

Correlation of Immune-inflammatory Response System (IRS) / Compensatory Immune-regulatory Reflex System (CIRS) with White Matter Integrity in First-Episode Patients with Schizophrenia

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Abstract

Several studies have reported compromised white matter integrity, and that some inflammatory mediators may underlie this functional dysconnectivity in brain of patients with schizophrenia. The immune-inflammatory response system and compensatory immune-regulatory reflex system (IRS/CIRS) are novel biomarkers for exploring the role of immune imbalance in the pathophysiological mechanism of schizophrenia. This study aimed to explore the little-known area regarding the composite score of peripheral cytokines, the IRS/CIRS, and its correlation with white matter integrity and the specific microstructures most affected in schizophrenia. First-episode patients with schizophrenia (FEPS, $n = 94$) and age- and sex-matched healthy controls (HCs, $n = 50$) were enrolled in this study. Plasma cytokine levels were measured using enzyme-linked immunosorbent assay (ELISA), and psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). The whole brain white matter integrity was measured by fractional anisotropy (FA) from diffusion tensor imaging (DTI) using a 3-T Prisma MRI scanner. The IRS/CIRS in FEPS was significantly higher than that in HCs ($p = 1.5 \times 10^{-5}$) and Cohen's d effect size was $d = 0.74$. FEPS had a significantly lower whole-brain white matter average FA ($p = 0.032$), which was negatively associated with IRS/CIRS ($p = 0.029$, adjusting for age, gender, years of education, BMI, and total intracranial volume), but not in the HCs ($p > 0.05$). Among the white matter microstructures, only the cortico-spinal tract was significantly correlated with IRS/CIRS in FEPS ($r = -0.543$, $p = 0.0009$). Therefore, elevated IRS/CIRS may affect the white matter in FEPS.

1. Introduction

Schizophrenia is a severe psychiatric disorder with unknown etiology[1], which may involve genetic, environmental, neurobiological (dopamine, serotonin, glutamine, and gamma aminobutyric acid hypotheses) factors, and brain structural abnormalities (such as gray matter loss and functional connectivity abnormalities in the white matter) [1–3]. Accumulating evidence has shown that these factors are associated with neuroinflammatory or peripheral cytokine alterations[4, 5]. Specifically, tumor necrosis factor α (TNF α) has been reported to influence the activation of microglia that is pivotal in mediating gray-matter loss in schizophrenia[1].

Cytokines, polypeptide signaling proteins, are secreted by immune cells to modulate the function of target cells or tissues. Through humoral and neural pathways, peripheral cytokines could cross over blood-brain barrier (BBB), activate microglia, and partake in the processes of synaptic plasticity and neurogenesis[6]. However, excessive peripheral cytokines or chronic microglial activation may harm neurons or oligodendrocyte precursor cells, resulting in the development of schizophrenia[6–8]. The relationship between single cytokines and symptoms of schizophrenia, such as the positive symptoms, negative symptoms, and cognition impairment, has been analyzed in numerous studies[9–12]. However, the complexity of schizophrenia may indicate the presence of complex cytokine networks. A meta-analysis[13] systematically compared the cytokine network alterations (interferon [IFN] γ , interleukin [IL] 1β , IL2, IL6, IL8, IL12, IL17, IL18, TNF α , IL1 receptor antagonist [IL1Ra], IL4, IL10, soluble IL2 receptor subunit alpha [sIL2Ra], sIL2R subunit beta [sIL2Rb], transforming growth factor- β 1 [TGF β 1], and TGF β 2)

in schizophrenia group and healthy controls and demonstrated the cytokine pattern of the acute phase of schizophrenia; this suggests the possibility of treating acute schizophrenia by decreasing proinflammatory cytokines and increasing anti-inflammatory cytokines[13]. In recent years, a few researchers have explored the imbalance between proinflammatory and anti-inflammatory cytokines and found that some severe mental diseases, including schizophrenia, bipolar disorder, and major depression disorder, have the characteristics of activation of the immune inflammatory response system (IRS) and mild immunosuppression. The latter is induced by IRS and plays a negative feedback role by elevating anti-inflammatory cytokines such as IL4, IL10 and TGF β [14, 15]. This novel concept was named compensatory immune-regulatory reflex system (CIRS)[16].

