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Unveiling the neurobiological underpinnings of cognitive dysfunction in patients with schizophrenia

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Unveiling the neurobiological underpinnings of cognitive dysfunction in patients with schizophrenia

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Table of contents

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Editorial: Unveiling the neurobiological underpinnings of cognitive dysfunction in patients with schizophrenia

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Editorial on the Research Topic
Unveiling the neurobiological underpinnings of cognitive dysfunction in patients with schizophrenia

Schizophrenia is a serious mental disorder that affects up to 1% of the population worldwide. Most patients with the illness suffer from disturbances of key aspects of cognitive function, e.g., neurocognition and social cognition, which worsen real-world functional outcomes. For example, neurocognitive impairment affects up to 75% of patients across multiple domains including processing speed, working memory, verbal memory, attention, executive functioning, while emotional processing, theory of mind, attributional bias, and social perception represent key domains of social cognition which are typically dysfunctional in schizophrenia. Several features of cognitive impairment are commonly found across schizophrenia and mood disorders, as well as their prodromal stages, indicating its transdiagnostic importance. Specifically, this *Topic* presents the cutting-edge knowledge on advanced assessments, neurobiological underpinnings, and interventional endeavors targeting cognitive impairment of schizophrenia.

Disturbances of neurocognition and social cognition of schizophrenia have been shown to be associated with both genetic and environmental factors. Among them, the genetic contribution is supported by Bae et al. who report poor performance on a test of facial emotion-recognition both in schizophrenia patients and their first-degree relatives. In this line, Deng et al. found an association between increased body mass index and neurocognition in first-episode drug-naive patients, also suggesting genetic susceptibility of cognitive impairment. On the other hand, the influence of socio-psychological (environmental) factors was reported by Peng et al. who observed an additive adverse effect of childhood trauma on cognition in patients with schizophrenia. Importantly, the association between cognitive symptoms and social function in individuals with at-risk mental states, as reported by Montemagni et al., underscore that cognitive impairment leads to poor functional outcome across stages of schizophrenia.

Neurobiological mechanisms of cognitive impairment of schizophrenia have been a Research Topic of intensive investigations based on data from a variety of research modalities. For example, Liang et al. employed resting-state functional magnetic resonance imaging and found increased levels of low-frequency fluctuation, an indicator of spontaneous and intrinsic neuronal activity, in childhood and adolescence-onset schizophrenia. Specifically, a relationship was noted between this imaging parameter and the performance on the tests of some cognitive domains. Another line of neurophysiological markers of cognitive function comes from magneto-electrical paradigms, e.g., electroencephalography and magnetoencephalography (MEG). By using MEG, Okazaki et al. reported altered auditory change-detection responses in patients with schizophrenia as a neural substrate for misattribution of inner experience to external agents. Based on the membrane phospholipid hypothesis, Higuchi et al. found associations between cognitive function and altered unsaturated fatty acid composition in the membrane of erythrocytes in antipsychotic-free schizophrenia patients.

Substantial efforts have been directed to the development of effective treatments of cognitive impairment of schizophrenia, with pharmacotherapy, non-invasive brain stimulation (NIBS) and cognitive rehabilitation as representative approaches. Accordingly, Li et al. presented data indicating domain-specific gender differences in cognitive improvements in patients with first-episode schizophrenia treated with antipsychotic drugs for two months. As a safe and feasible NIBS method, transcranial direct current stimulation was used by Yamada et al. who argued the advantage of stimulation of prefrontal cortical areas for enhancing neurocognition and higher levels of functional outcome, while disturbances of social cognition may be alleviated specifically when temporal brain regions are stimulated. A protocol of a randomized controlled study was introduced by Kubota et al., which aims to determine if combined treatment with cognitive remediation and a particular antipsychotic drug would improve neurocognitive function more effectively compared to the combination with another antipsychotic drug.

Overall, the papers contributed to this Research Topic provide a broad overview of the nature and underlying mechanisms of cognitive deficits of schizophrenia, as well as promising interventions to attain better outcomes for patients with this debilitating disorder.

Author contributions

TS: Writing – original draft, Writing – review & editing. LP: Writing – review & editing. SB: Writing – review & editing.

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Electrode montage for transcranial direct current stimulation governs its effect on symptoms and functionality in schizophrenia

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Backgrounds: Patients with schizophrenia suffer from cognitive impairment that worsens real-world functional outcomes. We previously reported that multi-session transcranial direct current stimulation (tDCS) delivered to the left dorsolateral prefrontal cortex (DLPFC) improved daily living skills, while stimulation on the left superior temporal sulcus (STS) enhanced performance on a test of social cognition in these patients. To examine the region-dependent influence of tDCS on daily-living skills, neurocognition, and psychotic symptoms, this study compared effects of anodal stimulation targeting either of these two brain areas in patients with schizophrenia.

Methods: Data were collected from open-label, single-arm trials with anodal electrodes placed over the left DLPFC (N = 28) or STS (N = 15). Daily-living skills, neurocognition, and psychotic symptoms were measured with the UCSD performance-based skills assessment-brief (UPSA-B), Brief Assessment of Cognition in Schizophrenia (BACS), and Positive and Negative Syndrome Scale (PANSS), respectively. After baseline evaluation, tDCS (2 mA × 20 min) were delivered two times per day for 5 consecutive days. One month after the final stimulation, clinical assessments were repeated.

Results: Performance on the UPSA-B was significantly improved in patients who received anodal tDCS at the left DLPFC ($d = 0.70$, $p < 0.001$), while this effect was absent in patients with anodal electrodes placed on the left STS ($d = 0.02$, $p = 0.939$). Significant improvement was also observed for scores on the BACS with anodal tDCS delivered to the DLPFC ($d = 0.49$, $p < 0.001$); however, such neurocognitive enhancement was absent when the STS was stimulated ($d = 0.05$, $p = 0.646$). Both methods of anodal stimulation showed a significant improvement of General Psychopathology scores on the PANSS (DLPFC, $d = 0.50$, $p = 0.027$; STS, $d = 0.44$, $p = 0.001$).

Conclusion: These results indicate the importance of selecting brain regions as a target for tDCS according to clinical features of individual patients. Anodal stimulation of the left DLPFC may be advantageous in improving higher level functional outcomes in patients with schizophrenia.

Trial registration: These studies were registered within the University hospital Medical Information Network Clinical Trials Registry [(24), UMIN000015953], and the Japan Registry of Clinical Trials [(28), jRCTs032180026].

KEYWORDS

neuromodulation, transcranial direct current stimulation (tDCS), schizophrenia, functional capacity, cognition

1. Introduction

Schizophrenia is one of the most prominent causes of disease burdens worldwide (1), with a prevalence of about 0.75% (2). The main symptoms of the disease include positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., apathy, anhedonia, and social withdrawal), and disturbances of several types of cognitive function (e.g., neurocognition and social cognition). Positive symptoms are well treated with antipsychotic drugs, whereas negative symptoms and cognitive dysfunctions are not adequately managed by pharmacotherapy (3). In particular, cognitive impairment leads to a decline in real-world functional outcome, and more than 70% of chronic patients are not employed (4, 5).

Impairments of neurocognition and social cognition have been implicated in social functioning in patients with schizophrenia (6, 7). Neurocognitive domains, such as attention/processing speed, working memory, learning memory, and reasoning and problem solving, are most severely affected (7). On the other hand, social cognition domains affected in schizophrenia includes theory of mind (ToM), emotion recognition, social perception, and attributional bias (8, 9). Several interventional methods, e.g., psychosocial and pharmacological approaches, have been tested to enhance neurocognition and social cognition in patients with schizophrenia (10–16).

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that modulates neural activity by applying electric currents, usually less than 2 mA, between an anode and cathode electrode for a short period of time (usually less than 30 min per session) (17). Previous meta-analyses reported that tDCS delivered to the dorsolateral prefrontal cortex (DLPFC) alleviates hallucinations (positive symptoms; Hedges' g = 0.86) and negative symptoms (0.41), and improves neurocognitive function, particularly working memory (0.41), in patients with schizophrenia (18–23). Recently, tDCS targeting the DLPFC has also been reported to improve daily-living skills (functional capacity) (24), insight into the illness (25), and metacognition (26). Regarding social cognition, data from our systematic review indicate tDCS on the prefrontal cortex enhances emotion recognition (27), while stimulation on the left superior temporal sulcus (STS) improved scores on the ToM in these patients (28–30). Therefore, the electrode montage of tDCS, especially the anodal stimulation site, may determine its effect on symptoms and functionality in patients with psychotic conditions, although controversy exists (31–33). Taken together, further considerations are needed to understand which brain regions should be stimulated to improve specific symptoms of schizophrenia (34).

In the present study, we compared effects of anodal tDCS targeting the left DLPFC or left STS on symptoms and functional outcomes in patients with schizophrenia. For this purpose, data from our previous studies targeting either of the two brain regions (24, 28), with the same placement of *cathodal* electrodes and stimulus frequency and intensity, were analyzed. The previous study targeting the left DLPFC (24) measured three indicators, i.e., psychotic symptoms, neurocognition, and daily-living skills (functional capacity), except social cognition, whereas another previous study targeting the left STS, independently conducted (28), measured all four indicators including social cognition. The latter study did not report the results of daily-living skills (28). Therefore, the present study provides new information, i.e., the effect of anodal tDCS targeting the left STS on daily-living skills, as accumulated evidence suggests the performance on the functional capacity provides important indicator of social functioning (35).

2. Materials and methods

2.1. Participants and procedure

Data were collected from previous studies (Narita et al., UMIN000015953; Yamada et al., jRCTs032180026) (24, 28). The protocols of these studies and demographic data of participants have been reported (24, 28, 29). Both studies were open-label, single-arm trials, conducted in a single-center at the National Center of Neurology and Psychiatry, Japan. Twenty-eight patients with schizophrenia (22 inpatients and 6 outpatients) received anodal stimulation delivered to the left DLPFC (24), while 15 outpatients received the stimulation to the left STS (28). The former study about the anodal stimulation of the DLPFC demonstrated improvements in daily-living skills. Therefore, the latter study targeting the STS implemented a sample size calculation which was based on the results of daily-living skills. Specifically, the minimum number of samples to achieve a value of p of 0.05 and 80% power was found 13, assuming a standard deviation of 15 and a mean difference of 11. Taking drop-outs into account, the sample size was set at 15 (28). Both studies were independent and data were derived from non-controlled trials. Inclusion and exclusion criteria are provided in Supplementary Tables 1, 2. The details of data collection have been described (29).

2.2. Intervention

Direct current was transmitted through 35 cm^2 saline-soaked sponge electrodes, and the intervention was performed by a 1 × 1 transcranial direct current low-intensity stimulator (Model 1,300 A; Soterix Medical Inc., New York, NY, United States). For tDCS montage, the anode was placed on F3 (the international 10–20 electroencephalography system) to deliver currents to the left DLPFC

or T3 to the left STS, while the cathode was placed on FP2 regions in both cases. We applied 10 sessions direct current of 2 mA for 20 min on 5 consecutive days (twice per day, with an interval of 30 min; Supplementary Table 3).

2.3. Outcomes

After being briefed on the purpose of the study and agreeing to participate, patients received psychological and clinical assessments, including the screening evaluation. Data were collected at baseline and 1 month after the final stimulus (Supplementary Table 3).

2.3.1. Daily-living skills (functional capacity)

Daily-living skills were assessed by the UCSD Performance-Based Skills Assessment-Brief (UPSA-B), which consists of financial and communication skills (36). Subscale scores of the two domains of the UPSA-B (i.e., finances and communication) were converted into the standard score ranging from 0 to 50 to make the maximum of the total score of 100. Higher scores indicate greater functional capacity.

2.3.2. Neurocognition

The Brief Assessment of Cognition in Schizophrenia (BACS) Japanese version was used to evaluate verbal memory (verbal memory list learning), working memory (digit sequencing task), speed of information processing (symbol coding), motor speed (token motor task), executive functions (tower of London) and verbal fluency (37). To provide a standard metric for combining test scores into domains and comparing performance over time, BACS scores were converted to z-scores to represent performance relative to that of healthy people (38).

2.3.3. Psychotic symptoms

The Positive and Negative Syndrome Scale (PANSS) was used to assess psychotic symptoms (39). The PANSS was a structured interview, consisting of positive, negative, and general psychopathology subscales (with scores ranging from 7 to 49, from 7 to 49, and from 16 to 112, respectively). The higher scores represent more severe psychotic symptoms.

2.4. Statistical analysis

Student's *t*-test was used for the clinical outcomes to evaluate the efficacy, while effect sizes were calculated as standardized mean difference (Cohen's d). Categorical variables were compared by the Chi-Squared test. Statistical analysis was conducted using IBM SPSS Statistics version 26.0.

3. Results

3.1. Participants

The demographic variables are shown in Table 1. There were no differences between participants in the two studies in potential parameters affecting cognitive/functional outcomes, i.e., age, duration of present illness, duration of education, estimated premorbid Intelligence Quotient (IQ), dose of antipsychotics, and *severity of psychotic symptoms*. No medication was changed, nor was cognitive rehabilitation performed during the study period.

TABLE 1 Clinical characteristics of patients [Narita et al. (24), Yamada et al. (28)].

Anodal stimulation sites	Left DLPFC	Left STS	
Variables	Mean (SD) or *n*	Mean (SD) or *n*	*p* Value
Inpatient/outpatient	22/6	0/15	**<0.001**
Male/female	16/12	7/8	0.510
Age (year)	40.9 (9.8)	40.1 (11.8)	0.813
Duration of present illness (year)	17.3 (9.9)	12.6 (10.2)	0.149
Duration of education (year)	13.8 (1.7)	13.6 (1.8)	0.720
Premorbid IQ	99.6 (12.0)	102.1 (11.0)	0.506
Chlorpromazine equivalent dose of antipsychotics (mg/day)	889.0 (587.1)	727.9 (323.1)	0.331
PANSS (positive syndrome)	15.7 (5.7)	16.2 (6.0)	0.792
PANSS (negative syndrome)	14.9 (8.0)	19.3 (6.4)	0.057
PANSS (general psychopathology)	32 (8.1)	37.5 (9.2)	0.062

DLPFC, dorsolateral prefrontal cortex; STS, superior temporal sulcus; SD, standard deviation; IQ, Intelligence Quotient; PANSS, Positive and Negative Syndrome Scale. Values reaching statistical significance are bolded.

3.2. Daily-living skills (functional capacity)

Performance on the UPSA-B was significantly improved in patients who received anodal tDCS at the left DLPFC ($d = 0.70$, $p < 0.001$), while this advantage was absent with anodal electrodes placed on the STS ($d = 0.02$, $p = 0.939$; Table 2). Similarly, anodal stimulation on the DLPFC significantly improved scores on the tests of financial skills ($d = 0.61$, $p = 0.002$) or communication skills ($d = 0.59$, $p = 0.001$) from the UPSA-B, while such changes were absent in patients with anodal electrodes for the STS (financial skills, $d = 0.14$, $p = 0.635$; communication skills, $d = 0.07$, $p = 0.760$; Table 2).

3.3. Neurocognition

Significant improvement was observed on the composite score of the BACS in patients who received anodal tDCS delivered to the left DLPFC ($d = 0.49$, $p < 0.001$), while such neurocognitive enhancement was absent with anodal stimulation targeting the left STS ($d = 0.05$, $p = 0.646$; Table 2). Similarly, anodal stimulation delivered to the DLPFC was associated with improvements in verbal memory ($d = 0.55$, $p < 0.001$), motor speed ($d = 0.44$, $p = 0.020$), and verbal

TABLE 2 Outcome measures at baseline and 1 month after the transcranial direct current stimulation (tDCS).

Anodal stimulation sites	Left DLPFC					Left STS				
	Baseline, mean (SD)	Follow-up, mean (SD)	*t* Value (Degree of freedom)	*p* Value	Effect size	Baseline, mean (SD)	Follow-up, mean (SD)	*t* Value (Degree of freedom)	*p* Value	Effect size
UPSA-B										
Total	68.4 (14.8)	79.0 (15.5)	$t = 5.89$ (27)	**<0.001**	**d = 0.70**	72.7 (10.3)	72.5 (16.0)	$t = 0.07$ (14)	0.939	$d = 0.02$
Financial skills	41.4 (8.1)	45.8 (6.2)	$t = 3.35$ (27)	**0.002**	**d = 0.61**	45.3 (4.4)	44.4 (7.3)	$t = 0.48$ (14)	0.635	$d = 0.14$
Communication skills	27.1 (9.6)	33.2 (11.1)	$t = 3.57$ (27)	**0.001**	**d = 0.59**	27.4 (9.2)	28.0 (10.3)	$t = -0.31$ (14)	0.760	$d = 0.07$
BACS (z-score)										
Composite score	−1.86 (0.92)	−1.40 (0.93)	$t = 4.23$ (27)	**<0.001**	**d = 0.49**	−1.85 (1.36)	−1.79 (1.29)	$t = -0.46$ (14)	0.646	$d = 0.05$
Verbal memory	−1.67 (1.06)	−1.06 (1.14)	$t = 4.53$ (27)	**<0.001**	**d = 0.55**	−1.00 (1.17)	−0.99 (1.15)	$t = -0.09$ (14)	0.929	$d = 0.01$
Working memory	−1.16 (1.38)	−0.95 (1.37)	$t = 1.52$ (27)	0.14	$d = 0.15$	−1.02 (1.18)	−0.90 (1.06)	$t = -0.06$ (14)	0.513	$d = 0.11$
Motor speed	−3.27 (1.25)	−2.73 (1.23)	$t = 2.47$ (27)	**0.020**	**d = 0.44**	−1.80 (0.93)	−1.81 (1.17)	$t = 0.04$ (14)	0.965	$d = 0.01$
Verbal fluency	−1.19 (1.05)	−0.84 (0.89)	$t = 2.10$ (27)	**0.046**	**d = 0.36**	−0.85 (0.97)	−0.66 (0.81)	$t = -1.48$ (14)	0.159	$d = 0.21$
Attention and speed	−2.25 (1.22)	−2.21 (1.44)	$t = 0.25$ (27)	0.80	$d = 0.03$	−1.35 (0.88)	−1.10 (0.95)	$t = -2.10$ (14)	0.054	$d = 0.27$
Executive functions	−1.76 (2.03)	−1.12 (2.16)	$t = 1.88$ (27)	0.071	$d = 0.31$	−0.18 (1.41)	−0.56 (1.20)	$t = 1.54$ (14)	0.143	$d = 0.29$
PANSS										
Positive syndrome	15.7 (5.7)	13.1 (4.8)	$t = 2.31$ (27)	**0.029**	**d = 0.48**	16.2 (6.0)	15.6 (6.3)	$t = 0.78$ (14)	0.444	$d = 0.10$
Negative syndrome	14.9 (8.0)	13.6 (6.7)	$t = 1.24$ (27)	0.23	$d = 0.17$	19.3 (6.4)	17.9 (6.2)	$t = 1.56$ (14)	0.139	$d = 0.22$
General psychopathology	32 (8.1)	28.3 (7.1)	$t = 2.35$ (27)	**0.027**	**d = 0.50**	37.5 (9.2)	33.4 (9.2)	$t = 4.07$ (14)	**0.001**	**d = 0.44**

tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; STS, superior temporal sulcus; SD, standard deviation; UPSA-B, the UCSD performance-based skills assessment-brief; BACS, Brief Assessment of Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale. Values reaching statistical significance are bolded.

fluency ($d = 0.36$, $p = 0.046$), while these benefits were absent when anodal stimulation was targeted to the STS (verbal memory, $d = 0.01$, $p = 0.929$; motor speed, $d = 0.01$, $p = 0.965$; verbal fluency, $d = 0.21$, $p = 0.159$; Table 2).

3.4. Psychotic symptoms

Anodal tDCS to either the left DLPFC ($d = 0.50$, $p = 0.027$) or STS ($d = 0.44$, $p = 0.001$) showed a significant improvement of general psychopathology scores on the PANSS. On the other hand, anodal stimulation delivered to the DLPFC ($d = 0.48$, $p = 0.029$), but not the STS ($d = 0.10$, $p = 0.444$) was associated with amelioration of positive symptoms. For negative symptoms, neither stimulation method was effective (DLPFC, $d = 0.17$, $p = 0.230$; STS, $d = 0.22$, $p = 0.139$).

4. Discussion

The results of the present study indicate that the placement of electrodes influences the ability of tDCS to ameliorate symptoms and improve functional outcome in patients with schizophrenia. This concept is supported by observations that anodal stimulation delivered to the left DLPFC, but not left STS was efficacious in enhancing daily-living skills and alleviating positive symptoms, while stimulation of the latter brain region was associated with improvement of social cognition.

Several neural substrates may explain the ability of anodal tDCS to enhance cognitive function and related functional capacity (daily-living skills). Altered structures in the brain of patients with schizophrenia has been reported, e.g., reduced grey matter in the frontotemporal lobe, thalamus, hippocampus, amygdala, insular cortex, and anterior cingulate cortex (40). Specifically, neurocognitive dysfunction is assumed to result from atrophy of the hippocampus and the DLPFC (40). The degree of change in brain morphology varies among individuals with schizophrenia, yielding variances of electric fields in brain cortical areas produced by tDCS with the same electrode montage (31–33).

Data from the present study indicate differential clinical benefits which depends on the placement of the anodal electrode. Traditionally, social cognitive function has been associated with the neural circuitry involving the STS, medial prefrontal cortex, and middle temporal gyrus (29). Despite previous observations (7, 9, 41, 42), the results of the present study suggest that social cognition does not appear to be directly linked to improvements in functional capacity, as indicated by the lack of efficacy anodal tDCS on the STS (28). In sum, the ability

of anodal stimulation on the DLPFC, but not STS to enhance functional capacity (daily-living skills) provides insight into neural mechanisms for therapeutics to improve higher functional outcomes in patients with schizophrenia.

The amelioration of positive symptoms by anodal tDCS delivered to the left DLPFC indicates the role for this brain region in the treatment of psychotic conditions. Specifically, the neural circuit with the hippocampus as a hub may play a role. Thus, anodal stimulation on the DLPFC is assumed to modulate the activities of hippocampus through this neural circuit, possibly via alterations of monoaminergic neurotransmissions (17). This concept is consistent with observations that increased activities of the hippocampus are related to positive symptoms (40). Therefore, the ability of anodal stimulation on the DLPFC to alleviate positive symptoms may be related to modulation of hyperactivity of the hippocampus.

Data from the current study suggest the importance of selecting brain areas to be targeted by tDCS according to clinical features of individual patients. The frontal brain regions, e.g., the left DLPFC, has been used in most studies showing improvement of psychotic symptoms and functionality in patients with schizophrenia (18, 19, 24), although some argued against this concept (31–33, 43, 44). However, these brain areas may not be ideal as a target for alleviating social cognitive impairment (27, 29, 30). Further study is warranted to confirm the present results with randomized controlled trial with target brain regions of the DLPFC or STS.

The limitations of this study should be mentioned. First, the small sample size may raise caution in generalizing the present results. Second, as we compared results from previous studies with different populations, e.g., the ratio of inpatient/outpatient number across the two studies, it cannot be ruled out that the characteristics of participants may have influenced the results. The modest internal validity and low external validity indicate the need for further validation before generalizing the present findings to clinical practice.

5. Conclusion

The results of the present study suggest that anodal stimulation site of tDCS may govern its effect on symptoms and functionality in patients with schizophrenia. For improving daily-living skills associated with neurocognition, the left DLPFC may provide an optimal brain region to be targeted.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the National Center of Neurology and Psychiatry Clinical Research Review Board (CRB3180006). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YYa and TS developed the original concept for the study and designed it. ZN advised on the statistical analysis, while KS advised on the outcome measures. AS, YYa, and ZN administered tDCS. TI and TS recruited participants. TS organized the team for this study. YYa wrote the original draft. All other authors reviewed and commented on the subsequent drafts, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1243859/full#supplementary-material

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Correlation of motor-auditory cross-modal and auditory unimodal N1 and mismatch responses of schizophrenic patients and normal subjects: an MEG study

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Introduction: It has been suggested that the positive symptoms of schizophrenic patients (hallucinations, delusions, and passivity experience) are caused by dysfunction of their internal and external sensory prediction errors. This is often discussed as related to dysfunction of the forward model that executes self-monitoring. Several reports have suggested that dysfunction of the forward model in schizophrenia causes misattributions of self-generated thoughts and actions to external sources. There is some evidence that the forward model can be measured using the electroencephalography (EEG) and magnetoencephalography (MEG) components such as N1 (m) and mismatch negativity (MMN) (m). The objective in this MEG study is to investigate differences in the N1m and MMNm-like activity generated in motor-auditory cross-modal tasks in normal control (NC) subjects and schizophrenic (SC) patients, and compared that activity with N1m and MMNm in the auditory unimodal task.

Methods: The N1m and MMNm/MMNm-like activity were recorded in 15 SC patients and 12 matched NC subjects. The N1m-attenuation effects and peak amplitude of MMNm/MMNm-like activity of the NC and SC groups were compared. Additionally, correlations between MEG measures (N1m suppression rate, MMNm, and MMNm-like activity) and clinical variables (Positive and Negative Syndrome Scale (PANSS) scores and antipsychotic drug (APD) dosages) in SC patients were investigated.

Results: It was found that (i) there was no significant difference in N1m-attenuation for the NC and SC groups, and that (ii) MMNm in the unimodal task in the SC group was significantly smaller than that in the NC group. Further, the MMNm-like activity in the cross-modal task was smaller than that of the MMNm in the unimodal task in the NC group, but there was no significant difference in the SC group. The PANSS positive symptoms and general psychopathology score were moderately negatively correlated with the amplitudes of the MMNm-like activity, and the APD dosage was moderately negatively correlated with the N1m suppression rate. However, none of these correlations reached statistical significance.

Discussion: The findings suggest that schizophrenic patients perform altered predictive processes differently from healthy subjects in latencies reflecting

MMNm, depending on whether they are under forward model generation or not. This may support the hypothesis that schizophrenic patients tend to misattribute their inner experience to external agents, thus leading to the characteristic schizophrenia symptoms.

KEYWORDS

schizophrenia, N1, mismatch negativity, magnetoencephalography (MEG), cross-modal context, forward model

Introduction

Most schizophrenic patients experience hallucinations, delusions, and passivity experiences as prominent symptoms (so-called positive symptoms) (1, 2). They often interpret apparently inexplicable experiences they have as "alien thoughts inserted into their mind" (3). These psychopathological descriptions have led to the idea that these symptoms come from patient interpretations of internally generated voices or thoughts as external voices and that their movements and speech as externally caused (1, 2). Frith (3) suggested that this misinterpretation is due to a failure of the self-monitoring system in schizophrenic patients who cannot distinguish between external events and perceptual changes caused by their own actions.

The execution of self-monitoring is often explained with a "forward model" system, in which an efference copy of a motor command is used to predict upcoming sensory consequences of self-initiated motor acts (corollary discharge). Several studies have suggested a dysfunction of the forward model in schizophrenic patients (1, 2, 4–10). Event-related potential studies in normal subjects found that the amplitudes of auditory N1 and its magnetoencephalographic (MEG) equivalent N1m component for self-initiated sounds were significantly attenuated compared with that for externally initiated sounds. These findings have been discussed in relation to the internal forward model mechanisms (11–13). Ford et al. (7) found that reduced N1 suppression to tones delivered by button pressing compared with tones played back was smaller in schizophrenic patients than in normal controls. They suggested that the results reflect failure of the forward model in schizophrenic patients. These reports have discussed that the dysfunction of the forward model in schizophrenia causes misattributions of self-generated thoughts and actions to external sources. For example, it has been hypothesized that this auditory dysfunction of the forward model causes schizophrenic patients to misattribute inner speech as external voices (i.e., auditory hallucinations).

However, it is also well-known finding that a reduction in a mismatch negativity (MMN) and its MEG counterpart MMNm, which is an auditory change-detection responses, was smaller in schizophrenic patients than in normal controls (14–17). Some reports have suggested that the reduction of MMN(m) in schizophrenia is related to impairment of prediction errors (18–20). The predictive coding model theory has also been applied to explanations of the psychopathological phenomena of schizophrenia (7, 21, 22). The MMN(m) in schizophrenic patients has also been discussed in relation to their psychiatric symptoms, especially positive symptoms whose main symptoms are hallucinations and delusional experiences (23–26).

The MMN(m) has usually been measured as a pre-attentive, automatic response in a unimodal paradigm. In an MEG study, Yumoto et al. (27) examined whether the deviant occurrences in the motor-auditory cross-modal oddball paradigm could elicit prediction-driven responses. In their experiment, subjects were asked to press either of two buttons based on their choice and pace and to listen to the tone (A or B) following the pressing of the button, with tones of A and B being, respectively, assigned beforehand to a specific button as the standard, within 15% deviance (switching of the tone). They found that normal subjects elicited MMNm-like activity when they performed a motor-auditory mismatch, and interpreted this reaction as a temporal internal model based on the motor-auditory rule and suggested that auditory perception is modulated by top-down prediction processes in motor-auditory contexts.

Randeniya et al. (28) suggested that both reduced N1-attenuation to self-generated sounds and MMN amplitudes in schizophrenic patients are symptomatic of aberrant internal and external sensory prediction errors, which explain their notion of imprecise belief formation (externally encroaching hallucinations and delusions). The N1(m)-attenuation to self-generated sounds and generation of MMN(m) are usually detected by different paradigms and have not been discussed as a series of responses even though they are very close components on the time scale. Differently, in the study of Yumoto et al. (27), it was possible to confirm MMN(m)-like activity under conditions following reduced N1(m)- attenuation to self-generated sounds due to the motion-related forward model. This MMN(m)-like activity, either by itself or compared to conventional unimodal MMN(m), may add new insights in the diagnosis or symptom assessment of schizophrenia.

When thinking about the above-mentioned hypotheses, it raises the question of how the MMNm-like activity is represented in schizophrenic patients compared to normal controls. The purpose of this study was to verify differences in N1m and MMNm-like activity generated in the motor-auditory cross-modal context between schizophrenic patients and normal controls and to compare that activity with the N1m and MMNm in the unimodal context. We hypothesized that MMNm-like activity itself or a comparison with MMNm in schizophrenic patients would present different patterns from normal controls and that it would also have some relevance to the clinical symptoms of schizophrenia, in addition to reproducing the findings on differences in N1m and MMNm between schizophrenic patients and healthy subjects described in previous studies.

Materials and methods

Participants

Fifteen patients diagnosed with schizophrenia (SC group) (10 women, 22–41 years old) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and 15 normal control subjects, sex- and age matched, (NC group) (10 women, 22–42 years old) were recruited to participate in this study. All subjects were right-handed and had no history of neurological or audiological disorders. The subjects of the NC group had no evidence of past or present psychiatric disorders (screened with the MINI interview, Japanese version; 29) and no history of schizophrenia or psychosis in a first-degree relative. Table 1 shows the demographic data of both subject groups. Only one patient in the SC group was not administered medications; the other 14 patients were being medicated with antipsychotic drugs (APD) at a mean dose of 529 mg (range 50–1,100 mg) per day of chlorpromazine (CPZ) equivalents (11 patients using atypical APD, 2 using typical APD), and the remaining one patient using 3 drugs including atypical and typical APDs.

After the experimental protocol was explained, written informed consent for participation was obtained from all subjects. This experiment was approved by the Ethics Committee of the National Center of Neurology and Psychiatry (Tokyo, Japan), where the study was conducted.

Procedures

The auditory stimuli consisted of two Shepard tones: I (110×2^n Hz) and II (155×2^n Hz). The two tones were synthesized by a sound editing program (Adobe Systems, San Jose, CA, United States). The auditory stimuli of the tones were delivered binaurally to the ears of the subject at a sound pressure level of 80 dB. Our experiment consisted of a motor-auditory (M-A) task and an auditory (A) task (27).

In the M-A task, subjects held a response pad with six buttons, on which only the two target buttons were colored, yellow and blue. They were asked to press either of the two target (yellow or blue) buttons at random with as equal probability (~50%) and interval (~2 s) as possible without counting with the index finger of their left hand. In 85% of the trials, a yellow button press was followed by tone I and a blue button press by tone II. In 15% of the trials (deviants), the I and II tones were reversed for the buttons. The M-A task was preceded by a rehearsal session of a few minutes. In this session, we confirmed that the subjects could execute our instructions and that they had noticed the regularities between their button pressing and the delivered tone.

In the A task, the subjects were asked to listen to tones delivered using a classical oddball paradigm. Standard (tone I, 85%) and deviant (tone II, 15%) tones were presented to the subjects in a pseudorandom order as an oddball paradigm.

During the MEG recording session, the subjects watched a silent movie. In the A task, following the method of measuring MMNm that is often used, the subjects were instructed to divert their attention on the tones. In the M-A task, to control the background activity with A task, the silent movie was presented in the same manner, but now the subjects were instructed to have a reason for the cause-and-effect logic between their choice of button press and the consequent self-generated tones. The presentation of the movie to the subjects was also meant to maintain their alertness, minimize boredom, and reduce eye movements. The screen was placed about 150 cm in front of the eyes of the subjects so that the center of the image was projected slightly below the horizontal line of sight. The response pad for the button pressing was set on the table in front of the subjects so that it would enter their visual field. No subject pushed buttons other than two target buttons in the array of six buttons due to carelessness or mistakes.

Data acquisition

Auditorily triggered neuromagnetic responses were recorded in a magnetically shielded room using VectorView (Elekta Neuromag, Helsinki, Finland), which has 204 first-order planar gradiometers at 102 measuring sites on a helmet-shaped surface that covers the entire scalp. Auditory stimulus-triggered epochs of 400-ms duration (including a 100-ms pre-stimulus baseline) were filtered online with a band pass of 1–200 Hz and recorded at a sampling rate of 600 Hz. The MEG responses to auditory stimuli, both matched and mismatched with the button presses, were selective averaged together for analysis. The subjects were continuously monitored through two monitoring cameras set up in the shielded room.

The waveforms were filtered offline using a 1- to 40-Hz band pass. The baseline for the waveforms in each MEG channel was defined by a mean amplitude between −100 and 0 ms. Epochs with artifacts exceeding 3 pT/cm in any MEG channel were discarded. Signal space separation (SSS) correction, head movement compensation, and bad

TABLE 1 Demographic data of the subjects.

	Control Subjects (n = 15)	Schizophrenia Patients (n = 15)
Age (years, range; mean ± SD)	22–42; 31.8 ± 7.29	22–41; 32.7 ± 5.86
Gender (male/female)	5 / 10	5 / 10
Educational History (years, range; mean ± SD)	15–16; 15.8 ± 0.43	12–16; 14.2 ± 1.74
CPZ Equivalent Dose of Antipsychotics (mg/day, range; mean ± SD)		0–1,100; 493.7 ± 340.0
PANSS score		
positive (range; mean ± SD)		10–22; 17.5 ± 3.78
negative (range; mean ± SD)		10–22; 19.5 ± 4.24
general (range; mean ± SD)		25–47; 38.8 ± 5.89

SD, standard deviation, CPZ, chlorpromazine, PANSS, Positive and Negative Syndrome Scale.

TABLE 2 Number of stimuli.

	Control Subjects (n = 15)	Schizophrenia Patients (n = 15)
Motor-auditory condition		
Frequent(range; mean ± SD)	347–489; 417.4 ± 53.7	348–623; 433.5 ± 78.2
Rare(range; mean ± SD)	74–104; 87.7 ± 10.6	71–131; 92.3 ± 16.1
Auditory condition		
Frequent(range; mean ± SD)	407–510; 443.4 ± 34.1	422–481; 449.7 ± 29.2
Rare(range; mean ± SD)	74–90; 78.9 ± 5.75	74–87; 78.7 ± 4.62

SD, standard deviation.

channel correction were applied using MaxFilter software (Elekta Neuromag). In addition, epochs were manually inspected and epochs with artifacts were rejected. Table 2 shows the number of stimuli that was finally used in the analysis. There was no significant difference in the number of stimuli in the various conditions of the two groups.

Data analysis

The peak latency of the main component (N1m to standard tones in the A task) was determined for each hemisphere by the time point at which the root mean square of the predefined left and right perisylvian channels reached the maximum between 70 and 140 ms after the onset of the auditory stimulus. The selected channel areas were presented in a prior study (30, 31). The source-strength waveforms in each hemisphere were calculated using the equivalent current dipoles of the main component in each subject. The responses to the auditory stimuli were selectively averaged for analysis. In the M-A task, the responses, both matched and mismatched with the button presses, were selectively averaged together for analysis, and were weighted according to the number of data acquisition. We looked into the delay between the timing of the button press and the auditory sound and found it to be 16 ms. We corrected for the delay before the data analysis.

The N1m responses were measured between 70 and 140 ms after the tone onset. To compare the attenuation effect of the N1m response by button pressing of the NC and SC groups, the responses were calculated by subtracting the value obtained for the standard tones in the M-A task from the value obtained for the standard tones in the A task (following Model 1). Prior to the statistical analysis, we confirmed the attenuation effect of the N1m response from the obtained data of each subject by visual inspection (following Model 0).

The MMNm response was measured between 100 and 250 ms after the tone onset. The latency of MMNm in our analysis was determined based on several reports (16, 18, 20, 32). The MMNm responses were calculated by subtracting the value obtained for standard tones from the deviant tones in the M-A and A tasks, respectively (following Model 2).

The following two types of mixed effect models were applied. Model 0: the maximum value of the N1m to standard tones in the range of latency [70,140(msec)] was included as the outcome, and the group (NC group, SC group), frequency (standard, deviant), left–right (left, right), condition (A task, M-A task), and interactions of these factors were included as fixed effects, and the subject identification data was specified as a random effect. Model 1: the maximum value of the difference of N1m to standard tones in the A task and the M-A task conditions in the range of latency [70,140(msec)] was included as the outcome, and the group (NC group, SC group), frequency (standard, deviant), left–right (left, right), and interactions of these factors were included as fixed effects, and the subject identification data was specified as a random effect. Model 2: the maximum value of MMNm (−like activity) between the standard and deviant conditions in the range of latencies [100,250(msec)] was included as the outcome, and the group (NC group, SC group), condition (A task and M-A task), left–right (left, right), and interactions of these factors were included as the fixed effects, and subject id was specified as a random effect. For the models, the inferences on least square means and their differences for each level of fixed factors were calculated. Significant levels for statistical tests were set as 0.05 and confidence levels were set as 0.95.

