-032, Date: March 30, 2020). Every study participant was given a clear explanation of the study protocol, and written informed consent was obtained afterward.

Participants were included in the observation group if (i) they were aged between 18 and 60, (ii) their diagnosis of primary SZ was made in conformance with the diagnostic standards set out in the DSM-V, and (iii) they had complete sMRI data and data records. Individuals with the following characteristics were excluded from this study: (i) patients with severe somatic diseases; (ii) pregnant women and parturients; (iii) patients with incomplete sMRI data; and (iv) patients with mental disorders caused by various factors.

In the control group, patients with the following characteristics were included: (i) patients aged between 18 and 60; (ii) patients without the history of mental diseases or family mental diseases; and (iii) patients without mental diseases as confirmed by DSM-V-based diagnosis. Patients with severe somatic diseases and incomplete sMRI data, as well as pregnant women and parturients were excluded.

Assessment of Clinical Symptoms and Cognitive Functions

Based on positive and negative syndrome scale (PANSS), the severity of mental diseases among SZ patients was assessed [15]. PANSS contains instruments to measure positive symptoms, negative symptoms, and general pathology. Of which, positive symptoms include delusion, hallucination, excitation, conception chaos, grandeur, suspiciousness or persecution, and hostility; negative symptoms encompass affective blunting, affective disorder, emotional retraction, passiveness or apathy, lack of spontaneity in conversation, abstract thinking, and rigid thinking; and general pathology covers 16 items, including the worry about physical health, anxiety, guilt, nervousness, mannerism, depression, and retardation. Each item in the above three components was scored in the range of 1 to 7 points. Points 1 to 7 represent no symptom, extremely mild symptom, mild symptom, moderate symptom, slightly severe symptom, severe symptom, and extremely severe symptom, respectively. In short, a higher PANSS score suggests the increasing severity of the symptom. MATRICS consensus cognitive battery (MCCB) [16] was employed to assess SZ patients' cognitive functions, including processing speed, attention or vigilance, working memory, word learning, visual learning, reasoning and problem-solving, and social cognition. Various tests were implemented, including even the line, code of symbol, fluency in speech, continuous operation, breath of space, sequence of numbers, memory of speech, visual memory, fan palace and emotional management. The total duration of the assessment was 63.5 minutes, and the duration of the entire experiment was measured in seconds.

Measurement of SAA, MCP-1, and YKL-40 Levels by ELISA

Four milliliters of blood was extracted from the cubital vein of each of the SZ patients under fasting state on the first day of admission or on the next day after admission. To obtain for serum, the blood specimens were centrifuged in a TD-4M centrifuge (Jinan Qiansi Biotechnology Co., Ltd., Jinan, China) at 3000 rpm and low temperature for 10 minutes. While performing the measurements, standard solutions were diluted and then added into the corresponding wells in the enzyme-linked immunosorbent assay (ELISA) plate. Next, the samples to be measured were added and incubated at 37 °C for 30 minutes. After that, the solutions were discarded and the plate was rinsed with scrubbing solution 5 times. Then, every well was added with 50 µL of enzyme conjugate reagent and then incubated at 37 °C for 30 minutes. The same washing step using scrubbing solution was then repeated. Subsequently, 50 µL of chromogenic reagents A and B were added and incubated at 37 °C for 15 minutes away from the light. After the 15-minute incubation, 50 µL of stop buffer was added to each well. Finally, the levels of SAA, MCP-1, and YKL-40 were measured using Multiskan FC microplate reader (ThermoScientific, USA) at 450 nm. The SAA, MCP-1, and YKL-40 ELISA kits were purchased from Shanghai Coibo Biotechnology Co., Ltd. (Shanghai, China).

Magnetic Resonance Imaging and Data Processing

All included subjects underwent magnetic resonance imaging (MRI) examination conducted using a superconducting magnetic resonance scanner (SIEMENS 3.0T VERO, Berlin, Germany). The subjects were instructed to assume a supine position while being examined. Full brain of each subject was scanned using T1W-3D-TFE sequence. The scanning parameters were set as follows: time of repetition time (TR) = 7.5 ms; time of echo (TE) = 3.7 ms; field of view (FOV) = 240 × 240 mm; slice thickness = 1 mm; flap angle = 8°; matrix size = 556 × 200; slice spacing = 0 mm; and number of slices = 180.