A meta-analysis demonstrated that IFN γ , IL6, TNF α , IL1 β , IL12 levels were elevated in first-episode psychosis[13] indicating the activation of IRS. Simultaneously, CIRS cytokine levels, such as IL10, sIL2R, TGF β , and IL1Ra, were also significantly increased in patients with first-episode psychosis, which attempts to counterbalance the IRS response. However, compared with healthy controls, IL4 levels were significantly decreased[17, 18], suggesting insufficient compensatory mechanisms. Recent studies have shown that reduced brain-derived neurotrophic factor (BDNF) levels are correlated with increased IRS and may be the result of IRS/CIRS responses in antipsychotic-naïve first-episode psychosis[17]. Moreover, after treatment with risperidone, the BDNF levels normalized[17] and Positive And Negative Syndrome Scale (PANSS) scores lowered[15] with decreasing IRS/CIRS composite score. Therefore, CIRS may be used as a medicinal target to facilitate the activation of drugs that inhibit IRS and promote injury repair.

Diffusion tensor imaging (DTI) is a noninvasive *in vivo* white matter assessment technique that uses a magnetic resonance imaging (MRI) scanner. Fractional anisotropy (FA) is one of the most commonly used indices for measuring the integrity of white matter and its microstructures. Reduced FA of the white matter has been reported in first-episode psychosis, which may indicate its role in the etiology of schizophrenia[6]. Several studies have reported that inflammatory mediators may underlie the functional dysconnectivity in brains of patients with schizophrenia. Elevated peripheral IFN γ and IL6 levels are associated with decreased FA of the corpus callosum in stable chronic schizophrenia[6, 19]. Plasma IL6 and CRP levels are inversely associated with FA of white matter microstructures, such as the forceps major, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus, in patients with schizophrenia[20]. It has been reported that the average FA of the white matter is decreased in first-episode schizophrenia and is negatively related to N-methyl-D-aspartate (NMDA) receptor antibody expressed in serum[21]. However, little is known about the composite score of peripheral cytokines, the IRS/CIRS, and its correlation with the integrity of white matter and specific microstructures that are majorly affected in first-episode patients with schizophrenia (FEPS). Therefore, our study aimed to test the following hypotheses: 1) plasma IRS/CIRS is significantly higher in FEPS than in healthy controls (HCs) and 2) elevated IRS/CIRS is inversely correlated with the average FA of white matter in FEPS; furthermore, the specific microstructures with correlation were explored.

2. Materials And Methods

2.1. Participants

In total, 94 FEPS were recruited from Beijing Huilongguan Hospital between 2017 and 2018. All patients met the following criteria: 1) diagnosis of schizophrenia in line with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); and 2) < 3 years of total illness duration and 2 weeks of antipsychotic medication. The medication status of the patients was as follows: drug naïve (6), risperidone (33), haloperidol combined with either risperidone or olanzapine (19), olanzapine (12), aripiprazole (9), paliperidone (5), iloperidone (3), haloperidol (2), olanzapine combined with aripiprazole (2), olanzapine combined with amisulpride (1), quetiapine (1), and ziprasidone (1). Every daily antipsychotic dose was converted to chlorpromazine equivalents. The exclusion criteria were as follows: 1) other psychiatric disorders diagnosed according to the DSM-IV Axis I; 2) severe physical illness; 3) recent infection or treatment with immunotherapy, physiotherapy, or psychotherapy; 4) mental retardation or serious nervous system disease; and 5) lactation or pregnancy. Methods of recruitment, inclusion criteria, and exclusion criteria of 50 healthy controls (HCs) were described in our previous article[22]; they were gender- and age-matched and without first-degree relatives diagnosed with psychiatric disorders according to DSM-IV Axis I. Demographic data of the participants are shown in Table 1.

Table 1
Demographics and clinical characteristics of FEPS and HCs

Characteristics	FEPS (n = 94) Mean (S.D.)	HCs (n = 50) Mean (S.D.)	Statistics (χ^2/t)	<i>p</i> value
Sex (M/F)	46/48	26/24	0.12	0.726
Age (years)	29.51 (9.52)	30.78 (8.11)	-0.80	0.425
Education (year)	12.52(3.51)	13.98(2.41)	-2.60*	0.010
BMI (kg/m ²)	21.49(3.28)	23.34(3.50)	-3.09*	0.002
Illness duration (month)	12.45(13.52)	NA	NA	NA
PANSS				
Total Score	77.77(14.08)	NA	NA	NA
P-Subscale	22.38(5.51)	NA	NA	NA
N-Subscale	17.38(6.37)	NA	NA	NA
G-Subscale	37.82(7.98)	NA	NA	NA
CPZ	322.17(224.01)	NA	NA	NA
FEPS: first-episode patients with schizophrenia; HCs: healthy controls; BMI: body mass index; PANSS, Positive and Negative Symptom Scale; CPZE: antipsychotic dosage by chlorpromazine equivalents; NA: not application.				
*Significant at $p < 0.05$				