In order to explore the relationships between MEG data and the clinical manifestation of schizophrenia, we also calculated Pearson's correlation coefficients between MEG measures and several clinical variables in the SC group. These included the PANSS scores (positive, negative and general psychopathology score) and APD dosage, which were translated into CPZ equivalent dosage levels. The MEG measures included the N1m suppression rate, MMNm, and MMNm-like activity. The N1m suppression rate was calculated by dividing N1m to standard tones in the M-A task conditions by that in the A task conditions. The values of N1m, MMNm, and MMNm-like activity were used with the peak amplitude of each component averaged over the left and right hemispheres. Significant levels for statistical tests were set as 0.05.

All statistical analyses were conducted with R software ver. 4.1 (R Core Team, Vienna) and SAS ver. 9.4 (SAS Institute Inc., Cary, NC).

Results

N1m-attenuation

Figure 1 shows the grand average of the distraction of N1m to the standard tones for the M-A and A task in both the NC and SC groups. By visual inspection of the N1m peak responses in NC group, 10 subjects showed the N1m-attenuation effect, 2 showed the opposite effect, i.e., the value of the standard tones in the M-A task was greater than that in the A task, and the remaining 3 showed no clear attenuation effect. In the SC group, 10 subjects showed the N1m-attenuation effect, 1 showed the opposite effect, and the remaining 4 showed no clear attenuation effect. The Model 0 mixed effect model showed that there was no statistically significant difference in the N1m of the standard tones in the M-A task and the A task in the NC group [−3.06 (−6.71, 0.59), $p = 0.097$, where (.) is 95% confidence interval], and that N1m in the M-A task was significantly smaller than that A in the task in SC group [−8.01 (−11.7, −4.42), $p < 0.001$]. The Model 1 mixed effect model showed

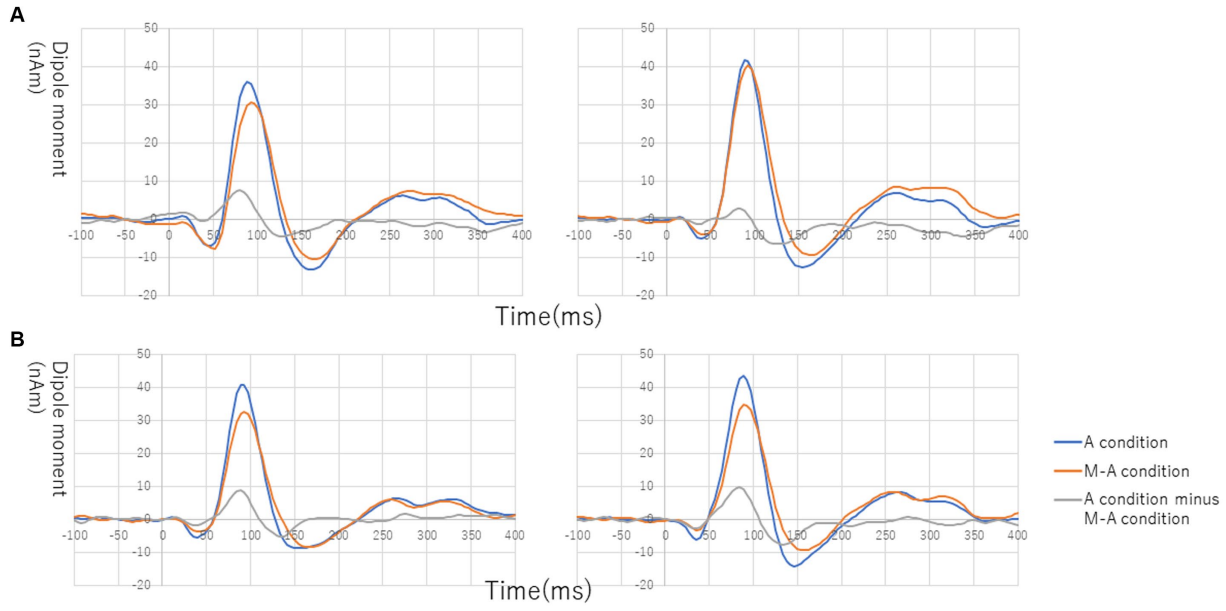

FIGURE 1
Grand average of source-strength waveforms for the N1m responses to the standard tones: **(A)** normal in the left hemisphere (left) and right hemisphere (right) and **(B)** schizophrenia in the left hemisphere (left) and right hemisphere (right). The blue and red curves plot the A (auditory)-condition and the M-A (motor-auditory) condition, respectively. The gray curve plots the difference between the A condition and the M-A condition.

that there was no statistically significant difference in the N1m-attenuation effects of the NC and SC groups but there was a significant trend towards smaller N1m-attenuation effects in the NC group [−4.43 (−9.44, −0.57), $p = 0.080$], which was the primary analysis target in our study (Figure 2).

MMNm

Figure 3 shows the grand average of MMNm (−like activity) (i.e., distraction of deviant minus standard tone) in the M-A and A task in both the NC and SC groups. The Model 2 mixed effect model shows that MMNm in the A task of the NC group was significantly larger than that in the other conditions (M-A task in the NC group [6.35 (2.93, 9.76), $p = 0.001$], M-A [6.27 (2.39, 10.16), $p = 0.003$] and A tasks in the SC group [4.58 (0.77, 8.38), $p = 0.020$]). There was no significant difference in the MMNm (−like activity) of the M-A and A task in the SC group. There was also no significant difference in the MMNm-like activity of the M-A task in the NC group and the various components in the SC group ($p > 0.05$) (Figure 4).

Overall, MMNm in the NC group was significantly larger than the other three components (MMNm-like activity in the NC group, MMNm-like activity in the SC group, and MMNm in the SC group), and there was no significant difference among the remaining three components.

Correlation

The PANSS positive symptoms and general psychopathology scores were moderately negatively correlated with amplitudes of MMNm-like activity (i.e., as scores increase, amplitudes decrease) ($r = -0.41$ and -0.40, respectively), and the APD dosage was also moderately negatively correlated with N1m suppression rate (i.e., as doses increase, the suppression rate decrease) ($r = -0.46$). However, none of these were statistically significant ($p > 0.05$) (Figure 5).

Discussion

The aim of this study was to compare N1m-attenuation and MMNm responses to self-initiated tones in a motor-auditory cross-modal context (i.e., the M-A task) with externally initiated tones in a classical oddball context (i.e., the A task) in NC (normal control) and SC (schizophrenic patient) groups.

The main MEG findings showed that (i) there was no significant difference in N1m-attenuation effect for the NC and SC groups, (ii) MMNm in the A task with the SC group was significantly smaller than that in the NC group, and the MMNm(−like activity) in the M-A task was smaller than that in the A task in the NC group, but there were no significant differences in the SC group.

First, we verified the attenuation effect of N1m around the peak latency (70–140 msec) to self-initiated tones in the NC and SC groups. We found that the N1m response was attenuated to self-initiated tones by the button pressing when compared to externally generated tones in both groups. However, some subjects deviated from this rule. This result is in line with that of previous studies (11, 12, 33) but does not fully reproduce them.

Martikainen et al. (12) found that the auditory N1m response was smaller with self-initiated sounds than with externally triggered sounds. This was explained as the existence of a motor-to-sensory forward model (1); and they suggested that this method could provide an objective test for schizophrenic patients, in which dysfunction of the forward model

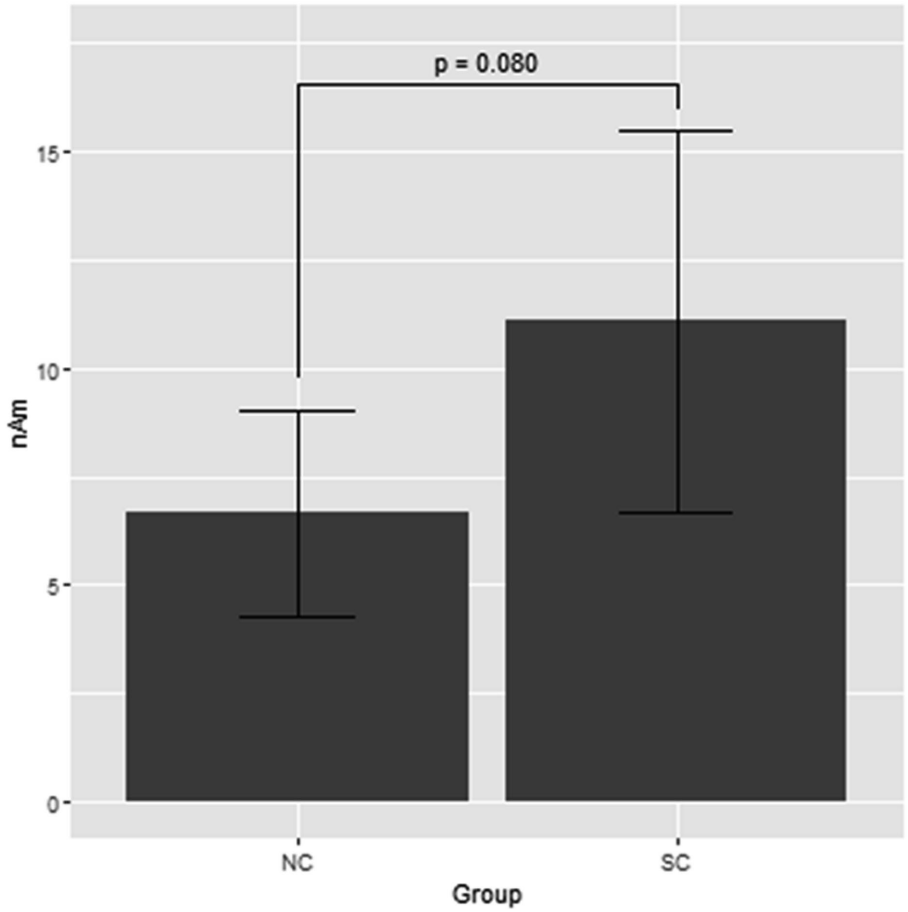

FIGURE 2
Least square means of attenuation effect of the N1m response to the standard tones with the mixed effect model 1. NC, normal; SC, schizophrenia.

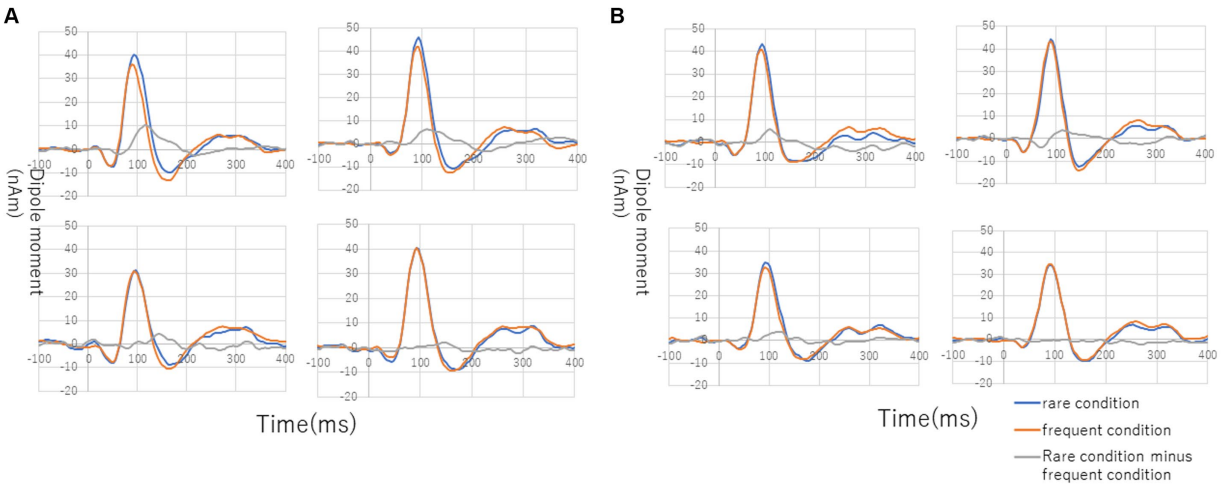

FIGURE 3
Grand average of source-strength waveforms for the MMNm responses: **(A)** normal in A (auditory) condition (left hemisphere, top left; right hemisphere, top right) and M-A (motor-auditory) condition (left hemisphere, bottom left; right hemisphere, bottom right) and **(B)** schizophrenia in A condition (left hemisphere, top left; right hemisphere, top right) and M-A condition (left hemisphere, bottom left; right hemisphere, bottom right). The blue and red curves indicate rare and frequent conditions, respectively. The gray curves indicate subtraction of frequent from rare conditions.

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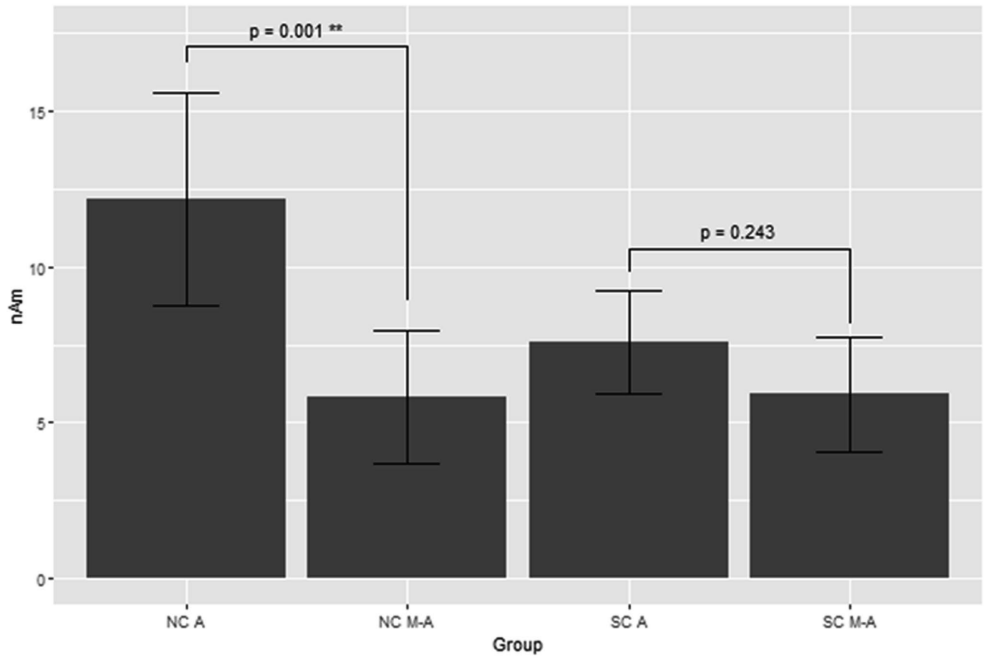

FIGURE 4
Least square means of the MMNm response with mixed effect model 2. NC A: A (auditory) condition in the normal control, NC M-A: M-A (motor-auditory) condition in the normal control, SC A: A condition in schizophrenia, SC M-A: M-A condition in schizophrenia.

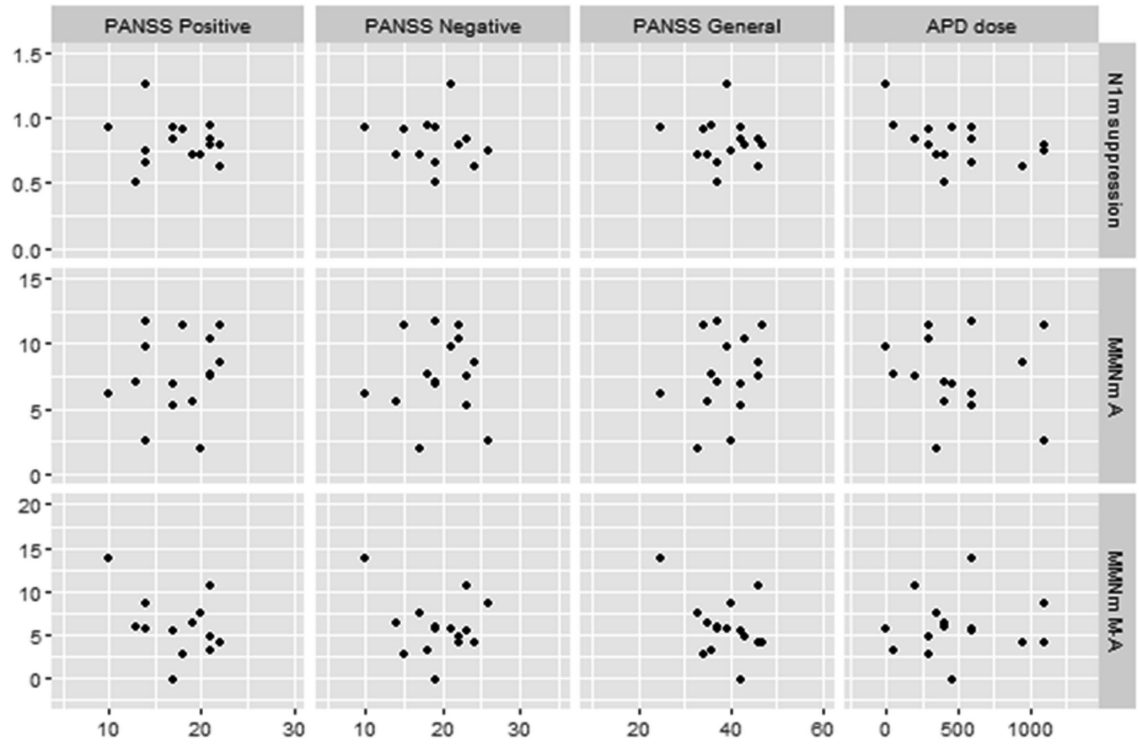

FIGURE 5
Scatterplots for correlations between MEG data and clinical data in schizophrenic patients. N1m suppression, N1m suppression score; MMN A, mismatch negativity in A (auditory) condition; MMN MA, mismatch negativity in M-A (motor-auditory) condition; PANSS, Positive and Negative Syndrome Scale; APD, antipsychotic drug. APD dose is converted to chlorpromazine equivalents.

could explain the generation of positive symptoms (1, 2). Ford et al. (7) suggested that reduced N1 suppression in schizophrenic patients reflects a deficit of corollary discharge action. In our study here, there was no significant difference in the N1m attenuation effect of the NC and SC groups, and the trend was rather towards the N1m attenuation effect as greater in the SC group. Therefore, our results are not consistent with their study. It is possible that the reduced auditory N1(m) component in the M-A task may be elicited under the conditions of the forward model, but we could not determine whether the dysfunction of the forward model in schizophrenic patients is present under this N1(m) suppression mechanism. There were some methodological differences between the study of Ford et al. (7) and our current study. That study measured using EEG and presented pure tones (1,000 Hz), while our study measured with MEG and presented Shepard tones and included two tones in the button-pressing task. Most importantly, our study also required a longer experimental time than the Ford et al. study to obtain MMNm in parallel. It may be difficult to obtain robust results that N1(m) attenuation is reduced in schizophrenic patients in the simple shared setting of comparing sounds delivered by button pressing and passive listening. To obtain reproducible results, it may be more reasonable to set up more methodologically rigorous rules or to adopt methods with more research, such as the "Talk/Listen" paradigm (34–36).

Second, we found that the MMNm was smaller in the schizophrenic patients than in the normal control subjects in the single oddball paradigm, in line with many previous studies. On the basis of the assumption of "better-known facts" (17, 37–40), we further tested whether there was a difference in the MMNm component in the M-A and A tasks between the NC and SC groups.

Auditory MMN(m) is elicited by infrequent (deviant) sounds occurring in a sequence of repetitive frequent (standard) sounds. It is believed that MMN(m) represents a neural process of mismatch detection between the deviant auditory input and a sensory memory trace developed by the standard stimuli (32, 41). Most studies have investigated MMN(m) in the auditory unimodal oddball paradigm, and MMN(m) has usually been studied as an automatic pre-attentive response under the passive listening conditions specified by an external context. However, some studies have reported that infrequent audiovisual incongruence also elicits "MMN(m)-like" activity (30, 31, 42). These results suggest that auditory expectant imagery from visual cues elicited MMNm-like activities when expectations were violated. Yumoto et al. (27) verified whether deviant occurrences in a motor-auditory cross-modal context could also mediate such prediction-driven MMNm-like activities. They reported that the deviant tones generated by arbitrary self-initiated button pressing also elicited MMNm-like activity, and suggested that the MMNm-like activity may represent a detection process for prediction errors relevant to internal model reformation.

In our present study, we found MMNm in the A (i.e., auditory listening) task and the MMNm-like activity in the M-A (i.e., motor-auditory cross-modal) task in both the NC and SC groups. In the NC group, the MMNm-like activity in the M-A task was significantly lower than MMNm in the A task. However, in the SC group, there was no significant difference between the MMNm-like activity in the M-A task and the MMNm in the A task. The MMNm-like activity in the M-A task in the SC group was smaller than the MMNm in the A task in the NC group, but there was no significant difference between the MMNm-like activity in the M-A task in the SC group and that in the M-A task in the NC group.

It is difficult to explain the reasons for the reduction in the MMNm-like activity compared to the MMNm in the NC group because there are few findings about this response to deviant occurrences in the motor-auditory cross-modal context even in normal subjects. One explanation could be that it is simply due to subject stimulus discrimination accuracy in the tasks. It is considered that it may be easier to detect deviant events and to match the previous sensory memory in the context of the unimodal oddball paradigm than the cross-modal context, and high-demand tasks could reduce the MMNm amplitude. However, Bendixen and Schröger (43) emphasized that the auditory system has the ability to extract and apply abstract rules in a fast and efficient manner and showed that on these grounds, changes in MMN were minimally affected, even on a complex paradigm assuming that deviant stimuli change over time. They also suggested that there is a dissociation between automatic detection (MMN data) and conscious detection (behavioral data), but it is not significant. Therefore, stimulus complexity may not be a valid explanation why the MMNm was attenuated in the NC group in our study. A further potential explanation could be that MMNm mainly operates as an automatically pre-conscious relevance filtering mechanism, and that it is more compatible with external stimuli regardless of the intentions of the responding subject, as many studies have shown. It is possible that the mismatch detection is also part of a forward model to discriminate self-generated deviance from an externally generated deviance. It is believed that MMN(m) involves a system for the detection of information crucial to survival, such as alerting to potential threats in the environment (28, 44). If the essential mechanism of MMN(m) is like this, the result of our study that the mismatch reaction generated from an external deviation is greater than that of a self-generated internal deviation in normal subjects could offer a possible explanation. We may infer that MMN(m) also plays some role in distinguishing between internal and external events (in other words, prevent excessive linkage between self-action and external events) under the forward model in normal subjects.

The sensory consequences of self-generated movements, such as a tone delivery following the pressing of a button, have been regarded as a model of internally generated experiences, with externally generated sensory inputs regarded as externally caused passive experiences (1, 2, 7, 34). Several studies have shown that the response to self-produced stimulation was attenuated compared to that of externally generated stimulation and that the degree of attenuation was smaller in schizophrenic patients than in normal subjects. These results were often discussed in relation to misattribution of inner experiences to external agents in schizophrenic patients. Synofzik et al. (45) suggested that compared to normal persons, schizophrenic patients tend to rely more strongly on external cues to realize predictions and that they may over-attribute external events to their own agency. Voss et al. (22) suggested that the predictive structuring link in schizophrenic patients is impaired, and therefore, that they show an over-strong linkage between internally generated actions and external sensory events. The results of Voss et al. (22) could support a finding that schizophrenic patients rely on feedback rather than on the forward model for their perceptions and taken together these studies may show that schizophrenic patients have difficulty in maintaining neutrality to external input. Possibly, schizophrenic patients display a dysfunction of the mechanism that clearly recognizes an external event as such (i.e., something that is "external, and not internal"), as would be the case with normal subjects. If this mismatch response difference also plays a role in the

discrimination between self-generated events and external events in normal subjects, the response pattern in schizophrenic patients could disrupt a precise discrimination between self and external experiences.

Our results would be in line with those of previous studies which suggest that the generation of prediction errors remain unchanged in most schizophrenic patients (20) and that they tend to depend on the estimates of prediction errors to deal with feedback from the outside (45). In other words, compared with the situation in normal subjects, the detection of prediction errors in schizophrenic patients tends to be influenced by internal self-generated rules derived from external cues, and that prediction errors may be uncertain in the passive automatically "echoic" conditions such as the methods used in traditional MMNm research. The excessive linkage between self-action and external events that causes a failure of the self-monitoring in schizophrenic patients could be attributed to a dysfunction of the forward model mechanisms in prediction errors rather than dysfunction of the prediction error itself. This may have led to the result in this study. At least, it cannot be concluded that the incomplete generation of MMN(m) in schizophrenic patients simply reflects a disability of their auditory change detection.

Here, the question arises as to the implications of behavioral differences of MMNm (−like activity) between normal subjects and the schizophrenic patients in our study. We found the attenuation of MMNm associated with the motion-related forward model paradigm in normal subjects. The fact that the attenuation of MMNm is decreased in schizophrenic patients is noteworthy. Recently, some studies suggest that the decreased MMN(m) in schizophrenic patients reflects their altered predictive coding (46–49) in which the brain is constantly trying to minimize the discrepancy between actual sensory input and internal representations of the environment (28). Our result may reflect that schizophrenic patients perform predictive coding differently from healthy controls after processing (or failing to process) sensory prediction errors in external factors and self-generated stimuli. It remains unclear why changes in MMN(m) responses during unimodal and cross-modal contexts differ in healthy controls and schizophrenic patients. However, there is little knowledge on the properties of MMN(m) in cross-modal contexts. It may be a secondary product of differences in information processing at the N1(m) level between healthy controls and schizophrenic patients, or may be due to dysfunction of MMN(m) itself in schizophrenic patients, or both.

It is possible that the difference in the waveforms of the MMNm-like activity in the M-A task in the present study can be interpreted as the later component of N1m rather than MMNm because the latency mainly, showing a significant difference from 100 to 130 msec (Figure 1, grand average). SanMiguel et al. (13) suggested that effects of N1 suppression due to prediction *via* the forward model were most related to the sensory- non-specific N1 components at the Cz electrode in EEG. In fact, there are competing hypotheses about the neural mechanisms of MMN(m) generation. The most common interpretation is that MMN(m) represents the change detection process involved in a memory-trace effect, which is functionally and spatially distinct from N1(m) generation (50). Another hypothesis is that MMN(m) results from differences in the adaptation of the N1(m) responses to standard and deviant stimuli (51). These conflicting ideas indicate that the relationship between N1(m) and MMN(m) have not been fully clarified although the predictive coding model could provide a common framework for accepting both hypotheses (52, 53). It is unknown whether the two mechanisms can be explained as a series of individual phenomena or as an overlap of mutually independent phenomena.

Additionally, we found several correlations between MEG data and clinical symptoms in schizophrenic patients. First, increases in APD dosage correlated with decreases in the N1m suppression rate. To our knowledge, there are no previous studies that have discussed the relationship between N1(m) suppression and APD doses. It is possible that APD administration may affect neuro-electro-magnetic data by its efficacy (improvement of psychosis) or side effects, such as drowsiness. However, we found no difference in N1m levels between normal controls and schizophrenic patients, as described above. Therefore, it is still unclear to what extent this result is relevant to the pathophysiology of schizophrenic patients. Second, we found that increases of PANSS positive and general psychopathology scores were correlated with decreased MMNm-like activity. However, the correlation did not reach statistical significance. Several previous studies have discussed the association between the PANSS score and MMN. Fisher et al. found that PANSS positive symptom scores were correlated with the duration of the MMN amplitude (24) and intensity MMN latencies (26). They further suggested that schizophrenic patients with auditory hallucinations which is the main symptom among positive symptoms showed significantly smaller MMN than the duration deviants without auditory hallucinations as well as than normal controls (23, 25). Riel et al. (54) suggested that lower PANSS general psychopathology scores were associated with larger MMN amplitudes. However, some reports found no significant association between MMN impairment and the severity of symptoms in schizophrenic patients (55). Although the results of our study cannot be simply compared with previous studies due to different modalities and analytical methods, our results suggest that MMNm-like activity and MMNm are not homologous in their correlation with individual patient psychiatric symptoms. Our results appear to infer that MMNm-like activity may need to be further investigated as an additional option and indicator of schizophrenic pathophysiology. The correlation analysis also mentions pairs that may not have been significant due to the small sample size. Verification of these results is a subject for future research.

Small sample size of subjects reduces the statistical power of the current study. This issue, however, also does not seem to correspond to the diversity of the diseases of schizophrenics. Considering the psychiatric symptom rating scale (PANSS score) and antipsychotic drug dosage regimen, we believe that the schizophrenic patients in our data are representative of outpatients who live in the community despite having some residual psychiatric symptoms. Still, the heterogeneous nature of schizophrenics including epidemiologically, symptomatically, and possibly genetically, will require data from a larger sample to obtain general findings for use as a biomarker. Further research is needed.

In conclusion, we could not find significant differences in the attenuation effect of the N1m to self-initiated sounds in both normal and schizophrenic subjects as discussed in previous studies. Therefore, we could not support the validity of the attenuation effect of the N1m as an indicator of dysfunction of the forward model in schizophrenic patients in this study. The auditory MMNm-like activity evoked by the self-triggered cross-modal events is attenuated compared to the MMNm evoked by the external events in the normal controls. The results could suggest that the auditory mismatch response plays some role in distinguishing between internal and external events. Moreover, we did not find this attenuation effect of MMNm in the schizophrenic patients. Differences in the response patterns of MMNm and MMNm-like activity between healthy controls and schizophrenic patients may reflect

differences in processing the predictive coding under forward model generation in both groups. This phenomenon could prompt schizophrenic patients to experience the boundaries of external and internal stimuli differently compared to healthy controls. This may support the hypothesis that schizophrenic patients tend to misattribute their inner experience to external agents, thus leading to their characteristic symptoms.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by National Center of Neurology and Psychiatry. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MO: conceptualization, methodology, recruit, software, writing-original draft preparation, writing-reviewing, and editing. MY: conceptualization, methodology, software, supervision. YK: Methodology, software, supervision. KM: statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor TS declared a past co-authorship with the author KM.

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Valuable interaction with cognitive remediation and optimal antipsychotics for recovery in schizophrenia (VICTORY-S): study protocol for an interventional, open-label, randomized comparison of combined treatment with cognitive remediation and lurasidone or paliperidone

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Background: Cognitive impairment, a core feature of schizophrenia, is associated with poor outcomes. Pharmacotherapy and psychosocial treatment, when used alone, have inadequate effect sizes for cognitive impairment, leading to recent interest in combination interventions. A previous study examined the additive effect of cognitive remediation on lurasidone in patients with schizophrenia, which was negative. Although improvement in cognitive function was suggested for lurasidone, it was inconclusive because there was no antipsychotic control in the study. To clarify whether lurasidone has a meaningful impact on cognitive function in combination with cognitive remediation, we use paliperidone as a control antipsychotic in this study. We hypothesize that combination with lurasidone will improve cognitive and social function to a greater extent than paliperidone.

Methods: The valuable interaction with cognitive remediation and optimal antipsychotics for recovery in schizophrenia study is a multicenter, interventional, open-label, rater-blind, randomized comparison study, comparing the effect of lurasidone plus cognitive remediation with that of paliperidone plus cognitive remediation in patients with schizophrenia. The Neuropsychological Educational Approach to Remediation (NEAR) is used for cognitive remediation. Eligible patients will be randomized 1:1 to receive lurasidone or paliperidone combined

with NEAR (6 weeks antipsychotic alone followed by 24 weeks combination antipsychotic plus NEAR). The primary endpoint is the change from baseline in the tablet-based Brief Assessment of Cognition in Schizophrenia composite T-score at the end of the NEAR combination treatment period. Secondary endpoints will include change from baseline in social function, schizophrenia symptoms, and quality of life at the end of the NEAR combination treatment period. Furthermore, change from baseline to the end of the pharmacotherapy period and change from the end of the pharmacotherapy period to the end of the NEAR combination treatment period will be assessed for all endpoints. Safety will also be evaluated.

Discussion: Achievement of adequate cognitive function is central to supporting social function, which is a key treatment goal for patients with schizophrenia. We think this study will fill in the gaps of the previous study and provide useful information regarding treatment decisions for patients with schizophrenia.

Clinical trial registration: Japan Registry of Clinical Trials ID, jRCTs031200338.

KEYWORDS

antipsychotics, cognitive impairment, cognitive remediation, lurasidone, Neuropsychological Educational Approach to Remediation (NEAR), paliperidone, schizophrenia

1 Introduction

Schizophrenia is a psychiatric disorder presenting with significant impairment in social function, which comprises functions related to a person's ability to interact with their environment, to live at home and in society, and to maintain communication with others (1, 2). Atypical (second-generation) antipsychotic drugs are effective for positive symptoms of schizophrenia and have comparatively fewer side effects than typical (first-generation) antipsychotics; however, negative symptoms remain in some cases, and they have limited efficacy in improving cognitive impairment (3, 4). Both the European Psychiatric Association and the Japanese society of Neuropsychopharmacology guidelines for schizophrenia primarily recommend atypical antipsychotic drugs (5, 6).

Cognitive impairment is a core feature of schizophrenia (7), which has led to an increased focus on the relationship between schizophrenia and cognitive function in treatment guidelines (5). Among patients with schizophrenia, cognitive impairment is associated with poor social function outcomes and disability, worse community functioning, lower patient quality of life, and increased burden on healthcare services (7–11). Cognitive impairment initially appears around the first schizophrenic episode and remains in the chronic phase, even after the patient reaches remission status (12–14). Cognitive function may deteriorate over time in patients with schizophrenia and can range from near-normal levels to a level of severe deficit (15–17). Up to 75% of patients with schizophrenia experience cognitive impairment (18), which, early in onset, is associated with reduced work-related social function (19). Together, the above information suggests that early intervention is important to improve schizophrenia-associated cognitive impairment.

Interventions available to improve cognitive impairment in patients with schizophrenia include pharmacotherapy and psychosocial treatment. The effect size of atypical antipsychotic drugs on cognitive impairment is reported to be approximately 0.17–0.46 (20), while that of cognitive remediation is around 0.45 (21). Given that the mean deficit in cognitive domains may be 1.0-3.0 standard deviations (SDs) below normal, a comprehensive care program may be important for a sufficient improvement in treatment effect size (22). This has led to recent interest in research aimed at improving cognitive function by combining cognitive remediation and cognition-enhancing drugs to effectively increase treatment effect size (23).

The atypical antipsychotic drug lurasidone is a novel benzisothiazole derivative that exhibits a high binding affinity and antagonistic effect on the dopamine D_2, serotonin $(5\text{-HT})_{2A}$ and 5-HT_7 receptors, a partial agonistic effect on the 5-HT_{1A} receptor, and no significant binding to histamine 1 and muscarinic acetylcholine receptors (24). In animal models, lurasidone treatment was associated with neuroprotective effects and better cognitive improvement compared with other antipsychotics (25, 26). Furthermore, results from a clinical study suggest that lurasidone may improve cognitive function in patients with schizophrenia (27). Recent preliminary clinical study findings have demonstrated improved cognitive function with lurasidone in patients with bipolar disorder (28, 29). A previous study has suggested that the combination of cognitive remediation with lurasidone had no greater therapeutic effect on cognitive function than the combination of lurasidone with nonspecific video games (30). Although improvement in cognitive function was suggested for lurasidone, the previous study did not adequately demonstrate whether lurasidone enhances the therapeutic effects of cognitive remediation, given that there was no comparison antipsychotic drug (30).

Herein, we describe the protocol for the valuable interaction with cognitive remediation and optimal antipsychotics for recovery in schizophrenia (VICTORY-S) study, which aims to examine the effects of lurasidone combined with cognitive remediation (the Neuropsychological Educational Approach to Remediation [NEAR]) on cognitive function using the tablet-based Brief Assessment of Cognition in Schizophrenia (BAC App) in patients with schizophrenia (31), by comparing with paliperidone combined with cognitive remediation.

2 Materials and methods

2.1 Study design

The VICTORY-S study is a multicenter, interventional, open-label, rater-blind, randomized comparison study. The study will be conducted at 17 sites in Japan between 2 February 2021 and 30 September 2025 (Table 1). The study will consist of two periods, a 6-week period of pharmacotherapy alone followed by a 24-week period of pharmacotherapy and NEAR combination treatment (Figure 1). Both patients and therapists will be aware of the group assignment (open-label study design). The allocation for each patient will be disclosed to the therapists, and the endpoint rater will be blinded. Eligible patients will be randomly assigned in a 1:1 ratio to either the lurasidone group (6-week lurasidone alone plus 24-week lurasidone and NEAR combination) or the paliperidone group (6-week paliperidone alone plus 24-week paliperidone and NEAR combination) using the minimization method, with balancing for age (≤39 years and ≥40 years), sex, and severity of cognitive impairment measured using the symbol coding task from the tablet-based BAC App (cutoff: 55 points). The cutoff for the BAC App symbol coding was determined by calculating the mean–one standard deviation of the symbol coding scores obtained when the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J) was being developed (calculation: 67.4 points [mean] − 12.4 points [SD] = 55 points) (32). An electronic data capture system (HOPE eACReSS) managed by a central data center will be used for randomization.

The study protocol was approved by the Clinical Research Review Board of the National Center of Neurology and Psychiatry, National Research and Development Agency (CRB3200004), and written informed consent will be obtained from patients before enrollment. The study will be conducted in accordance with the principles of the Declaration of Helsinki and the Clinical Trials Act in Japan, and is registered under the identifier jRCTs031200338.[1]

TABLE 1 List of study sites and principal investigators.