The collected MRI images were processed according to MATLAB7.1 protocols. MRI images were standardized, segmented, and adjusted using voxel-based morphometry to obtain the unadjusted MRI images of brain's gray and white matters. The volume of gray matter (GM) was calculated.

Statistical Analysis

The data were processed and analyzed using SPSS 20.0 software (IBM Corp., Chicago, IL, USA) and subjected to normality assessment using Kolmogorov–Smirnov test. Normally distributed data are expressed as mean ± standard deviation and were analyzed by *t*-test. Categorical data are presented as percentage (%) and were analyzed by Chi-squared test. Pearson's correlation tests were carried out to analyze the correlation between immunoinflammatory factor levels and cognitive functions as well as brain sMRI features. A difference was considered statistically significant if $p < 0.05$.

Table 1. Comparison of the baseline and clinical characteristics between observation and control groups.

Variable	Observation group (n = 21)	Control group (n = 30)	χ^2/t value	*p*-value
Age	22.83 ± 3.54	23.21 ± 3.87	0.357	0.723
Sex (male/female)	12/9	18/12	0.042	0.838
Education duration (years)	13.33 ± 3.59	13.81 ± 2.98	0.520	0.605
Course of disease (months)	10.74 ± 5.42	/	/	/
PANSS scores				
Positive symptom score (points)	18.21 ± 3.52	/	/	/
Negative symptom score (points)	19.67 ± 3.88	/	/	/
General pathology score (points)	40.13 ± 3.49	/	/	/
Total score (points)	78.01 ± 8.85	/	/	/

PANSS, positive and negative syndrome scale.

Results

Comparison of Baseline and Clinical Characteristics

The baseline characteristics such as age, sex, education duration, course of disease and PANSS score between observation group and control group were compared (Table 1). PANSS scores of positive symptoms, negative symptoms and general pathology in the observation group were 18.21 ± 3.52, 19.67 ± 3.88 and 40.13 ± 3.49, respectively, with a total score of 78.01 ± 8.85. The average course of disease in observation group was 10.74 ± 5.42 months. There were no statistical differences between the two groups in age, gender ratio, and education duration ($p > 0.05$).

Comparison of Cognitive Functions

The scores of even the line, code of symbol, fluency in speech, continuous operation, breath of space, sequence of numbers, memory of speech, visual memory, fan palace and emotional management in the observation group were significantly lower than those in the control group (all $p < 0.05$). The total score of MCCB was 196.47 ± 15.2 in the observation group and 269.27 ± 18.13 in the control group, and the difference was statistically significant ($p < 0.001$) (Fig. 1).

Comparison of Immunoinflammatory Factor Levels

The serum levels of immunoinflammatory factors of observation and control groups are depicted in Fig. 2. Our comparison revealed that the MCP-1 level was not significantly different between observation and control groups ($t = 1.380$, $p > 0.05$). However, significant differences in YKL-40 ($t = 3.406$, $p < 0.05$) and SAA levels ($t = 5.656$, $p < 0.001$) were observed between the observation and control groups.

Comparison of GM Volumes

The GM volumes between the observation and control groups were compared (Fig. 3). Compared to the control group, the observation group displayed reductions in the volumes of left and right insular lobes, left and right anterior cingulate cortexes, left and right hippocampi, right parahippocampal gyrus, right amygdala, left inferior occipital lobe, left superior temporal lobe, left temporal pole, and left middle and inferior temporal lobes (all $p < 0.05$).

Analysis of the Correlation between Immunoinflammatory Factors and Cognitive Functions

The YKL-40 and SAA levels were negatively correlated with the MCCB scores in observation group ($r = –0.3668$, $p = 0.004$; $r = –0.8495$, $p < 0.001$; respectively) (Figs. 4,5).