2.2. Peripheral cytokine measurement

Peripheral plasma samples were collected between 8 am and 9 am in EDTA-K₂ disposable vacuum collection tubes (Beijing Dongfang Jianfeng Technology Co., Ltd. Beijing, China). The samples were centrifuged at 4°C with a speed of 3000 rpm for 10 minutes (Thermo Fisher Scientific, Waltham, Massachusetts, USA) and then aliquoted and stored at -80°C. The selection of cytokine markers was based on a meta-analysis of blood cytokine network alteration in schizophrenia[13]. Sandwich enzyme-linked immunosorbent assay (ELISA) kits (Beijing Rongxin Zhihe Biotechnology Co. Ltd., Beijing, China) and 800TMTS Absorbance Reader (BioTek Instruments, Vermont, USA) were used to determine the concentration of plasma cytokine markers (IFN γ , IL1 β , IL2, IL6, IL8, IL12, IL17, IL18, TNF α , IL1Ra, IL4, IL10, sIL2Ra, sIL2Rb, TGF β 1, and TGF β 2). The procedures were performed according to the protocol of the assay kit as described in our previous article[22]. The case-control status was blinded to the assay performers. The intra- and inter-assay coefficients of variation were 4.75% and 11.96%, respectively.

2.3. Measurement of clinical characteristics

FEPS and HCs were interviewed by one of the two independent psychiatrists. The psychotic symptom of patients was assessed using the PANSS; the intraclass correlation coefficient of the psychiatrists was ≥ 0.75 .

2.4. Imaging and data processing

The integrity of the whole-brain white matter was measured using FA from DTI. A 3-T Prisma MRI scanner (Siemens Medical Solutions, Berlin, Germany) with a 64-channel radio frequency head coil was used to acquire imaging data at the Beijing Huilongguan Hospital Imaging Research Center. The parameters of the structural T1-weighted and DTI imaging data collection have been previously reported[21, 23]. We used padding to retrain and minimize patient movement during the MRI scans. The ENIGMA-DTI analysis pipeline was used to process DTI data[24]. All data passed the ENIGMA-DTI quality assurance and control criteria. Based on the ENIGMA-DTI atlas, 21 major regional white matter FA were generated and averaged across hemispheres.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 20.0 (IBM Corp., New York, USA) and GraphPad Prism 8.0 (Graphpad Software, Inc., San Diego, CA) was used to prepare graphs. Between group comparison for categorical variables, such as sex, were performed using the chi-square test. All continuous data were tested for normality using the Shapiro-Wilk test. Continuous variables with normal distribution, such as age, education years, body mass index (BMI), and some cytokines, were compared between FEPS and HCs using an unpaired t-test, and the effect size was calculated using JASP 0.16.1 (JASP Team, Amsterdam, The Netherlands). Other non-normally distributed continuous variables were compared using the Mann-Whitney U-test. General linear regression analysis was used to evaluate relationships between biological indicators and FA of white matter, with age, sex, years of education, BMI, and total intracranial volume taken as covariates^{8,15}. The significance level was set at $\alpha < 0.05$ (for white matter microstructures regression $\alpha < 0.05/21$). Data are presented as means and standard deviations (mean \pm SD).

According to previous studies[14, 15], the z-unit weighted composite score for the cytokine profiles was calculated as follows:

IRS, computed as $z\text{-value of IFN}\gamma (z\text{IFN}\gamma) + z\text{IL}1\beta + z\text{IL}2 + z\text{IL}6 + z\text{IL}8 + z\text{IL}12 + z\text{IL}17 + z\text{IL}18 + z\text{TNF}\alpha$.

CIRS, computed as $z\text{IL}1\text{Ra} + z\text{IL}4 + z\text{IL}10 + z\text{sIL}2\text{Ra} + z\text{sIL}2\text{Rb} + z\text{TGF}\beta 1 + z\text{TGF}\beta 2$.

IRS/CIRS, computed as $z(\text{IRS}) - z(\text{CIRS})$.

3. Results

3.1 Demographic and clinical characteristics

Compared with the HCs, there was no significant difference in the age and sex ratio among the FEPS. FEPS acquired fewer years of education and a lower BMI than HCs ($p = 0.01$, $p = 0.002$, respectively). The mean illness duration of FEPS was 12.45 months. The total PANSS score, subscale scores, and antipsychotic dosage by chlorpromazine equivalents (CPZ) are shown in Table 1.

3.2 Peripheral cytokine levels and different types of cytokine profiles comparisons

The FEPS group had elevated IFN γ , IL1 β , IL6, IL18, TNF α , and sIL2Ra and reduced IL4 expression levels (all $p < 0.05$; Table 2). Subsequently, we calculated the z-score of all these cytokines and the composite scores comprising three cytokine profiles (IRS, CIRS, and IRS/CIRS) were computed as described in Materials and Methods. IRS and IRS/CIRS in FEPS were significantly higher than those in HCs ($p = 0.014$ and $p = 1.5 \times 10^{-5}$, respectively); however, CIRS was not ($p = 0.708$). We compared the effect sizes of the differences between the FEPS and HCs in cytokines included in this study and three cytokine profiles. The largest effect size was observed for IRS/CIRS ($d = 0.74$), which almost reached a large effect (Fig. 1).