Study site	Principal investigator
National Center of Neurology and Psychiatry	Kazuyuki Nakagome[a]
Hokkaido University Hospital	Naoki Hashimoto
Kohnodai Hospital, National Center for Global Health and Medicine	Toshihiko Ito
Takatsuki Hospital	Yukihiro Nagase
Kanagawa Psychiatric Center	Hisako Taguchi
Kawaguchi Hospital	Taro Takahashi
Inuyama Hospital	Satoru Takazawa
Ainohanazono Hospital	Nobuo Shimizu
Yamaguchi University Hospital	Shin Nakagawa
Kochi Medical School Hospital	Hidetoshi Takahashi
Umibeno-mori Hospital	Kazushi Okada
Amekudai Hospital	Naoki Taira
Fukushima Medical Center, Kokoro no Mori	Yuki Inoue
Hizen Psychiatric Center	Takefumi Ueno
Aoi Clinic	Hiroshi Terada
Tosa Hospital	Yasuhiko Sudo
Shimane Prefectural Psychiatric Medical Center	Hazama Gen-i

[a]Principal investigator of the study.

2.2 Eligibility criteria

The following inclusion criteria must be met for enrollment in the study: Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria for schizophrenia; ability to provide in-person written informed consent; outpatient; aged 18–55 years at the time of informed consent; express a preference to switch antipsychotic drug and obtain agreement for this switch by the primary care physician; have presented no risk for self-harm or harming others in the 6 months prior to the date of informed consent; no acute illness requiring treatment; any chronic condition (e.g., hypertension) must be stable with treatment that has been continued for at least 1 month prior to participation; ability to participate in cognitive remediation sessions twice weekly (60–75 min per session); ability to undergo neuropsychological assessment (BAC App); chlorpromazine (CP) equivalent dose(s) of the prior antipsychotic drug(s) not more than 1,000 mg/day in the 30 days prior to the date of informed consent; and no change in the type of main agent of prior antipsychotic medication in the 30 days prior to the date of informed consent.

Exclusion criteria are as follows: a premorbid IQ of less than 70 on the Japanese Adult Reading Test-25 (33, 34); hearing or visual disability; non-native speaker of Japanese; currently receiving lurasidone, paliperidone, or clozapine; currently using three or more antipsychotic drugs; a history of treatment resistance, as evidenced by a failure to respond to at least two antipsychotic drugs when administered for at least 6 weeks at the dose specified on the package insert in the 12 months prior to the date of informed consent; receiving psychotropic drugs known to affect cognitive function, such as methamphetamine; administration of long-acting injections of antipsychotic drugs in the 6 weeks prior to the date of informed consent; a history of electroconvulsive therapy (ECT) in the 6 months prior to the date of informed consent or are expected to require ECT during participation in this study; a likelihood to attempt suicide during participation in this study; a history of intracranial disease or central nervous system disease (e.g., stroke, traumatic brain injury, epilepsy, Parkinson's disease); a clinically significant abnormality in physical condition; a history of alcohol or drug abuse or addiction in the 6 months prior to the date of informed consent; pregnant or planning to become pregnant; breastfeeding; received cognitive remediation in the 6 months prior to the date of screening; any contraindication to lurasidone or paliperidone; and deemed ineligible for the study in the opinion of the investigator or subinvestigator.

2.3 Intervention

During the pharmacotherapy alone period, 40 mg of lurasidone hydrochloride will be administered orally once daily after a meal. The

1 https://jrct.niph.go.jp/en-latest-detail/jRCTs031200338

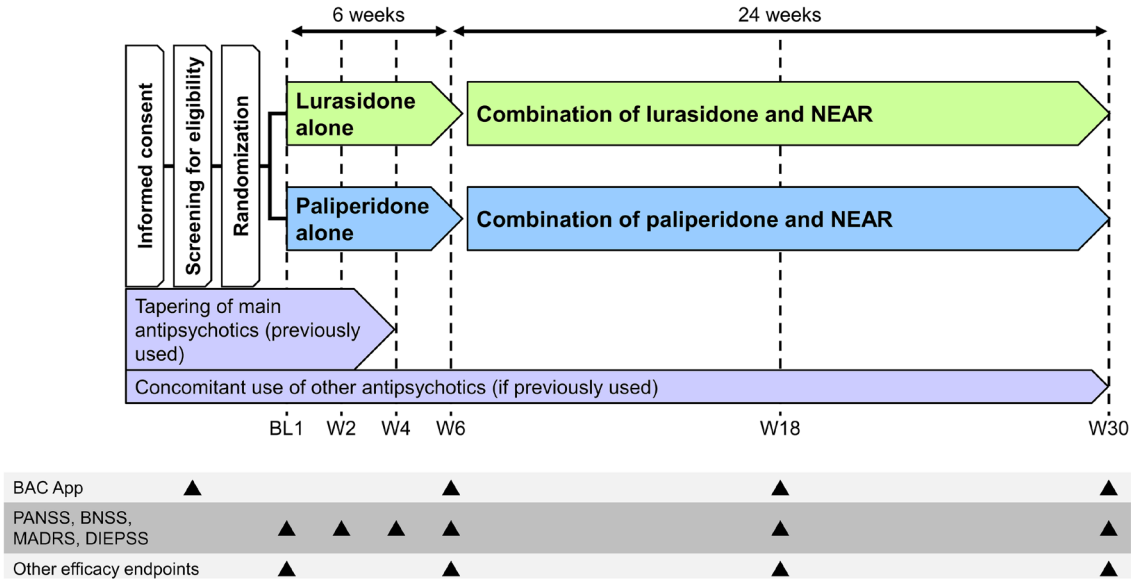

FIGURE 1
Study design. BAC App, tablet-based Brief Assessment of Cognition in Schizophrenia; BL, baseline; BNSS, Brief Negative Symptom Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; MADRS, Montgomery Åsberg Depression Rating Scale; NEAR, Neuropsychological Educational Approach to Remediation; PANSS, Positive and Negative Syndrome Scale; W, Week.

dose will be adjusted as necessary depending on the age and symptoms of the patient; however, the dose should not exceed 80 mg/day. In the paliperidone group, patients will receive 6 mg of oral paliperidone once daily after breakfast. The dose will be adjusted as necessary, not to exceed 12 mg/day and using a daily dose increment of 3 mg with an interval of at least 5 days. In general, tapering of the prior antipsychotic medication (main agent) will be started simultaneously with the start of study drug treatment, initiating the switch from prior medication to study drug. Monitoring of the patient's condition should be used as a guide for tapering the prior antipsychotic medication (main agent), which should be tapered and discontinued by Week 4. The study drug dose should remain unchanged during the first 4 to 6 weeks following treatment initiation. For drugs included as part of a patient's prior antipsychotic treatment regimen other than the main agent, continuation of only one drug will be allowed during the study. The main agent is defined as an antipsychotic used at a dose greater than 50% of the daily CP equivalent. The dose should remain the same throughout the study and the drug must have been used for at least 30 days prior to the date of informed consent. The total antipsychotic dose, including the dose of the study drug, should not exceed a CP equivalent dose of 1,000 mg/day. The study drugs will be administered in accordance with the Japanese package insert. The dosage will be adjusted at the discretion of the attending physician within the range specified by the package insert.

Following the pharmacotherapy alone period, the NEAR combination treatment period will begin. NEAR will consist of cognitive task sessions lasting 45–60 min and bridging sessions lasting for 10 to 20 min. These sessions will be conducted twice weekly for 24 weeks. At least one of the practitioners at each site will have received training approved by the developer of NEAR, Alice Medalia (35). To ensure NEAR is being implemented correctly, on-site monitoring will be conducted for some sites using a fidelity scale. Regular supervision meetings will be held by the NEAR practitioners at each facility, either onsite or online. In this period, the dose of the study drug and other concomitant drugs will be maintained without change from the dose used during the pharmacotherapy alone period, but the dose of these drugs can be changed if the attending physician judges it necessary to do so.

2.4 Prohibited and restricted concomitant medications and therapies

Prohibited concomitant medications are as follows: as-needed but regular use of antipsychotic medications; adrenaline; strong inhibitors and inducers of cytochrome P450 3A4; and drugs that affect dopaminergic nerve activity, such as psychostimulants and prokinetic agents. Prohibited concomitant therapies are as follows: neuromodulation therapies such as ECT and repetitive transcranial magnetic stimulation therapy, any new psychotherapy other than NEAR, and psychosocial approaches that may affect cognitive function such as daycare and occupational therapy.

Restricted concomitant medications include antipsychotic drugs, psychotropic drugs, and antiparkinsonian drugs. Restrictions for antipsychotic drugs are as follows: antipsychotic drugs for treatment of adverse events (AEs) will be permitted on an as-needed basis up to three times weekly.

Psychotropic drugs are permitted under the following conditions. In general, psychotropic drugs (including antipsychotic drugs other than the main agent) that have been used for at least 30 days prior to the date of informed consent will be continued at the same dose during study participation. If any other psychotropic drug is used on an as-needed basis for treatment of AEs, lorazepam may be used up to 5 times weekly at a dose of ≤1 mg/day. Patients with insomnia may be treated up to 5 times weekly with zolpidem (≤10 mg/dose), eszopiclone (≤2 mg/dose), or zopiclone (≤10 mg/dose). However,

none of these drugs should be used within the 12 h prior to cognitive function testing. Antiparkinsonian drugs may be used at an equivalent biperiden hydrochloride dose of ≤3 mg/day. Any concomitant therapy that has been used for at least 30 days prior to the date of informed consent may be continued at the same dosage during participation in the study.

2.5 Endpoints

The primary endpoint is the change from baseline in BAC App composite T-score at the end of the NEAR combination treatment period. BACS is a tool to assess both the composite and individual domain scores of cognitive function that are most frequently impaired and most strongly associated with outcomes in schizophrenia (36). The domains assessed include verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency. BACS-J is the validated, Japanese version of BACS (37). The BAC App, which will be used in this study, is a tablet version of BACS/BACS-J (31).

Secondary endpoints include the change from baseline at the end of the NEAR combination treatment period in the Positive and Negative Syndrome Scale (PANSS) (38, 39), Brief Negative Symptom Scale (BNSS) (40, 41), Montgomery Åsberg Depression Rating Scale (MADRS) (42), BAC App subscale T-score, University of California San Diego Performance-based Skills Assessment-Brief (UPSA-B) (43, 44), Specific Levels of Functioning Scale (SLOF) (45, 46), Schizophrenia Quality of Life Scale (47, 48), EQ-5D-5L (49–51), Work Productivity and Activity Impairment Questionnaire (52), and Defeatist Performance Belief (53–55). Change from baseline to the end of the pharmacotherapy alone period and change from the end of the pharmacotherapy alone period to the end of the NEAR combination treatment period in each of these scale scores will also be included as secondary endpoints. Additional endpoints will include the proportion of patients who successfully switch from their prior antipsychotic treatment to the study drugs, the proportion of patients who discontinue the study treatments, the total number of NEAR sessions performed as part of the study treatment, and the proportion of patients who discontinue NEAR. All study raters will have received training in the use of PANSS, BNSS, MADRS, SLOF, UPSA-B, and BACS-J, as well as operational training for the BAC App (VeraSci).

Safety endpoints will include AEs, change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) from baseline and the pharmacotherapy alone period to the NEAR combination treatment period (56, 57), change in DIEPSS from baseline to the pharmacotherapy alone period, vital signs, height, body weight, and laboratory tests.

2.6 Sample size

Assuming the standardized group difference of 0.5 based on the effect size (0.82 and 0.32) of previous studies (20, 27, 29, 30), the mixed models for repeated measures (MMRM) requires 64 patients for each group to achieve 80% power to detect a group difference of 0.5 at a two-sided significance level of 0.05 (58). With the anticipation that some patients would fail to switch from their prior antipsychotic drug to the study treatment, a dropout rate of 25% was assumed (27). Based on the above, the target sample size of this study was determined to be 170 patients (85 per group).

2.7 Statistical analyses

The efficacy and safety analyses will be based on the full analysis set, which will include all patients who are randomly allocated, undergo treatment, and are evaluated at least once. The per-protocol set will also be analyzed. Two-sided p-values will be presented; $p < 0.05$ will be considered statistically significant.

The primary endpoint, change from baseline to end of the NEAR combination treatment period in BAC App composite T-score, will be analyzed using the MMRM to estimate the difference between the groups. Covariates will be allocated group, time point, interaction term of the allocated group and time point, and baseline score. For all other scores of change, the repeated measures will be analyzed using the MMRM, and one-point measures will be analyzed using the linear models.

As a secondary analysis of changes from the end of the pharmacotherapy alone period, MMRM with the inverse probability weighting method will be used to adjust the imbalance between the groups caused by dropouts during the pharmacotherapy alone period. Weights will be estimated using logistic regression with explanatory variables that will be selected from treatment group, patient characteristics, baseline scale scores, occurrence of serious adverse effects, and their interaction terms.

The proportion of patients who complete the switch to the study drug, discontinue the pharmacotherapy alone period, and discontinue the NEAR combination treatment period will be compared between treatment groups using Fisher's exact test. The number of NEAR sessions completed will be compared between treatment groups using the Wilcoxon test. Subgroup analyses will be performed by baseline BAC App composite T-score, age, sex, duration of disease, and baseline BAC App symbol coding score. Missing data will not be imputed.

AEs will be coded by System Organ Class and Preferred Term per the Medical Dictionary for Regulatory Activities, version J.25.1 or higher. The frequency and proportion of patients reporting AEs will be summarized by time point and group.

All statistical analyses will be conducted using SAS version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or R version 3.6 or higher.

3 Discussion

The VICTORY-S study will examine the effects of treatment with either lurasidone or paliperidone combined with cognitive remediation on cognitive function in patients with schizophrenia. A network meta-analysis of 54 randomized controlled trials that included 5,866 patients with schizophrenia found that lurasidone treatment, when compared with other antipsychotic agents, elicited the greatest improvement in attentional function, working memory, and cognitive composite score (59). Recent efforts aimed at enhancing improvement in cognitive function with treatment have explored combining pharmacological interventions with cognitive remediation; to our knowledge, only one study to date has evaluated the efficacy of combining lurasidone and cognitive remediation for the treatment of

schizophrenia (30). In that study, patients received lurasidone combined with either cognitive remediation or video game use. However, cognitive function had recovered by the time cognitive remediation was initiated, and there was no antipsychotic control. For those reasons, the previous study was not able to assess whether lurasidone enhances the therapeutic effects of cognitive remediation. Given the reported beneficial effects of lurasidone on cognitive function (25–29), we hypothesize that the lurasidone plus NEAR combination group may experience a greater improvement in cognitive and social function than the paliperidone combination group. VICTORY-S is the first study to examine the potential of lurasidone to facilitate the therapeutic effects of cognitive remediation for schizophrenia.

Adequate social function supports the ability of patients with schizophrenia to live in social communities. Together with improvement of subjective satisfaction, improvement of social function is considered an important treatment goal for schizophrenia. Given that cognitive function is the factor most related to social function (7), treatment is often aimed at its improvement. Studies have shown that neither pharmacological nor psychosocial treatment alone have adequate effect sizes (0.17–0.46) (20, 21). Though there are few reports of the effectiveness of combination therapy, many clinicians treat their patients with a combination of pharmacological and psychosocial therapy. Cognitive remediation has been shown to improve social function when added to other psychosocial treatments; however, the time and effort needed to maintain combination psychosocial treatments can be a barrier to patient participation (21). Therefore, we plan to examine the efficacy of a combination of cognitive remediation and lurasidone, an approved antipsychotic that has been suggested to improve cognitive function. The results of this study are expected to help guide treatment choices in daily clinical practice. In addition, if combined lurasidone and cognitive remediation therapies elicit stronger improvement in social function than monotherapy, then there is greater hope that patients with schizophrenia will be able to participate in social activities while continuing treatment for cognitive function.

Green et al. proposed a path diagram of (1) cognitive function; (2) defeatist beliefs; (3) negative symptoms; and (4) social function as a mechanism by which cognitive function affects social function (60). With this in mind, we set the change from baseline in BAC App composite T-score as the primary endpoint of this study and set the endpoints in the path diagram as secondary outcomes. This strategy may reveal which parts of the mechanism are affected by pharmacotherapy and which parts are affected by the addition of cognitive remediation. Thus, the results of this study are expected to be comparable with previously published studies. The assumed treatment period for cognitive remediation is 3 to 6 months, based on the average of 16.7 weeks reported in the meta-analysis (21); the present study will evaluate study endpoints at both 18 and 30 weeks, allowing for the evaluation of treatment duration. From this, we hope that the findings of this study will assist clinicians in implementing NEAR more strategically.

Paliperidone was selected as the active comparator for use in this study. Paliperidone, the major active metabolite of risperidone (9-hydroxy-risperidone), has inhibitory effects on D_2 and 5-HT_{2A} receptors; as such, it is classified as a serotonin–dopamine antagonist (61). Paliperidone is currently approved for the treatment of schizophrenia in various regions, including the United States, the European Union, and Japan, and is considered to be a standard treatment for schizophrenia. In a network meta-analysis of 34 randomized controlled trials of antipsychotic treatment for schizophrenia (62), paliperidone was significantly superior to placebo in all-cause discontinuation rates and ranked highest among the other antipsychotic agents with respect to Surface Under the Cumulative Ranking Curves, indicating the usefulness of this drug in schizophrenia treatment. It has also been shown that paliperidone does not have an adverse effect on cognitive function (63). Based on this information, we chose paliperidone as the active comparator for use in this study.

Based on the results of previous phase 3 clinical trials of lurasidone and paliperidone, the pharmacotherapy alone period is set to 6 weeks in this study. In the previous clinical trials, the PANSS total score significantly improved after 6 weeks of lurasidone or paliperidone treatment compared to placebo (64–67). Furthermore, a previous study of lurasidone reported a significant improvement in cognitive function compared to placebo at 6 weeks (27). The present study will examine not only the effects of the combination of lurasidone and paliperidone with NEAR, but also these monotherapies. Therefore, the efficacy of these study drugs should have reached a steady state prior to the initiation of the NEAR combination treatment, and 6 weeks is considered sufficient as the pharmacotherapy alone period.

Cognitive function in patients with schizophrenia is also thought to be influenced by daily lifestyle, and it has been suggested that aerobic exercise and aerobic exercise combined with cognitive remediation may improve cognitive function (68, 69). It may be worthwhile to discuss the improvement effects on cognitive function between the results of this study (combination of lurasidone with cognitive remediation) and combination of aerobic exercise and cognitive remediation in the future.

4 Conclusion

The VICTORY-S study will be the first to examine the potential of lurasidone to enhance the therapeutic effects of cognitive remediation for schizophrenia. The findings from this study are expected to provide useful insight for clinicians who treat patients with schizophrenia.

Ethics statement

The study protocol was approved by the Clinical Research Review Board of the National Center of Neurology and Psychiatry, National Research and Development Agency (CRB3200004), and written informed consent will be obtained from patients before enrollment. The study will be conducted in accordance with the principles of the Declaration of Helsinki and the Clinical Trials Act in Japan, and is registered under the identifier jRCTs031200338.

Author contributions

RK: Investigation, Writing – original draft, Writing – review & editing. SaI: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. HO: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – original draft,

Writing – review & editing. MO: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – original draft, Writing – review & editing. ShI: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – original draft, Writing – review & editing. RT: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – original draft, Writing – review & editing. LA: Investigation, Writing – original draft, Writing – review & editing. MM: Investigation, Writing – original draft, Writing – review & editing. ST: Conceptualization, Writing – original draft, Writing – review & editing. YN: Conceptualization, Writing – original draft, Writing – review & editing. DH: Conceptualization, Writing – original draft, Writing – review & editing. TI: Conceptualization, Writing – original draft, Writing – review & editing. KN: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

RK received honoraria from Sumitomo Pharma Co., Ltd. SaI received honoraria from Nippon Boehringer Ingelheim Co., Ltd., Lundbeck Japan K.K., Sumitomo Pharma Co., Ltd., and Takeda Pharmaceutical Co., Ltd. HO received research funding from Otsuka Pharmaceutical Co., Ltd.; and is the director of Japan Society of Clinical Trials and Research and The Japanese Association of Pharmaceutical Medicine. MO received honoraria from Pfizer Japan Inc., AstraZeneca K.K., and EP-SOGO Co., Ltd. ST and YN are employees of Sumitomo Pharma Co., Ltd. KN received honoraria from Sumitomo Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corp., Takeda Pharmaceutical Co., Ltd., Lundbeck Japan K.K., Viatris Inc., Eisai Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Mochida Pharmaceutical Co., Ltd.; support for transportation to attend meetings from Sumitomo Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corp., Takeda Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Mochida Pharmaceutical Co., Ltd.; and his institution received grants from Shionogi & Co., Ltd., Sumitomo Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corp., Nippon Boehringer Ingelheim Co., Ltd., and Mochida Pharmaceutical Co., Ltd.

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Investigating amplitude of low-frequency fluctuation and possible links with cognitive impairment in childhood and adolescence onset schizophrenia: a correlation study

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Background: Cognitive impairment (CI) is a distinctive characteristic of schizophrenia, with evidence suggesting that childhood and adolescence onset schizophrenia (CAOS), representing severe but rare forms of schizophrenia, share continuity with adult-onset conditions. While relationships between altered brain function and CI have been identified in adults with schizophrenia, the extent of brain function abnormalities in CAOS remains largely unknown. In this study, we employed resting-state functional magnetic resonance imaging (rs-fMRI) to investigate functional alterations in brain areas among patients with CAOS. To assess CI across multiple cognitive domains, we utilized the Stroop Color and Word Tests (SCWT) and MATRICS Consensus Cognitive Battery (MCCB) tests. Our objective was to explore the associations between functional CI and the amplitude of low-frequency fluctuation (ALFF) levels in these patients.

Methods: We enrolled 50 patients diagnosed with CAOS and 33 healthy controls (HCs) matched for sex and age. Cognitive functions were assessed using the MCCB and SCWT methods. Rs-fMRI data were acquired using gradient-echo echo-planar imaging sequences. Voxel-based ALFF group maps were compared through two-sample t-tests in SPM8. Subsequently, correlation analyses were conducted to identify associations between ALFF levels and cognitive scores.

Results: In comparison to HCs, patients exhibited significantly increased ALFF levels in the right fusiform gyrus, frontal lobe, and caudate, as well as the left frontal lobe and caudate. Conversely, reduced ALFF levels were observed in the temporal and left medial frontal lobes. Significant differences were identified between HCs and patients in terms of total cognitive scores, ALFF levels, and domain scores. All test scores were decreased, except for TMA. Correlation analyses between ALFF levels and cognitive functions in patients with CAOS differed from those in HCs. Pearson correlation analyses revealed positive associations between Brief Visuospatial Memory Test - Revised (BVMT-R)

scores and ALFF levels in the left medial frontal gyrus. Digital Span Test (DST) scores were negatively correlated with ALFF levels in the right caudate, and Maze Test values were negatively correlated with levels in the left caudate. However, Pearson correlation analyses in HCs indicated that color and Hopkins Verbal Learning Test (HVLT-R) scores positively correlated with ALFF levels in the left frontal lobe, while color-word and symbol coding scores negatively correlated with levels in the right caudate.

Conclusions: Altered ALFF levels in the brain may be linked to cognitive impairment (CI) in patients with CAOS. We highlighted the pathophysiology of schizophrenia and provide imaging evidence that could potentially aid in the diagnosis of CAOS.

KEYWORDS

amplitude of low-frequency fluctuation, children and adolescence onset schizophrenia, cognitive function, schizophrenia, RS-fMRI

Introduction

Schizophrenia, as a mental disorder, still lacks a well-characterized etiology. Research has defined it as a neurodevelopmental disorder with a complex genetic basis (1, 2). Individuals with schizophrenia often exhibit cognitive dysfunction and negative symptoms that are frequently resistant to therapeutic interventions (3). Extensive studies have explored the relationships between brain structures and cognitive functions in schizophrenia, with cognitive remediation investigations focusing on both functional and connectivity changes (4, 5). Previous research has identified significant associations between overall brain structures and eight MATRICS-inspired cognitive domains, suggesting a potential functional network architecture underlying brain structure-cognition relationships (6). Other studies have provided comprehensive evidence of functional, structural, and neurochemical changes in the brain, particularly in subcortical regions and the association cortex (7). Social cognition, a significant research area in understanding cognitive impairment (CI) in schizophrenia, has linked changes in social cognition to structural and functional disturbances in areas known as the social brain (8). Cognitive remediation efforts have shown the ability to protect gray matter volume (GMV) in specific medial temporal lobes, such as the para-hippocampus, amygdala, and hippocampus, as well as thalamus regions. Meanwhile, functional alterations primarily impact the dorsolateral prefrontal lobe and insular cortex, both associated with improved cognitive ability (9). Notably, improvements in cognitive remediation have been observed in thalamic and prefrontal regions (10). Critically, neuroimaging facilitates the examination of affected brain areas linked with CI, and thus seeks to identify brain function alterations.

Childhood and adolescence onset schizophrenia (CAOS) represents a challenging psychiatric condition that is resistant to treatment, characterized by its chronic and severe nature, often surpassing the severity seen in adult-onset cases. Onset before adolescence is uncommon, but early age onset can predict worse prognosis (11). Unfortunately, there is a significant gap in the availability of safe and effective antipsychotics designed specifically for children and adolescents, making comprehensive research and development crucial for addressing CAOS. The rarity of CAOS is evident in a record-linkage study of hospital admissions in the UK. However, it is noteworthy that incidence rates of schizophrenia and non-affective psychoses have substantially increased among adolescents (12). Schizophrenia is widely regarded as a reflection of abnormal brain development, and its manifestation is particularly severe in patients with CAOS. Previous research on CAOS has suggested that developmental events may contribute to the onset of the condition (13). In comparative investigations focusing on CAOS, it has been observed that the severity of negative symptoms and the age of onset serve as pertinent predictors of the disease (14).

Previous advancements in neuroimaging have shed light on neural and functional abnormalities in early-stage schizophrenia, emphasizing the understanding of disease development in the maturing brain (15). In recent years, many neuroimaging-related schizophrenia investigations have reported that abnormal brain structures are related to pathophysiological actions underpinning schizophrenia (16, 17). In the present study, significant alterations in ALFF levels were recorded in the spontaneous oscillation of functional resting-state magnetic resonance images (rs-fMRI) (18, 19), and we observed that ALFF was a potential, biologically significant parameter for regional brain function assessment (20). Measuring ALFF levels through blood oxygenation-dependent signals has provided valuable insights into regional neural functions, showing correlations with local field potential activity (21). Importantly, few investigations have focused on CAOS in terms of both brain structure and function. Therefore, this

investigation aims to contribute new insights into the pathophysiology of CAOS and scrutinize the diagnostic criteria for this complex disorder.

Cognitive dysfunction is a prominent feature in the majority of schizophrenia cases and is closely associated with the degree of social function prognosis in affected individuals. Patients commonly exhibit deficits in working memory, processing speed, attention, visual and verbal learning, as well as substantial impairments in reasoning, planning, problem-solving, and abstract thinking (22). In adults with schizophrenia, evidence suggests that mild cognitive impairment (CI) in those who later develop schizophrenia or related disorders may manifest in early childhood, potentially increasing the risk of schizophrenia in adulthood (23, 24). Compared to adult-onset schizophrenia, CAOS patients often experience more pronounced neurocognitive deficits, heightened disability levels, diminished socio-occupational functioning, and increased levels of self-stigma (25). A previous schizophrenia investigation reported that patients had poorer cognitive and social functioning during childhood and adolescence as well as present-state social cognition and cognitive functioning scores when compared to healthy controls (HCs) (26). While aberrant ALFF levels in brain areas and cognitive dysfunction are frequently reported in schizophrenia, the connections between ALFF and CI remain inadequately explored in patients with CAOS.

Materials and methods

Participants

Between October 2013 and March 2018, we recruited a total of 80 right-handed subjects after a thorough screening process, comprising 50 patients diagnosed with CAOS and 33 HCs. Ethical approval was obtained, and written informed consent was provided by all participants. CAOS diagnoses were determined using the Structured Clinical Interview for DSM-IV (SCID-IV), involving diagnostic discussions among at least two experienced clinicians. Patients with CAOS were aged between 8-18 years old, had a disease duration of less than 1 year, and were treatment-naïve to antipsychotic therapy. HCs from a local school underwent Structured Clinical Interview non-patient edition (SCID-NP) screening to ensure the absence of psychiatric and neurological illnesses in themselves and their immediate relatives. Clinical characteristics and demographics are presented in Table 1. Exclusion criteria included: (a) Intellectual Disability, (b) organic brain disorder, and (c) physical illness, including brain tumor, hepatitis or epilepsy as indicated by medical records. Brain MR ALFF BOLD data were assessed by experienced clinical personnel, and no gross abnormalities were identified.

Data gathering

Functional and structural MRI scans were conducted using a 3T MR scanner (TIM Trio, Siemens, Erlangen, Germany) in a single session. For the generation of three-dimensional (3D) head images, rapid acquisition gradient echo sequences were employed with the following parameters: slice thickness of 1 mm, field of view (FOV) of 56 × 256 mm^2, repetition time (TR)/echo time (TE) of 530 ms/2.43 ms, and a flip angle of 7°. BOLD signal-sensitive MRIs were generated using gradient echo-planar imaging (EPI) sequences (TR/TE of 2000 ms/30 ms and a flip angle of 90°).

Computing ALFF and preprocessing data

From each functional time series, we eliminated the first five volumes due to initial MRI signal instability and participant adaption to study conditions. Throughout rs-fMRI scans, head translation movement data of > 2 mm or > 2° rotation were removed. We slice-time-corrected EPI images, realigned them to initial first series images, and spatially normalized data to the Montreal Neurological Institute (MNI) EPI format, with voxels resampled to 3 × 3 × 3 mm^3. We used the REST toolbox to perform T1-weighting, fMRI preprocessing, and ALFF image computation (26). After band-pass filtering (0.01–0.08 Hz)[10] and linear trend removal, we converted time series' to frequency domains using fast Fourier transformations (FFTs) (FFT length; shortest and taper percent; 0) to generate power spectra. As frequency power was proportional to component frequency amplitude squared, we square-rooted and averaged FFT power spectra across 0.01-0.08 Hz at each voxel to generate ALFF levels. For

TABLE 1 Participant clinical characteristics and demographics.

Characteristics	CAOS (n=50)	HCs (n=33)	*t*	χ^2	*P*
Age (years)	14.22 ± 2.48	14.33 ± 2.70	-0.20	—	0.84
Sex, F:M	23:27	15:18	—	0.002	0.96
Education level (years)	8.22 ± 2.48	8.33 ± 2.70	-0.20	—	0.84
Illness duration (months)	5.26 ± 3.40	—	—	—	—

F, female; M, male; CAOS, childhood and adolescence onset schizophrenia; HCs, healthy controls.
"-" represents a value that does not exist.

standardization, voxel ALFF levels were divided by global mean ALFF levels.

Statistical analyses

The data were expressed as mean ± SD. Group comparisons were conducted using chi-squared tests and ANOVA in SPSS (version 17.0, IBM Corp, Armonk, NY, USA). Statistical significance was set at p<0.05.

Results

Demographic information

For sex (P=0.96), age (P=0.84), educational levels (P=0.84), handedness or head motion, no significant differences were observed between groups (Table 1). Participant movements were < 2 mm and < 2° for rotation.

ALFF differences between groups

We identified ALFF levels in the typical 0.01-0.08 Hz frequency band. In comparison to HCs, patients recorded significantly elevated ALFF levels in the left frontal lobe and caudate, as well as the right fusiform gyrus, caudate, and frontal lobe. Conversely, patients had significantly reduced ALFF levels in temporal and left medial frontal lobes (Table 2; Figure 1). Red areas indicated elevated ALFF levels in patients with respect to HCs, and blue areas showed lower levels in patients compared to HCs.

Cognitive outcomes

In comparison to HCs, patients with CAOS displayed significantly impaired total scores which were impaired across all domains. All test scores were reduced with the exception of TMA (P<0.001) (Table 3).

Correlations between cognitive function and ALFF

Correlations between ALFF levels and cognitive functions were examined in patients. Pearson correlation analyses indicated that BVMT-R scores positively correlated with ALFF levels in the left medial frontal gyrus (r=0.41, P<0.01). Digital Span Test (DST) scores negatively correlated with ALFF levels in the right caudate (r=-0.30, P<0.05) and Groton Maze Learning (GML) scores negatively correlated with ALFF levels in the left caudate (r=-0.28, P<0.05). Multiple correlation coefficient analyses were statistically significant (Table 4; Figure 2).

Correlations in HCs were also examined; Pearson correlation analyses indicated that color-naming and HVLT-R scores positively correlated with ALFF levels in the left frontal lobe (r=0.37, 0.38, P<0.05). Conversely, named color-word scores and symbol coding negatively correlated with ALFF levels in the right caudate (r=-5.48, -0.40, P<0.05). The findings from multiple correlation coefficient analyses were also statistically significant (Table 5; Figure 3).

Discussion

In previous years, researchers have used the ALFF method to examiners local brain activity in adult patients with schizophrenia and identified links between CI and altered brain functions (18, 21). In our investigations, ALFF differences and CI levels were identified between our groups. When compared with HCs, patients displayed elevated ALFF levels in the left frontal lobe and caudate, as well as the right fusiform gyrus, frontal lobe, and caudate, Conversely, decreased levels were noted in the temporal and left medial frontal lobes. In patients with CAOS, we identified positive correlations between BVMT-R scores and ALFF levels in the left medial frontal

TABLE 2 ALFF (0.01-0.08 Hz) differences in HCs and patient brain areas.

Brain region	Cluster size	Peak coordinates (MNI)			T-values
		x	y	z	
L frontal lobe	42	-39	45	0	4.5848
L caudate	44	-18	15	15	4.8055
R fusiform gyrus	26	33	-18	-42	4.6110
R frontal lobe	17	39	-24	33	4.1542
R caudate	29	15	15	12	4.5811
L medial frontal	29	-3	-30	69	-4.6610
L temporal lobe	32	-51	-24	0	-4.9389

ALFF, amplitude of low frequency fluctuations; MNI, Montreal Neurological Institute; x, y, z, coordinates of peak locations in the MNI space.

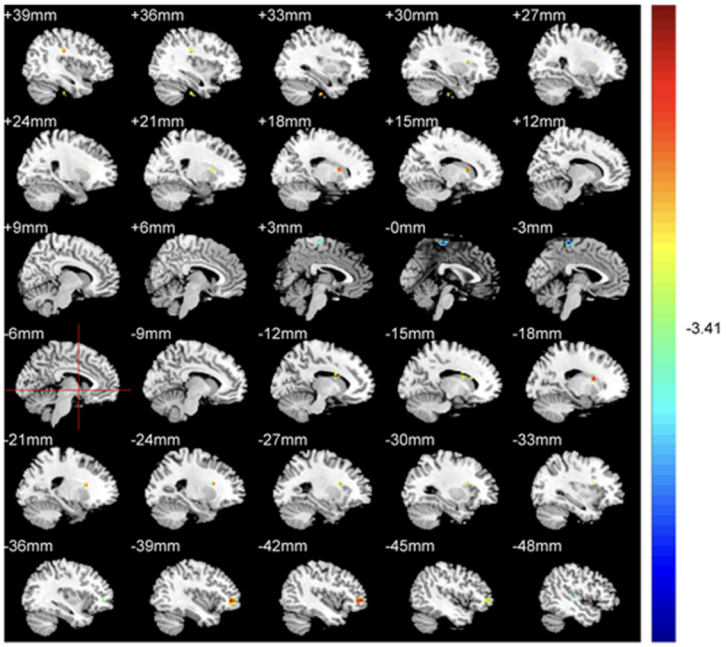

FIGURE 1
ALFF comparisons between patients with CAOS and HCs (P<0.05, AlphaSim corrected). Elevated ALFF levels in patients with COAS are red, while blue indicates reduced levels. When compared with HCs, patients recorded significantly elevated ALFF levels in the left frontal lobe and caudate, and right fusiform gyrus, frontal lobe, and caudate, while decreased levels were recorded in temporal and left medial frontal lobes.

gyrus, but negative correlations were present between DST scores and ALFF levels in the right caudate, and GML scores and ALFF levels in the left caudate. We also examined correlations in HCs; color-naming and HVLT-R scores positively correlated with ALFF levels in the left frontal lobe, whereas color-word scores and symbol coding negatively correlated with ALFF levels in the right caudate. Importantly, our study marked the first exploration of relationships between cognitive function and ALFF levels in patients with CAOS.

ALFF levels serve as indicators of spontaneous and intrinsic neuronal activity, commonly used to highlight abnormalities in conditions like schizophrenia (19). In our study, when compared with HCs, patients with CAOS displayed aberrant ALFF levels in numerous brain areas. A previous meta-analysis reported that spontaneous brain activity alterations in drug-naïve first-episode schizophrenia predominantly included the frontal lobe, putamen, and cerebellum (27). Our findings aligned with this, revealing

TABLE 3 Comparing cognitive functions in HCs and patients.

MCCB/SCWT	Patient group	Control group	*t*	*P*
TMA	63.74 ± 36.58	38.73 ± 13.35	4.41	<0.001
SC	37.64 ± 12.93	56.85 ± 9.57	-7.31	<0.001
HVLT-R	19.40 ± 6.07	26.85 ± 3.92	-6.79	<0.001
BVMT-R	18.60 ± 8.14	30.58 ± 2.76	-9.60	<0.001
FCF	14.32 ± 3.90	19.85 ± 4.12	-6.18	<0.001
DST	43.98 ± 14.52	78.03 ± 18.08	-9.48	<0.001
GML	11.32 ± 5.31	19.82 ± 4.25	-8.07	<0.001
word reading	63.72 ± 16.04	92.00 ± 16.39	-7.80	<0.001
color naming	42.24 ± 11.75	64.03 ± 13.95	-7.67	<0.001
named color-word	24.86 ± 8.77	35.42 ± 8.03	-5.55	<0.001

MCCB, MATRICS Consensus Cognitive Battery; SCWT, Stroop Color and Word Test; TMA, Trail Making Test: Part A; SC, Symbol coding; HVLT-R, Hopkins Verbal Learning Test-Revised; BVMT-R, Brief Visuospatial Memory Test-Revised; FCF, Fluency Category Fluency: Animal Naming; DST, Digital Span Test; GML, Groton Maze Learning; SCWT, Stroop Test conditions (word reading, color naming, named color-word).

TABLE 4 ALFF and cognitive function correlations in patients.