Analysis of the Correlation between Inflammatory Factors and sMRI GM Volumes

The correlation between immunoinflammatory factor levels (YKL-40 and SAA) and GM volumes was analyzed (Table 2). The GM volumes of right insular lobe, left and right anterior cingulate cortexes, right parahippocampal gyrus, right amygdala, and left middle temporal lobe were all negatively correlated with YKL-40 and SAA levels ($p < 0.05$). The GM volume of left and right anterior cingulate cortexes were significantly negatively correlated with SAA level ($p < 0.01$). On the other hand, the GM volume of right insular lobe was negatively correlated with YKL-40 level ($r = –0.501$, $p < 0.01$).

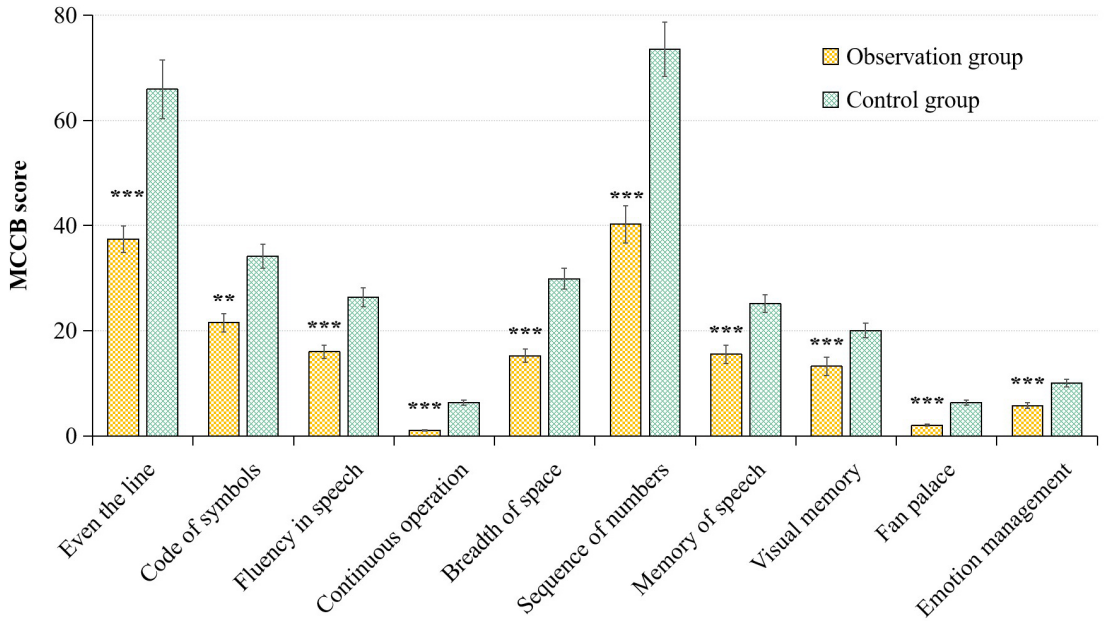

Fig. 1. Comparison of MCCB scores between the observation and control groups. ** $p < 0.01$, *** $p < 0.001$. Abbreviation: MCCB, MATRICS consensus cognitive battery.

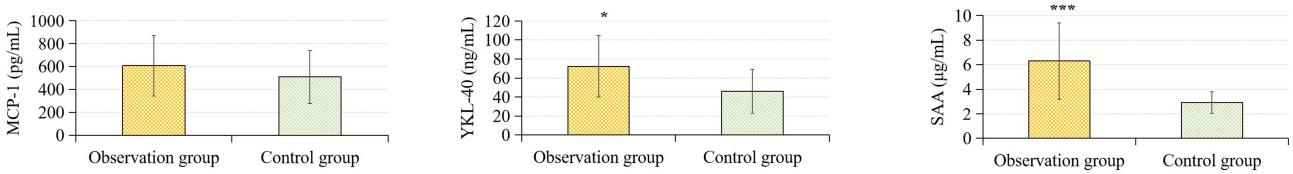

Fig. 2. Comparison of immunoinflammatory factor levels between the observation and control groups. * $p < 0.05$, *** $p < 0.001$. Abbreviations: MCP-1, monocyte chemoattractant protein 1; YKL-40, chitinase-3-like protein 1; SAA, serum amyloid A.