Table 2
Cytokine levels and different types of cytokine profiles expressed in plasma of FEPS and HCs

	FEPS(n = 94)	Controls(n = 50)	Statistics	p value
	Mean (S.D.)	Mean (S.D.)	(F/t)	
IRS	3.72(8.95)	0.00(7.52)	2.50*	0.014
CIRS	0.38(5.74)	0.00(5.72)	0.38	0.708
IRS/CIRS	3.52(5.64)	0.00(3.67)	3.98***	1.5×10 ⁻⁵
IFN γ (pg/ml)	945.3(302.57)	822.11 (265.50)	2.42*	0.017
IL1 β (pg/ml)	116.43(40.47)	94.60 (31.86)	3.30***	0.001
IL2 (ng/ml)	10.24(5.04)	9.24 (2.28)	1.62	0.108
IL6 (pg/ml)	58.11(18.28)	48.54 (14.61)	3.19**	0.002
IL8 (pg/ml)	127.48(40.17)	117.01 (28.40)	1.81	0.073
IL12 (pg/ml)	42.75(13.38)	42.45 (13.55)	0.13	0.898
IL17 (pg/ml)	329.01(98.7)	330.36 (143.29)	-0.07	0.947
IL18 (pg/ml)	377.41(101.23)	339.50 (83.20)	2.27*	0.025
TNF α (pg/ml)	91.77(30.41)	77.35 (22.52)	2.94**	0.004
IL1Ra (pg/ml)	214.96(94.48)	202.36 (57.20)	0.99	0.323
IL4 (pg/ml)	44.55(15.04)	53.39 (15.62)	-3.31***	0.001
IL10 (pg/ml)	822.04(193.86)	901.47 (361.19)	-1.45	0.153
sIL2Ra (pg/ml)	417.22(117.61)	377.23 (104.89)	2.01*	0.047
sIL2Rb (pg/ml)	4 898.35(1 858.8)	4 721.53 (2 060.92)	0.52	0.602
TGF β 1 (ng/ml)	270.83(105.44)	245.61 (94.26)	1.41	0.160
TGF β 2 (pg/ml)	3 774.96(764.93)	3 623.23 (1 034.71)	0.99	0.322
IRS: immune inflammatory response system, computed as z value of interferon (IFN) γ (zIFN γ) + zIL(interleukin)1 β + zIL2 + z IL6 + z IL8 + zIL12 + zIL17 + zIL18 + zTNF(tumor necrosis factor) α .				
CIRS: compensatory immune regulatory system, computed as zIL1Ra (IL1 receptor antagonist) + zIL4 + zIL10 + zsIL2Ra (soluble IL2 receptor subunit alpha) + zsIL2Rb (sIL2R subunit beta) + zTGF β 1(transforming growth factor- β 1) + zTGF β 2.				
IRS/CIRS: computed as z(IRS) – z(CIRS).				
*Significant at $p < 0.05$ **significant at $p < 0.01$ ***significant at $p < 0.001$				

3.3 Relationship between IRS/CIRS and whole-brain white matter average FA

The number of participants who completed the measurement of peripheral cytokines and had valid imaging data was 39 FEPS and 41 HCs. Compared with HCs, FEPS had significantly lower whole-brain white matter average FA ($t=-2.18$, $p = 0.032$) (Fig. 2A). Only in FEPS, whole-brain average FA negatively correlated with IRS/CIRS ($p = 0.029$, after adjusting for age, sex, education, BMI, and total intracranial volume), but not in the HCs group ($p > 0.05$) (Fig. 2B). To identify whether IRS/CIRS was the most relevant to white matter average FA, we measured the effect size of the correlation between average FA and different kinds of cytokines or cytokine profiles in the FEPS group. The IRS/CIRS had the largest and only significant value ($r=-0.374$, $p = 0.029$) (Fig. 2C).

3.4 Specific white matter region and IRS/CIRS

To determine whether all white matter regions were negatively associated with IRS/CIRS, we compared 21 whole-brain white matter regions with IRS/CIRS. The correlation results showed a negative trend for almost every region. Eight tracts, the body of the corpus callosum, cingulum, corticospinal tract, external capsule, genu of the corpus callosum, superior fronto-occipital fasciculus, and superior longitudinal fasciculus, were nominally significantly associated with IRS/CIRS (all $p < 0.05$), but only the corticospinal tract (CST) was statistically significant after Bonferroni correction (Fig. 3A). The partial correlation scatter plots of IRS/CIRS and FA of the CST in FEPS ($r=-0.543$, $p = 0.0009$) and HCs ($r=-0.029$, $p = 0.867$) are displayed in Fig. 3B.