	RFG	LFL	LTL	RC	LC	RFL	LMF
TMA	-0.02	0.04	0.03	0.04	0.08	0.13	0.02
SC	-0.06	0.10	-0.15	-0.07	-0.10	-0.13	0.03
HVLT-R	0.20	-0.10	-0.13	-0.08	-0.08	0.00	0.14
BVMT-R	-0.06	-0.06	-0.08	-0.14	-0.05	-0.10	**0.41****
FCF	0.04	-0.04	0.01	-0.15	-0.03	0.12	-0.04
DST	0.00	0.02	-0.05	**-0.30***	-0.22	0.05	0.05
GML	-0.01	-0.15	0.00	-0.16	**-0.28***	0.00	0.25
word reading	0.14	0.17	-0.08	0.05	0.01	0.15	0.05
color naming	0.08	0.21	-0.07	-0.03	-0.05	-0.22	0.26
named color-word	0.08	0.06	-0.11	-0.14	-0.14	-0.03	0.12

*P<0.05, ** P<0.01; RFG, R fusiform gyrus; LFL, L frontal lobe; LTL, L temporal lobe; RC, R caudate; LC, L caudate; RFL, R frontal lobe; LMF, L medial frontal; TMA, Trail Making Test: Part A; SC, Symbol coding; HVLT-R, Hopkins Verbal Learning Test-Revised; BVMT-R, Brief Visuospatial Memory Test-Revised; FCF, Fluency Category Fluency: Animal Naming; DST, Digital Span Test; GML, Groton Maze Learning; SCWT, Stroop Test conditions (word reading, color naming, named color-word).
Bold values means the correlation between the scores of cognitive function test items and the ALFF values of brain regions with significant differences. * denotes P < 0.05.

significantly elevated ALFF levels in the frontal lobe, consistent with previous studies. Our rs-fMRI data further indicated increased elevated ALFF levels in the bilateral caudate, consistent with patients with schizophrenia (28, 29). Also, previous investigations described elevated ALFF levels in the right hippocampus and left caudate (30, 31). In comparison with HCs, patients with schizophrenia had lowered ALFF levels in the left angular gyrus and fusiform gyrus (32). Our study also identified elevated ALFF levels in the right fusiform gyrus and reduced levels in the left temporal lobe, which partly agreed with Alonso-Solís et al. (33), although they also reported elevated ALFF levels in the temporal pole, in contrast with our observations. A previous rs-fMRI investigation identified elevated ALFF levels in the medial frontal gyrus, and these data were confirmed in a first-episode

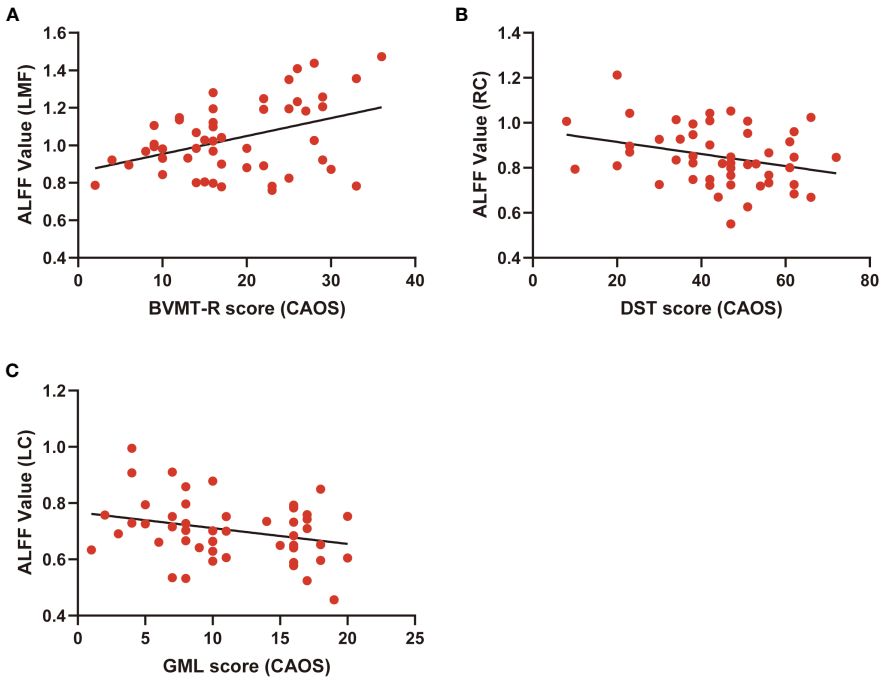

FIGURE 2
Scatter diagram showing relevant LMF trends in ALFF cluster levels, BVMT-R scores **(A)**, cluster RC of ALFF levels and DST scores **(B)**, LC of ALFF cluster levels, and GML scores **(C)**.

TABLE 5 ALFF and cognitive function correlations in HCs.

	RFG	LFL	LTL	RC	LC	RFL	LMF
TMA	0.26	-0.11	0.15	0.07	0.23	-0.05	0.31
SC	-0.21	0.10	0.01	**-0.55***	-0.24	0.04	0.30
HVLT-R	-0.16	**0.37***	0.23	-0.17	-0.21	-0.06	0.01
BVMT-R	0.19	0.08	0.12	0.26	0.21	0.18	-0.07
FCF	-0.01	0.01	0.08	0.02	-0.07	-0.21	0.26
DST	-0.10	0.07	-0.08	0.10	0.00	-0.05	-0.04
GML	-0.04	-0.11	0.30	-0.09	-0.03	-0.20	0.21
word reading	-0.02	0.30	-0.02	-0.18	-0.06	-0.17	0.04
color naming	0.13	**0.38***	0.05	-0.24	-0.07	-0.02	0.26
named color-word	0.21	0.23	0.11	-0.40*	-0.22	0.01	0.12

*P<0.05; RFG, R fusiform gyrus; LFL, L frontal lobe; LTL, L temporal lobe; RC, R caudate; LC, L caudate; RFL, R frontal lobe; LMF, L medial frontal; TMA, Trail Making Test: Part A; SC, Symbol coding; HVLT-R, Hopkins Verbal Learning Test-Revised; BVMT-R, Brief Visuospatial Memory Test-Revised; FCF, Fluency Category Fluency: Animal Naming; DST, Digital Span Test; GML, Groton Maze Learning; SCWT, Stroop Test conditions (word reading, color naming, named color-word).
Bold values means the correlation between the scores of cognitive function test items and the ALFF values of brain regions with significant differences. * denotes $P < 0.05$.

schizophrenic patient investigation (34, 35). However, in our investigation, we identified reduced ALFF levels in the left medial frontal gyrus. These heterogeneous observations are unfortunate and may be reflected by medication effects, age, or illness duration. To limit such factors, we selected first-episode children and adolescents. Importantly, our findings suggested that abnormal ALFF levels in patients with COAS could distinguish these patients from healthy children and adolescents.

Cognitive Impairment (CI) is a fundamental trait in schizophrenia, characterized by consistent deficits across various cognitive domains (23, 25). Numerous reviews have highlighted that individuals with schizophrenia exhibit heightened CI compared to both HCs and individuals with affective disorders, particularly in memory and processing speed domains (36). A previous review also reported that presence of mild CI in early childhood among individuals who later develop schizophrenia, with a notable increase in CI during adolescence, the prodrome, and the first psychotic episodes (24). In our study, the impaired cognitive functions observed in patients with COAS concurred with previous investigations showing CI in all domains in schizophrenia patients. The MATRICS Consensus Cognitive Battery (MCCB) was used to assess the following cognitive domains: 1) visual learning 2) vigilance/attention, 3) working memory, 4) social cognition, 5) processing speeds, 6) problem solving/reasoning, and 7) verbal learning (37). Stroop word-reading reflected visual-search speed, Stroop color-naming indicated working memory and visual-search speed, and Stroop color-word referred to working memory, conflict monitoring, and visual-search speed (38). When MCCB and Stroop Color and Word Test (SCWT) methods were used to measure cognitive functions, all test scores were lower except for TMA. A recent investigation indicated that cognitive profiles in childhood and adolescence could be used to differentiate between psychiatric disease spectra (39). Our data further suggested that CI could serve as a distinguishing factor for patients with COAS compared to healthy children and adolescents, and the degree of impairment may contribute to prognosis considerations.

Individuals with schizophrenia commonly exhibit cognitive domain deficits, yet the neurobiological underpinnings of these impairments remain largely unknown (3). Neuroimaging studies have highlighted the neurobiological foundation of cognitive function in schizophrenia, and facilitated exploration of affected brain areas associated with such CI's. Recently, it was reported that neurocognition was associated with brain structures which was characterized by higher immediate recall scores which were linked to elevated GMV in the left temporal pole, elevated verbal fluency scores associated with elevated GMV in the left temporal pole, middle temporal gyrus, and elevated Stroop-word scores linked to raised GMV in the right middle frontal gyrus (40). Previous findings also reported that executive function impairments were linked to prefrontal cortex thickness and volume, cognitive control impairments were correlated with elevated anterior cingulate cortex activation, and episodic memory impairments were related to hippocampal reduction (10). From fMRI analyses, BVMT-R scores in patients were positively linked to ALFF levels in the left medial frontal gyrus. Also, prefrontal cortical deficits occurred during schizophrenia and reflected neural working-memory pathway deficits, consistent with elements of our investigation (41, 42). Moreover, HVLT-R and color-naming scores in HCs were positively linked with ALFF levels in the left frontal lobe. Importantly, these aforementioned research studies exemplified the relationship between the frontal lobe and cognition.

While early investigations in schizophrenia indicated that ALFF levels in the left precentral gyrus negatively correlated with several MCCB cognitive domains, and opposite results in the left cortex/precuneus (31). Compared to HCs, patients exhibited decreased ALFF in the bilateral postcentral gyri and paracentral lobule, and

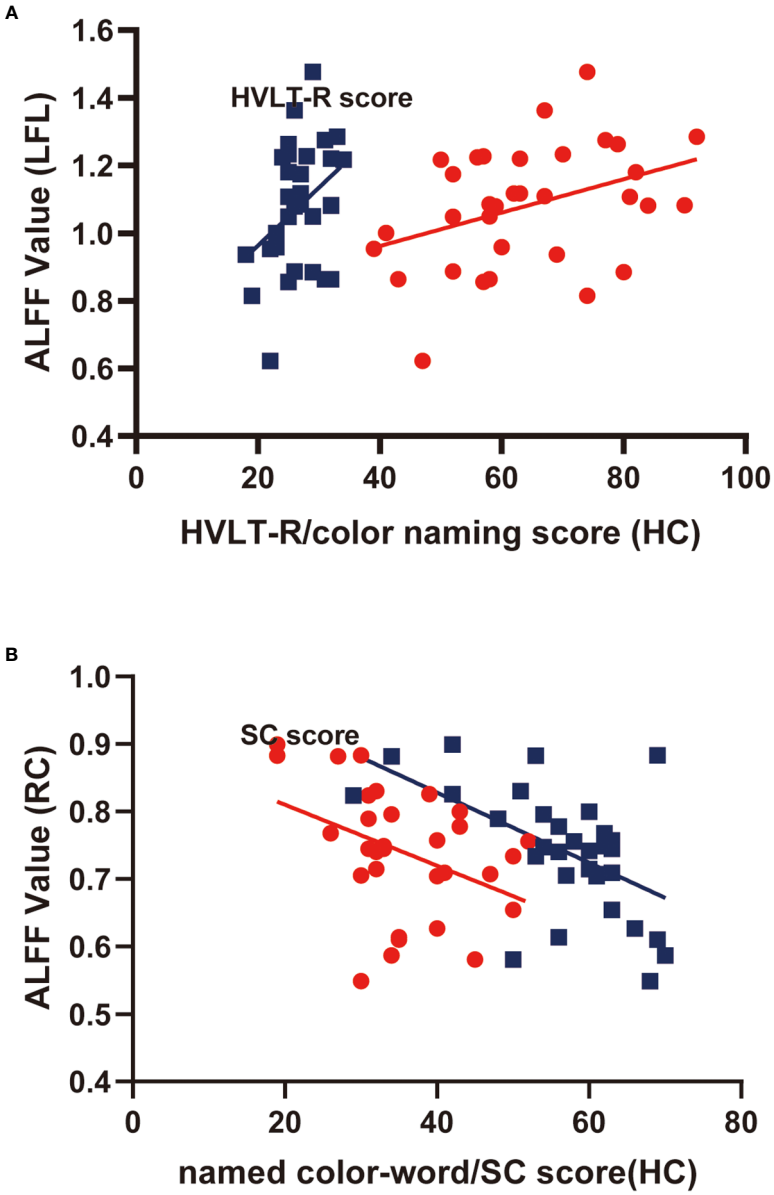

FIGURE 3
Scatter diagram showing relevant LFL trends in ALFF cluster levels, HVLT-R scores, color-naming scores **(A)**; RC of ALFF cluster levels, named color-word scores, and SC scores **(B)**.

these reductions were negatively correlated with the symbol coding sub-tests of MCCB (28). Additionally, in patients, DST scores negatively correlated with ALFF levels in the right caudate, while GML scores negatively correlated with levels in the left caudate. However, overall, research findings in this area are inconsistent across studies, and our understanding of the relationships between functional CI and ALFF remains limited.

Our study presented several strengths. Firstly, links between ALFF levels and CI in patients with COAS have never been studied before. Secondly, our study circumvented confounding factors, such as medication effects, illness chronicity, and educational background, in affected individuals. Finally, we examined relationships between brain function and CI in patients with COAS to better understand the pathophysiology underlying schizophrenia and improve prognostic social functioning. Nevertheless, our investigation had certain limitations. Firstly, COAS is a rare mental disorder, therefore subject recruitment was limited, and sample size was low. Secondly, we were unable to eliminate all physiological noise effects. Thirdly, some participants may not have shut their eyes during resting sessions. Lastly, while we limited head movements as much as possible, a previous investigation indicated that minimal head motion affected ALFF measurements during rs-fMRI (43). Therefore our future aim is to expand sample sizes and comprehensively address these limitations.

Conclusions

CI is prominent in patients with CAOS who presented with ALFF alterations in several brain areas during our investigations - these changes may be linked to CI in these patients. Critically, our investigation provides new information on the pathophysiology of schizophrenia and provides improved diagnostic and predictive insights for patients with CAOS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Second Affiliated Hospital of Xinxiang Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

YiL: Data curation, Formal Analysis, Writing – original draft. RS: Formal Analysis, Software, Writing – original draft. YX: Methodology, Project administration, Visualization, Writing – original draft. YaL: Data curation, Formal Analysis, Writing – original draft. SG: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Association between increased BMI and cognitive function in first-episode drug-naïve male schizophrenia

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Objective: Although the adverse effects of obesity in schizophrenia are documented, there is limited research exists on the implications for untreated initial schizophrenia. Our investigation aimed to explore the connections between BMI and cognitive function in first-episode drug-naïve (FEDN)schizophrenia.

Methods: We enrolled 143 FEDN schizophrenia patients, and collected data on their body mass index, fasting blood glucose and lipid levels. Cognitive function was measured with the MATRICS Consensus Cognitive Battery (MCCB). Using correlation and regression analysis to assess the relationship between BMI and cognitive performance.

Results: The prevalence rate of overweight plus obesity in FEDN schizophrenia patients was 33.57%. Patients with FEDN schizophrenia exhibited extensive cognitive impairment, and those who were overweight/obesity demonstrated more severe impairments in working memory and visual learning when compared to normal/under weight counterparts. Correlation analysis indicated a negative association between working memory and BMI and TG, as well as a link between visual learning and BMI and LDL-C. Multiple linear regression analysis revealed that a higher BMI predicted a decrease in working memory in FEDN schizophrenia patients.

Conclusion: Our results indicate that the rate of overweight plus obesity is high in FEDN schizophrenia patients, and there is an association between BMI and cognitive function in schizophrenia, particularly in relation to working memory.

KEYWORDS

schizophrenia, cognitive function, BMI, overweight/obesity, normal/under weight

Introduction

Schizophrenia is a chronic disease with an unclear etiopathogenesis and poor prognosis, representing a heavy economic burden (1). According to epidemiological studies, up to 50% of patients with schizophrenia experience obesity problems (2), and approximately 44% of untreated first-episode schizophrenia patients are overweight or obese (3), which is higher than the rate among general population (2, 3). Furthermore, obesity in individuals with schizophrenia not only increases their vulnerability to physical ailments like cardiovascular disease but also diminishes their life expectancy by approximately a decade (4, 5).

Cognitive impairment is a significant and prevalent issue in schizophrenia (6). A number of studies consistently underscored that cognitive impairment hinders the recovery of social functioning in schizophrenia and is the most challenging core symptom to significantly improve (7–9). Previous research has discovered a connection between obesity and cognitive dysfunction. For instance, obese mice displayed poorer learning and memory capabilities than non-obese counterparts (10, 11). A recent study found that schizophrenia patients had lower working memory, motor speed, and cognitive composite scores as BMI increased (12). Another study pointed out that elevated BMI may detrimentally affect neurocognitive function by disrupting white matter integrity in schizophrenia (13). However, C. W. Wei et al. discovered a positive correlation between BMI and verbal and visuospatial abilities in schizophrenia (14). Furthermore, Rashid et al. suggested that obesity does not exert a direct impact on cognitive function in schizophrenia (15).

However, the aforementioned studies primarily focused on chronic schizophrenia patients, and the results could be influenced by prolonged psychiatric symptoms and the administration of antipsychotic medications (16–18). Antipsychotic medications, especially atypical antipsychotics, have been indisputably linked to obesity-related metabolic disturbances (17, 18). There is also intense debate regarding the impact of antipsychotic drugs on cognitive function (19). Furthermore, there are gender differences in the psychiatric symptoms and cognitive functions of patients with schizophrenia (20). Similarly, Zhu Y et al. found that attentional bias during social information processing also exhibits gender differences (21). There is little research examining the association between obesity and cognition in first-episode drug-naïve (FEDN) schizophrenia patients. Therefore, the insufficient evidence regarding the cognitive implications of obesity in schizophrenia calls for further investigation to establish a clearer understanding.

Considering the sex differences in schizophrenia (20, 21) and the effect of antipsychotic medication (16, 17, 22), we recruited first-episode drug-naïve male patients with schizophrenia to control for these confounding factors. We collected metabolic indicators, including BMI, fasting plasma glucose, and lipids, as well as symptom dimensions and cognitive assessment scores. The primary objective of this study was to investigate the differences in cognitive function between overweight/obesity and normal/under weight FEDN male patients with schizophrenia, followed by an investigation into the correlation between BMI and cognitive function. We postulated that a significant correlation would exist between BMI and cognitive ability in FEDN male schizophrenia. Building upon prior research, we recruited drug-naïve male patients with first-episode schizophrenia to control for these confounding factors.

Materials and methods

Participants

Our study subjects were 143 patients enrolled in the outpatient clinic and inpatient departments of the Affiliated Brain Hospital of Nanjing Medical University from May 2017 to October 2022. All patients were unanimously assessed by two highly experienced associate chief psychiatrists or chief psychiatrists, in accordance with the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5. All study participants were diagnosed with schizophrenia after at least 1 year of follow-up. The inclusion criteria for schizophrenic patients were as follows: (1) the Chinese Han population, right-handed, aged 16-44; (2) Education years ≥ 8 years, intelligence quotient (IQ) ≥ 70; (3) First onset, duration of first psychotic symptoms ≤ 24 months, drug naïve (i.e., no previous exposure to antipsychotics), no prior exposure to physical therapy; (4) Positive and Negative Syndrome Scale (PANSS) total score ≥ 60 points. Exclusion criteria included major somatic disorders, organic mental disorder, dementia/mental retardation, alcohol or substance abuse. Participants provided written consent, and the Medical Research Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University approved this consent procedure.

Clinical and psychological assessments

Age, sex, and years of education were self-reported. Height and weight were measured, and body mass index (BMI) was calculated using the formula BMI = weight (kg)/height squared (m^2). Based on the Chinese metabolic abnormality criteria (23), individuals with a BMI≥24 kg/m^2 were considered overweight/obesity group, while those with a BMI < 24 kg/m^2 were classified as normal/under weight group.

Fasting blood samples were collected between 6:30-7:30 in the morning. The levels of fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using Beckman AU5821 automatic biochemical analyzer.

We computed duration of illness (DUI) from onset of illness to the date of assessment. Intellectual quotient (IQ) was measured using the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS), which includes four subtests: Knowledge Quiz, Similarity Test, Picture Filling Test, and Block Diagram Test. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS), which was administered by two experienced psychiatrists who received an intra-class correlation coefficient (ICC) above 0.8 prior to the study inception. All data collection was completed in 5 days.

Measures of cognitive function

The cognitive functions were assessed using the Chinese version of the MATRICS Consensus Cognitive Battery (MCCB) (24). MCCB included 9 sub-items, which were Trail Making Test, Symbol Coding, Hopkins Verbal Learning-Revised, Spatial Span, Mazes, Brief Visuospatial Memory Test-Revised, Fluency, Managing Emotions, and Continuous Performance Test-Identical Pairs. Standardized T scores were calculated for each subtest to assess composite scores and the following seven cognitive domains: speed of processing, attention and vigilance, working memory, visual learning, verbal learning, problem solving, and social cognition (25).

Statistical analyzes

The analysis was conducted using SPSS 27.0. The normality of the data distribution was assessed using the Shapiro-Wilk test. After conducting this test, it was found that all quantitative data adhered to a normal distribution. Independent samples t-test was employed to compare the demographic, clinical characteristics, and cognitive function between groups. The cognitive function of norm and patients was compared using one sample t-test. Pearson correlation analysis was used to explore preliminary associations between BMI and cognitive function. Multiple linear regression analysis was employed to further explore the relationship. In this analysis, cognitive function served as the dependent variable, while meaningful indicators identified through correlation analysis were considered independent variables. Additionally, we controlled for covariates such as age, IQ, and DUI.

Results

Demographic and clinical characteristics

The demographic, metabolic characteristics and PANSS scores are shown in Table 1. The rate of overweight/obesity among FEDN patients with schizophrenia was 33.57% (48/143), which was higher than that of the general population aged 25-33 years (19.10%) (26). Compared to normal/under weight patients, overweight/obesity patients showed significantly elevated levels of BMI, TG and LDL-C (all p <0.05). However, HDL-C is lower in the overweight/obesity group than in the normal/under weight group (p <0.05). There were no significant differences in the remaining demographic variables and PANSS scores between the two groups.

Cognitive function

FEDN schizophrenia patients exhibited significant cognitive deficits compared to Chinese MCCB norms (n = 656, mean = 50, SD = 10) (24), as stated in Table 2 (all $p < 0.001$). And the cognitive

TABLE 1 Demographic, metabolic characteristics and PANSS scores of first-episode drug-naïve schizophrenia patients.

	Schizophrenia (n = 143)	groups		t	p
		normal/under weight (n = 95)	overweight/obesity (n = 48)		
Age (years)	25.73 ± 7.31	24.94 ± 7.05	27.31 ± 7.64	t = -1.850	0.066
Years of Education	13.07 ± 2.72	12.89 ± 2.93	13.42 ± 2.26	t = -1.178	0.241
IQ	107.90 ± 11.70	107.92 ± 11.83	107.86 ± 11.58	t = 0.029	0.977
DUI (months)	11.29 ± 8.18	10.93 ± 8.10	12.00 ± 8.38	t = -0.740	0.461
BMI (kg/m^2)	22.75 ± 4.01	20.42 ± 1.96	27.35 ± 2.87	t = -17.010	<0.001***
FBG (mmol/L)	4.51 ± 0.56	4.51 ± 0.57	4.51 ± 0.55	t = 0.017	0.986
TG (mmol/L)	1.15 ± 0.79	0.98 ± 0.61	1.50 ± 1.00	t = -3.292	0.002**
TC (mmol/L)	4.06 ± 0.88	3.97 ± 0.74	4.23 ± 1.09	t = -1.490	0.141
LDL-C (mmol/L)	2.29 ± 0.74	2.17 ± 0.63	2.51 ± 0.88	t = -2.388	0.020*
HDL-C (mmol/L)	1.15 ± 0.25	1.23 ± 0.23	1.00 ± 0.22	t = 5.660	<0.001***
PANSS					
Positive symptom	23.76 ± 3.59	23.48 ± 3.75	24.29 ± 3.22	t = -1.274	0.205
Negative symptom	19.35 ± 3.85	19.36 ± 3.95	19.33 ± 3.67	t = 0.036	0.971
General psychopathology	45.24 ± 3.44	45.01 ± 3.38	45.69 ± 3.54	t = -1.112	0.268
Total symptom	88.30 ± 7.25	87.85 ± 7.28	89.19 ± 7.170	t = -1.041	0.300

Means ± SD value, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
IQ, intelligence quotient; DUI, duration of illness; BMI, body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PANSS, Positive and Negative Syndrome Scale.

TABLE 2 Cognitive function in FEDN schizophrenia patients and controls.

	N	Mean	SD	Controls Mean	t	95% CI	*P*
speed of processing	143	39.56	10.94	50.00	-11.417	-12.25, -8.63	<0.001***
attention and vigilance	143	37.42	10.29	50.00	-14.617	-14.28, -10.88	<0.001***
working memory	143	36.43	10.24	50.00	-15.844	-15.27, -11.88	<0.001***
verbal learning	143	38.57	11.57	50.00	-11.807	-13.34, -9.51	<0.001***
visual learning	143	42.20	11.26	50.00	-8.286	-9.67, -5.94	<0.001***
problem solving	143	43.92	11.01	50.00	-6.607	-7.90, -4.26	<0.001***
social cognition	143	35.34	10.18	50.00	-17.220	-16.34, -12.97	<0.001***
composite scores	143	32.29	11.23	50.00	-18.863	-19.57, -15.86	<0.001***

CI, confidence interval.
***$p < 0.001$.

differences between overweight/obesity and normal/under weight FEDN schizophrenia patients were demonstrated in Table 3. overweight/obesity patients exhibited markedly inferior performance in working memory and visual learning compared to normal/under weight patients. Box plots depicting significant differences between the two groups are presented in Figure 1. However, no significant differences were observed between the two groups in the remaining cognitive domains.

Association between BMI and cognitive function

Pearson correlation analysis revealed a significant negative association between working memory and BMI (r = -0.191, $p = 0.022$) as well as TG (r = -0.246, $p = 0.003$). Similarly, visual learning exhibited a significant negative correlation with both BMI (r = -0.168, $p = 0.045$) and LDL-C levels (r = -0196, $p = 0.019$). There was a negative correlation between TG and problem solving (r = -0191, $p = 0.023$), as well as composite scores (r = -0204, $p = 0.014$). Results of correlation analysis are shown in a heatmap in Figure 2. The scatter plot of BMI and cognitive function are shown in Supplementary Figure S2. Further multiple regression analysis revealed that only a higher BMI predicted a decrease in working memory ($\beta = -0.439$, $p = 0.044$, Table 4).

Discussion

The primary findings of this study were as follows: (1) the rate of overweight/obesity among FEDN schizophrenia patients was 33.57%. (2) FEDN schizophrenia patients had extensive cognitive impairment. And overweight/obesity patients exhibited markedly inferior performance in working memory and visual learning compared to normal/under weight patients. (3) Correlation analysis indicated a significant association between lower working memory and higher BMI and TG, as well as a link between poorer visual learning and elevated BMI and LDL-C in FEDN schizophrenia patients. Further regression analysis revealed that BMI significantly and negatively influenced working memory among FEDN schizophrenia patients.

In this study, we observed a higher overweight/obesity rate (33.57%) among FEDN schizophrenia patients (age 25.73 ± 7.31) compared to the general population aged 15-24 years old (7.50%) and 25-33 years old (19.10%) (26). Our findings are consistent with the previous study by Y. Tian et al., which reported an increased prevalence of overweight and obesity among first-episode schizophrenia in contrast to healthy control (3). Moreover, metabolic syndrome is more likely to develop in both drug-naïve schizophrenia patients and their siblings, regardless of antipsychotic effects (27). The findings suggest a greater propensity for overweight and obesity among individuals with schizophrenia, independent of antipsychotic medication impact.

The increased prevalence of overweight/obesity in first-episode schizophrenia could be attributed to a combination of factors, including unhealthy lifestyles, gut microbiota dysbiosis, and genetic susceptibility. Unhealthy lifestyles, such as reduced time spent on complex activities (28) and excessive consumption of nonalcoholic beverages (i.e., high sugar intake) (29), are common among patients with early-stage schizophrenia and contribute to the elevated obesity rate in this population. In addition, dysbiosis of the gut microbiota may provide a common biological basis for the etiology of schizophrenia and obesity. Both conditions are associated with a reduction in anti-inflammatory bacteria and an increase in proinflammatory and pathogenic bacteria (30). The inflammatory signals produced by gut microbiota may serve as a potential link between schizophrenia and obesity.

More interestingly, several studies suggest that the higher obesity rate among first-episode schizophrenia patients may be attributed to genetic susceptibility. The 22q11.2 deletion syndrome, for instance, is the strongest risk factor for schizophrenia (31, 32) and is also associated with a higher risk of developing obesity (33, 34). A study found a strong correlation between schizophrenia and BMI at 18 different genetic loci, with 16q12.11 being the primary locus (35). The duplication or deletion of 16p11.2 can cause various physical and mental symptoms, including schizophrenia and obesity (36–39). The shared genetic loci between BMI and schizophrenia are linked to 20 significantly enriched pathways,

TABLE 3 Cognitive function in normal/under weight and overweight/obesity schizophrenia patients.

	normal/under weight (n = 95)	overweight/obesity (n = 48)	t	*p*
Speed Of Processing	39.60 ± 10.75	39.48 ± 11.41	t = 0.062	0.951
Attention And Vigilance	38.02 ± 10.16	36.23 ± 10.55	t = 0.983	0.327
Working Memory	37.98 ± 10.52	33.35 ± 9.02	t = 2.600	0.010*
Verbal Learning	38.54 ± 11.39	38.65 ± 12.04	t = -0.053	0.958
Visual Learning	43.81 ± 10.84	39.00 ± 11.50	t = 2.454	0.015*
Problem Solving	43.87 ± 10.84	44.00 ± 11.47	t = -0.065	0.949
Social Cognition	35.61 ± 10.38	34.81 ± 9.85	t = 0.441	0.660
Composite Scores	33.22 ± 10.94	30.44 ± 11.67	t = 1.405	0.162

*$p < 0.05$.

with the proton pump inhibitor pathway and AKT phosphorylation targets in the nuclear pathway being particularly significant (40). These pathways have an impact on neurodevelopment (40), providing insights into the biological mechanisms underlying the relationship between schizophrenia and obesity in terms of genetic susceptibility.

In this study, our second finding is that FEDN schizophrenia patients had significantly lower cognitive function than the norm across multiple domains. This is consistent with previous research (41–43), which demonstrated that early-stage schizophrenia patients suffer from widespread cognitive impairment. Moreover, overweight/obesity schizophrenia patients performed significantly worse than normal/under weight patients in working memory and visual learning. This phenomenon may be related to the detrimental effects of obesity on cognitive function, which has also been corroborated by prior studies (10–13).

However, the exact mechanism underlying the association between obesity and cognitive impairments in schizophrenia is complex and not fully understood. Obesity may lead to inflammation, insulin resistance, vascular changes, and alterations in brain structure and function. It can trigger inflammation pathways in microglial cells, causing abnormalities in cerebral blood vessels and potentially leading to cognitive decline (44, 45). Obesity-related insulin resistance can disrupt gene expression in the hippocampus, impairing cognitive functions (46). Obesity is also associated with increased amyloid-β protein deposition and neurofibrillary tangles, hallmarks of Alzheimer's disease (47). Hormones and cytokines secreted by adipose tissue can affect brain energy metabolism, neuronal survival, emotional states, and cognitive processes, and may cause neuroinflammation and neuronal damage (48–52). Research has linked obesity to gray matter atrophy in various brain regions, notably the prefrontal cortex, which is associated with schizophrenia and cognitive functioning (53, 54). Addressing obesity and its related metabolic effects may be important in managing cognitive impairments in individuals with schizophrenia.

Further correlation analysis revealed a negative association between working memory and BMI and TG, as well as a connection between visual learning and BMI and LDL-C in FEDN schizophrenia patients. Multiple linear regression analysis also revealed that a higher BMI predicted a decrease in working memory in FEDN schizophrenia patients. These findings underscore the potential harm of overweight/obesity on cognitive function in the early stage of schizophrenia, especially in specific cognitive domains such as executive function. However, due to limited relevant studies in FEDN schizophrenia patients, more research is needed to replicate our findings.

Additionally, the research results regarding the association between obesity and cognitive function in patients with schizophrenia who have received antipsychotic medication for a certain period are inconsistent. X. Guo et al. observed a significant association between higher BMI and lower scores on the visual reproduction and digit symbol tests (55). Likewise, S. Hidese et al. detected a negative correlation between BMI and the composite score of Brief Assessment of Cognition in Schizophrenia (BACS) (12). However, C. W. Wei et al.'s study revealed a positive correlation between BMI and language and visuospatial domains (14). Moreover, another study suggests that there is no association between obesity and cognitive impairment in individuals with schizophrenia (56). One speculation is that the more severe

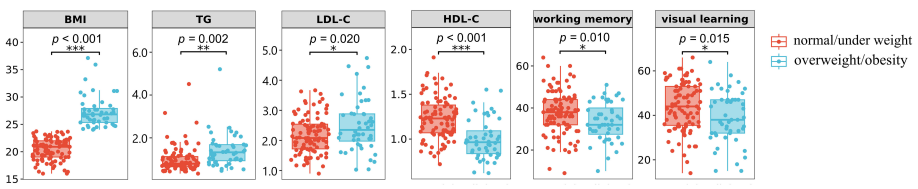

FIGURE 1
Box plots of significant differences between normal/under weight and overweight/obesity schizophrenia.

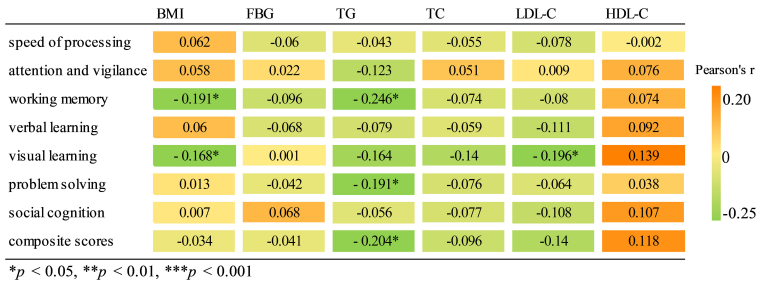

FIGURE 2
Pearson correlation heatmap among cognitive function and metabolic parameters.

cognitive impairments in patients with schizophrenia may obscure the potential correlation between cognitive impairment and other risk factors. For instance, Rashid employed structural equation modeling to unveil the deleterious impact of obesity on the condition of patients with schizophrenia, thereby affecting cognition (15). Another speculation is that the association between obesity and cognition may be related to the 'obesity paradox' (57), where higher BMI in younger years is associated with decreased cognitive abilities, but higher BMI in later years is associated with improved cognition. Furthermore, these inconsistent results may also be attributed to the differences in assessment tools, disease progression, frequency of psychiatric episodes, use of antipsychotic medications, and family economic capacity. Therefore, more research is needed to explore the complex and dynamic relationship between obesity and cognitive function in patients with schizophrenia, especially in specific cognitive domains and different stages of the illness.

The strengths of this study lie in the examination of first-episode drug-naïve schizophrenia patients, and the absence of confounding factors, such as antipsychotic intervention and sex effects. However, this study had several limitations. First, due to its cross-sectional design, we were unable to track changes within each patient and determine causal relationships or moderating effects between variables. Therefore, future studies should focus on longitudinal studies of BMI changes in the same individual to more accurately assess the dynamic relationship between BMI and cognitive function, as well as their association with disease progression and treatment outcomes. We hope that such research will provide more evidence and guidance for cognitive rehabilitation in patients with FEDN schizophrenia. Second, our study solely focused on male schizophrenia patients, which limits generalization to the entire population with schizophrenia. To enhance the inclusivity and comprehensiveness of our observation, it is imperative to improve sample diversity by incorporating female patients and healthy individuals. Third, the sample size of this study was relatively small, which could increase the likelihood of obtaining false-negative results. Four, in this study, relying solely on BMI as a measure of obesity has limitations because it does not account for factors such as body fat percentage and differences in body shape. Future research could consider combining multiple methods to measure obesity, such as waist circumference and waist-to-height ratio (WHtR), and conducting more detailed subgroup analyses to comprehensively assess the relationship between the type and severity of obesity and schizophrenia. Finally, the possibility of selection bias cannot be ruled out, since our analysis only included subjects who were tested for all variables. Despite adjusting for various known confounders in our analyzes, there may still exist residual confounding.

Conclusions

In conclusion, our findings indicate that the rate of overweight/obesity among FEDN schizophrenia patients was high. Additionally, overweight/obesity patients exhibited markedly inferior performance in working memory and visual learning compared to normal/under weight patients. Furthermore, regression analysis revealed that BMI significantly and negatively influenced working memory of FEDN schizophrenia patients. These results underscore the potential utility of markers for overweight/obesity as targets for both improvement and prevention strategies in addressing cognitive function in schizophrenia. This study provides more clues for clinical and

TABLE 4 Results of the regression analysis.

	BMI	TG	LDL-C	Age	IQ	DUI	R^2
working memory	-0.439*	-2.185	-	0.166	0.209**	-0.095	0.142
visual learning	-0.399	-	-1.963	0.037	0.337***	-0.133	0.193

*p < 0.05, **p < 0.01, ***p < 0.001.
BMI, body mass index; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; IQ, intelligence quotient; DUI, duration of illness.

scientific investigation of this intricate and multifaceted psychiatric disorder.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Medical Research Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

XD: Data curation, Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Methodology, Software. SL: Data curation, Writing – original draft, Writing – review & editing, Funding acquisition. YL: Data curation, Writing – review & editing. XF: Conceptualization, Methodology, Software, Writing – review & editing. RZ: Data curation, Investigation, Writing – review & editing. XS: Data curation, Writing – review & editing. JD: Funding acquisition, Project administration, Resources, Validation, Writing – review & editing. SX: Funding acquisition, Project administration, Resources, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Independent effects of early life adversity on social cognitive function in patients with schizophrenia

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Objective: The aim of this study was to investigate the impact of early life adversity on cognitive function in patients with schizophrenia, with a focus on social cognition (SC).