Discussion

At present, it is generally believed that the scores for cognitive functions are lower in SZ patients than in healthy individuals. In this research, MCCB was employed to measure the cognitive functions of SZ patients and the subjects in control group. It was demonstrated that the scores for even the line, fluency in speech, continuous operation, breadth of space, sequence of numbers, memory of speech, visual memory, fan palace, and emotion management in observation group were notably inferior to those in the control group. Total MCCB score was remarkably lower in the observation group than in the control group, suggesting that SZ patients had significantly reduced cognitive functions. Besides, the level of neurocognitive injury, a main clinical symptom of SZ, was found to be significantly correlated with SZ dysfunction. Nonetheless, the mechanism and process relating to neurocognitive injury remain unclear [17]. A study has demonstrated that the level of cognitive function impairment in SZ is associated with age, course of disease, severity of disease, and drug therapy [18]. It is known that cognitive dysfunction occurs before the development of SZ, allowing for early disease evaluation and prediction of disease progression based on the scores for cognitive levels. Furthermore, patients receiving treatment for SZ in early stage generally have remarkable prognosis. It has also been reported that regions with less GM volume at different stages of SZ can be pinpointed using sMRI. A previous study has also found that reduction in total brain volume occurs at the early stage of SZ, accompanied by brain ventricle expansion [19]. Our findings also align well with other study demonstrating the reductions in GM volumes of left superior temporal lobe, medial temporal lobe, anterior cingulate, right subparietal cortex, and insular lobe in SZ patients [20]. Moreover, Dziwota *et al.* [21] showed that the volumes of left superior and middle temporal gyri, left middle frontal gyrus, right inferior frontal gyrus, anterior cingulate, medial temporal lobe, and bilateral parietal cortex in SZ patients decreased, relative to those in healthy people. In this study, we found that the volumes of left and right

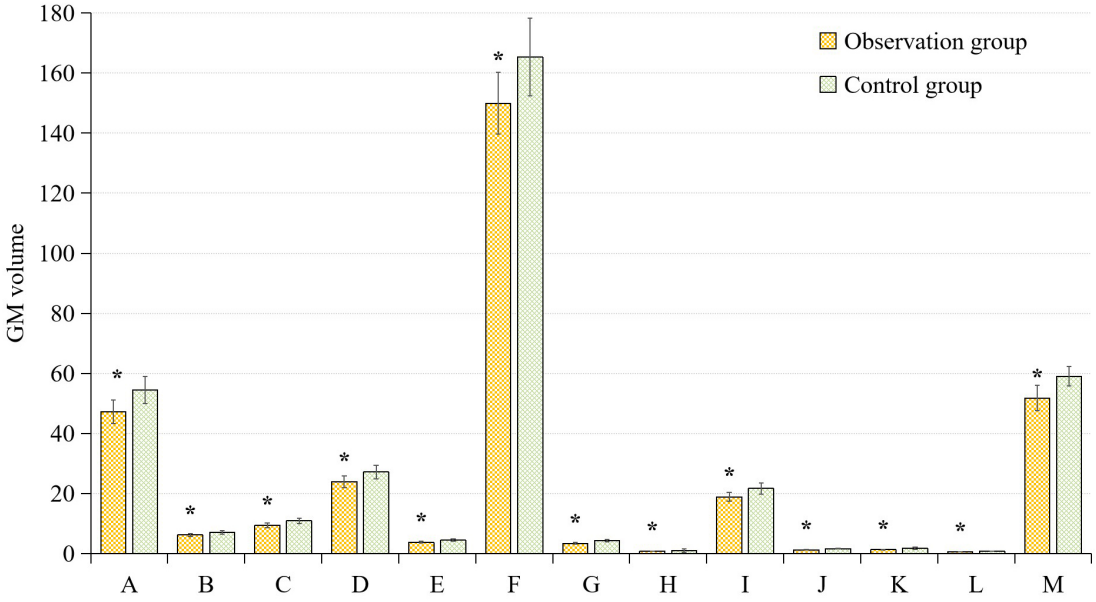

Fig. 3. Comparison of GM volumes in different parts of the brain between the observation and control groups. (A) left insular lobe, (B) right insular lobe, (C) left anterior cingulate cortex, (D) right anterior cingulate cortex, (E) right hippocampus, (F) left hippocampus, (G) right parahippocampal gyrus, (H) right amygdala, (I) left inferior occipital lobe, (J) left superior temporal lobe, (K) left temporal pole, (L) left middle temporal lobe, and (M) left inferior temporal lobe. *$p < 0.05$. Abbreviation: GM, gray matter.