3.5 PANSS score, illness duration, and IRS/CIRS

Considering age, sex, education, and BMI as covariates, there was no correlation between IRS/CIRS and PANSS total scores or subscale scores and illness duration (all $p > 0.05$).

4. Discussion

This study identified a novel cytokine profile, IRS/CIRS, to be significantly higher in the FEPS group and its negative association with whole-brain white matter average FA. Among the white matter microstructures, only CST showed significant correlation with IRS/CIRS in FEPS. These findings suggest that IRS/CIRS could be a novel biomarker for exploring the role of immune imbalance in the pathophysiological mechanism of schizophrenia.

Our first hypothesis that plasma IRS/CIRS is significantly higher in FEPS than in HCs was strongly supported by previous studies[5, 6, 13, 15, 17]. Maes et al. had shown the expression level of IRS/CIRS to be significantly elevated in antipsychotic naïve first-episode psychosis, with activation of the IRS and CIRS response[15, 17]. Compared with CIRS, the IRS response was relatively greater for IL6, IFN γ , and TNF α levels in the serum samples. Our findings were in line with those of Maes et al.; however, we incorporated another proinflammatory cytokine, IL1 β , in the IRS profile. The present results were

consistent with a previous report that IL1 β is elevated in first-episode psychosis[25]. This cytokine decreased following treatment and was exacerbated with acute relapse of chronic schizophrenia[13], indicating that IL1 β is closely correlated with changes occurring in schizophrenia. It was reported that IL1 β could stimulate the production of kynurenic acid which was associated with schizophrenia symptoms and cognitive dysfunction[25]. Additionally, IL1 β can make for aberrant release and accumulation of glutamate, which reportedly results in the death of neurons and oligodendrocytes[26]. Therefore, we believe that it is necessary to include IL1 β in IRS profile along with IL6, IFN γ , and TNF α .

Table 2 demonstrates that contrary to the significantly high IRS in FEPS, CIRS showed only a slight upward trend. Therefore, it is obvious that compensatory mechanisms were insufficient. IL4 was decreased in FEPS, consistent with the meta-analysis results[13]. IL4 may act as an immune regulator and is a major player in CIRS[18]. IL4 activates M2 macrophages to promote the production of IL10 and TGF β and suppresses the production of IL1 β , IL6, and TNF α [14]. Additionally, the release of IL1Ra is enhanced by IL10. These cytokines are all present in the CIRS profile and attenuate the proinflammatory function[14]. For example, proinflammatory cytokines could reduce the production of BDNF mRNA in astrocytes and IL4 could reverse this effect and directly induce astrocytes to produce BDNF mRNA[27]. The decreasing expression of IL4 may result in severe cognitive impairment[27].

Most cytokines and the three cytokine profiles analyzed were highly associated with each other ($p < 0.01$; Supplementary Fig. S1). These results were consistent with those of Chutima et al.[18] and indicate generalized immune activation. It is reasonable to believe that computing profiles of cytokines would perform better than single inflammatory markers to explore the effects of immune abnormalities on schizophrenia. The present results of Cohen's d also showed that among all the included cytokines and the three types of cytokine profiles, the largest effect size of the difference between the FEPS and HCs groups was for IRS/CIRS ($d = 0.74$).

Additionally, we had hypothesized that a higher IRS/CIRS was negatively associated with whole-brain white matter average FA in FEPS, unlike HCs. The results of our study showed that the integrity of the white matter measured by FA was significantly lower in the FEPS compared with the HCs. In schizophrenia, cognitive function was impaired in all domains measured by the MATRICS Consensus Cognitive Battery[22], which may indicate widespread reduction in the integrity of whole brain white matter. This consistent with other research results that the combined function of pro- and anti-inflammatory factors could result in the decreased integrity of the white matter fiber tracts[28], attributable to pathological changes in myelin and neurofilament[20]. Through regulating oligodendrocyte, the most important myelinating cell[29], cytokines play a vital role in moderating inflammation that alters white matter development[30]. The specific function of cytokines in oligodendrocytes and neurons could explain this.