Methods: Two groups of patients with schizophrenia were recruited and matched on sociodemographic and clinical characteristics. One group consisted of 32 patients with a history of childhood trauma (SCZ-ct), and the other group consisted of 30 patients without a history of childhood trauma (SCZ-nct). In addition, 39 healthy controls without a history of childhood trauma (HC-nct) were also recruited. The intelligence of the three groups was assessed using the Wechsler Abbreviated Scale of Intelligence (WAIS—RC) short version. The cognitive function evaluation was conducted using the MATRICS Consensus Cognitive Battery (MCCB), and early life adversity was measured using the Childhood Trauma Questionnaire-Short Form (CTQ) and Bullying Scale for Adults (BSA).

Results: Patients with schizophrenia endosed significantly higher scores on the CTQ ($F=67.61$, $p<0.001$) and BSA ($F=9.84$, $p<0.001$) compared to the HC-nct. Analysis of covariance (ANCOVA) and *post-hoc* analyses revealed that SCZ-ct ($F=11.20$, $p<0.001$) exhibited the most pronounced cognitive impairment among the three groups, as indicated in MCCB total scores and in the domain score of SC. CTQ exhibited a negative correlation with MCCB ($r=-0.405$, $p< 0.001$); SC was negatively correlated with physical abuse (PA) of CTQ ($r=-0.271$, $p=0.030$) and emotional abuse (EA) of BSA ($r=-0.265$, $p=0.034$) in the whole patient sample. Higher SC performance was significantly predicted

by CT_total (Beta =-0.582, p<0.001, 95% CI -0.96-0.46), and years of education (Beta=0.260, p =0.014, 95% CI 0.20-1.75) in schizophrenia.

Conclusions: Besides familial trauma, schizophrenia patients appear to have a higher likelihood of experiencing bullying in their early life. These experiences seem to contribute significantly to their severe impairments in SC.

KEYWORDS

early life adversity, childhood trauma, bullying, schizophrenia, social cognition

1 Introduction

Schizophrenia is recognized as a severe and complex mental disorder (1, 2) that is often associated with impairments in social cognitive (SC) function (3–5). Patients with schizophrenia may experience difficulties in accurately understanding the emotions, intentions, and social norms of others (6, 7). These issues frequently lead to conflicts and instances of aggressive behavior between patients with schizophrenia and their close caregivers, resulting in strained interpersonal relationships (8, 9). Consequently, these factors disrupt normal social interactions and significantly impact the individual's quality of life and career development (10, 11).

The pathogenic mechanisms underlying schizophrenia are not yet fully elucidated. Besides genetic dispositions, previous research has focused on sociopsychological factors (5, 12). Among these factors, childhood trauma (CT) has been proposed as a potential risk factor for schizophrenia onset (13–15). This includes experiences such as physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect (14, 16, 17). These traumatic experiences may not only potentially heighten the risk of adolescents exhibiting psychotic symptoms (17–19) but also increase their vulnerability to the development of schizophrenia (20).

Furthermore, experiences of bullying during adolescence may serve as another potential factor in the onset of schizophrenia (12, 21). A study found that boys who frequently engage in bullying behaviors, or those who frequently find themselves the victims of such behaviors, are more susceptible to developing schizophrenia in early adulthood (22). This finding is further substantiated by a longitudinal investigation involving 4,720 participants, which concluded that regardless of whether one is a perpetrator or victim of bullying, experiencing bullying during adolescence increases the risk of developing mental disorders (23). This body of evidence points toward a discernable connection between bullying and mental illness, specifically schizophrenia.

The cognitive function of patients with schizophrenia is impaired, as established by previous research (3, 4, 24, 25). However, limited studies have implemented the threshold value of the Childhood Trauma Questionnaire-Short Form (CTQ) to differentiate patients with schizophrenia who have experienced childhood trauma from those who have not and to investigate potential differences in cognitive functioning between these two groups. This is particularly significant in the context of their social cognition function, which significantly impacts their quality of life and successful reintegration into society. Existing literature suggests that exposure to social adversity during childhood may contribute to the formation of negative internal working models, selective attention toward emotional stimuli and greater difficulties with emotional self-regulation (26). Moreover, studies have revealed that CT can affect an individual's social cognitive functioning, particularly in terms of their intimate relationship with their mother (5). The presence of physical neglect significantly influences the intimacy between patients with schizophrenia and their parents, standing as the most potent predictor for their challenges in emotional recognition (5).

The purpose of the present study was to explore the effects of self-reported CT and bullying on the cognitive function of schizophrenia patients, with a focus on social cognition. The hypotheses formulated for this study were as follows (1): Patients with schizophrenia are likely to have endured more adversities during their early life - as quantified by the CTQ and the Bullying Scale for Adults (BSA) - in comparison to those without any such diagnosis (2); Experiencing adversities during early life could potentially impair cognitive function, with a particular impact on SC.

2 Methods

2.1 Participant enrollment

A total of 32 schizophrenia patients with a history of childhood trauma (SCZ-ct), 30 schizophrenia patients without a history of childhood trauma (SCZ-nct), and 39 healthy controls (HC-nct) without childhood trauma or any form of mental illness were recruited for this study (see Table 1). Eligible patients were referred to the study from both inpatient and outpatient departments at Beijing Anding Hospital, Capital Medical University. The inclusion criteria for the study were as follows

TABLE 1 Sociodemographic characteristics and early life adversities among the three groups of participants ($\bar{x}$ S).

Variables	SCZ-ct (n=32)	SCZ-nct (n=30)	HC-nct (n=39)	$t/F/\chi^2$	P
Gender (male/female)	20/18	23/12	18/21	2.92	0.230
Age (years)	30.43 ± 8.70	30.94 ± 9.24	28.97 ± 6.92	1.73	0.841
Years of education	14.61 ± 3.72	14.40 ± 3.67	16.00 ± 2.38	2.63	0.080
IQ	99.91 ± 13.47	108.81 ± 12.19	118.46 ± 9.92	22.83	<0.001
Duration of illness (months)	93.88 ± 87.76	85.14 ± 75.83	–	0.44	0.659
OLZeq (mg)	12.87 ± 7.15	13.34 ± 8.59	–	-0.22	0.830
PANSS	63.46 ± 19.27	64.14 ± 13.43	–	-0.17	0.863
Positive	16.62 ± 6.48	17.54 ± 5.01	–	-0.65	0.519
Negative	17.14 ± 7.28	16.60 ± 6.10	–	0.34	0.737
General Psychopathology	29.70 ± 8.76	30.00 ± 6.39	–	-0.16	0.870
CT_total	46.92 ± 9.85	31.54 ± 4.83	29.64 ± 5.39	67.61	<0.001
CT_EA	8.13 ± 3.03	6.23 ± 1.68	6.36 ± 1.93	6.54	0.002
CT_PA	7.11 ± 2.92	5.45 ± 0.85	5.41 ± 0.75	10.59	<0.001
CT_SA	6.42 ± 2.32	5.37 ± 0.97	5.17 ± 0.45	18.77	0.001
CT_EN	14.92 ± 5.43	8.00 ± 2.97	7.05 ± 2.33	8.41	<0.001
CT_PN	10.34 ± 3.20	6.08 ± 1.36	5.64 ± 1.16	7.80	0.001
BSA	13.66 ± 10.21	11.00 ± 10.87	4.59 ± 6.05	9.84	<0.001
EA	7.74 ± 5.65	5.89 ± 6.07	2.67 ± 3.09	9.88	<0.001
ID	3.71 ± 4.15	3.60 ± 4.94	1.10 ± 2.11	5.54	0.005
PA	2.05 ± 2.36	1.26 ± 1.52	0.59 ± 1.50	6.08	0.003
SH	0.16 ± 0.49	0.26 ± 0.70	0.23 ± 0.87	0.19	0.832

SCZ-ct, schizophrenia patients with a history of childhood trauma; SCZ-nct, schizophrenia patients without a history of childhood trauma; HC-nct, healthy controls without a history of childhood trauma; IQ, Intelligence Quotient; OLZeq, Olanzapine equivalent dose of antipsychotics; PANSS, Positive and Negative Syndrome Scale; CT_total, total childhood trauma; CT_EA, Emotional Abuse; CT_PA, Physical Abuse; CT_SA, Sexual Abuse; CT_EN, Emotional Neglect; CT_PN, Physical Neglect; BSA, Bullying Scale for Adults; EA, Emotional Abuse; ID, Interpersonal Difficulties; PA, Physical Abuse; SH, Sexual Harassment.
The symbol "–" means inapplicable.

(1): a diagnosis of schizophrenia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (2); a minimum of 9 years of education (3), an IQ of at least 80 (4), native Chinese speakers, and (5) aged between 18 and 60. Patients were excluded from the study if they had a history of substance abuse or had undergone any form of brain stimulation therapies within the 3 months prior to the study. The HCs were recruited from nearby communities. Prior to their participation, informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University, and North China University of Science and Technology.

2.2 Assessment

2.2.1 Clinical Assessments

The diagnosis of schizophrenia in patients was conducted using the Chinese version of the MINI International Neuropsychiatric Interview (MINI) (7.0.2) (27–29). The Chinese version of the Positive and Negative Syndrome Scale (PANSS) (30, 31) was administered to assess the clinical symptoms of patients with schizophrenia.

2.2.2 Cognitive Assessments

The Wechsler Abbreviated Scale of Intelligence (WAIS—RC) short version (32, 33) was utilized to evaluate the intelligence of the three groups.

The MATRICS Consensus Cognitive Battery (MCCB) (34–37) was administered to measure cognitive function across the three groups. The MCCB has been developed for assessing the cognitive functions of schizophrenia and related disorders and has exhibited good reliability and small practice effects in a wide range of clinical studies in individuals with psychosis. There are 10 subtests in the Chinese version of MCCB (35) which are organized into the following 7 domains: 1. Speed of Processing (SP): Trail Making Test: Part A (TMT), Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding, and Category Fluency Test: Animal naming

(Fluency); 2. Attention/Vigilance (A/V): Continuous Performance Test-Identical Pairs (CPT-IP); 3. Working Memory (WM): Wechsler Memory Scale—Third Edition (WMS-III): Spatial Span; 4. Verbal Learning (VEL): Hopkins Verbal Learning Test—Revised (HVLT-R); 5. Visual Learning (VIL): Brief Visuospatial Memory Test-Revised (BVMT-R); 6. Reasoning and Problem Solving (RPS): Neuropsychological Assessment Battery (NAB): Mazes; 7. Social Cognition (SC): Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions.

In particular, the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) serves as a social cognitive measurement that evaluates the participant's capacity to perceive, use, understand, and regulate emotions through a series of questions. The MSCEIT applies questions based on everyday situations to gauge the ability with which individuals navigate social tasks, interpret facial expressions, and address emotionally-charged problems (38, 39).

2.3 The childhood trauma questionnaire-short form

The CTQ developed by Bernstein and Fink (40, 41) was utilized in our study. The CTQ is a widely recognized self-assessment tool specifically designed to retrospectively evaluate experiences of maltreatment and neglect during childhood. This tool is composed of 28 items, each rated on a five-point Likert scale, with response options extending from "0" (indicating 'never') to "4" (indicating 'very often').

The CTQ assigns different threshold scores for each of its subscales: emotional abuse (EA) has a threshold of 13, physical abuse (PA) is set at 10, sexual abuse (SA) requires a minimum of 8, emotional neglect (EN) is set at 15, and physical neglect (PN) has a threshold of 10 (42). Patients with scores meeting or exceeding the designated threshold on any dimension are classified as SCZ-ct (42).

2.4 The Bullying Scale for Adults

The BSA, derived from the Bully Survey (43), was developed as a modified version to assess adults' past experiences of bullying (44). The BSA comprises three distinct parts. Part A concentrates on personal experiences related to bullying. It includes 13 items representing four types of bullying behavior, namely Emotional Abuse (EA), Interpersonal Difficulties (ID), Physical Abuse (PA), and Sexual Harassment (SH). Participants rate each item using a five-point Likert scale, ranging from "0" (never) to "4" (always), with an additional option of "don't know". If a score other than "0" is selected, respondents are required to provide more detailed information regarding the perpetrator, time, and duration of the incidents. Part B examines the personal consequences of bullying, encompassing six items measured on a five-point Likert scale ("0-Never a problem" to "4-Always a problem"). Last, Part C includes two items that inquire about the experience of acting as a bullying perpetrator. Our previous study yielded favorable outcomes in terms of reliability and validity in the Chinese version of the BSA (45).

2.5 Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Categorical data were analyzed by the chi-square test. Analysis of covariance (ANCOVA) was employed to compare the differences in cognitive function among the groups, with IQ as a covariate. To understand the relationships between the variables, the Pearson correlation was applied. To investigate the influencing factors of SC, relevant sociodemographic and clinical variables were entered as independent variables in a stepwise multiple linear regression analysis. Numerical data are expressed as the mean ± standard deviation d. Multiple comparisons were adjusted using the Bonferroni correction, $P<0.05$ means the difference is statistically significant, and a two-tailed test is adopted.

3 Results

3.1 Sociodemographic characteristics and early life adversities

Six patients were excluded from the SCZ-ct group and 5 patients were excluded from the SCZ-nct group due to low IQ scores (IQ<80). Consequently, 32 SCZ-ct patients, 30 SCZ-nct patients and 39 heathy controls were included in the analyses. There was a significant difference in the scores of IQ among the three groups (Table 1). *Post-hoc* analyses revealed that individuals in SCZ-ct group had the lowest IQ scores (Supplementary Table 1). Apart from IQ, no statistically significant differences were observed in sociodemographic among the three groups or in the clinical features between the two groups of patients.

The BSA total score and dimensional scores were compared between SCZ-ct, SCZ-nct, and HC. One-way ANOVA and *post hoc* analyses showed that SCZ-ct had significantly higher scores in BSA ($F=9.84$, $p<0.001$), EA ($F=9.88$, $p<0.001$), ID ($F=5.54$, $p =0.005$), and PA ($F=6.08$, $p =0.003$) than HC-nct. SCZ-ct and SCZ-nct had comparable scores in BSA and all dimensional scores.

In the whole patient sample, the mean scores of BSA ($F=9.84$, $p< 0.001$) and ID ($F=5.54$, $p=0.005$) were significantly higher than that of HC-nct (Table 1; Supplementary Figure 1).

3.2 Cognitive result

Analysis of Covariance (ANCOVA) was conducted with IQ as a covariate, revealing significant differences in MCCB total score among the three groups ($F=11.20$, $p<0.001$). *Post-hoc* analyses indicated that SCZ-ct exhibited the most severe cognitive impairment with the lowest scores. Similar results were observed in several domain scores, including SP ($F=17.62$, $p<0.001$), A/V ($F=7.28$, $p<0.001$), WM ($F=5.02$, $p=0.008$), VEL ($F=5.68$, $p=0.005$), RPS ($F=3.63$, $p=0.030$), and SC ($F=4.17$, $p=0.018$). In terms of SC, the score of SCZ-nct was not significantly different from that of HC-nct ($p=1.000$) but was significantly higher than that of SCZ-ct ($p=0.030$) (Table 2; Figure 1).

3.3 Correlation between CT, BSA and MCCB results

In the whole sample of schizophrenia patients, CTQ showed a significant negative correlation with MCCB (r = -0.405, p< 0.001), and CTQ_PA exhibited a negative association with the SC scores (r = -0.271, p = 0.030) on the MCCB. Furthermore, the BSA_EA exhibited a negative correlation with the SC scores (r = -0.265, p = 0.034) on the MCCB (Supplementary Table 2).

3.4 Exploring factors that predict SC function

In the stepwise linear regression analyses, SC was entered as the dependent variable, and the scores of CTQ, CTQ_PA, BSA_EA, and education were entered as independent variables. The results suggested that higher SC score was significantly predicted by CTQ (Beta =-0.582, p<0.001, 95% CI -0.96-0.46) and education (Beta = 0.260, p =0.014, 95% CI 0.20-1.75) in schizophrenia patients (Table 3).

TABLE 2 Comparisons of MCCB scores among three groups of participants ($\bar{x}\pm S$).

Variables	SCZ-ct (n=32)	SCZ-nct (n=30)	HC-nct (n=39)	*F*	*P*	η^2	*Post-hoc* *p*, Bonferroni-adjusted		
							SCZ-ct vs. SCZ-nct	SCZ-ct vs. HC-nct	SCZ-nct vs. HC-nct
MCCB	43.70 ± 1.77	46.76 ± 1.67	55.16 ± 1.60	11.20	<0.001	0.188	0.756	<0.001	0.001
SP	44.59 ± 1.45	44.65 ± 1.37	55.01 ± 1.31	17.62	<0.001	0.266	1.000	<0.001	<0.001
A/V	45.44 ± 1.95	45.86 ± 1.84	54.64 ± 1.77	7.28	<0.001	0.130	1.000	0.005	0.003
WM	44.13 ± 1.86	45.91 ± 1.76	52.29 ± 1.69	5.02	0.008	0.094	1.000	0.013	0.033
VEL	44.47 ± 1.95	47.60 ± 1.85	53.80 ± 1.77	5.68	0.005	0.105	0.725	0.004	0.056
VIL	48.30 ± 1.81	50.36 ± 1.71	52.70 ± 1.64	1.40	0.253	0.028	1.000	0.296	0.996
RPS	49.42 ± 1.90	47.19 ± 1.79	53.90 ± 1.72	3.63	0.030	0.070	1.000	0.322	0.026
SC	43.85 ± 2.23	51.83 ± 2.11	51.87 ± 2.03	4.17	0.018	0.079	0.030	0.046	1.000

MCCB, SCZ-ct, schizophrenia patients with a history of childhood trauma; SCZ-nct, schizophrenia patients without a history of childhood trauma; HC-nct, healthy controls without a history of childhood trauma; MATRICS Consensus Cognitive Battery; SP, Speed of Processing; A/V, Attention/Vigilance; WM, Working Memory; VEL, Verbal Learning; VIL, Visual Learning; RPS, Reasoning and Problem Solving; SC, Social Cognition.

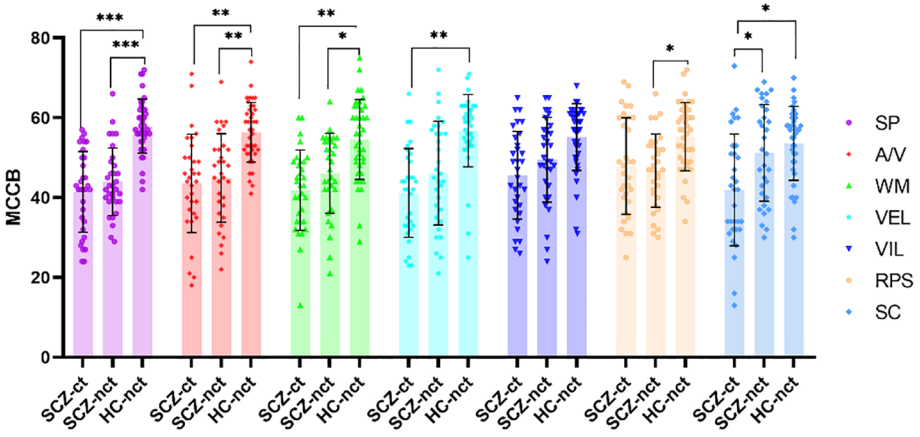

FIGURE 1
Comparisons of MCCB among three groups of participants. SCZ-ct, schizophrenia patients with a history of childhood trauma; SCZ-nct, schizophrenia patients without a history of childhood trauma; HC-nct, healthy controls without a history of childhood trauma; MCCB, MATRICS Consensus Cognitive Battery; SP, Speed of Processing; A/V, Attention/Vigilance; WM: Working Memory; VEL, Verbal Learning; VIL, Visual Learning; RPS, Reasoning and Problem Solving; SC, Social Cognition. *p<0.05; **p<0.01; ***p<0.001.

4 Discussion

To the best of our knowledge, this is the first study in which the CTQ, BSA, and MCCB have been employed to examine the impact of early life adversity on cognitive functioning, particularly in the domain of SC, in patients with schizophrenia. The findings of the study have confirmed our hypothesis that, compared to healthy controls, patients with schizophrenia experience more early life adversity, including bullying. These early life adversities are associated with poorer cognitive functioning, especially SC, which has been considered to be closely related to quality of life and occupational development of the patients.

As hypothesized, patients with schizophrenia had significantly higher scores on the CTQ and BSA than healthy controls, which means that patients with schizophrenia experience more early life adversities. The study findings are in line with previous research studies. A meta-analysis of 36 studies (46) revealed that, compared to healthy controls, the odds ratio (OR) for CT in patients with schizophrenia was 2.78 (95% CI: 2.34-3.31). Specific forms of trauma showed an OR of 2.90 (95% CI: 1.71-4.92) for neglect, 3.40 (95% CI: 2.06-5.62) for emotional abuse, 2.95 (95% CI: 2.25-3.88) for physical abuse, and 2.38 (95% CI: 1.98-2.87) for sexual abuse. Another study (47) indicated that patients with schizophrenia had higher scores on measures of sexual abuse than healthy controls. According to a prospective cohort study (23) of 4720 children aged 8 to 11 years, children who reported bullying had a higher likelihood of developing a mental illness by age 18 than children who did not (OR=2.4, 95% CI: 1.6-3.4). A case-control study (12) also found that schizophrenia patients were bullied twice as much as healthy controls. According to revictimization theory (48–50), individuals who experience childhood trauma may be more likely to become targets of bullying and attacks and are more likely to experience further trauma. A longitudinal study (51) validated this theory, as 213 (11.1%) out of 1915 young adults who experienced sexual abuse before adulthood reported experiencing sexual abuse again in adulthood.

SCZ-ct group was observed to have the lowest IQ scores among the three groups in the current study. This finding aligns with a 6-year follow-up study involving 1,119 patients with schizophrenia spectrum disorders. The study revealed that patients with schizophrenia spectrum disorders who had a history of childhood trauma exhibited the least progress in intellectual abilities, suggesting the lowest learning effect (52). Similar results were found in a study examining the impact of childhood trauma on intellectual functioning in patients with bipolar disorder, indicating that the presence of childhood trauma further impairs their intellectual abilities (53). This may be attributed to the negative effect of trauma on neural development, leading to alterations in brain structure and function (7, 54, 55).

In terms of SC, patients with schizophrenia have difficulty accurately understanding others' emotions, intentions, and social signals when communicating with caregivers (5) or during social interactions. They may misunderstand others' facial expressions, language, and nonverbal cues (6, 56), leading to poor communication and interpersonal tension. The results confirm our hypothesis that SC was significantly associated with childhood trauma, as indicated in the stepwise linear regression analyses. We found that the factors of "physical abuse" in CTQ and "emotional abuse" in BSA (bullying scales for adult) were significantly anti-correlated with social cognitive function (r = -0.271 and -0.265, respectively). In the multivariate regression, no specific type of trauma or bullying experience were identified to be independent predictors for social cognition, and the only contributor was the total score of CTQ (Beta=-0.582). This suggests that the social cognition impairments would better be explained by a cumulative effects of various kinds of childhood adversities.

Previous studies have shown that cognitive function is impaired in patients with schizophrenia (3, 4, 24, 25), with CT playing an important role in SC impairment in schizophrenia (5, 7, 26, 56–58). One study showed that schizophrenia patients had significantly lower scores in parental relationships and SC than healthy controls, with physical neglect being the strongest predictor of emotional recognition impairment. Good parental relationships were found to alleviate this emotional problem (5). Another survey involving 204 children aged 8-11 found that victims of bullying had difficulty in some moral judgment tasks (59), indicating that bullying has a negative impact on individuals' SC. Furthermore, CT was found not only to affect the SC of schizophrenia patients but also to contribute to the cognitive impairment of bipolar disorder patients, specifically in working memory and executive function (60). A comprehensive review of 1,723 mood disorders and 797 healthy controls also confirmed that CT has a certain impact on the cognitive and executive functions of mood disorders (61).

Schizophrenia is a complex and severe mental disorder that involves various biological, psychological, social, and environmental factors (1, 2, 62–65), and CT increases the risk of developing this illness. Long-term and repeated exposure to negative environments, such as trauma and bullying, disrupts the balance of neurohormones (particularly glucocorticoids) (66), which can affect neuronal development and connectivity while altering epigenetic modifications (67). This process also impacts synaptic pruning during critical periods of early brain development (68, 69), as early life is a crucial period for individual brain development (53, 70, 71). Therefore, early-life adversities, including childhood

TABLE 3 Results of the stepwise multiple regression analysis (patients; n=62).

Social cognition	Predictor	Beta	p-value	95% CI
Adjusted R^2 = 0.360; $F_{(2, 59)}$= 18.19; p<0.001	**CT_total**	-0.582	<0.001	-0.96, -0.46
	Years of education	0.260	0.014	0.20,1.75

CT_total, total childhood trauma; CT_PA, Physical Abuse; BSA_EA, Emotional Abuse.

trauma, disturb the balance of neurohormone secretion and lead to structural changes in the brain. These structural alterations can affect the cognitive functioning of patients with schizophrenia.

Notably, we found that the SC scores of SCZ-ct were significantly lower than those of SCZ-nct, while there was no significant difference in neural cognition dimensions (58, 72). It appears that CT independently contributes to the shaping of SC. Childhood is considered an important stage for both individual neural development and SC development (53, 70, 71, 73). During this period, the social environment in which children exist has a profound impact on their SC and behavioral patterns (74). According to Bowlby's attachment theory (75), developing a secure attachment with a caregiver, especially one related to the mother, during childhood enables individuals to form a positive and secure "internal working model" in their interactions with others. This secure attachment relationship is an important prerequisite for successful social interactions. In contrast, experiencing adverse traumatic events during childhood, such as low levels of care and neglect, hinder the development of a secure attachment relationship, leading to difficulties in trusting others, exhibiting poor adaptability to the environment in adulthood (76), and even manifesting psychotic symptoms. Bowlby's attachment theory (75) provides a cognitive-developmental framework for understanding the potential mechanisms by which early-life adversity may impact SC abilities later in life.

4.1 Limitations

There are some limitations to this study that need to be mentioned. First, the sample size employed was relatively small, thereby resulting in a decrease in statistical power. For example, no effort was made to match the intelligence levels among the three groups, although a covariance analysis was undertaken to mitigate the effects of intellectual impairment on the differences in cognitive function. Second, the study's reliance on the self-assessment retrospective nature of the childhood trauma questionnaire introduces the possibility of potential recall biases in the patients' reported experiences of childhood trauma. Furthermore, SC is a complex set of mental abilities that involve many aspects. A limitation of the MCCB is that there is only one test in the domain of SC. Future studies should consider the utilization of an integrated social cognition battery to assess various aspects of this cognitive function. Last but not least, additional variables such as genetic factors and psychiatric comorbidities could potentially confound the result but were not collected in the present study. These factors should be taken into consideration for a more comprehensive interpretation of the results in the future.

5 Conclusion

In addition to familial trauma, patients with schizophrenia are more susceptible to experiencing bullying during their early life. Both factors contribute significantly to the exacerbation of their social cognitive impairments. Our research enhances the understanding of the impact of early life adversity on cognitive functioning, specifically social cognitive function, in individuals with schizophrenia.

Moreover, the findings of this study offer valuable insights for the development of innovative psychological interventions. These interventions aim at alleviating the long-term repercussions of early life adversity for individuals with schizophrenia. This underscores not only the importance of childhood trauma experiences, which are currently considered during clinical assessments and treatment plans but also elevates the significance of bullying experiences in individuals with schizophrenia.

Therefore, to prevent and mitigate the lasting effects of childhood trauma and bullying on individual development and potential psychiatric disorders in individuals with schizophrenia, the development of new social-psychological intervention strategies is essential. These would facilitate their recovery and social reintegration.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Medical Ethics Committee of North China University of Science and Technology and the Ethics Committee of Beijing Anding Hospital, Capital Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. W-PH: Writing – review & editing, Writing – original draft. Y-SD: Writing – review & editing, Writing – original draft. QW: Writing – review & editing, Data curation. FL: Writing – review & editing, Funding acquisition. SS: Writing – review & editing. C-CY: Writing – review & editing. X-JZ: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. F-CZ: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. C-YW: Conceptualization, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1343188/full#supplementary-material

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Facial emotion-recognition deficits in patients with schizophrenia and unaffected first-degree relatives

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Introduction: This study aimed to determine trait- and state-dependent markers of schizophrenia by investigating facial emotion-recognition (FER) deficits in remitted patients with schizophrenia and their first-degree relatives (FR).

Methods: Three groups were included: the Schizophrenia group (n=66), their unaffected FR group (n=40), and healthy controls (n=50) who were matched for age, sex, and years of education. A facial-labeling task was used to examine FER deficits using the following eight standardized expressions: happy, fearful, disgusted, angry, sad, contemptuous, surprised, and neutral.

Results: There was a poorer accuracy in the recognition of sadness and anger in the Schizophrenia group as well as in contempt in both the Schizophrenia and FR groups compared with healthy controls. The response times for the recognition of contempt, sadness, and neutral emotion were delayed in the Schizophrenia group and those for fear were delayed in the Schizophrenia and FR groups compared with healthy controls.

Conclusion: Concerning the accuracy in FER, sadness and anger can be considered state-dependent markers of remitted schizophrenia, and contempt is a trait-dependent marker of schizophrenia. Similarly, for response times in FER, contempt, sadness, and neutral emotion can be considered state-dependent markers of remitted schizophrenia, while fear is considered a trait-dependent marker of schizophrenia. These findings may contribute to the early diagnosis of schizophrenia and the development of relevant therapeutic interventions.

KEYWORDS

schizophrenia, emotion recognition, facial emotion, 1st degree relatives, high-risk group

1 Introduction

Among the various symptoms of schizophrenia, impairment of social function has garnered considerable interest (1), particularly concerning difficulties in interpreting social signals and recognizing other aspects of the social environment. This may be partly related to cognitive impairment in facial recognition (2). Communication of emotions through facial expressions is closely related to practical functional outcomes that are essential to social communication (3). Facial expressions are responses to internal and external stimuli caused by complex neural networks in the brain (4) and represent an immediate, observable, easy-to-evaluate, and inexpensive biomarker for brain disorders, particularly social communication disorders. Facial emotion (or expression) recognition (FER) is a domain of affective cognition impaired across various psychiatric conditions, including schizophrenia, bipolar disorder, major depressive disorder, autism, post-traumatic stress disorder, attention deficient hyperactive disorder, borderline personality disorder, etc (5). A systematic review and meta-analysis revealed differences in accuracy in the identification of each type of emotion during a FER task in several psychiatric disorders and showed that FER is a potential integrative instrument for guiding diagnosis by enabling discrimination between schizophrenia, bipolar disorder, and major depressive disorder (6).

FER deficits have been consistently reported in patients with schizophrenia. In particular, these patients show significant deficits in recognizing negative emotions (anger, fear, and sadness) compared to controls (7, 8). These relative deficits are present in the prodromal phase of psychosis (9), during the first episode of schizophrenia (10, 11), and under chronic schizophrenic conditions (12).

Interestingly, this affect-recognition deficit has also been observed in individuals with a high familial risk of developing schizophrenia (13). Studies on FER deficits among first-degree relatives of patients with schizophrenia (FR) have found significant impairment in recognizing negative emotions, particularly fear (14, 15). Other studies have shown that the ability to recognize negative emotions such as disgust and neutral emotions (16) or disgust and anger (17) was impaired in FR compared to healthy controls (HC). Furthermore, a reduced ability to recognize neutral emotions and higher accuracy in identifying fearful emotions were predictors of the transition to a psychotic disorder in ultra-high-risk participants (18). Pena-Garijo et al. (19) reported the results of an interesting study in which FER was conducted on HC who were at low or high risk for psychosis, a group with first-episode psychosis, and a group with multi-episode schizophrenia spectrum disorders. They reported that FER is early impaired in high-risk individuals and increases along the psychosis continuum. Similarly, fear recognition is impaired throughout the illness period, suggesting a possible vulnerability marker. Recently, the European Network of National Networks Studying Gene–Environment Interactions in Schizophrenia (EU-GEI) (20) published a report indicating that FER is probably an intermediate phenotype of psychosis. In South Korea, Kang et al. (21) reported that FR have FER deficits for negative emotions, such as fear and sadness.

Conversely, other reports have revealed no deficits in FER ability in families with a genetic burden of schizophrenia or psychosis. Siblings of patients with schizophrenia demonstrated similar accuracy and speed in all FER tasks compared to HC (22). Addington et al. (23) conducted longitudinal studies in high-risk clinical groups. They reported no differences in facial affect-recognition tasks between patients who did and did not convert to psychosis. The authors concluded that poorer affect recognition may be associated with vulnerability to psychosis; however, it may not be a marker for the development of psychotic illness. Park (24) conducted a FER-processing study on HC and FR with a high genetic burden of schizophrenia, using functional magnetic resonance imaging. The study reported that when performing affect-recognition tasks for fear and neutral emotion, relatives displayed abnormal brain activity in the occipito-temporo-limbic-frontal network, which is involved in FER processing. However, the two groups had no differences in the behavioral results. Based on these findings, FER deficits may either be present primarily during psychosis (i.e., state-dependent), form an integral part of the disorder (i.e., trait-dependent), or be a combination of the two (i.e., state- and trait-dependent). Trait markers represent the characteristics of biological processes that act as antecedents and play a causative role in the pathophysiology of mental illness. Trait-dependent markers are most useful when presented in clinically unaffected FR (co-familial traits) and are not limited to those who co-segregate with psychosis (25).

The heterogeneous findings regarding FER in schizophrenia may reflect the complexity of the disorder, the diversity of the participants' characteristics, and the research methods used. To perform a well-designed FER test, several points must be considered. First, there is a need to evaluate a variety of emotions. Early studies evaluated only three emotion categories (positive, neutral, and negative) by assessing various standardized emotions, such as Ekman's six basic emotions (sadness, happiness, surprise, anger, disgust, and fear); these were used to identify emotion-specific characteristics (26). Second, several studies have shown that poor emotional performance in patients with schizophrenia is associated with more severe symptoms (27–29). Our previous study (30) reported that the degree of the deficiency in emotional perception in patients with early schizophrenia varies depending on the severity of psychotic symptoms. Therefore, it is necessary to control the severity of psychotic symptoms. Third, mood states lead to a bias in emotional recognition (31, 32). Other conditions, such as mood symptoms or mood disorders, are often observed in patients with schizophrenia and must be controlled. Fourth, accuracy and response time are two important measures for cognitive test evaluations, including FER tasks. Most emotion-recognition studies have evaluated only the hit rate of correct responses; however, it is also necessary to evaluate the response time in patients with schizophrenia who can cooperate with performing the tests. Fifth, if patients can recognize faces of their race better than those of other races, it may be meaningful to evaluate FER tasks using faces of their race and individuals from the same country (33). Furthermore, previous studies did not use appropriate expressions to deal with various emotions or consider cultural backgrounds, such as the participant's race. Considering

these factors, FER tests using standardized facial photographs of individuals of the same cultural backgrounds or races as the participants may be more useful.

This study aimed to clarify the state- and trait-dependent markers of remitted schizophrenia by investigating FER deficits in remitted patients with schizophrenia, FR, and HC. Specifically, this study evaluated the accuracy and response times for recognizing standardized Korean facial expressions depicting eight types of emotions after controlling for several factors that can affect emotion perception.

2 Materials and methods

2.1 Participants

The study was conducted between July 2014 and December 2019. It included patients with schizophrenia (Schizophrenia group) and FR groups recruited from among the outpatients in the psychiatric department of Kyungpook National University Hospital. Patients with schizophrenia and their primary relatives volunteered for the study after learning about it through the hospital advertisement.

The diagnosis of schizophrenia for patients and probands was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (34) after a review of medical records and interviews with two psychiatrists.

Psychotic symptoms can potentially impair performance on the FER test, ultimately undermining test reliability. Correct response times cannot be calculated when the accuracy value is zero, making patient compliance a critical factor in evaluating response times. To ensure stable test cooperation, we specifically recruited patients in remission from the Schizophrenia group. The remission status is defined as follows: 1) Brief Psychiatric Rating Scale (BPRS) (35) scores of ≤3 points concurrently on each of seven BPRS items (grandiosity, suspiciousness, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, and blunted affect); 2) Scale for the Assessment of Negative Symptoms (SANS) (36, 37) scores of ≤2 points concurrently on the global rating items of the four domains of SANS (affective flattening, avolition-apathy, anhedonia-asociality, alogia); 3) maintenance over 6 months of simultaneous ratings of mild or less on all items is required. 4) the aforementioned symptom severity must be maintained for a minimum of 6 months (38). However, in this study, the maintenance of remission at 6 months was determined by two psychiatrists assessing the severity of symptoms through retrospective medical record review and interviews with patients and caregivers. Patients had experienced no changes in antipsychotic medication dosage for at least the last 2 months.

The relatives were first-degree biological relatives of probands without a personal history of psychiatric disorder. 90% of the participants were the proband's siblings (age range: 18 to 49 years), and 10% were children (age range: 20 to 28 years). A complete family history of the first-degree relatives was obtained from each proband and at least one other first-degree relative. HC without a personal and family history of DSM-IV axis I or II disorders were recruited through a local advertisement. The Korean version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (39) was administered to all participants to confirm their diagnostic eligibility.

All participants had to be aged between 18 and 50 years. To minimize natural cognitive decline or physical conditions that may affect cognitive function (e.g., menopause), the age was set to 50 years.

For inclusion in the study, all participants had to be euthymic, as evaluated by the Korean version of the Montgomery–Åsberg Depression Rating Scale (K-MADRS) (40) (clinical cut-off level: ≤8) and the Korean version of the Young Mania Rating Scale (YMRS-K) (41) (clinical cut-off level: ≤6) and not be psychotic, as evaluated by the BPRS (clinical cut-off level: ≤30). Additional exclusion criteria for the participants included head trauma, neurologic disorders, a history of alcohol or drug abuse within the previous year, mental retardation (intelligence quotient <70), physical illness that may affect cognitive function, and serious medical conditions.