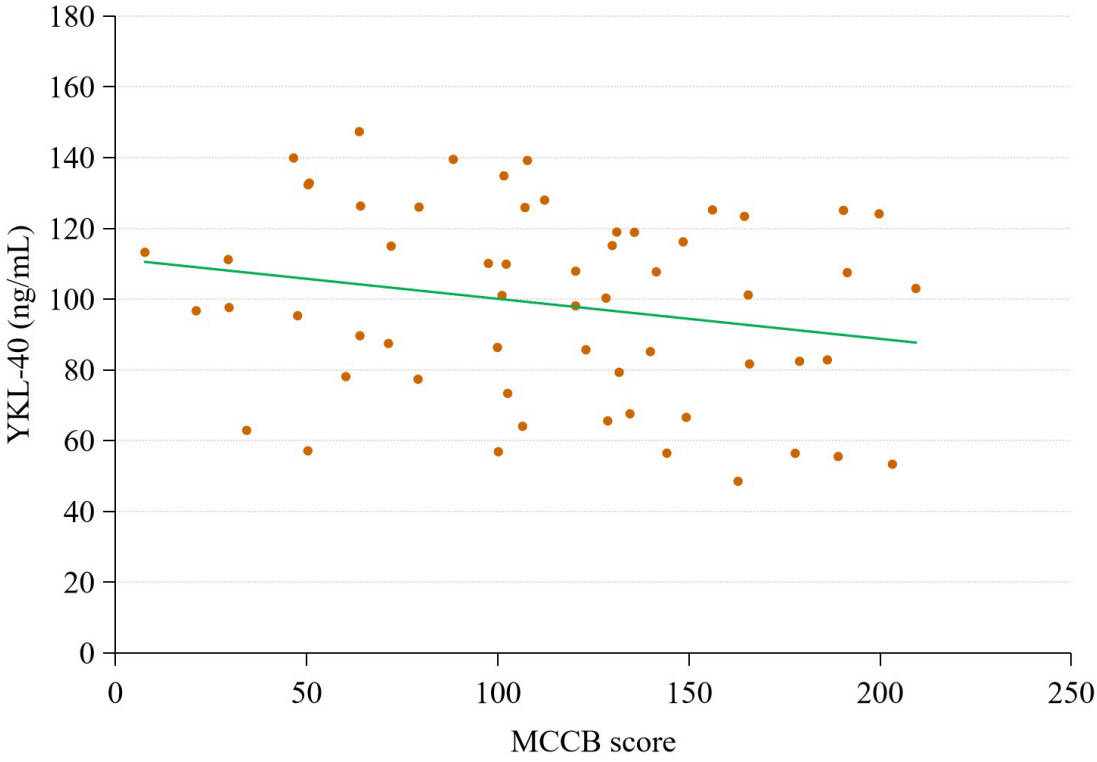

Fig. 4. Analysis of the correlation between YKL-40 and MCCB scores in observation group. Abbreviations: YKL-40, chitinase-3-like protein 1; MCCB, MATRICS consensus cognitive battery.