TNF α targets the TNF receptor expressed by oligodendrocyte progenitors and exerts an inhibitory role in the survival and differentiation of this cell type[28]. Furthermore, TNF α can hinder the development of oligodendrocytes and the expression of myelin basic protein mRNA[31], which can maintain the stability

of myelin structure and function. IL-1 β impedes oligodendrocyte progenitor cell (OPC) recruitment by targeting IL-1R1 to inhibit white matter restoration and functional renewal[32]. Elevated IL-6 levels induce demyelination and are correlated with neurofilament damage[20]. IL4 plays an indispensable role in facilitating white matter integrity and repairing injured white matter. It acts directly on peroxisome proliferator-activated receptor gamma to promote OPC into mature oligodendrocytes that produce myelin[33]. Although previous studies found that elevated peripheral IL10 was associated with reduced white matter FA[34], we believe that it is the compensatory mechanism of CIRS in response to IRS, which is the initial factor related to the decrease in FA. Inflammation suppression, IL10, and TGF- β have been reported to promote re-myelination and neuron/axonal growth[34] by mediating the expression of growth arrest-specific gene 6 as a therapeutic intervention for demyelination and glial cell development[35].

The IRS profile cytokines, IL1 β , IL6, IFN γ , and TNF α , transferred from the periphery or secreted from chronically activated microglia, could exert deleterious effects on oligodendrocytes and neurons by stimulating kinases and caspase cascades, leading to cell death[20, 36]. CIRS profiles, including IL4, IL10, and TGF- β , could promote healing and limit neuronal injury[37]. The IRS/CIRS ratio reflects the general effects of cytokines on oligodendrocytes and neurons.

CST was significantly associated with IRS/CIRS, suggesting that some white matter tracts may be more assailable to proinflammatory cytokines in FEPS[20]. A Chinese study demonstrated the association of decreased FA in the CST with voluntary motor function in patients with severe negative symptoms[38]. Moreover, low FA in the CST exists in patients with treatment-resistant schizophrenia and explains their poor performance in complex motor tasks[39]. Combined with the findings of our study, it may be suggested the effects of IRS/CIRS on motor deficits may have already occurred during schizophrenia onset.

Although we did not find the correlation between PANSS scores and IRS/CIRS in FEPS, it is promising to find an association in chronic schizophrenia, as IRS/CIRS imbalance also exists in chronic psychosis[18] and illness duration may promote the influence of cytokines on white matter integrity[40]. In chronic disease, the corpus callosum is vulnerable to inflammatory markers[6, 21]. We intend to explore the relationship of IRS/CIRS and white matter in chronic disease and its difference with FEPS in our future research.

Our study has some limitations. First, this was a cross-sectional study, and the effects of IRS/CIRS on white matter integrity were not examined. Further studies in patients with chronic schizophrenia are needed. Second, the number of participants who completed all experiments, especially for acquiring valid imaging data, was small. This may have resulted in some promising associations being missed, such as genu of corpus callosum with IRS/CIRS. Third, the high sensitivity and specificity of the multi-cytokine detection ELISA kit, which aided in acquiring raw expression data in a short time, could have resulted in decreased variation coefficients.

In conclusion, our findings suggest that IRS/CIRS was significantly higher in FEPS and was negatively correlated with whole-brain white matter average FA. This indicates that IRS/CIRS is a novel biomarker for

exploring the role of immune imbalance in the pathophysiological mechanism of schizophrenia.

Declarations

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Author Contributions Li Tian, Yunlong Tan, and L. Elliot Hong designed the project and obtained the funding for this study. Mengzhuang Gou, Wei Li, Jinghui Tong, Yanfang Zhou, Ting Xie, Ting Yu, Wei Feng, Yanli Li, Song Chen, Shujuan Pan, Ping Zhang, and Junchao Huang were responsible for recruiting patients, performing clinical ratings, neuroimaging, and collecting samples. Mengzhuang Gou analyzed all the data and wrote the paper. Yunlong Tan and Li Tian are responsible for the integrity of data and the accuracy of data analysis. Baopeng Tian, Zhiren Wang, Shuping Tan, Xingguang Luo, Chiang-Shan R. Li, and L. Elliot Hong were invited in evolving the ideas and editing the manuscript. All authors have contributed to and have approved the final manuscript.

Data Availability The datasets generated during the current study will be made available from the corresponding author on reasonable request once the dataset has been fully exploited by the authors.

Ethics Approval and Consent to Participate All study-related procedures were performed only after the participants enrolled in this study provided written informed consent. The study protocol was approved by the Ethics Committee of Beijing Huilongguan Hospital.

Consent for publication Not applicable.