All participants, including the primary relatives, are South Korean and are of the same ethnicity. All patients with schizophrenia underwent usual outpatient treatment and did not participate in formal group therapy or individual psychotherapy. Patients were prescribed second-generation antipsychotics (either one or two drugs, excluding clozapine), benzodiazepines, anticholinergics, β-blockers, and antidepressants, and they were not requested to discontinue their medications for the study. No participants continued their medications for physical illnesses.

2.1.1 Ethical consideration

This study was approved by the Institutional Review Board of Kyungpook National University Hospital (KNUH-2011-01-042). All participants were briefed on the purpose and process of the study, and they provided written informed consent for participation.

2.2 Assessment tools

2.2.1 Evaluation of clinical symptoms

In patients with schizophrenia, remission status was evaluated using BPRS and SANS. In addition, all the psychotic symptoms of the participants were assessed using BPRS, manic symptoms using YMRS-K, depressive symptoms using K-MADRS, and diagnostic eligibility using SCID-I.

2.2.1.1 SCID-I

This is a semi-structured interview guide to establish DSM-IV Axis-I disorders (42). The clinician used SCID-I to confirm the diagnosis. An approved Korean version of SCID-I was used in this study (39).

2.2.1.2 BPRS

This scale is based on the clinician's interview with the patient and observations of the patient's behavior over the previous 2–3 days (35). The patient's family can also provide the behavior report. The BPRS consists of positivity, negativity, and affectivity subscales. It has

18 items with a 7-point scale from 1 (not present) to 7 (extremely severe). The scores range from 18 to 126, with <31, >31, >41, and >53 indicating "illness not significant," "mildly ill," "moderately ill," and "markedly ill," respectively.

2.2.1.3 SANS

The 25-item SANS is used to assess negative symptoms; the scores range from 0 (no abnormality) to 5 (severe) (36, 37). This scale is divided into five symptom dimensions: affective flattening, alogia, avolition–apathy, anhedonia–asociality, and attention.

2.2.1.4 K-MADRS

MADRS (43) is a 10-item, clinician-administered scale designed to measure the overall severity of depressive symptoms. Using the MADRS with a 7-point scale from 0 (not present) to 6 (extremely severe), the intensity of depressive symptoms during the past week can be measured. The Korean version of the MADRS (40) was standardized and exhibited good reliability and validity for the measurement of the severity of depressive symptoms (Cronbach's alpha = 0.79). The total score ranges from 0 to 60, and the clinical cutoff level is 8.

2.2.1.5 YMRS-K

The YMRS (44) is a clinical interview scale used to assess the severity of manic states. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Additional information is based on the clinical observations made during the clinical interview. The Korean version of the YMRS (YMRS-K) (41) was standardized and exhibited good reliability and validity for the measurement of the severity of manic symptoms (Cronbach's alpha = 0.73). The total score ranges from 0 to 60, and the clinical cutoff level is 6 or less.

2.2.2 Evaluation of intelligence and motor performance

2.2.2.1 Intelligence

The Korean Wechsler Adult Intelligence Scale (45) consisted of six verbal and five performance subtexts. The verbal tests were as follows: information, comprehension, arithmetic, digit span, similarities, and vocabulary. The performance subtexts were picture arrangement, picture completion, block design, object assembly, and digit symbol. Verbal IQ, performance IQ, and full-scale IQ were obtained. We administered only two subtexts (vocabulary and block design) and calculated the total IQ using an estimation method (46).

2.2.2.2 Motor performance

The finger-tapping test (47) measured psychomotor speed. This test examines finger motor ability, motor concentration, and motor execution ability and measures movement speed entirely. In general, when a contralateral prefrontal disorder is present, a delay in movement speed can be observed. Using the index finger of the dominant hand, the desk is tapped as quickly as possible for 10 seconds, five times in a row. The same is done with the non-dominant hand, and the test results are compared for each hand.

2.2.3 Facial emotion-recognition task

A facial-labeling task (48) was used as the FER test to examine FER deficits. This forced-choice emotion identification task displayed eight standardized facial expressions on a computer screen: happy, sad, angry, fearful, contemptuous, disgusted, surprised, and neutral emotion. Facial stimuli were valid and reliable images (the accuracy for each emotion is 0.7 or higher, the emotional intensity is 100%) obtained from the Korean Facial Expressions of Emotion database (49), with an established set of photographs based on the characteristic facial configurations by Ekman and Friesen (50, 51).

Participants were briefed on the names of the eight emotions that would be displayed. Next, they were instructed to react to the faces shown by clicking a button corresponding to the name of an emotion on the screen as quickly as possible, using a mouse. The pictures were randomly displayed in one block (16 images in total, one male and one female model for each of the eight emotions). For the practice session, one block was performed, and participants were allowed to try the same block one more time only if they did not fully understand the test process. After confirming that the participants fully understood the procedure, the actual test was conducted in four blocks (64 images in total, other models used in practice). Participants were allowed to take a short break between blocks. Before, during, and after this task, participants were instructed to return to a stable emotional state. Facial stimuli were presented for 750ms, with an interval of 4,500ms (3,000ms of reaction time and 1,500ms of feedback time). This study measured two primary measures: the accuracy of responses indicated by mean commission error rates (percentage of wrong hit responses) and response times indicated by mean correct response time for each emotion. Only responses falling within the valid response time range of 200 to 3,000ms were included in the analysis. Any correct response shown after 3,000ms elapsed was considered missing data.

2.3 Statistical analyses

Categorical data are expressed as frequency counts, and continuous data are expressed as means and standard deviations. Regarding the analysis of demographic homogeneity between the groups, the chi-square test was used for sex ratio analysis, and the analysis of variance (ANOVA) test was used for age and level of education analysis. When comparing the three groups in the analysis of psychopathologies, accuracy, and response times, employing a non-parametric method is appropriate because most outcome variables did not follow a normal distribution. However, Analysis of covariance (ANCOVA) was used since the three groups needed to be compared after controlling for YMRS-K and K-MADRS. Since it was confirmed that the significant results of the ANOVA and Kruskal-Wallis tests did not differ, we accepted the results of ANCOVA as valid to some extent.

In cases of significance in the ANOVA, the *post hoc* comparisons were analyzed using Tukey–Kramer's method, and in cases of significance in the ANCOVA, the *post hoc* comparisons were analyzed using Bonferroni method. We calculated the effect size for each emotion. The effect sizes (Cohen's *d*) were calculated based on the average standard deviation of the two means. Values of 0.2, 0.5, and 0.8 indicated small, medium, and large effect sizes, respectively (52). All statistical analyses were performed using IBM SPS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA), and a *P*-value <0.05 was considered significant.

3 Results

3.1 Information on participant recruitment and screening

After meeting the inclusion and exclusion criteria in the dataset and matching the three groups for age, gender, and years of education, 79 participants were allocated to the Schizophrenia group, 46 to the FR group, and 53 to the HC group.

When the accuracy of a participant's response to a specific emotion is zero, it is impossible to accurately calculate the response time for that emotion. This can significantly impact the comparison of the response times for the eight emotions, leading to distorted results. To ensure accurate calculation of the mean response times, participants with zero accuracy in any of the eight emotions were excluded from the analysis. A total of 13 (16.5%), 6 (13.0%), and 3 (5.7%) participants from the Schizophrenia, FR, and HC groups, respectively, were excluded from the data analysis due to the inability to measure any of the eight emotions; no significant difference was observed between the groups (P = 0.178). Among the emotions excluded because of having zero accuracy, fear had the largest number of emotions in the Schizophrenia, FR, and HC groups, with 8, 5, and 3 participants, respectively, and exhibited no statistical significance (P = 0.594). The rest of the excluded emotions were out of the measurement range for one to two participants. In the final analysis, 66, 40, and 50 participants from the Schizophrenia, FR, and HC groups, respectively, were included for accuracy and response times on the FER tests.

3.2 Demographic characteristics, psychopathology, and neurocognitive function tests

Table 1 shows the results of the demographic characteristics and neurocognitive function tests for the three groups. There were no significant differences among the three groups in terms of sex (χ^2 = 1.41, P=0.49), mean age (F=0.14, P=0.87), and duration of education (F=0.97, P= 0.38). The mean scores of BPRS (F=20.81, P<0.01) were significantly higher in the Schizophrenia group (24.80 ± 5.75 points) than those in the other groups, and YMRS-K (F=3.43, P=0.04) and K-MADRS (F=6.36, P<0.01) mean scores were significantly higher in the Schizophrenia group (YMRS-K: 1.05 ± 1.68; K-MADRS: 3.30 ± 3.00 points) compared with those in HC group (YMRS-K: 0.40 ± 0.78; K-MADRS: 1.52 ± 2.10 points). Notably, all three indicators' values lay within the significant clinical cut-off levels. The overall intelligence score on the neurocognitive function tests was significantly lower in the Schizophrenia group (108.0 ± 15.4 points) than that in HC group (115.8 ± 11.8 points) (F=4.79, P=0.01). No significant differences were observed between the three groups for the evaluation of psychomotor speed, as measured by the finger-tapping test; this was true for both dominant (F=1.16, P=0.32) and non-dominant hands (F=0.97, P=0.38).

3.3 Accuracy

Table 2 lists the mean commission error rates for each emotion. Compared to HC group, the Schizophrenia group showed significantly higher error rates for the recognition of sadness (F=11.35, P<0.01) and anger (F=5.69, P<0.01). The Schizophrenia and FR groups had a significantly higher error rate in recognition of contempt than the HC group (F=7.88, P<0.01). No significant differences were observed in the error rates for the recognition of happiness, fear, disgust, surprise, and neutral emotion among the three groups.

Figure 1 summarizes the effect sizes of the commission error rates for recognizing the eight emotions in the Schizophrenia and FR groups compared with the HC group as well as in the Schizophrenia group compared with the FR group. In the comparison between the Schizophrenia and HC groups, large effect sizes were observed for the stimuli depicting contempt (d=-0.93), medium effect sizes were noted for sadness (d=-0.78) and anger(d=-0.58), and small effect sizes were noted for fear (d=-0.47), and neutral emotion (d=-0.46). Notably, the effect size for surprise was small, which was in the opposite direction (d=0.24). In the FR versus HC groups, large effect sizes were observed for the stimuli depicting contempt (d=-0.92) whereas small effect sizes were noted for those depicting neutral emotion (d=-0.31) and disgust (d=-0.20). In the Schizophrenia versus FR groups, medium effect sizes were observed for the stimuli depicting sadness (d=-0.74), whereas small effect sizes were noted for anger (d=-0.49), fear (d=-0.39), contempt (d=-0.26), and happiness (d=-0.23).

3.4 Response times

No significant differences were observed in the correct mean response times for the recognition of stimuli depicting happiness, anger, and disgust among the three groups. The correct response times were significantly delayed for stimuli depicting sadness (F=3.42, P=0.04) and contempt (F=3.83, P=0.02) in the Schizophrenia group compared to the HC group. The Schizophrenia and FR groups showed significantly delayed correct response times for stimuli depicting fear (F=4.19, P=0.02)

TABLE 1 Demographic data and clinical characteristics of the participants.

	Schizophrenia group (*n*=66)	FR group (*n*=40)	HC group (*n*=50)	*F* or χ	*P*	*post hoc**
Sex (men/women)	29/37	15/25	25/25	1.41	0.494	
Age (years)	30.1 ± 7.1	29.4 ± 8.1	29.6 ± 5.3	0.14	0.865	
Duration of education (years)	14.3 ± 2.0	14.3 ± 1.8	14.7 ± 1.7	0.97	0.383	
Onset age (years)	23.8 ± 5.5					
Duration of illness (years)	6.35 ± 6.00					
Number of admissions	1.08 ± 1.11					
Medications						
2nd generation antipsychotics, n (%)	66 (100.0)					
Monotherapy, n (%)	58 (87.9)					
Combined therapy, n (%)	8 (12.1)					
CPZ equivalents†, mg	322.9 ± 225.2					
Benzodiazepines, n (%)	31 (47.0)					
Anticholinergics, n (%)	41 (62.1)					
ß-blocker, n (%)	17 (25.8)					
Antidepressants, n (%)	6 (9.0)					
Psychopathology						
BPRS	24.80 ± 5.75	20.40 ± 4.61	19.66 ± 2.52	20.81	**<0.001**	1>2,3
YMRS-K	1.05 ± 1.68	0.70 ± 1.18	0.40 ± 0.78	3.43	**0.035**	1>3
K-MADRS	3.30 ± 3.00	2.50 ± 2.71	1.52 ± 2.10	6.36	**0.002**	1>3
Neurocognition						
IQ	108.0 ± 15.4	112.6 ± 12.9	115.8 ± 11.8	4.79	**0.010**	1<3
Finger-tapping test						
Dominant hand	65.6 ± 15.0	69.2 ± 10.5	68.0 ± 10.5	1.16	0.315	
Non-dominant hand	66.8 ± 15.5	70.6 ± 11.5	68.5 ± 11.8	0.97	0.380	

FR, first-degree relatives of patients with schizophrenia; HC, healthy controls; BPRS, Brief Psychiatric Rating Scale; YMRS-K, Young Mania Rating Scale (Korean version); K-MADRS, Montgomery–Åsberg Depression Rating Scale (Korean version); IQ, intelligence quotient. †Dosage equivalents of chlorpromazine. Values are presented as means ± standard deviations. Analysis of variance (ANOVA) was used. *Using Tukey–Kramer's method. The significant values are shown in bold.

compared to HC group. Furthermore, the Schizophrenia group showed a significantly delayed correct response time for stimuli depicting surprise compared to FR group (F=3.10, P<0.05) and for stimuli depicting neutral emotion compared to other groups (F=6.13, P<0.01) (Table 3).

Figure 2 summarizes the effect sizes for the response times for eight emotions in the Schizophrenia and FR groups compared with the HC group as well as in the Schizophrenia group compared with the FR group. In the comparison between the Schizophrenia and HC groups, medium effect sizes were observed for the recognition of contempt (d=-0.76), neutral emotion (d=-0.74), sadness (d=-0.65), fear (d=-0.57), and happiness (d=-0.54) whereas small effect sizes were observed for the recognition of disgust (d=-0.45), anger (d=-0.40), and surprise (d=-0.36). In FR versus HC groups, medium effect sizes were observed for the recognition of fear (d=-0.68) and contempt (d=-0.55) whereas small effect sizes were observed for the recognition of sadness (d=-0.31) and anger (d=-0.21). The surprise was the small effect size, which was in the opposite direction (d=0.22). In the Schizophrenia versus FR groups, medium effect sizes were observed for the stimuli depicting neutral emotion (d=-0.59), and surprise (d=-0.55), and small effect sizes were noted for happiness (d=-0.40), sadness (d=-0.36), and disgust (d=-0.32).

4 Discussion

To identify the state and trait markers of schizophrenia, this study compared the degree and type of FER deficits in remitted schizophrenia, FR, and HC. To account for potential factors that could impact emotional recognition, we controlled for age, sex, education level, psychopathology, psychomotor speed, culture, and race. Standardized facial expressions representing eight distinct

TABLE 2 Mean commission error rates by participant and emotion type in the facial emotion-recognition test.

Emotion depicted in the facial stimuli	Schizophrenia group (*n*=66)	FR group (*n*=40)	HC group (*n*=50)	*F*	*P*	*post hoc**
Happiness	0.021 ± 0.060	0.009 ± 0.044	0.018 ± 0.057	0.64	0.531	
Sadness	0.320 ± 0.225	0.182 ± 0.140	0.170 ± 0.152	11.35	**<0.001**	1>2,3
Anger	0.379 ± 0.251	0.267 ± 0.199	0.251 ± 0.190	5.69	**0.004**	1>2,3
Fear	0.605 ± 0.208	0.512 ± 0.265	0.504 ± 0.222	2.81	0.064	
Contempt	0.219 ± 0.263	0.162 ± 0.172	0.040 ± 0.074	7.88	**0.001**	1,2>3
Disgust	0.478 ± 0.231	0.485 ± 0.230	0.437 ± 0.250	0.92	0.401	
Surprise	0.055 ± 0.105	0.063 ± 0.098	0.082 ± 0.120	1.30	0.276	
Neutral	0.047 ± 0.087	0.037 ± 0.090	0.015 ± 0.048	1.80	0.168	

FR group, first-degree relatives of patients with schizophrenia; HC, healthy controls. Values are presented as means ± standard deviations. Analysis of covariance (ANCOVA) was performed to control the values of the YMRS-K (Young Mania Rating Scale [Korean version]) and K-MADRS (Montgomery–Åsberg Depression Rating Scale [Korean version]). *Using Tukey–Kramer's method. The significant values are shown in bold.

emotions were presented as facial stimuli. The facial expressions were modeled by individuals of the same culture and race as the study participants. In addition to measuring the accuracy of recognition of the individual emotions, differences between them in reaction times were also recorded.

There were no significant group differences in sex, age, or duration of education, indicating that the main variables that may affect cognitive function were well-adjusted. Patients` average duration of illness was 6.35 years, and the average number of hospitalizations was 1.08, indicating that most patients were not in a chronic state and remained stable with medication administered through the outpatient facility. Intelligence was estimated using two subtests; while it was high in all groups, it was lower in the Schizophrenia group than in HC group, in agreement with the results of other studies. The mean BPRS values were significantly higher in the Schizophrenia group than in the other groups. The YMRS-K and K-MADRS mean scores were significantly higher in the Schizophrenia group than in HC group. However, all values were within the clinical cut-off levels, indicating that the patients with schizophrenia were in remission and that psychotic and mood symptoms were stable. Thus, it can be suggested that the associated psychopathology was well-controlled. However, to minimize the effect of psychopathology on cognitive function, we treated the values of the YMRS-K and K-MADRS as covariates in the analysis of the results of the FER tasks. Furthermore, no differences in the psychomotor speed of the dominant and non-dominant hands were observed among the three groups, indicating that this parameter was also well-controlled.

With respect to the accuracy of FER, the commission error rates for stimuli depicting contempt, sadness, and anger were significantly higher in the Schizophrenia group than those in HC group; however, no differences in the rates for stimuli depicting happiness, fear, neutral emotion, surprise, and disgust were observed between the two groups. Among the three significant emotions, large effect sizes were observed for the stimuli depicting contempt, while medium effect sizes were noted for those of sadness and anger. In a comparison between the Schizophrenia and FR

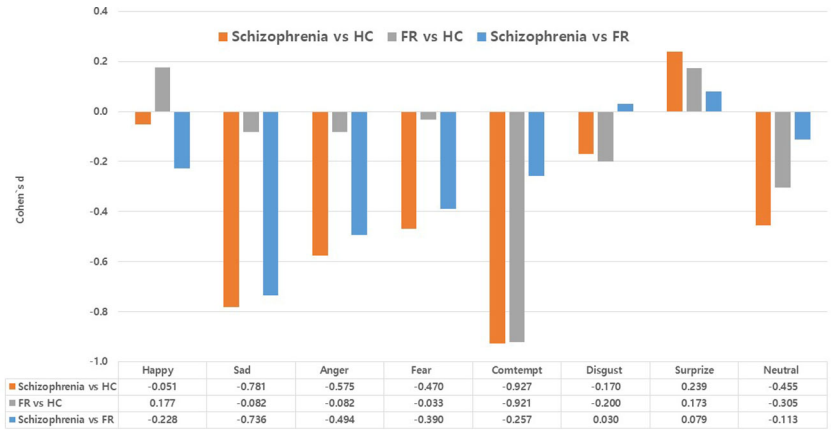

FIGURE 1
Effect size (Cohen's d) of accuracy (commission error rates) in the facial emotion-recognition test: comparison between the Schizophrenia and healthy control (HC) groups, the first-degree relatives of patients with schizophrenia (FR) and HC groups, and the comparison between the Schizophrenia and FR groups. Values are expressed as mean with standard error.

TABLE 3 Mean correct response times by participant and emotion type in the facial emotion-recognition test.

Emotion depicted in the facial stimuli	Schizophrenia group (*n*=66)	FR group (*n*=40)	HC group (*n*=50)	*F*	*P*	*post hoc**
Happiness	1402 ± 259	1300 ± 248	1277 ± 201	2.96	0.055	
Sadness	1755 ± 346	1636 ± 310	1541 ± 308	3.42	**0.035**	1>3
Anger	1855 ± 513	1764 ± 409	1686 ± 314	1.35	0.264	
Fear	2037 ± 492	2039 ± 358	1783 ± 394	4.19	**0.017**	1,2>3
Contempt	1675 ± 495	1581 ± 471	1365 ± 293	3.83	**0.024**	1>3
Disgust	2156 ± 517	2006 ± 426	1928 ± 504	1.85	0.161	
Surprise	1548 ± 300	1395 ± 257	1451± 242	3.10	**0.048**	1>2
Neutral	1344 ± 236	1218 ± 190	1191 ± 171	6.13	**0.003**	1>2,3

FR group, first-degree relatives of patients with schizophrenia; HC, healthy controls. Values are presented as means ± standard deviations. Analysis of covariance (ANCOVA) was performed to control the values of the YMRS-K (Young Mania Rating Scale [Korean version]) and K-MADRS (Montgomery–Åsberg Depression Rating Scale [Korean version]). *Using Tukey–Kramer's method. The significant values are shown in bold.

groups, the error rates for sadness and anger were significantly higher in the Schizophrenia group than in FR group, and both emotions showed medium effect sizes.

Most previous studies have consistently reported that patients with schizophrenia have relative deficits in their ability to recognize negative emotions (7, 8, 10, 30, 53), which is similar to our findings. Kohler et al. (27) conducted a meta-analysis and found that facial emotion recognition and discrimination abilities of patients with schizophrenia were worse than those of non-psychotic controls and were specific to negative emotions, such as fear and anger. In a meta-analysis of early schizophrenia, a large effect size was observed for the recognition of disgust, fear, and surprise, while a medium effect size was observed for the recognition of sadness and happiness. However, no differences were observed in the effect sizes for faces showing anger and neutral emotion (54). Meanwhile, Allot et al. (15) conducted an emotion-labeling task using seven emotions (excluding contempt), which is a higher number of emotions than those used in previous studies. They reported that participants with a first episode of schizophrenia performed significantly poorly in recognizing anger, disgust, and fear compared to HC. These differences in research outcomes may be attributed to methodological diversity and cultural differences. Our study is significant in that it used a total of eight emotions, including contempt, which was not evaluated in other studies, and it also controlled for several factors that could affect emotional recognition.

In this study's analysis of FR group, the incidence of deficits in recognition of contempt in the Schizophrenia and FR groups was significantly lower than that in the HC group. In a comparison between FR and HC groups, large effect sizes were observed for the stimuli depicting contempt. As mentioned earlier, studies have investigated whether FER deficits are present in FR, and their ability to recognize different types of emotions varies across studies. Some studies have shown a deficit in recognizing fear in FR (14, 15). Others have shown differences in recognizing disgust and neutral emotion (16) and disgust and anger (17). The EU-GEI study reported that anger might serve as an intermediate phenotype for psychosis (55). A South Korean study on FR revealed a relative accuracy deficit in recognizing sadness and fear (21). These

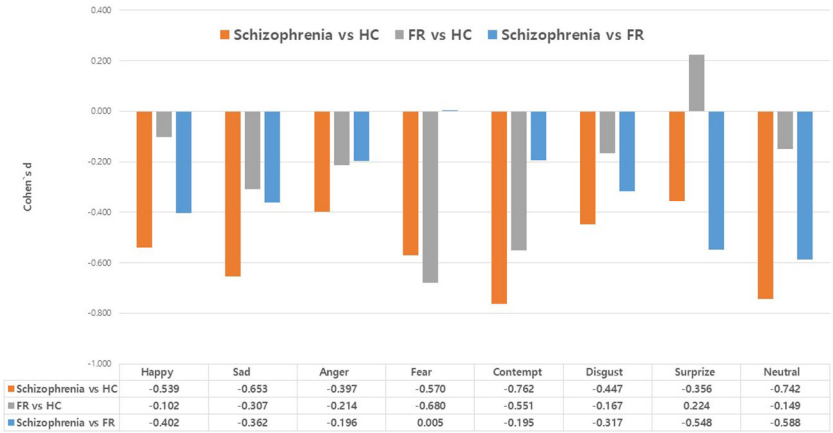

FIGURE 2
Effect size (Cohen's d) of the response times in the facial emotion-recognition test: comparison between the Schizophrenia and healthy control (HC) groups, the first-degree relatives of patients with schizophrenia (FR) and HC groups, and the comparison between the Schizophrenia and FR groups. Values are expressed as mean with standard error.

differences in the results of several studies on FR may also be attributed to variations in research methods or cultural differences. A few years ago, our research team reported differences in FER according to the severity of psychotic symptoms in patients with early-stage schizophrenia. The aforementioned study employed the same research method as the present study. The previous study showed that deficits in recognizing contempt, anger, and fear persisted in individuals regardless of the severity of psychotic symptoms, with a moderate effect size. These findings suggest that trait-dependent characteristics may exist among these emotions (30). Based on the results of the present study, for the accuracy of FER tests, sadness, and anger can be considered state-dependent markers in remitted patients with schizophrenia. In contrast, contempt can be considered a trait-dependent marker in schizophrenia.

This study found that the Schizophrenia group had significantly slower response times than HC group when presented with stimuli depicting contempt, neutral emotion, and sadness (the effect sizes of all emotions were medium) in FER. The responses to stimuli depicting fear were slower in both the Schizophrenia and FR groups than those in HC group (the effect size of fear was medium). The response time to stimuli depicting surprise was slower in the Schizophrenia group than in FR group (the effect size of surprise was medium). Most previous FER studies have focused on accuracy variables rather than response time. Further, only a few studies have focused on the response times of families with a genetic load for schizophrenia and psychosis. Reports found that the response for all emotions, regardless of the detailed emotion, was delayed in patients with schizophrenia (22) and their primary families (22, 24). Evaluating the response time is useful in several cognitive research areas, such as semantic and perceptual priming, implicit serial, sequence, and learning. Measuring the response times of correct responses by assigning a time limit may reflect real-life situations more closely (56). Many scientists seem to religiously adhere to the study of either accuracy or response time; rarely are both investigated simultaneously in a given experimental design.

Furthermore, accuracy and response time data are often critical for distinguishing between theories of cognition, and using only one of these measures may generate a skewed interpretation. Therefore, both accuracy and response time are significant values to be measured (56–58). Brain imaging studies involving patients with schizophrenia and their primary families have revealed abnormalities in processing FER information. A recent meta-analysis of existing brain imaging studies related to facial emotion processing capabilities of patients with schizophrenia revealed the following: a significant under-recruitment of the amygdala and a substantial limitation in activation throughout the ventral temporal-basal ganglia-prefrontal cortex 'social brain' system is responsible for difficulties faced by participants when processing facial emotion (22). Additionally, dysfunction was observed in facial expression processing in non-psychotic siblings of patients with schizophrenia similar to that of the patients, and abnormal activation was observed in both groups in the precentral and superior frontal gyri (59). This study's results suggest that contempt, sadness, and neutral emotion are state-dependent markers for response times of FER tests in remitted patients with schizophrenia. At the same time, fear is a trait-dependent marker of schizophrenia.

This study has some limitations. First, the possibility of drug-induced cognitive impairment could not be completely ruled out, owing to the use of psychiatric medications, such as antipsychotics, benzodiazepines, and other psychotropics, in the patient group. Second, as this is a cross-sectional study, it is important to track whether these state and trait characteristics are maintained over time to investigate the recurrence of symptoms in remitted patients with schizophrenia or the onset of psychotic symptoms in FR using longitudinal follow-up studies. Third, our study lacks generalizability as it included a sample population of only one ethnicity. Consequently, FER deficits in individuals with schizophrenia from various ethnic and cultural backgrounds should be analyzed using the same research methods. Differences in FER deficits between cultures and countries have been reported in healthy individuals (60). FER deficits among patients with schizophrenia in all cultures share the same characteristics, although there are differences in FER deficits for specific emotions (61). Fourth, according to criterion (38), maintenance of a 6-month remission must be confirmed through monthly evaluations using relevant measures. However, in this study, scale evaluations were conducted once upon registration, and the maintenance of remission was clinically determined by two psychiatrists who assessed symptom severity through a retrospective review of medical records and interviews with patients and caregivers. Finally, we have a system for conducting training and evaluation using standard videos to maintain interrater reliability. However, since data were collected over a long period of time, there is a possibility of environmental or evaluator bias occurring.

Nevertheless, this study had several strengths. First, demographic variables (age, sex, and education level), psychopathology (psychotic symptoms and mood symptoms), and psychomotor ability that can affect cognitive function were controlled. Second, we used standardized facial stimuli (i.e., facial expressions of models of those of the same culture and race as that of the participants) in the study. This was considered based on the other-race effect, considering that patients with schizophrenia can recognize faces of their race better than those of other races (33). Third, this study employed eight emotions, the most examined among the studies reported. Fourth, response time, one of the major indicators of FER inadequately investigated in previous studies, was measured for each emotion. Fifth, the target patients with schizophrenia were not in a chronic disease state, did not have recent onsets of schizophrenia, and had experienced remission in terms of psychotic symptoms.

A range of phenomenological symptoms characterizes schizophrenia, and it is crucial to identify the associated risk factors for its development. Early diagnosis and therapeutic intervention in high-risk groups are among the most effective approaches for preventing and treating schizophrenia. Our findings may contribute to the early diagnosis of schizophrenia and the development of relevant therapeutic interventions. Future research is essential to determine the possibility of making novel

predictions regarding the transition to schizophrenia, including factors such as neurocognitive function, which can affect FER tests.

In conclusion, our study was conducted using a facial-labeling task to compare the degree of FER deficits among patients with schizophrenia, FR, and HC and to investigate the state- and trait-dependent markers of remitted patients with schizophrenia. The Schizophrenia group showed reduced recognition accuracy for emotions of sadness and anger; both the Schizophrenia and FR groups showed reduced recognition accuracy for the emotion of contempt. Regarding the response times of FER tasks, emotions of contempt, sadness, and neutral emotion were delayed in the Schizophrenia group; and emotions of fear were delayed in the Schizophrenia and FR groups. Therefore, sadness and anger can be considered state-dependent markers for accuracy in FER in remitted patients with schizophrenia, and contempt is a trait-dependent marker of schizophrenia. Furthermore, for response times in FER, contempt, sadness, and neutral emotion can be considered state-dependent markers in remitted patients with schizophrenia, and fear as trait-dependent markers of schizophrenia. Therefore, it is necessary to consider the deficits in FER in the evaluation and follow-up of clinical progression in patients with schizophrenia and high-risk groups. In remitted schizophrenia, the deficiency in FER is a mixture of state- and trait-dependent markers, depending on the measured variable (accuracy or response time) and the type of emotion.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Institutional Review Board of Kyungpook National University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MB: Visualization, Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Data curation. JC: Writing – review & editing, Software, Project administration, Investigation, Data curation. SW: Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Relationships between erythrocyte membrane mono- and poly- unsaturated fatty acid composition and clinical/cognitive indices in antipsychotic-free schizophrenia patients

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Introduction: Membrane phospholipid abnormalities are considered a pathophysiological background for schizophrenia. The aim of the study was to explore in detail the fatty acid (FA) composition in patients with antipsychotic-free schizophrenia and its association with clinical symptoms and cognitive function.

Materials and methods: Erythrocyte membrane FAs were measured in 29 antipsychotic-free patients with schizophrenia (male/female = 11/18; mean [standard deviation] age=26.7 [7.9] years) and age and sex-matched 32 healthy volunteers. Clinical symptoms and cognitive function were assessed using the Positive and Negative Syndrome Scale (PANSS), Brief Assessment of Cognition in Schizophrenia (BACS), and the Schizophrenia Cognition Rating Scale (SCoRS).

Results: Eicosapentaenoic acid levels were lower in the schizophrenia group than in the healthy control group. In contrast, arachidonic acid and nervonic acid levels were higher in the schizophrenia group than in the control group. Nervonic acid levels were significantly associated with depression scores as measured by the PANSS. No FA levels were correlated with BACS score; however, oleic acid levels were significantly related to cognitive dysfunction, as measured by the SCoRS.

Conclusion: These findings suggest that depressive symptoms along with cognitive dysfunction in daily living in schizophrenia may be linked to the FA composition abnormalities. Further studies will be needed to examine potential longitudinal FA changes during the course of schizophrenia as well as disease specificity.

KEYWORDS

cognitive function, depression, erythrocyte membrane, monounsaturated fatty acid, polyunsaturated fatty acid, nervonic acid, oleic acid, schizophrenia

Introduction

It has been suggested that the altered composition of phospholipids (composed of the sphingosine skeleton, fatty acid (FA), phosphoric acid, and alcohol), a major component of neural membranes, may be related to the pathophysiology of schizophrenia (1–4). As the phospholipid components likely influence the fluidity and elasticity of cell membranes (5, 6), their changes may lead to an increased membrane rigidity and consequently alter the conformation and function of proteins, receptors, and ion channels (7). Among the constituents of phospholipids, saturated FA e.g. palmitic acid (PA) and stearic acid (SA), as well as monounsaturated FAs (MUFAs), e.g. oleic acid (OA) and nervonic acid (NA), can be synthesized *de novo*. Conversely, some polyunsaturated fatty acids (PUFAs), e.g. n-3 (omega-3) and n-6 (omega-6) PUFAs are called essential unsaturated fatty acids because they must be acquired from the diet. n-3 PUFAs contain eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). n-6 PUFAs contain linoleic acid (LA), dihomogammalinolenic acid (DGLA), and arachidonic acid (AA). PUFAs play important roles in the regulation of neuronal migration, pruning, and synaptic plasticity (8). Moreover, n-6 PUFAs are pro-inflammatory bioactive lipids, whereas n-3 PUFAs are anti-inflammatory bioactive lipids (9–11). In this context, n-6/n-3 ratio has been frequently used, since it has been found to be related to several negative health consequences, such as promotion of chronic inflammation (12, 13). Meanwhile, OA can also exert anti-inflammatory effects (14) and NA can activate the antioxidant system (15), these are considered to compensate for deficiencies in essential FAs and their metabolites.

While not consistently replicated, decreased n-3 PUFAs, alteration of n-6 PUFAs and increased n-9 MUFAs in the erythrocyte membrane have been observed in patients with schizophrenia and related conditions (4, 7, 16–20). Several but no all studies also demonstrated an association between PUFAs deficiency and the severity of the negative symptoms of schizophrenia (21–23). Sumiyoshi et al. reported that a decrease in n-3 and n-6 PUFA levels was associated with impaired social cognition in chronically ill patients with schizophrenia (24), while we failed to replicate such relationship in anti-psychotic free first-episode patients (25). Recent studies suggested similar FA abnormalities in at-risk mental state (ARMS) individuals (8, 25) irrespective of outcome (i.e., later psychosis onset), where FA levels were associated with prodromal symptomatology and global functioning. These findings may suggest the role of erythrocyte membrane FA abnormalities as a biomarker associated with vulnerability to psychopathology, but reported FA findings in schizophrenia might also be affected by other factors such as environmental factors after the onset (e.g., dietary habits, physical condition), antipsychotic medication, and chronic oxidative stress. Therefore, further research in patients with less confounding factors is needed to better understand the pathophysiological role of membrane FA composition and its relation to clinical characteristics in schizophrenia.

As human brain is generally inaccessible for direct FA analysis *in vivo*, alternative approaches such as peripheral cell models and neuroimaging techniques have been used as surrogate biomarkers of membrane FAs in the central nervous system (16). Peripheral cell models, especially those of erythrocyte membranes, are frequently used to study brain lipid metabolism due to high correlation between peripheral erythrocyte membrane and brain tissue FA levels (r = 0.86) (26). Erythrocyte membrane FA composition is, as compared to plasma FA levels, less affected by food intake prior to blood sampling as a marker of long-term lipid storage (27–29) and also better reflects neural cell membrane FAs in human (30–32) and animals (33, 34).

This study comprehensively measured erythrocyte membrane FAs in antipsychotic-free patients with schizophrenia and healthy controls. The FAs assessed in this study included saturated FAs (PA and SA), n-9 MUFAs (OA and NA), n-3 PUFAs (EPA, DPA, and DHA), and n-6 PUFAs (LA, DGLA, and AA). These FAs were essential for a comprehensive analysis because of their importance as major constituents, accounting for more than 90% of the total FA content in erythrocytes and the brain (5, 18). Based on previous findings, we predicted that patient group would have an altered FA composition (especially decreased n-3 PUFA and increased n-9 MUFA) and that such alterations would contribute to their symptom severity and cognitive functions.

Methods

Participants

Twenty-nine Japanese patients with schizophrenia recruited from the University of Toyama Hospital, participated in this study. None of the patients took antipsychotic medications within the two weeks before blood sampling, and 20 of the 29 patients were antipsychotic-naïve. Eleven of the 29 patients had first-episode schizophrenia, defined as an illness duration of fewer than two years with a single psychotic episode. Thirty-two healthy volunteers were recruited from university students, hospital staff, and acquaintances. The patients diagnosed with schizophrenia underwent diagnostic interviews using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) Patient Edition (35). Eleven of the 29 patients with schizophrenia and all the healthy volunteers overlapped with the subjects in our previous report (25).

Information on clinical history was collected through interviews with the patients, their families, or medical records. Physical examinations and standard laboratory tests confirmed that the participants were physically healthy. The exclusion criteria included being 40 years of age or older, a history of substance abuse or dependence, seizures, head injury, and an estimated premorbid IQ of less than 70 based on the Japanese Adult Reading Test (JART) (36). The JART is the Japanese version of The National Adult Reading Test (Nelson, 1982). It comprises several irregular Japanese words, and the participants' premorbid IQ is estimated based on their reading performance (36). Additional

criteria for healthy controls were; i) no Axis I disorders based on the SCID-I Non-patient Edition (35), and ii) no personal or family (within first-degree relatives) history of psychiatric disorders.

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Committee on Medical Ethics of Toyama University (no. I2013006) on February 5, 2014. Written informed consent was obtained from all participants after a full explanation of the purpose and procedure of the study was provided. Written consent was obtained from the parents or guardians of participants under 20 years of age.