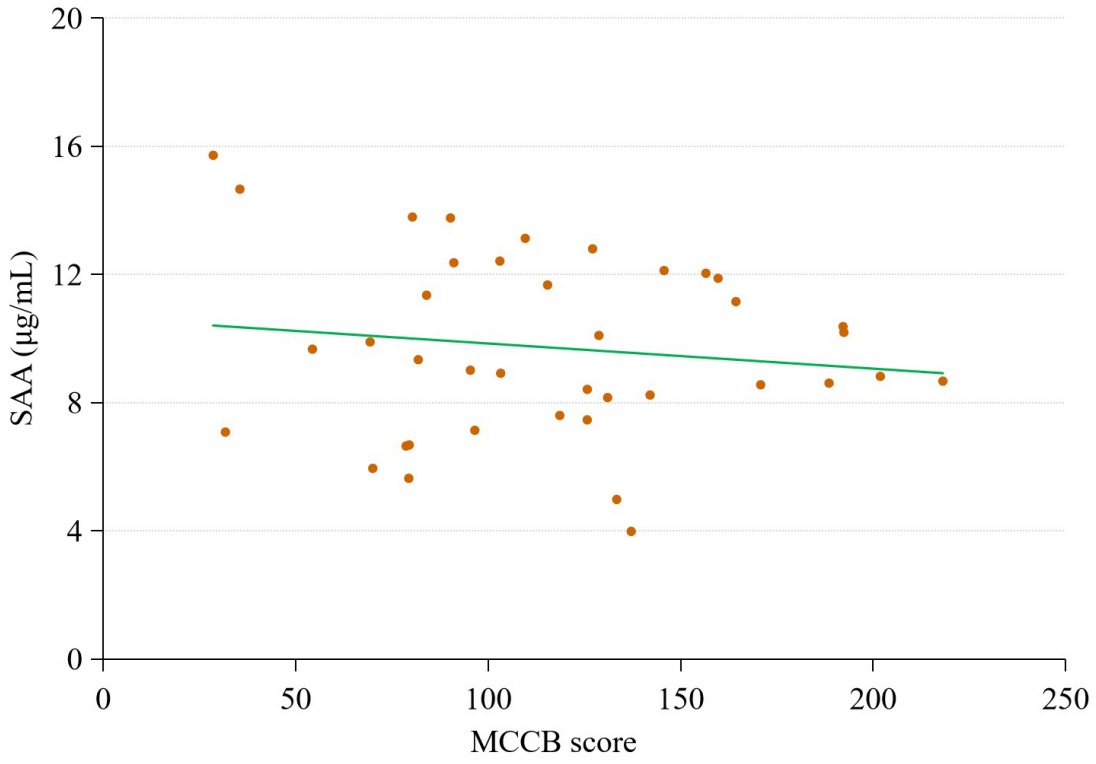

Fig. 5. Analysis of the correlation between SAA and MCCB scores in observation group. Abbreviations: SAA, serum amyloid A; MCCB, MATRICS consensus cognitive battery.

insular lobes, left and right anterior cingulate cortexes, left and right hippocampi, right parahippocampal gyrus, right amygdala, left inferior occipital lobe, left superior temporal lobe, left temporal pole, and left middle and inferior temporal lobes were decreased in the observation group, a finding consistent with the existing research results. Taken together, these findings demonstrated that the GM volumes are generally reduced in SZ patients. Nonetheless, there is no unified conclusion regarding the lowered GM volumes in specific parts of the brain, which might be caused by the deteriorating severity and progression of SZ. However, albeit rare, some clinical studies shed light on the association between GM volumes and specific parts of brain. For instance, a study has found that the reduction of insular lobe GM volume is correlating with the clinical features of mental diseases, potentially serving as a clinical hallmark [22].

A growing body of studies have demonstrated that SZ patients are constantly suffering from oxidative damage and inflammation. According to the existing research, immune dysfunction and abnormal cellular and humoral immunity are also a commonplace among SZ patients. Additionally, reduced IL-1 and IL-1β levels in serum and cerebrospinal fluid have been noted in SZ patients, as compared to those in healthy individuals [23]. As an essential regulator of leukocyte chemotaxis in inflammation, MCP-1 plays an important role in inflammatory reaction and cell migration, in addition to modulating T-assisted cell development by stimulating Th2 polarization. Thus, MCP-1 might be involved in SZ pathogenesis since neuroinflammation is a common feature in SZ [24]. Ma *et al.* [25] reported that the serum levels of MCP-1 and IL-8 in SZ patients were apparently higher than those in the controls and were positively correlated with the severity of clinical symptoms. Different from their study, we, however, detected no significant difference in MCP-1 level between observation and control groups, probably due to the different severity levels of SZ patients recruited to this study. YKL-40 is mainly secreted by activated macrophage, playing a vital role in inflammation. A prior study has established the association of YKL-40 level with the occurrence and development of cardiovascular diseases [26]. Orhan *et al.* [27] indicated that MCP-1 and YKL-40 levels in cerebrospinal fluid and serum were higher among SZ patients than among healthy controls, suggesting that the occurrence of SZ is correlated with monocyte activation and immune dysfunction. SAA represents a group of pleomorphic proteins encoded by the same gene cluster and is expressed by mammals and birds. The synthesis of SAA is regulated by IL-1, IL-6, and TNF-α, indicating its high specificity to a diverse range of triggers.