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 41. **Statements and Declarations**

Figures

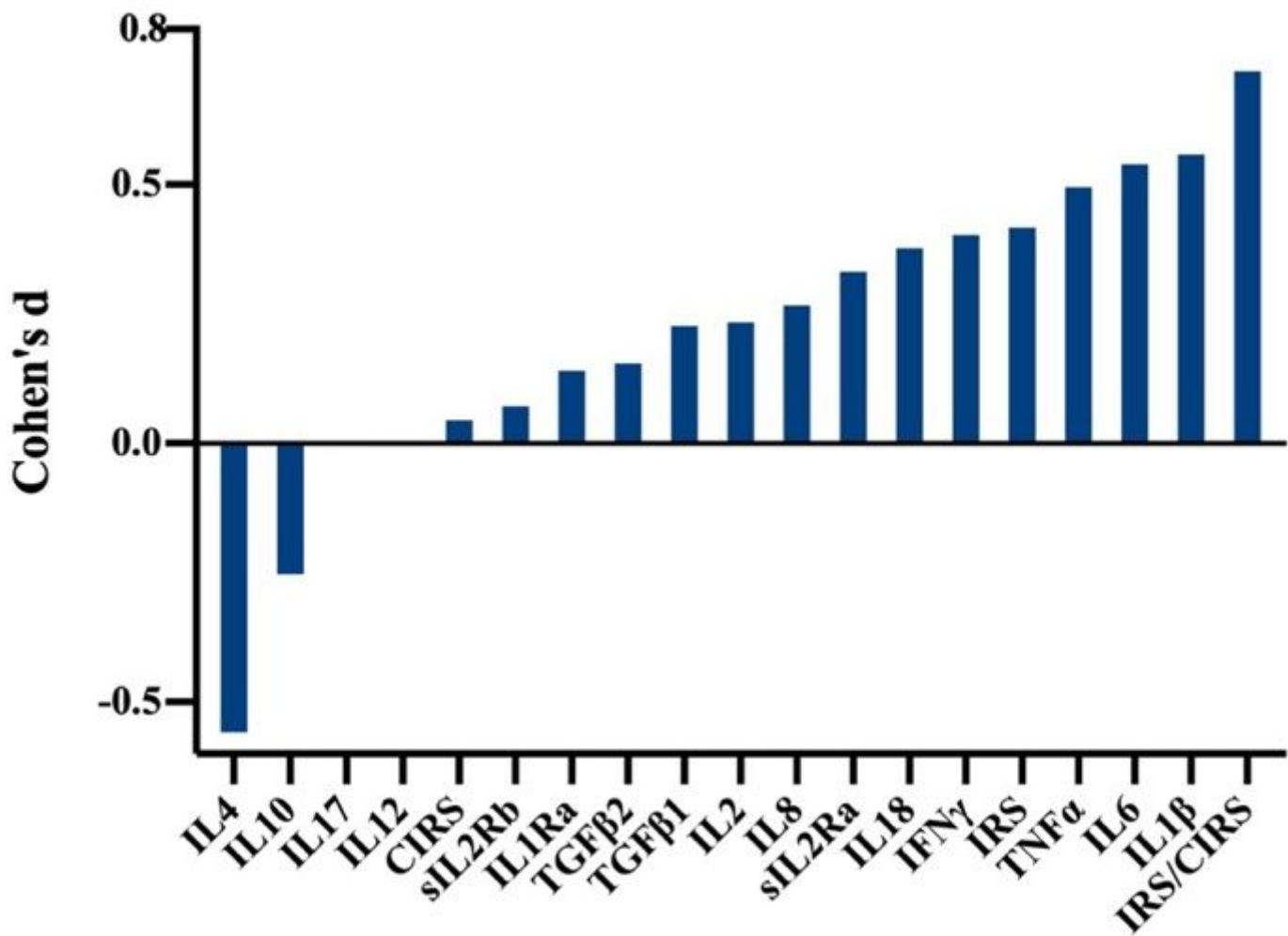


Figure 1

Effect sizes of difference between FEPS group and HCs group in kinds of cytokine and three types of cytokine profiles. The largest effect size was in IRS/CIRS ($d=0.74$).