Clinical assessment

Experienced psychiatrists or psychologists evaluated clinical symptoms, cognitive function, and social function using the Positive and Negative Syndrome Scale (PANSS) (37), Brief Assessment of Cognition in Schizophrenia (BACS) (38, 39), Schizophrenia Cognition Rating Scale (SCoRS) (40, 41), and the modified Global Assessment of Functioning (mGAF) (42). The BACS composite scores were obtained by averaging the z-scores of the six subtests (39). Socio-economic status (SES) was measured by the Hollingshead-Redlich scale (43). Clinical assessments were performed on the same day as or within two weeks of blood collection.

FA analysis

Blood samples were collected from the study participants between 08:30 and 10:00 after at least two hours of fasting for FA measurements and general blood and biochemical examinations. Erythrocyte membrane FA levels were analyzed by gas chromatography based on an established method (18, 24, 25, 44). Briefly, 1 mL of red blood cells obtained from the subjects was collected in a 15-mL screw cap vial. Erythrocytes and plasma were separated by centrifugation and only erythrocytes were extracted and washed with saline. The vial was filled with 4.0 mL of 0.6 N methanolic HCl containing 4 µL of 0.5% butyl hydroxytoluene (BHT) as an internal standard and was then sealed and incubated at 80°C for two hours. Methylated FAs were extracted twice with hexane and the layers were separated by centrifugation in a swinging rotor at 3000 g for 15 min at room temperature. The hexane layer was carefully removed and the residue was collected in separate vials. The hexane extract was dried entirely by passing it through argon and it was then stored at -40°C until use. The methylated FAs were resuspended in 150 µL hexane, and aliquots (1 µL) were used for FA analysis by a Shimadzu gas chromatograph (Model GC-2010, Japan), using a capillary column with dimensions 30 m×0.32 mm×0.20 µm (Supelco, USA). A flame ionization detector was used with a column oven temperature of 160°C for 10 min, programmed at 10°C rise/min up to 175°C, and held at 220°C for 10 min was used. The injector and detector temperatures were set to 240°C and 275°C, respectively. The column was calibrated by injecting standard FA mixtures in approximately equal proportions. Peaks in the recorded data were identified based on the retention times of standard FAs under identical conditions.

The FA data were categorized into four groups: i) saturated FAs (PA and SA), ii) n-9 series MUFAs (OA and NA), iii) n-3 PUFAs (EPA, DPA, and DHA), and iv) n-6 series PUFAs (LA, DGLA, and AA). The FA levels were expressed as relative values measured as 100% of the 11 FAs, which included the 10 FAs mentioned above, with BHT as an internal standard (5). We calculated the following parameters as indices to assess the inflammatory response: i) n-6/n-3 ratio (AA/[EPA + DHA]) and ii) omega-3 index (EPA + DHA), based on previous literature (8, 45, 46).

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 25 (SPSS Japan Inc.) and Jamovi Software (https://www.jamovi.org). The analyses covered FA composition and the PANSS, BACS and SCoRS scores and their subscale scores. The mGAF was measured as it is a well-known tool for determining the level of functioning of patients with general mental illness, however was not included in the present analysis due to its strong correlation with SCoRS. As most demographic/clinical data (age, PANSS subscale scores, BACS, SCoRS) had skewed distributions, the nonparametric Mann-Whitney U test was used to compare group differences. Similarly, nonparametric tests were employed to determine group differences in the FA composition, which had non-normal distributions. Spearman's rho with semi-partial correlation was used to calculate the correlation between FA composition and clinical data, with only FA indices being controlled for by age, because age significantly affected FA composition in previous literature (47, 48) as well as our data (data not shown). For correlation analyses between FA composition and clinical variables, the Benjamini–Hochberg false discovery rate (FDR) procedure was used because there were many items to be compared (49). Statistical significance was set at p less than 0.05.

Results

Subjects' profile

Demographic data are shown in Table 1. The age and sex ratios of the groups were matched; however, there were significant differences in personal/parental socioeconomic status (controls > patients with schizophrenia). Body mass index (BMI) was higher in the schizophrenia than in the healthy group; however, it was within the normal range (18.5–25) in both groups. The estimated premorbid IQ measured by the JART was within the normal range. Some patients with schizophrenia were taking anxiolytics (n=2) and hypnotics (n=2). These medications did not affect clinical or cognitive indices, or the FAs composition (data not shown). None were taking antidepressant. Regarding cognitive function, patients with schizophrenia performed approximately one standard deviation lower on the composite score calculated from the BACS than those in the healthy group. SCoRS scores were high in the current dataset and exceeded the reported average of first-episode and chronic schizophrenia (3.8 ± 1.8 and 4.4 ± 1.9, respectively)

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TABLE 1 Demographic and clinical data.

	H	Sch	Group difference[a]
	n=32	n=29	
Age [years]	26.9(3.4)	26.7(7.9)	$U_{32,29} = 439$, p=0.72
Gender [male/female]	17/15	11/18	$\chi^2 = 1.41$, p=0.23
Age at onset [years]	–	23.2(6.9)	–
Duration of illness [years]	–	3.5(5.9)	–
Socioeconomic status	6.6(0.6)	4.4(1.2)	$U_{32,29} = 49$, p<0.001
Parental Socioeconomic status	6.3(0.9)	5.1(0.9)	$U_{13,24} = 53.5$, p<0.001
BMI [kg/m^2]	20.2(1.6)	22.7(3.4)	$U_{13,28} = 105$, p=0.03
JART	–	100.5(10.2)	–
PANSS	–		–
:positive	–	15.5(5.7)	–
:negative	–	16.3(6.7)	–
:general psychopathology	–	33.3(8.8)	–
:total	–	65.7(17.3)	–
mGAF[b]	–	34.4(10.8)	–
BACS[c]	–	-1.1(1.1)	–
SCoRS[d]	–	6.4(2.3)	–

Values are shown as means (standard deviations).
BACS; Brief Assessment of Cognition in Schizophrenia, BMI; body mass index, H; healthy control, JART; Japanese Adult Reading Test, mGAF; modified Global Assessment Functioning, PANSS; Positive and Negative Syndrome Scale, Sch; schizophrenia, SCoRS; Schizophrenia Cognition Rating Scale.
[a]Demographic differences between groups were examined by Mann-Whitney U t-test or chi-square (χ^2) test. The subscript two numbers written after U are the sample size in each group.
[b]Data are ranging from 0 to 100. Healthy subjects generally have a score ranging from 90 to 100.
[c]BACS composite score was calculated by averaging all z-scores of the six primary measures from the BACS.
[d]Data are ranging from 0 to 10, with larger number representing more worse function.

(41). Social functioning measured by the mGAF was approximately 30 points, indicating major impairment in several areas of functioning (42).

FA composition

Table 2 and Figure 1 present the results of FA composition analysis. The NA levels were significantly higher in the schizophrenia group than in the healthy group. EPA levels were lower and AA levels were higher in the schizophrenia group than in healthy controls. There was a significant difference in DPA levels and the n-6/n-3 ratio between controls and patients with schizophrenia; however, this did not persist after post-hoc analysis for multiple comparisons. These findings remained consistent even when we analyzed only antipsychotic-naïve or only first-episode patients (data not shown).

Relationships between FAs and clinical symptoms

No correlations were found between the FAs and PANSS total or positive/negative scores. Only NA was weakly correlated with PANSS general psychopathology scores (*rho*=0.47, *p*=0.017), however this correlation did not survive after multiple comparisons (Table 3A). Regarding the subscales, a significant positive correlation was found between NA level and "depression" score (G6) as presented in Table 3B and Figure 2. NA level was also correlated with "anxiety" (G2) and "poor attention" (G11) scores, but they did not survive post-hoc analysis for multiple comparisons. There were no significant correlations between the other FAs or the summary values (the n6/n3 ratio and n-3 index) and PANSS subscale scores (data not shown).

Relationships between FAs and cognitive scales

The relationships between FAs and cognitive scales are presented in Table 4. A significant positive correlation was found between OA level and SCoRS score. The BACS composite score correlated with SA level; however, this correlation did not persist after post-hoc analysis for multiple comparisons. There were no significant correlations between the other FAs or summary values (the n6/n3 ratio and n-3 index) and cognitive scales.

The correlation results between the OA and SCoRS subscales are presented in Table 5 and Figure 3. There were significant positive correlations between OA level and items 8 (remembering what you were going to say)?, 11 (concentrating sufficiently to read newspapers or books)?, and 20 (following conversations in a group)?.

Discussion

The present study investigated the erythrocyte membrane FA composition and its relationship with symptom severity, social, and cognitive functioning in antipsychotic-free patients with schizophrenia. Our findings showed that patients with schizophrenia had decreased levels of EPA (an n-3 PUFA), increased levels of AA (an n-6 PUFA), and a markedly increased level of NA (an n-9 MUFA), compared to controls. We also found that NA levels were predominantly associated with depression and related symptoms in patients with schizophrenia. Moreover, OA, an n-9 PUFA, was significantly and positively related to cognitive dysfunction related to daily living, as measured by the SCoRS in schizophrenia. These results suggest an association with specific aspects of symptomatology, suggesting FA composition may contribute.

The decreased EPA level in the current schizophrenia group is consistent with previous research (4, 7, 18), indicating that this change may be a characteristic trait of schizophrenia. FA levels including EPA composition are known to be affected by various confounding factors, such as antipsychotics (5, 7, 23, 50–53), aging

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TABLE 2 Fatty acid composition.

		H	Sch	Statistic	*p*	*q*	effect size
		n=32	n=29				
saturated	PA	21.17 (0.98)	21.17 (1.01)	$U_{32,29}$=439	0.72	0.79	0.05
	SA	19.80 (0.65)	19.56 (0.99)	$U_{32,29}$=400	0.36	0.48	0.14
monounsaturated	OA	14.69 (1.09)	14.72 (1.03)	$U_{32,29}$=455	0.90	0.90	0.02
	NA	0.53 (0.07)	0.94 (0.33)	$U_{32,29}$=39	<0.001	**<0.001***	0.92
n3 polyunsaturated	EPA	1.22 (1.42)	0.96 (0.42)	$U_{32,29}$=287	0.01	**0.04***	0.38
	DPA	3.00 (0.35)	2.85 (0.34)	$U_{32,29}$=328	0.05	0.12	0.29
	DHA	8.16 (1.23)	7.94 (1.35)	$U_{32,29}$=385	0.26	0.45	0.17
n6 polyunsaturated	LA	10.22 (0.93)	10.02 (0.96)	$U_{32,29}$=425	0.58	0.70	0.08
	DGLA	1.44 (0.19)	1.51 (0.30)	$U_{32,29}$=399	0.35	0.53	0.14
	AA	15.44 (1.42)	16.36 (1.52)	$U_{32,29}$=280	0.007	**0.04***	0.40
Summary value	n6/n3 ratio[a]	1.72 (0.47)	1.92 (0.47)	$U_{32,29}$=326	0.05	0.14	0.30
	Omega3 Index[b]	9.38 (1.55)	8.90 (1.69)	$U_{32,29}$=348	0.10	0.19	0.25

All values are shown as means (standard deviations).
Differences between groups were examined by Mann-Whitney U t-test. The subscript two numbers written after U are the sample size in each group.
*False discovery rate adjusted *p* value (*q*) < 0.05 (bold letter).
AA, arachidonic acid (20:4 n-6); DGLA, dihomogammalinolenic acid (20:3 n-6); DHA, docosahexaenoic acid (22:6 n-3); DPA, docosapentaenoic acid (22:5 n-3); EPA, eicosapentaenoic acid (20:5 n-3); H, healthy control; LA, linoleic acid (18:2 n-6); NA, nervonic acid (24:1 n-9); OA, oleic acid (18:1 n-9); PA, palmitic acid (16:0); SA, stearic acid (18:0); Sch, schizophrenia.
[a]n-6/n-3 ratio=AA/(EPA+DHA).
[b]omega-3 index=EPA+DHA.

(47, 48), dietary intake (54), and smoking (54). For this reason, this study examined only antipsychotic-free schizophrenia patients with early illness stages matched for age with control subjects, who likely have fewer confounding factors compared to previous studies. We also observed increased levels of AA, an n-6 PUFA. Previous studies consistently found an Increased n-6/n-3 ratio in schizophrenia (4, 5, 20). AA-derived eicosanoids have more prominent inflammatory activity than n-3 PUFAs, and an imbalance between n-6 and n-3 PUFAs, as indicated by the increased n-6/n-3 ratio, may cause neuroinflammatory pathology in neuropsychiatric disorders (55, 56). In other words, AA is a precursor of inflammatory bioactive lipids such as prostaglandins and thromboxane, which act in a pro-inflammatory direction (9, 10). Conversely, EPA is a known precursor of anti-inflammatory bioactive lipids, particularly resolvins E1/2, which are potent anti-inflammatory mediators and act in the direction of converging inflammation (11). Our findings suggest that patients with schizophrenia may have an excess of induced inflammation, resulting in damage to neurons or other organs. Furthermore, animal and experimental studies have suggested that PUFA abnormalities affect membrane properties in the central nervous system (e.g., fluidity, elasticity, and thickness) (6) and dopaminergic transmission (57), which might underlie vulnerability to psychosis (58). A combination of these factors may shape the pathophysiology of schizophrenia.

The role of PUFAs in the pathophysiology of schizophrenia led to the hypothesis that n-3 PUFAs (EPA and DHA) could be administered to patients with ARMS to prevent the onset of overt psychosis. Accordingly, the worldwide multicenter RCT,

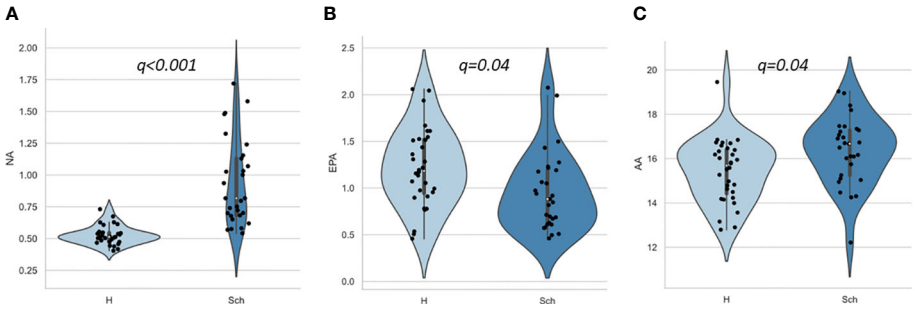

FIGURE 1
Scatter and violin plots of fatty acid composition. **(A)**, **(B)**, and **(C)** represent NA, EPA and AA compositions for H and Sch, respectively. The y-axis shows the percentage of each fatty acid when all (ten) fatty acids plus the internal standard, are adjusted to 100%. Values indicate false discovery rate adjusted p value (*q*). AA, arachidonic acid (20:4 n-6); EPA, eicosapentaenoic acid (20:5 n-3); H, healthy control; NA, nervonic acid (24:1 n-9); Sch, schizophrenia.

TABLE 3 Relationships between Fatty acid concentration and PANSS scores in schizophrenia.

A. FATTY ACID COMPOSITIONS AND PANSS TOTAL, POSITIVE, NEGATIVE, AND GENERAL PSYCHOPATHOLOGY

	PANSS total			PANSS Positive			PANSS Negative			PANSS General Psychopathology		
	rho	*p*	*q*	rho	*p*	*q*	rho	*p*	*q*	rho	*p*	*q*
PA	0.37	0.07	0.42	0.07	0.73	1.75	0.40	0.05	0.29	0.32	0.12	0.47
SA	-0.42	0.04	0.45	-0.02	0.93	1.01	-0.40	0.05	0.54	-0.37	0.07	0.41
OA	0.23	0.28	0.67	0.13	0.53	1.59	0.34	0.10	0.39	0.07	0.75	1.12
NA	0.35	0.09	0.35	-0.03	0.89	1.18	0.23	0.28	0.67	0.49	0.01	0.16
EPA	-0.17	0.41	0.82	-0.15	0.46	1.85	-0.15	0.47	0.95	-0.09	0.65	1.57
DPA	-0.27	0.19	0.58	-0.24	0.23	2.75	-0.23	0.27	0.81	-0.17	0.42	1.25
DHA	0.02	0.91	1.21	-0.01	0.96	0.96	-0.04	0.85	1.13	0.07	0.74	1.27
LA	-0.03	0.90	1.35	0.16	0.43	2.59	-0.14	0.51	0.88	-0.05	0.80	1.07
DGLA	0.06	0.80	1.36	0.06	0.76	1.51	-0.03	0.89	1.07	0.03	0.90	0.90
AA	0.01	0.96	1.15	-0.05	0.82	1.23	-0.04	0.84	1.27	0.08	0.69	1.38
n6/n3ratio[a]	0.00	0.99	0.99	-0.02	0.91	1.09	-0.01	0.95	0.95	0.03	0.88	0.96
Omega3 Index[b]	0.00	0.98	1.07	-0.05	0.80	1.37	-0.03	0.90	0.98	0.04	0.87	1.04

B. NA AND PANSS SUBSCALES

		rho	*p*	*q*
PANSS Positive	**1**[c]	0.03	0.89	0.91
	2	0.09	0.67	0.89
	3	0.04	0.86	0.89
	4	-0.08	0.71	0.38
	5	-0.36	0.08	0.89
	6	0.06	0.77	0.33
	7	0.32	0.11	0.89
PANSS Negative	**1**	0.32	0.11	0.37
	2	0.17	0.42	0.73
	3	0.21	0.32	0.63
	4	0.39	0.05	0.41
	5	-0.14	0.50	0.78
	6	0.23	0.27	0.59
	7	-0.34	0.09	0.40
PANSS General Psychopathology	**1**	0.39	0.06	0.33
	2	0.45	0.02	0.33
	3	-0.05	0.81	0.86
	4	-0.34	0.10	0.36
	5	0.17	0.42	0.78
	6	0.68	<0.001	**0.03***

(Continued)

B. NA AND PANSS SUBSCALES Continued

		rho	*p*	*q*
	7	0.29	0.16	0.43
	8	-0.07	0.76	0.91
	9	0.11	0.62	0.88
	10	0.05	0.80	0.89
	11	0.45	0.03	0.25
	12	0.28	0.17	0.43
	13	0.17	0.42	0.70
	14	-0.13	0.53	0.80
	15	0.25	0.23	0.53
	16	0.09	0.68	0.89

Values are Spearman's rank correlation coefficient, calculated using semi-partial correlation analysis that only fatty acid was controlled by age as a covariate.
*False discovery rate adjusted *p* value (*q*) < 0.05 (bold letter).
AA, arachidonic acid (20:4 n-6); DGLA, dihomogammalinolenic acid (20:3 n-6); DHA, docosahexaenoic acid (22:6 n-3); DPA, docosapentaenoic acid (22:5 n-3); EPA, eicosapentaenoic acid (20:5 n-3); H, healthy control; LA, linoleic acid (18:2 n-6); NA, nervonic acid (24:1 n-9); OA, oleic acid (18:1 n-9); PA, palmitic acid (16:0); PANSS; Positive and Negative Syndrome Scale, SA, stearic acid (18:0).
[a]n-6/n-3 ratio=AA/(EPA+DHA).
[b]omega-3 index=EPA+DHA.
[c]The numbers represent the following items, respectively:
Positive;1=Delusions, 2=Conceptual disorganization, 3=Hallucinations, 4=Excitement, 5=Grandiosity, 6=Suspiciousness/persecution, 7=Hostility.
Negative; 1=Blunted affect, 2= Emotional withdrawal, 3= Poor rapport, 4= Passive/apathetic social withdrawal, 5= Difficulty in abstract thinking, 6= Lack of spontaneity and flow of conversation, 7=Stereotyped thinking.
General Psychopathology; 1=Somatic concern, 2=Anxiety, 3=Guilt feelings, 4=Tension, 5=Mannerisms and posturing, **6=Depression,** 7=Motor retardation, 8=Uncooperativeness, 9=Unusual thought content, 10=Disorientation, 11=Poor attention, 12=Lack of judgment and insight, 13=Disturbance of volition, 14=Poor impulse control, 15=Preoccupation, 16=Active social avoidance.

NEURAPRO, was conducted (59). However, n-3 PUFA did not provide additional benefits for psychosis prevention. Considering this finding, the role of n-3 PUFAs in schizophrenia remain unclear, suggesting that the changes observed in the present study also might be a secondary phenomenon rather than pathophysiology of schizophrenia. Conversely, a recently published network meta-analysis concluding that n-3 PUFAs helped in preventing transitions to psychosis as compared to in controls (60). Currently, Other large-scale studies have been conducted (https://clinicaltrials.gov/ct2/show/NCT01429454; https://clinicaltrials.gov/ct2/show/record/NCT02597439), and their conclusions are expected to further our understanding of the role of FAs in schizophrenia.

Another important finding in this study was a markedly high level of NA, an n-9 MUFA, in the schizophrenia group. This finding is consistent with previous studies that indicated increased NA levels in patients with schizophrenia and ARMS (16, 20, 25). We also found a positive correlation between NA and depressive symptoms as measured by the PANSS subscale. Anxiety and poor attention, which are common symptoms with patients with depression (61, 62) also showed trend-level correlation with an increased NA level. NA is an essential molecule for the growth and

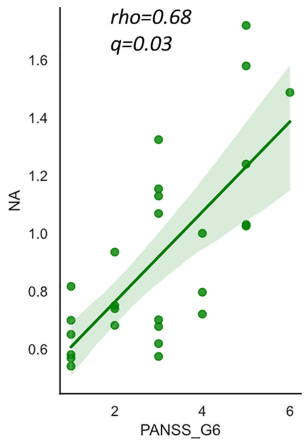

FIGURE 2
The relationship between nervonic acid (NA) and PANSS_G6 (depression) score in schizophrenia. The y-axis shows the percentage of each fatty acid when all (ten) fatty acids plus the internal standard, are adjusted to 100%. Values represent Spearman's rho and false discovery rate adjusted p value (q). The shaded area represents 95% confidence interval. NA, nervonic acid (24:1 n-9), PANSS, Positive and Negative Syndrome Scale.

TABLE 4 Relationships between fatty acid composition and cognitive and social functions in schizophrenia.

		BACS			SCoRS		
		rho	*p*	*q*	rho	*p*	*q*
saturated	PA	-0.10	0.62	0.99	0.19	0.38	0.83
	SA	0.44	0.02[†]	0.24	-0.37	0.09	0.52
n-9 monounsaturated	OA	-0.32	0.10	0.47	0.60	0.002	**0.048***
	NA	-0.37	0.06	0.46	-0.07	0.76	1.02
n-3 polyunsaturated	EPA	-0.17	0.39	0.67	0.04	0.87	0.99
	DPA	-0.19	0.33	0.80	-0.19	0.38	0.76
	DHA	-0.22	0.28	0.74	-0.02	0.94	1.03
n-6 polyunsaturated	LA	0.25	0.20	0.81	-0.19	0.39	0.71
	DGLA	-0.001	0.99	0.99	-0.07	0.75	1.12
	AA	0.06	0.78	0.98	-0.01	0.98	1.02
Summary value	n-6/n-3 ratio[a]	0.22	0.26	0.79	-0.07	0.75	1.06
	omega-3 index[b]	-0.24	0.23	0.78	0.05	0.81	0.97

Values are Spearman's rho, calculated using semi-partial correlation analysis that only fatty acid indices were controlled by age as a covariate.
*False discovery rate adjusted *p* value (*q*) < 0.05 (bold letter).
AA, arachidonic acid (20:4 n-6); BACS, Brief Assessment of Cognition in Schizophrenia; DGLA, dihomogammalinolenic acid (20:3 n-6); DHA, docosahexaenoic acid (22:6 n-3); DPA, docosapentaenoic acid (22:5 n-3); EPA, eicosapentaenoic acid (20:5 n-3); FES, first episode schizophrenia; H, healthy control; LA, linoleic acid (18:2 n-6); NA, nervonic acid (24:1 n-9); OA, oleic acid (18:1 n-9); PA, palmitic acid (16:0); SA, stearic acid (18:0); SCoRS, Schizophrenia Cognition Rating Scale.
[a]n-6/n-3 ratio=AA/(EPA+DHA).
[b]omega-3 index=EPA+DHA.

TABLE 5 Relationships between OA concentration and SCoRS subscores in schizophrenia.

SCoRS subscale	rho	*p*	*q*
1. Remembering names of people you know or meet?	0.20	0.36	0.40
2. Remembering how to get places?	0.33	0.13	0.18
3. Following a TV show?	0.31	0.15	0.18
4. Remembering where you put things?	0.41	0.05	0.10
5. Remembering your chores and responsibilities?	0.44	0.04	0.09
6. Learning how to use new gadgets and equipment?	0.07	0.76	0.76
7. Remembering information and/or instructions recently given to you?	0.46	0.03	0.08
8. Remembering what you were going to say?	0.56	0.006	**0.037***
9. Keeping track of your money?	0.34	0.11	0.18
10. Keeping your words from being jumbled together?	0.35	0.10	0.17
11. Concentrating well enough to read a newspaper or a book?	0.54	0.008	**0.039***
12. With familiar tasks?	0.25	0.25	0.29
13. Staying focused?	0.56	0.01	0.05
14. Learning new things?	0.49	0.02	0.06
15. Speaking as fast as you would like?	0.33	0.13	0.17
16. Doing things quickly?	0.35	0.10	0.18
17. Handling changes in your daily routine?	0.41	0.05	0.11
18. Understanding what people mean when they are talking to you?	0.56	0.005	0.11
19. Understanding how other people feel about things?	0.08	0.73	0.77
20. Following conversations in a group?	0.52	0.01	**0.047***

(Continued)

TABLE 5 Continued

Values are Spearman's rank correlation coefficient, calculated using semi-partial correlation analysis that only OA was controlled by age as a covariate.
*False discovery rate adjusted *p* value (*q*) < 0.05 (bold letter).
OA, oleic acid (18:1 n-9); SCoRS, Schizophrenia Cognition Rating Scale.

maintenance of integrity in the white matter and peripheral nervous tissue enriched by sphingomyelin (63) and is suggested to be related to psychiatric disorders (64). Our results may be partly in line with the neuroimaging evidence that abnormalities in brain connectivity contribute to the trait characteristics of schizophrenia (65), such as negative symptomatology (66) and cognitive deficits (67). Because the impaired integrity of white matter is also reported in depression (68–70), it may be possible that NA abnormalities commonly contribute to the pathophysiology of both schizophrenia and depression.

In this study, we found for the first time that OA and n-9 MUFA levels were significantly related to cognitive dysfunction related to daily living, as measured by the SCoRS, in patients with

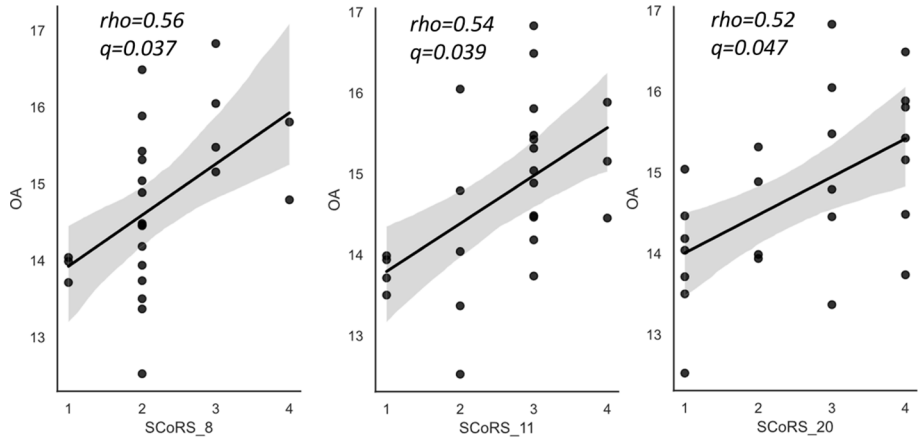

FIGURE 3
The relationships between oleic acid (OA) and SCoRS subscales in schizophrenia. SCoRS_8; 'Remembering what you were going to say?'; SCoRS_11, 'Concentrating well enough to read a newspaper or a book?'; SCoRS_20, 'Following conversations in a group?'. The y-axis shows the percentage of each fatty acid when all (ten) fatty acids plus the internal standard, are adjusted to 100%. Values represent Spearman's rho and false discovery rate adjusted p value (q). The shaded areas represent 95% confidence interval. OA, oleic acid (18:1 n-9); SCoRS, Schizophrenia Cognition Rating Scale.

schizophrenia. As far as we know, no previous study has shown significant association between OA levels and schizophrenia; however, previous OA studies have shown associations with depression (71, 72), Parkinson's disease (73) and Alzheimer's disease (74). Notably, a recent large-scale study on depression (n=4459) (75) suggested that serum OA levels were positively associated with depression and that for every 1 mmol/L increase in OA levels, the prevalence of depression increased by 40%. OA is an important FA as the most abundant FA in plasma, accounting for approximately 80% of the plasma phospholipid MUFAs (76). Since stearoyl-CoA desaturase, the rate-limiting enzyme of OA, has been found to cause neurotoxicity by producing MUFAs and impairing microglia and macrophages (77), the possibility exists that this mechanism affects cognitive function in patients with schizophrenia.

The present study had several potential limitations. First, the sample size of the study was rather small by including only antipsychotic-free patients, which may have limited the generalizability and statistical power of our results. Second, we did not control for participants' dietary habits and cigarette smoking that could affect FA results. All participants had normal blood test results and standard BMIs; however, the BMIs were higher in the patients than in the controls, whereas the SES was higher in the controls than in the patients. The SES score did not always reflect the exact nutritional status of the young patients included in this study; thus, we should have conducted a nutritional questionnaire survey in addition to the assessments of SES, BMI, and blood chemistry. Differences in the nutritional status potentially led to differences in the lifestyle habits and physical conditions between the groups. The possibility that this further affected the results of the symptom/cognition measures in each group cannot be ruled out. Third, as our study was cross-sectional, future longitudinal studies are needed to confirm the role of FA changes as a trait marker and to investigate the influence of illness stage. Finally, as FA abnormalities and their contribution to clinical symptoms were reported also in other neuropsychiatric disorders, such as depression [63], disease specificity of our findings should be tested in future studies.

In conclusion, this study expanded our previous FA findings in schizophrenia and confirmed the increase in EPA levels and decrease in AA levels in the affected patients. It further showed that erythrocyte membrane level of NA, an n-9 MUFA elevated in patients with possibility of impaired white matter integrity (65, 68–70), was significantly correlated with the severity of depressive symptoms in a cohort of antipsychotic free patients with relatively early stages. We also demonstrated for the first time that membrane OA, an n-9 MUFA abundantly exists in the human body, is associated with cognitive dysfunction in schizophrenia. Further studies on FA abnormalities in various illness stages of schizophrenia, potential influencing factors, and disease specificity will be needed to clarify the role of FA abnormalities in the pathophysiology of schizophrenia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Committee on Medical Ethics of the University of Toyama. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

YH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project

administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TT: Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing. HI: Data curation, Investigation, Writing – review & editing. DS: Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing. TS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. MS: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing, Data curation, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Gender differences in cognitive improvements after two months of atypical antipsychotic treatment in first episode schizophrenia

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Aims: This study aims to explore the gender differences in cognitive improvements after two months of atypical antipsychotic treatment in first episode schizophrenia (FES).

Methods: 82 patients with FES, including 50 male patients and 32 female patients, were enrolled in the present study. Positive and Negative Syndrome Scale (PANSS) and MATRICS Consensus Cognitive Battery (MCCB) were respectively conducted to evaluate the clinical symptoms and cognitive function of patients with FES at baseline and after treatment. Repeated measure ANOVA was performed to compare gender differences in cognitive domains scores between baseline and 2-month follow-up. Stepwise liner regression model was performed to explore the effect factors of cognitive improvements in patients.

Results: There was no significant difference in age of onset, education years, PANSS scores, duration of untreated psychosis and Olanzapine equivalent doses between male and female patients (all $p > 0.05$). In the comparisons of cognition function, male patients exhibited better performance in social cognition compared with female patients at baseline ($t = 3.20$, $p < 0.05$). After treatment, improvements of attention/vigilance and working memory were both found in male patients and female patients (attention/vigilance, $F = 11.867$, $p < 0.05$; working memory, $F = 18.265$, $p < 0.05$). In addition, improvement of speed of information processing was only found in female patients ($F = 11.65$, $p < 0.01$). Significant interaction between time and gender was found in speed information of processing ($F = 4.140$, $p = 0.045$). Stepwise liner regression model revealed that improvements of negative symptoms promote improvements of cognitive function in female patients (all $p < 0.05$).

Conclusions: Our findings revealed gender differences of cognitive improvements in patients with FES after 2-month treatment. It provides new evidence for gender differences in cognitive symptoms of schizophrenia, and also provides preliminary clues for further individualized cognitive intervention strategies.

KEYWORDS

first episode schizophrenia, cognitive function, gender difference, follow-up study, MCCB

Introduction

Gender is one of the most important heterogeneity factors in schizophrenia (1). Over the past few decades, numerous studies have explored difference between male and female patients in several aspects of the disease. For example, male patients with schizophrenia appear to exhibit an earlier age of onset, severer negative symptoms and a higher frequency of alcohol/substance abuse than female patients (2, 3). Female patients display superior occupational, interpersonal and psychosocial function compared with male patients (4). Studies also found gender difference in response to antipsychotic drugs. Male patients tend to respond more poorly to antipsychotic medications, exhibit poorer medication adherence, and therefore have more disabilities (5). Inversely, in a 4-18 years follow-up study, female patients with schizophrenia had both better remission of symptoms and functional outcomes after treatments (6). Gender-related characteristics may play a crucial role in the progression and outcome of schizophrenia. Identifying these differences benefits to specify and implement gender-specific intervention strategies.

As the core features of schizophrenia, cognitive deficits occur early and persist across the course of schizophrenia (7, 8), which may be associated with long-term disability and heavy economic burden on society (9). Several studies have devoted to investigate gender difference of cognitive function in schizophrenia. Evidence indicated that gender differences exhibit in the whole course of schizophrenia, including the prodromal, acute and chronic stages (10, 11). Zhao et al (12) have demonstrated that female patients with FES performed better in speed of processing and verbal learning than male patients. However, Zhang et al (13) also reported no gender difference in the comparisons of cognitive function in first episode schizophrenia. Given the inconsistent results on gender difference in cognitive function, one of the reasons may be the heterogeneity of sample size and methods of analyses. The other may be the different tools of cognitive assessment used in the previous studies. Measurement and Treatment of Schizophrenia Cognition Research (MATRICS) Consensus Cognitive Battery (MCCB) (14, 15), which is considered the gold standard for assessing cognitive function in patients with schizophrenia. Based on these reason, this study adopted appropriate assessment tools to further explore gender differences in cognitive function of schizophrenia.

It's worth noting that previous studies have shown that gender difference in outcome indicators may affect by the time of evaluation. One of the studies reported that more female patients reached a state of recovery compared to male patients after a 5-year follow-up (16). A 10-year follow-up study indicated that gender differences in outcome were attenuated (17, 18). However, the majority of previous studies have mostly employed long-term longitudinal designs (up to 1 year), and the results of short-term study on gender difference in cognitive improvements remain unclear. Study on gender difference in cognitive function after short-term treatment is beneficial to the formulation of individualized intervention strategies for early schizophrenia. Previous studies have reported about 91.4% schizophrenia with FES had improvements in cognitive function after 2 months of atypical antipsychotic treatment (19). And 2 months is seen as a early time window to observe cognitive improvements (20, 21). Up to now, no study has investigated gender difference in cognitive improvements after 2 months of atypical antipsychotic treatment in Chinese Han population. Whether this cognitive improvement may be influenced by gender remains unknown.

In the present study, the main objective was to investigate gender difference in cognitive improvements of schizophrenia with FES after 2-month treatment. We hypothesize that there is gender difference in cognitive improvement of schizophrenia after 2-month treatment and this difference may be related to the improvement of clinical symptoms.

Materials and methods

Subjects

Patients with FES were recruited from the inpatient and outpatient of Nanjing brain hospital, Jiangsu, China, from

January 2017 to September 2023. Patients were diagnosed by two psychiatrists using the DSM-V who were experienced and involved in the usual care process of patients. All patients meets the following criteria: (1) right handed; (2) age between 16 to 45; (3) Intelligence quotient (IQ)>70 the Wechsler Adult Scale of Intelligence (WAIS) was adopted to test the Intelligence Quotient (IQ); (4) Duration of untreated time ≤ 24 months, never treated with antipsychotic medication or physical therapy. Exclusion criteria included: (1) Mental retardation or other serious mental disorders; (2) Serious physical diseases; (3) History of drug or alcohol abuse.

The study was approved by the Medical Research Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University(No. 2021-KY075-01). All participants provided written informed consent.

Nueropsychologic and Clinical measurement

Basic clinical measurements such as age of onset, education years, duration of untreated psychosis were provided by patients and their caregivers. In this study, cognitive assessment was performed using the MCCB, comprised of seven cognitive domains, including speed of information processing, attention and vigilance, verbal learning, working memory, problem solving, visual learning and social cognition (22, 23). Clinical symptoms assessment was performed using the Positive and Negative Syndrome Scale (PANSS), comprising positive symptoms, negative symptoms and general symptoms, and carried out by two experienced psychiatrists (24). All patients were medicated with atypical antipsychotic medication based on routine clinical practice. Seventeen patients were treated with risperidon, thirteen with olanzapine, twenty-one with aripiprazole, fourteen with paliperidone and seventeen with amisulpiride. All drug doses are converted to olanzapine equivalents (25), and cumulative antipsychotic dose was defined as the sum of all daily doses from the start of antipsychotic therapy to the day of retesting MCCB at 2 months follow-up.

Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences version 25.0 (SPSS 25.0). The normality of data distribution was assessed with the Kolmogorov-Smirnov test and Shapiro-Wilk test. Mann-Whitney U test was adopted to compare difference of education years, age of onset and duration of untreated psychosis. Independent t-test was used to compare PANSS scores, MCCB scores at baseline and olanzapine equivalent doses between male and female patients. Repeated measure ANOVA was performed to compare cognitive domain scores between groups. Stepwise liner regression model was performed to explore the effect factors of cognitive improvements in patients.