Table 2. Analysis of the correlation between immunoinflammatory factor levels and GM volumes in different parts of brain.

Variable	YKL-40		SAA	
	r value	*p*-value	r value	*p*-value
Right insular lobe	–0.501	0.002	–0.385	0.015
Left anterior cingulate cortex	–0.493	0.019	–0.432	0.003
Right anterior cingulate cortex	–0.282	0.031	–0.462	0.006
Right parahippocampal gyrus	–0.416	0.015	–0.302	0.043
Right amygdala	–0.331	0.045	–0.323	0.043
Left middle temporal lobe	–0.290	0.032	–0.234	0.041

Abbreviations: YKL-40, chitinase-3-like protein 1; SAA, serum amyloid A.

When the body system is stimulated by various inflammatory factors, SAA level will rise dramatically and return to normal level upon the successful control of inflammation. Therefore, based on its association with the severity of inflammatory reaction, SAA level can be utilized to predict the course of SZ [28]. In the current study, SAA level in the observation group was higher than that in the control group, indicating an obvious inflammatory response in the SZ patients. Such response can be alleviated through SZ treatment for SZ, as demonstrated by Sobiś *et al.* [29] who found that the SAA levels notably declined after treatment. Our correlation analyses revealed that YKL-40 and SAA levels were negatively correlated with MCCB scores and with the GM volumes of right insular lobe, left and right anterior cingulate cortexes, right parahippocampal gyrus, right amygdala, and left middle temporal lobe. We also found that the biochemical parameters investigated in this study were correlated with select brain sMRI features in an exclusive manner: for instance, SAA level was negatively correlated with GM volumes of left and right anterior cingulate cortexes, while YKL-40 level was negatively correlated with GM volume of right insular lobe. Taken together, these findings portray the inverse correlations of key biochemical parameters (i.e., YKL-40 and SAA levels) with the cognitive functions and GM volumes among SZ patients.

Several limitations of this study should be acknowledged. The sample size of this retrospective cross-sectional study is relatively small. Firstly, the generalizability of the results to other populations may be limited. Secondly, the statistical power of the correlation analysis may also be compromised due to the restricted sample size. Future research should focus on conducting studies on larger sample size so as to validate the correlations of immunoinflammatory levels with the scores for cognitive functions and GM volumes.

Conclusion

Cognitive impairment in SZ is characterized by an abnormal increase in serum levels of immunoinflammatory factors and a reduction in GM volume. The current study offers a comprehensive perspective encompassing biochemical and imaging assessment as well as patients' clinical scores, laying a solid basis for exploring the pathogenesis of cognitive dysfunction in SZ.

Abbreviations

SZ, Schizophrenia; sMRI, structural magnetic resonance imaging; DSM-V, Diagnostic and Statistical Manual, Fifth Edition; MCCB, MATRICS consensus cognitive battery; ELISA, enzyme-linked immunosorbent assay; SAA, serum amyloid A; MCP-1, monocyte chemoattractant protein 1; YKL-40, chitinase-3-like protein 1; GM, gray matter; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α; IFN-7, interferon-7; PANSS, positive and negative syndrome scale; TR, time of repetition time; TE, time of echo; FOV, field of view.

Availability of Data and Materials

The data for this study can be obtained from the corresponding author upon request.

Author Contributions

XP and WS designed the research study. ZW performed the research. ZC and HJ provided help and advice on the ELISA experiments. XJ and HC analyzed the data. All authors contributed to the drafting or important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Huzhou Third Municipal Hospital, (approval number: 2020-032, Date:30/3/2020). All study participants or their legal guardian provided their consent to participate after being informed of the study's purpose.

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Conflict of Interest

The authors declare no conflict of interest.

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