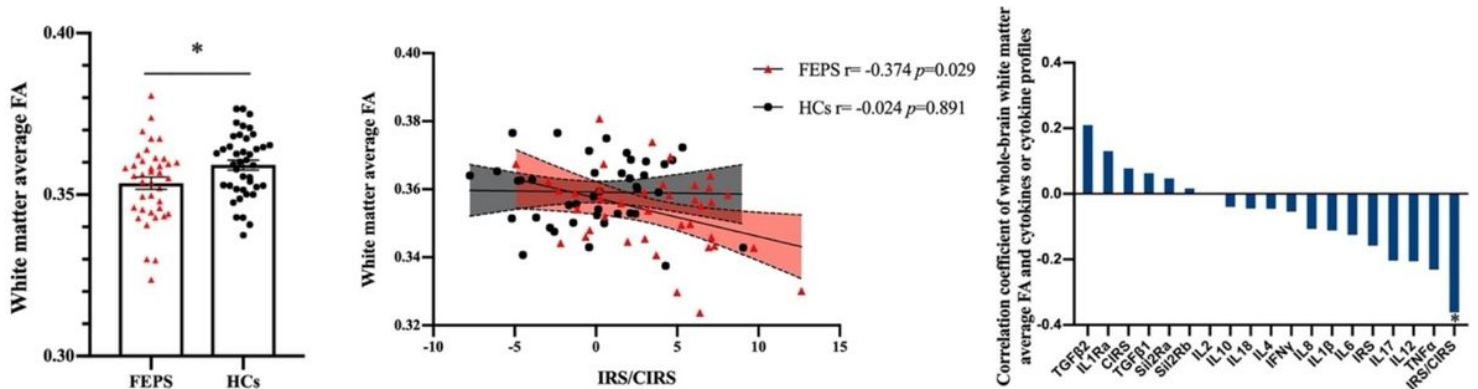


Figure 2

Relationship between IRS/CIRS and whole-brain white matter average FA (fractional anisotropy) in FEPS and HCs. (A) The whole-brain white matter average FA of FEPS group was significantly lower than that of HCs group ($t=-2.18, p=0.032$) (B) The average FA of whole-brain white matter was negatively associated with IRS/CIRS only in FEPS ($p=0.029$, adjusting for age, gender, education, BMI and total intracranial volume), but not in HCs group ($p>0.05$). (C) Effect sizes of correlation between whole-brain white matter average FA and different kinds of cytokines or cytokine profiles in FEPS group. The effect size of relationship between whole-brain white matter average FA and IRS/CIRS was the largest and only significant one ($r=-0.374, p=0.029$).

*Significant at $p<0.05$

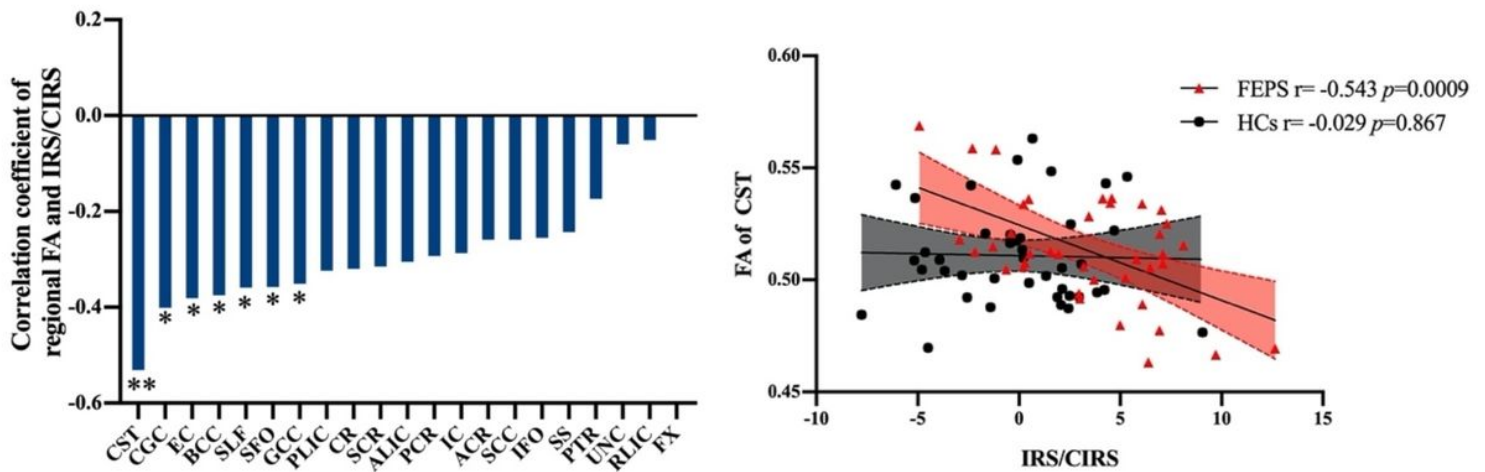


Figure 3

Relationship between tract-specific FA and IRS/CIRS in FEPS group (A). FA of CST (cortico-spinal tract) and IRS/CIRS was significantly negatively correlated in FEPS ($p=0.0009$, significant after Bonferroni correction), but not in HCs ($p>0.05$) (B). Abbreviations: ACR, anterior corona radiata; ALIC, anterior limb of internal capsule; BCC, body of corpus callosum; CGC, cingulum; CR, corona radiata; CST, cortico-spinal tract; EC, external capsule; FX, fornix; GCC, genu of corpus callosum; IC, internal capsule; IFO, inferior frontal occipital fasciculus; PCR, posterior corona radiata; PLIC, posterior limb of internal capsule; PTR, posterior thalamic radiation; RLIC, retrolenticular limb of the internal capsule; SCC, splenium of corpus callosum; SCR, superior corona radiata; SFO, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; UNC, uncinate fasciculus; SS, sagittal striatum.

*Significant at $p<0.05$ **significant after Bonferroni correction.

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