Results

Demographic and clinical characteristics

A total of 82 schizophrenia with FES (52 males, 30 females) were enrolled in the present study. Compared to normative data from the Chinese population (26), patients with FES showed deficits in all cognitive domains (all $p < 0.05$, see Table 1 for details).

There were no significant differences in age of onset, education years, PANSS scores (including positive scores, negative scores and general psychopathology scores) and duration of untreated psychosis between male and female at baseline. There was also no significant differences in Olanzapine equivalent doses between groups (all $p > 0.05$). In the comparisons of cognition function, male patients exhibited better performance in social cognition

TABLE 1 Cognitive impairments in schizophrenia with FES.

	N	Mean (SD)	Controls Mean	*t*	*p*
Speed of processing	82	38.45 (11.12)	50	-9.39	0.00
Attention/vigilance	82	39.04 (11.01)	50	-9.01	0.00
Working memory	82	36.48 (10.69)	50	-11.45	0.00
Verbal learning	82	37.56 (11.27)	50	-9.98	0.00
Visual learning	82	41.85 (12.28)	50	-6.00	0.00
Problems solving	82	46.76 (11.42)	50	-2.57	0.01
Social cognition	82	33.46 (10.83)	50	-13.81	0.00
Composite scores	82	32.37 (12.39)	50	-12.88	0.00

FES, First episode schizophrenia.
N, Total number of schizophrenia.
Mean:,All data were stated as Mean (SD).
t, Independent t-test.
P, p < 0.05 indicates statistical significance.

compared with female patients at baseline (t = 3.20, $p < 0.05$, see Table 2 for detalis).

Gender difference in cognitive function at baseline and 2-month follow-up

After 2-month treatment, both male and female patients exhibited improvements in attention/vigilance and working memory (attention/vigilance, F = 11.867, $p < 0.05$; working memory, F = 18.265, $p < 0.05$). Furthermore, only female patients showed improvement in speed of information processing (F = 11.65, $p < 0.01$). All enrolled patients demonstrated significant enhancements in overall cognitive function after 2 months of treatment with atypical antipsychotics (F = 9.708, $p < 0.01$). Notably, a significant interaction between time and gender was observed in terms of speed of information processing (F = 4.140, $p = 0.045$). (see Figure 1 for details).

Gender difference in effect factors of cognitive improvements

Stepwise liner regression model revealed that improvements of negative symptoms promote improvements of cognitive function in female patients. (all $p < 0.05$, see details in Table 3). No significant effect factor of cognitive improvements was found in male patients.

Discussion

In the present study, we explored gender differences in cognitive improvements of first episode schizophrenia after 2 months of treatment. The main findings emerged 1) Male patients had better social cognition than female patients at baseline. 2) Improvement of speed of processing was only found in female patients. Significant interaction between time and gender was found in speed information of processing. 3) Negative symptoms improvement may promote cognitive improvements in female patients.

Evidence shows that individuals with schizophrenia exhibit different psychiatric symptoms based on gender. Males tend to experience more severe negative symptoms, while females tend to experience more severe positive symptoms (13, 27–29). However, the present study found no gender differences in psychiatric symptoms of first episode schizophrenia, which was inconsistent with previous research findings. A global study had revealed that gender differences in psychotic symptoms displayed regional heterogeneity, possibly associate with psychosocial and cultural factors in different residential regions (30). Additionally, the

TABLE 2 Gender differences in demographic and clinical characteristics in schizophrenia with FES.

	Male (n=50)	Female (n=32)	*t/U*	*P*
Age of onset (years)[a]	22.50 (18.75-30.25)	21.00 (18.00-29.00)	-0.78	0.43
Education years [a]	13.00 (11.00-15.25)	13.00 (11.00-15.00)	-0.46	0.64
Dup (months)[a]	6.00 (3.75-12.00)	10.00 (6.00-12.00)	-0.75	0.45
Olanzapine equivalent doses [b]	14.08 (4.41)	12.45 (3.87)	1.70	0.09
Baseline symptoms severity				
PANSS-positive scores [b]	21.72 (3.36)	21.31 (3.28)	0.53	0.59
PANSS-negative scores [b]	18.98 (4.05)	19.31 (4.66)	-0.14	0.88
PANSS-general scores [b]	44.10 (3.85)	43.97 (3.65)	0.15	0.87
PANSS-total scores [b]	84.78 (7.35)	84.38 (9.30)	0.21	0.82
Baseline cognitive impairment severity				
Speed of information processing [b]	39.14 (11.26)	37.38 (10.99)	0.70	0.48
Attention/vigilance [b]	37.88 (11.81)	40.84 (9.52)	-1.19	0.23
Verbal learning [b]	37.74 (11.43)	37.28 (11.20)	0.18	0.85
Working memory [b]	36.60 (10.78)	36.28 (10.72)	0.13	0.89
Visual learning [b]	40.94 (11.97)	43.28 (12.83)	-0.84	0.40
Problem solving [b]	45.70 (11.04)	48.41 (11.98)	-1.04	0.29
Social cognition [b]	36.22 (11.10)	29.16 (8.97)	3.02	0.00*

FES, first episode schizophrenia.
Dup, duration of untreated psychosis.
PANSS, Positive and Negative Syndrome Scale.
[a]Independent t-test; [b]Mann-Whitney U test.

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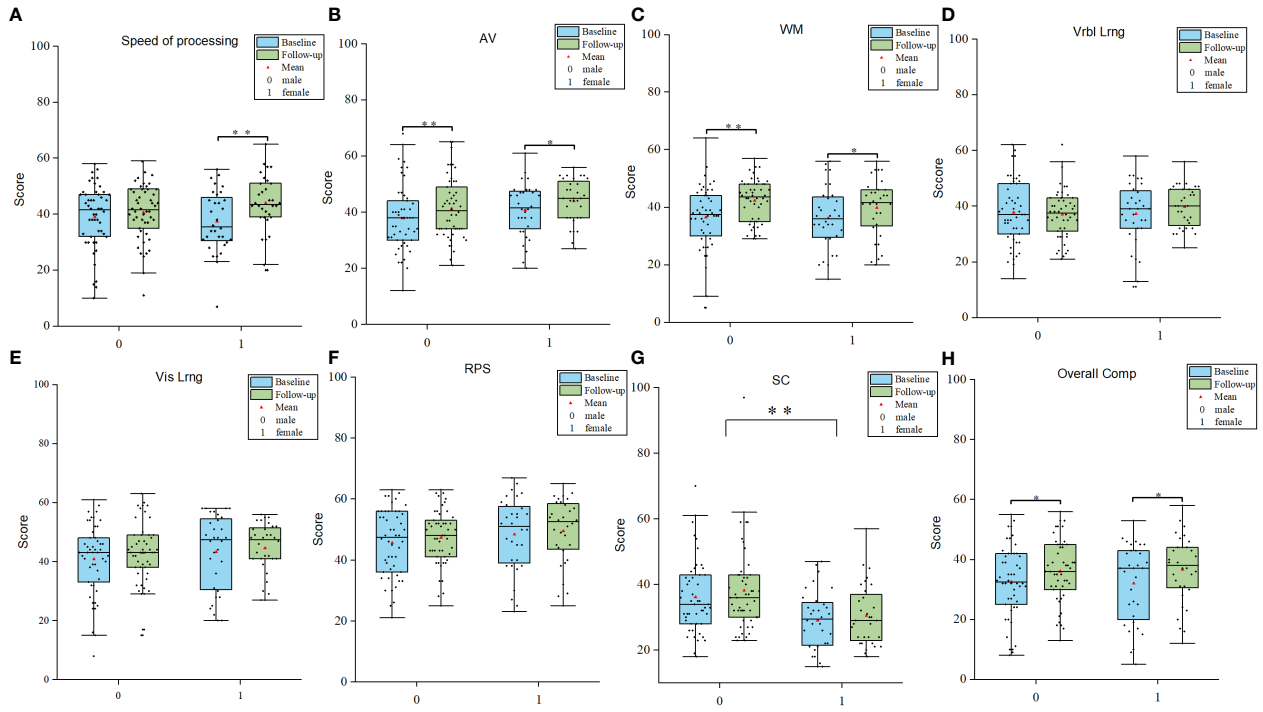

FIGURE 1
Gender differences in cognitive improvements. **(A-H)** Comparisions of different cognitive domains between male and female patients. AV Attention/Vigilance; WM Working memory; Vrbl lrng Verbal learning; Vis lrng Visual learning; PRS Problem solving; SC Social cognition. *$p < 0.05$, **$p < 0.01$.

heterogeneity in sample size and assessments tools adopted may contribute to potential discrepancies in research outcomes.

Previous studies have reported cognitive impairments in patients with schizophrenia during the early stages of this illness (7, 31–33). In our study, we found that first episode schizophrenia exhibited extensive cognitive deficits compared to normative data from the Chinese population. These findings provide additional evidence to support this viewpoint and further enhance its reliability. When analyzing the data by gender grouping, a noteworthy trend emerged among patients, showing that males scored higher in social cognition, indicating better social function compared to females. However, the conclusions regarding gender differences in social cognition still remain controversial. For instance, previous researches indicated that males exhibited superior social cognition compared to females at the early and chronic stages of schizophrenia (27, 34). It is important to note that some studies suggested there was no significant difference in social cognitive function between gender (13). A potential explanation for the inconsistent of our results could be the complexity of the social cognition functional construct (35). Prior investigations have revealed that social cognition encompasses diverse abilities, including theory of Mind, emotional processing (EP), social perception, and attribution style (36). However, the MCCB used in the present study primarily assessed the EP aspect of individual

TABLE 3 Gender difference in effect factors of cognitive improvements in schizophrenia.

Cognitive improvement	PANSS symptoms improvement	B	β	t	p
Speed of information processing	Negative symptoms	-1.90	-0.713	-5.56	<.01
Attention/vigilance	Negative symptoms	-1.26	-0.59	-4.09	<.01
Verbal learning	Negative symptoms	-2.10	-0.68	-5.08	<.01
Working memory	Negative symptoms	-1.27	-0.54	-3.60	<.01
Visual learning	Negative symptoms	-2.10	-0.68	-5.08	<.01
Problem solving	Negative symptoms	-1.57	-0.58	-3.90	<.01
Social cognition	Negative symptoms	-1.47	-0.58	-3.95	<.01
Overall Composite scores	Negative symptoms	-2.56	-0.77	-6.75	<.01

PANSS, Positive and Negative Syndrome Scale.

social cognition. Furthermore, a 10-year follow-up study provided evidence that male patients with schizophrenia exhibited poorer social cognition than female patients (37).Combined with the results of this study, it is possible to speculate that the female advantage in social cognition might become apparent later in the disease course. However, relevant studies need to be further verified.

The present study found that only female patients exhibited improvements in processing speed, which consistent with findings from previous research (34, 38, 39). Notably, a rodent study simulating schizophrenia-like behavior also revealed that female mice demonstrated better processing speed than male mice (40). Nevertheless, the pathophysiological mechanism underlying gender differences in speed of processing improvements in schizophrenia remains inconclusive. Currently, the most widely accepted explanation is that estrogen has a protective impact on cognitive function in patients with schizophrenia (41–43). And previous study also reported that there is an inverse correlation between psychotic symptoms and estrogen levels (44). Some females with psychotic tendencies experience more pronounced symptoms after menopause (45, 46). Estrogen diminished psychotic symptoms by modulating major neurotransmitter systems associated with schizophrenia, such as the dopamine signaling system. However, this protection primarily prevents further cognitive deterioration over time in schizophrenia, rather than preventing damage from the disease itself, as evidenced by the absence of gender differences in processing speed improvements among patients with FES at baseline. Furthermore, the superior response of female patients to antipsychotic drugs may provide an additional explanation. Specifically, estrogen influences the activity of CYP1A2, a major enzyme involved in olanzapine metabolism (47). Consequently, With the same dosage, the drug plasma concentration of olanzapine in female patients with schizophrenia was higher than that in males with schizophrenia and produce better results (48). Numerous prior studies have demonstrated that gender may change brain structure through mediating neurodevelopment, resulting in various psychiatric symptom (49–52). Future magnetic resonance findings should be included to explore gender differences in cognitive structure of processing speed in schizophrenia.

Previous studies have identified a convergence between negative symptoms and cognitive impairments in individuals with schizophrenia (53, 54). Oliver et al. (55) investigated that cognitive changes were associated with negative factors in a one-year follow-up study. Chen et al. also reported that negative symptoms were associated with longitudinal changes of cognitive function (56). Overlapping etiologies may exited between negative symptom subdomains and cognitive function. Cognitive function and clinical symptoms are not independent but affects each other. However, we only found that negative symptoms improvements were correlated with cognitive improvements in female patients, which suggested there may be gender specificity in curative effect. The earlier the intervention for negative symptoms, the greater may be cognitive improvements in female patients.

Cognitive remediation (CR) is an important therapeutic method for cognitive impairments in schizophrenia. CR as a type of behavioral training aims to improve cognitive function with the goal of persistence and generalization in everyday life. CR is effective in promoting the improvement of cognitive function, social and daily living function in patients with schizophrenia (57). Exsting MRI research conducted on individuals in the early stages of schizophrenia has revealed that CR interventions are associated with structural and functional alterations in the brain, particularly in the frontal and limbic regions (58, 59). CR may have a slowing or reversing effect on progressive brain volume deterioration in the early stages of schizophrenia, especially in areas critical to higher cognitive processes (58, 60). Vita et al. also reported that long-term improvement of psychosocial functioning after CR can be observed with significant gender differences, and females exihibited more significant improvements in cognitive function (61). Currently, only a few studies have concentrated on gender differences in cognitive improvements after CR intervention, and the results have been inconsistent. Thus, in the future studies, gender differences in cognitive improvement and brain structure changes after CR interventions need to be further explored at the early stage of the disease by using multimodal techniques. Longitudinal studies are also needed to clarify gender differences in cognitive training and whether its positive effects persist over time.

Limitation

This research has some limitations. First, our study lasted only 2 months, which is much shorter than previous studies. The findings from longitudinal investigations suggested that the duration of 1-3 years may not be sufficient to detect significant changes in cognitive function (62). In our future studies, we intend to conduct ongoing follow-up assessments of the participants who have been enrolled in our study. Second, our research is an observational study, the pathological mechanisms of gender differences in cognitive function in schizophrenia are not yet clear. We need to incorporate magnetic resonance data for further study. Third, the study employed inconsistent drug interventions. Previous research has demonstrated varying degrees of improvement in cognitive function depending on the type of antipsychotic medication utilized (63). Fourth, the sample size after the gender-stratified analysis was relatively small, and our stratified results should be validated in larger studies in the future. Finally, women's neuropsychological performance has been shown to fluctuate with the menstrual cycle, which was not controlled for in our study (64).

Conclusion

In summary, our results indicated that gender differences of cognitive function exhibited at baseline and 2-month follow-up, which provides some clues for the personalized treatment of schizophrenia patients. Understanding these differences may help develop more precise treatment strategies for individuals with schizophrenia.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Medical Research Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WL: Writing – review & editing, Writing – original draft, Methodology, Data curation. XC: Writing – original draft. QL: Writing – review & editing, Data curation. YL: Writing – review & editing, Data curation. CZ: Writing – review & editing, Methodology, Formal Analysis. JD: Writing – review & editing, Supervision, Resources, Funding acquisition. SX: Writing – review & editing, Supervision, Resources, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1369532/full#supplementary-material

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Factorial structure of the Comprehensive Assessment of At-Risk Mental States in help-seeking individuals: mapping the structure and the prediction of subsequent transition to psychosis

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Objectives: The aim of the current study was 3-fold: 1) to examine the factorial structure of the Comprehensive Assessment of At-Risk Mental States (CAARMS) in help-seeking individuals undergoing an assessment on suspicion of psychosis risk; 2) to investigate the association of CAARMS factors with functioning; 3) and to test the association of any derived factors with the longitudinal outcome of transition to psychosis.

Methods: The study included 101 patients. First, a principal component analysis (PCA) was conducted using the Varimax rotation method. A minimum initial eigenvalues of greater than or equal to 1.0, analysis of Scree plots, percentage of variance explained by each component, reliability (Cronbach's alpha) of factors above 0.7 and Parallel Analysis were the criteria used to determine the appropriate number of factors Second, Spearman correlations were run to analyze the relationship between CAARMS factors and sociodemographic and functional variables (i.e. age, schooling, Social and Occupational Functioning Assessment Scale-SOFAS- and Health of the Nation Outcome Scales-HoNOS-scores). Third, we performed a Logistic regression analysis to evaluate the association between baseline CAARMS factors and the risk of transition to psychosis at the 6-month follow-up.

Results: A total of 101 consecutive patiens were recruited. We found that: 1) a 6 factor model solution as the most appropriate, jointly accounting for 65% of the variance; 2) factors 1 ("negative-interpersonal"), 2 ("cognitive-disorganization"), 3 ("positive"), and 4 ("motor-physical changes") were negatively correlated with SOFAS total score; factors 1, 2, and 3 showed positive correlations with HoNOS total score; factors 2 and 3 present similar patterns of correlations, factor 3 manifesting the strongest association with HoNOS symptoms, HONOS and SOFAS total score. Both factors 5 and 6 show significant associations with HoNOS behavioral impairment; 3) after 6 months 28 participants (30.1%) converted to psychosis. Factors 2 and 3 were positively associated with the risk

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of transition to psychosis; whereas, the factor 5 ("affective factor") was negatively associated with the outcome variable.

Conclusions: It is thus crucial to recognize the type and severity of psychopathology in help-seeking individuals in order to intensive clinical monitoring of subclinical psychopathology risk profiles, and design specific care pathways.

KEYWORDS

help seeking, CAARMS, principal component analysis (PCA), disorganization, HoNOS, SOFAS

1 Introduction

Primary psychosis usually arises from earlier stages that already indicate a requirement for care, and tends to coincide with other comorbid disorders and functional impairment. The concept of early intervention in psychosis has laid the groundwork for the development of clinical staging: this model aims to determine an individual's placement on a continuum of illness, with the primary objective being to offer a more precise roadmap for treatment decisions, prognosis, and outcome prediction (1, 2). Interventions implemented during the subthreshold symptoms phase of disorder not only decrease the risk of transition for a minimum of 1–2 years, but also enhance functional outcomes (1, 2).

Over the last two decades, a critical clinical and research issue has been to define reliable and validated criteria to identify help-seeking subjects with subthreshold positive psychotic symptoms at high risk of developing a psychotic disorder such as the at-risk mental state (ARMS) (3) or clinical high-risk (UHR) (4).

These criteria comprise a combination of trait and state risk factors that allow the identification of individuals with an enhanced 36% risk of developing a psychotic illness within a year (5, 6), although declining transition rates to 15% have been found in specialized early intervention settings (7–9).

Even though the majority of individuals with ARMS will not actually transition to full-blown psychosis or even remit from an ARMS state, they manifest mental difficulties that are distressing and disabling *per se*, such as negative symptoms and persistent depressive and anxiety features that are associated with functional deficits at baseline and follow-up (9, 10). Indeed, psychiatric symptoms other than subthreshold psychotic ones represent the most common subjective distress eliciting the search for mental help in the general population (11–14).

In this scenario, a dimensional approach defining the extent to which, i.e., "how much", a specific characteristic occurs could be a suitable method to interpret the proteiform phenomenology in ARMS help-seekers and to identify, describe, and map the emergent needs of this population. Indeed, it would serve as both an alternative and complement to the mainstream categorical approach based on all-or-nothing conditions determined by the "presence/absence" of specific symptoms, e.g., perceptual aberrations. This is already possible since the first and most widely used instrument, i.e., the Comprehensive Assessment of At-Risk Mental States [CAARMS] (15), allows one not only to rate positive symptoms (disorders of thought content, perceptual abnormalities, and disorganized speech) to classify the young person as non/UHR/affected by psychosis, but also to evaluate other valuable psychopathological domains such as cognitive-attentional changes, emotional disturbances, negative symptoms, impaired tolerance to normal stress, impulsive behaviors, behavioral changes, motor and physical changes, and general psychopathology, which appear to be associated with the emerging disability of young help-seekers (15). In detail, the CAARMS enables the assessment of subclinical symptoms that are below the sensitivity threshold of commonly used psychopathological scales. From this point of view, the exploration of the dimensional structure of the CAARMS might represent a useful way to describe the subclinical symptomatology in the UHR population (16–19).

To our knowledge, only three studies have explored the dimensional structure of CAARMS to better understand the UHR subjects' psychopathology, suggesting the presence of three (17) or five (18, 20) factors.

In light of this, the aim of the current study was threefold (1): to examine the factorial structure of the CAARMS in help-seeking individuals undergoing an assessment on suspicion of psychosis risk, for an accurate representation of sub-threshold clinical manifestation in UHR (2); to investigate the association of CAARMS factors with other important variables such as global functioning (3); and to test the association of any derived factors with the longitudinal outcome of transition to psychosis, operatively defined as daily positive psychotic symptoms lasting longer than 1 week (6, 21).

2 Methods

2.1 Subjects and procedures

The present study includes all consecutive help-seekers on suspicion of psychosis risk referred to the Struttura Complessa Psichiatria Universitaria, Dipartimento di Neuroscienze e Salute Mentale, Azienda Ospedaliero-Universitaria "Città della Salute e della Scienza di Torino," Turin, Italy, in the period January 2020–December 2023, for assessment and diagnosis, within the project named "Modello di riconoscimento e cura delle persone con esordio psicotico o ad alto rischio di psicosi nei giovani tra i 14 e i 30 anni, con un approccio fortemente orientato alla prevenzione" ("Model of recognition and care of people with onset psychotic or at high risk of psychosis in young people aged between 14 and 30 years, with a strongly oriented approach to prevention").

Help-seekers were mainly sent by general practitioners, child neuropsychiatry centers, psychology/adolescent centers, other mental health services, hospital emergency rooms, school and college counselors, relatives, and self-referral. A very low threshold for the referral from any potential sender was chosen to favor the most inclusive accessibility.

Eligible patients fulfilled the following inclusion criteria (1): age between 14 and 30 years (2); seeking help for a mental distress with onset within the previous 12 months in association with substantial psychosocial functional decay [>25% decrease in the Global Assessment of Functioning (GAF) in the past 12 months] (3); fluent in Italian; and (4) being able to complete a full questionnaire. Exclusion criteria were the following (1): history of frank psychotic episodes (2); history of treatment with antipsychotics (3); substance abuse or dependence in the past 6 months (4); no consent from the adolescent or his/her parents (5); known intellectual disability (IQ < 70); and (6) anamnesis positive for a severe head injury (coma ≥ 48 h), neurological disorders, or any other medical condition associated with psychiatric symptoms. The presence of psychiatric comorbidity and substance use disorders (SUDs) was assessed using the SCID-5-TR.

All participants volunteered for the study and gave their written informed consent prior to participation. For individuals under 18, in addition to the informed consent, parents were informed and gave their written consent. The study complies with the Declaration of Helsinki and was conducted according to ethics committee approval (protocol number: 0057625).

Two experienced psychiatrists (AC and CM) conducted a semistructured interview to collect demographic and clinical data (age, gender, and years of education) and administered CAARMS, Social and Occupational Functioning Assessment Scale (SOFAS), and Health of the Nation Outcome Scales (HoNOS). The CAARMS rating was independently conducted by the two psychiatrists in the assessment of 25 individuals. The ICC for the CAARMS-K total score was 0.89, and those for the seven subscales (positive symptoms, cognitive changes, emotional disturbance, negative symptoms, behavioral change, motor/physical changes, and general symptoms) showed acceptable results (0.75, 0.74, 0.71, 0.68, 0.79, 0.61, and 0.85, respectively). To reduce inter-rater variability, all interviewers met for training workshops before the study began. The training procedure consisted of didactic sessions, observation, and supervised practice. In addition, procedure manuals and web-based instructional videos were always available for all interviewers.

2.2 Measures

The CAARMS is a semistructured interview developed at the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne and designed to assess prodromal symptoms (15). It consists of 27 items [each one calculated in terms of frequency/duration (0–6) and intensity (0–6)], which are grouped into seven subscales: (a) positive symptoms; (b) cognitive change, attention, and concentration; (c) emotional disturbances; (d) negative symptoms; (e) behavioral changes; (f) motor/physical changes; and (g) general psychopathology. In the present study, we used the approved Italian translation of the CAARMS (22), which showed good to excellent inter-rater reliability in Italian clinical samples (22–24).

The SOFAS is a 100-point single-item scale administered to assess the individual's level of social and occupational functioning across a continuum ranging from optimum functioning to important functional impairment (25). The SOFAS is based on the GAF scale, but aims to separate functioning from symptoms.

The HoNOS is an observer-rated scale that covers psychological and behavioral symptoms and organic and social problems, and it has been developed for use with general psychiatric patients. It is composed of 12 items each scored 0 ± 4, yielding a total score in the range of 0 ± 48 (26). Higher scores indicate greater levels of impairment.

2.3 Procedure

Participants were re-interviewed 6 months after baseline assessment.

2.4 Data analysis

Statistical analysis was performed using SPSS Statistics (IBM) 28.0 with a critical *p*-value of 0.05. Mean ± standard deviation (SD) and percentages were calculated.

To examine the CAARMS underlying structure in the data from a help-seeking sample at first presentation, a principal component analysis (PCA) was conducted using the Varimax rotation method. PCA enabled researchers to reduce the number of dimensions in complex datasets. The principal components are ordered by their eigenvalues, which represent the variance in all the variables accounted for by a component. Only components with an eigenvalue > 1.0 were saved for subsequent analyses. After the first extraction, a varimax rotation of the components was performed.

There is no single optimal way of performing rotations. Our choice of using the varimax procedure was influenced by the purpose of this study—to identify distinct categories of symptoms that will elucidate the clinical picture of help-seeking individuals. Thus, a statistical technique that achieves the aim of making the

pattern of loadings clearer and more definite (27–30) appeared more appropriate. In varimax rotation, the total amount of variation explained does not change and the components are adjusted in a way that makes the loadings either high positive (or negative) or zero, while keeping the components uncorrelated or orthogonal. Moreover, as varimax rotation is probably the most common approach to performing rotations, its use allows comparison with previous studies (18, 31, 32).

The validity of the factor analysis was analyzed using Bartlett's sphericity test and the Kaiser–Meyer–Olkin (KMO) coefficient, with $p < 0.05$ and KMO > 0.6 as the cutoff levels, respectively.

The reliability of the questionnaire and the produced factors was evaluated using Cronbach's alpha index, assuming 0.70 as the cutoff value (33).

Minimum initial eigenvalues of greater than or equal to 1.0 (KaiserGuttman rule) (34), analysis of Scree plots (the point of inflection on the scree plot), percentage of variance explained by each component (only factors that explained an additional 5% of the proportion of variance were retained), reliability (Cronbach's alpha) of factors above 0.7, and parallel analysis (35) were the criteria used to determine the appropriate number of factors (36–38). The Horn's parallel analysis is an inferential method that produces a huge number of random correlation matrices with the same number of variables and sample size as the actual matrix, and then makes comparisons between the mean eigenvalues from the random correlation matrices and the eigenvalues from the real data correlation matrix. Previous studies have shown that this analysis is the most accurate rule for identifying the correct number of factors (39, 40).

To be included in a given factor, an item had to possess a factor loading greater than 0.45 in its factor (41). If two items crossloaded to more than one factor with loadings >0.45, then all those were chosen and the item was considered to load on multiple factors. If only loadings below 0.45 exist, then all those >0.30 were chosen and the item was considered to load on multiple factors.

The normal distribution of the continuous variables was verified with the Kolmogorov–Smirnov test.

As the explored variables were non-normally distributed, we run Spearman correlations between CAARMS factors and baseline demographic, behavioral, and functioning variables.

Lastly, we performed a logistic regression analysis using a forward procedure to evaluate the association between baseline CAARMS factors and the risk of transition to psychosis at the 6-month follow-up.

Variance inflation factor (VIF) was used to detect the amount of multicollinearity.

3 Results

3.1 Sociodemographic sample characteristics

Among the 128 individuals who accessed the recruitment center during the investigation period, 101 completed the 6-month assessment. Among them, 51 were men and 50 were women; aged 20.6 ± 5.1 years; with 12.5 average years (± 2.3 years) of formal education; 17 not (engaged) in education, employment, or training (16.7%); 24 employed (23.5%); and 61 students (59.8%). Most of the patients were unmarried (69.6%).

Drop-outs showed higher scores in the fifth factor ("affective factor") as compared with the completers.

3.2 Analyses on the whole sample

3.2.1 Principal component analysis

The factor analysis' validity has been proved by the Bartlett's Test of Sphericity, with highly significant results ($\chi^2 = 1{,}815.60$, df = 378, $p < 0.001$), which showed adequate sampling and nonlinearity of factors. Moreover, the KMO measure of sampling adequacy > 0.5 (0.638) highlighted both that there were relationships between the components and that they were selected appropriately. Both findings prove that the variables entered were adequate for factor analysis (29, 42).

The overall Cronbach's alpha index of the CAARMS was 0.870, which confirms that the questionnaire is reliable (value > 0.70), while the item-total corrections varied from 0.125 to 0.602, except for item 7.6, which showed a correlation of −0.41 (Table 1). Median and mode values are also provided (see Table 2). Out of the 28 items, 3 items had 4 (moderately severe) as the most recurring score (mode), 5 items had 3 (moderate), 4 items had 2 (mild), and 16 items had 0 (absent).

A PCA of the 28 items identified produced eight distinct and interpretable factors with eigenvalues greater than 1, overall explaining 75.9% of the variance. However, the scree plot representing the eigenvalues of the factors ordered by magnitude demonstrated a sharp point of inflection after the first seven factors. Of these, only the first six factors accounted for more than 5% of the variance. This finding was confirmed by the Horn's parallel analysis (35), which showed only six components with eigenvalues exceeding the corresponding criterion values for a randomly generated data matrix of the same size. Taking these results into account, the findings of this study provide stronger support for a six-factor model solution as the most appropriate, jointly accounting for more than 65%, which is considered to be an acceptable result. The seventh factor (with modest loading on 5.4 and 7.4 items) explained 4.97% of the variance; the eighth one (with modest loadings positively on 7.8 and negatively on 3.2 items) explained only 4.75% of the variance. Both the seventh and eighth factors were excluded after examination of the parallel analysis.

Table 3 presents the rotated component matrix of the CAARMS, percent variances explained, and items loading on each factor.

In detail, the first factor explained 16.9% of the variance and included nine items ("anhedonia", "impaired role function", "social isolation", "avolition", "impaired tolerance to normal stress", "subjective emotional experience", "disorganized behavior", "non-bizarre ideas", and "observed blunted affect"), corresponding to a "negative-interpersonal factor" (Table 3). A second factor explained 14.17% of the total variance and was composed of seven items ("observed cognitive change", "disorganized speech", "mania",

10.3389/fpsyt.2024.1381133

TABLE 1 Corrected item-total correlations of the 28 CAARMS items and Cronbach's alphas if the item is deleted.

	Corrected item-total correlation	Cronbach's alpha if the item is deleted
1.1 Unusual thought content	0.571	0.861
1.2 Non-bizarre ideas	0.555	0.862
1.3 Perceptual abnormalities	0.314	0.870
1.4 Disorganized speech	0.580	0.861
2.1 Subjective cognitive change	0.508	0.865
2.2 Observed cognitive change	0.529	0.864
3.1 Subjective emotional experience	0.593	0.861
3.2 Observed blunter affect	0.454	0.865
3.3 Observed inappropriate affect	0.514	0.863
4.1 Alogia	0.589	0.863
4.2 Avolition/apathy	0.591	0.861
4.3 Anhedonia	0.559	0.863
5.1 Social isolation	0.576	0.862
5.2 Impaired role function	0.602	0.861
5.3 Disorganizing/odd/stigmatizing behavior	0.592	0.862
5.4 Aggression/dangerous behavior	0.198	0.872
6.1 Subjective complaints of impaired motor functioning	0.435	0.866
6.2 Informant reported or observed changes in motor functioning	0.497	0.866
6.3 Subjective complaints of impaired bodily sensation	0.411	0.866
6.4 Subjective complaints of impaired autonomic functioning	0.314	0.869
7.1 Mania	0.231	0.870
7.2 Depression	0.130	0.873
7.3 Suicidality and self-harm	0.125	0.877
7.4 Mood swings/lability	0.171	0.872
7.5 Anxiety	0.291	0.869
7.6 Obsessive–compulsive symptoms	−0.041	0.878
7.7 Dissociative symptoms	0.391	0.867
7.8 Impaired tolerance to normal stress	0.575	0.862

"subjective cognitive change", "alogia", "unusual thought content", and "disorganized behavior"), identifying a "cognitive-disorganization" factor. A third factor explaining 9.77% of the variance included four items ("perceptual abnormalities", "subjective complaints of impaired bodily sensations", "non-bizarre ideas", and "unusual thought content"), representing a "positive" factor. A fourth factor explained 8.55% of the variance and included three items ("subjective complaints of impaired motor functioning", "informant reported or observed changes in motor functioning", and "observed inappropriate affect"), representing the "motor-physical changes" factor. Factor 5 explained 8.26% of the total variance and was defined by high loadings on three items ("suicidality and self-harm", "depression", and "dissociative symptoms"), reflecting a "mood-affective-emotional" domain. A sixth factor explained 7.4% of the variance and comprised three items ("subjective complaints of impaired autonomic functioning", "anxiety", and "obsessive–compulsive symptoms"). Factor complexity was observed; more than one item cross-loaded on more than one factor (item "disorganized behavior" on factors 1 and 2 and item "unusual thought content" on factors 2 and 3).

3.2.2 Associations between CAARMS dimensions and demographic-functioning dimensions at baseline

Table 4 presents the correlations between the CAARMS factors and baseline demographic, behavioral, and functioning variables.

TABLE 2 CAARMS item scores at first assessment (n = 101): descriptive statistics.

	Minimum	Maximum	Mean	SD	Median	Mode
1.1 Unusual thought content	0	6	2.13	1.902	2	0
1.2 Non-bizarre ideas	0	6	2.14	1.802	2	0
1.3 Perceptual abnormalities	0	6	1.63	1.985	0	0
1.4 Disorganized speech	0	6	1.52	1.59	1	0
2.1 Subjective cognitive change	0	4	1.95	0.976	2	2
2.2 Observed cognitive change	0	5	0.62	1.137	0	0
3.1 Subjective emotional experience	0	5	2.07	1.381	2	2
3.2 Observed blunter affect	0	4	1.18	1.231	1	0
3.3 Observed inappropriate affect	0	5	1.33	1.446	1	0
4.1 Alogia	0	3	0.73	0.985	0	0
4.2 Avolition/apathy	0	5	2.57	1.507	2	4
4.3 Anhedonia	0	4	2.25	1.306	3	3
5.1 Social isolation	0	5	2.17	1.281	2	3
5.2 Impaired role function	0	5	2.51	1.6	3	4
5.3 Disorganizing/odd/stigmatizing behavior	0	4	1.32	1.292	2	0
5.4 Aggression/dangerous behavior	0	5	2.03	1.418	2	3
6.1 Subjective complaints of impaired motor functioning	0	4	0.62	1.088	0	0
6.2 Informant reported or observed changes in motor functioning	0	3	0.39	0.811	0	0
6.3 Subjective complaints of impaired bodily sensation	0	5	0.91	1.442	0	0
6.4 Subjective complaints of impaired autonomic functioning	0	5	1.41	1.446	2	0
7.1 Mania	0	3	0.20	0.65	0	0
7.2 Depression	0	6	2.63	1.324	3	2
7.3 Suicidality and self-harm	0	6	2.32	1.855	2	2
7.4 Mood swings/lability	0	5	2.70	1.264	3	3
7.5 Anxiety	0	5	3.02	1.398	3	3
7.6 Obsessive–compulsive symptoms	0	5	1.04	1.489	0	0
7.7 Dissociative symptoms	0	5	1.39	1.382	2	0
7.8 Impaired tolerance to normal stress	0	5	2.91	1.457	3	4

CAARMS, The Comprehensive Assessment of At-Risk Mental States; severity scores: 0 = Absent; 1 = Questionable; 2 = Mild; 3 = Moderate; 4 = Moderately severe; 5 = Severe; 6 = Extreme (i.e., psychotic intensity).

The level of statistical significance was set at $p < 0.01$ to compensate for multiple testing.

Correlations with age and schooling were all negative as regards factors 5 and 6, with CAARMS factor 5 having the strongest association with education and CAARMS factor 6 with age.

As regards functioning dimensions, factors 1, 2, 3, and 4 were negatively correlated with SOFAS total score; factors 1, 2, and 3 showed positive correlations with HoNOS total score. Factors 2 and 3 present similar patterns of correlations, with factor 3 manifesting the strongest association with HoNOS symptoms and HoNOS and SOFAS total score. Both factors 5 and 6 show significant associations with HoNOS behavioral impairment.

3.2.3 Associations between CAARMS dimensions and transitions to psychosis

Participants were evaluated 6 months after baseline to assess whether psychosis had occurred.

During this time period, 28 out of 101 completers (30.1%) converted to psychosis. Only 1 out of 27 subjects who dropped out at follow-up transitioned to psychosis (clinical information

10.3389/fpsyt.2024.1381133

TABLE 3 Component loadings for the 28 CAARMS items.

	CAARMS factors					
	1	2	3	4	5	6
4.3 Anhedonia	0.834					
5.2 Impaired role function	0.772					
5.1 Social isolation	0.740					
4.2 Avolition/apathy	0.733					
7.8 Impaired tolerance to normal stress	0.649					
3.1 Subjective emotional experience	0.629					
5.3 Disorganizing/odd/stigmatizing behavior	0.599	0.451				
2.2 Observed cognitive change		0.866				
1.4 Disorganized speech		0.804				
7.1 Mania		0.735				
2.1 Subjective cognitive change		0.729				
4.1 Alogia		0.608				
1.1 Unusual thought content		0.530	0.518			
1.3 Perceptual abnormalities			0.800			
6.3 Subjective complaints of impaired bodily sensation			0.727			
1.2 Non-bizarre ideas	0.498		0.581			
6.1 Subjective complaints of impaired motor functioning				0.810		
6.2 Informant reported or observed changes in motor functioning				0.765		
3.3 Observed inappropriate affect				0.693		
7.3 Suicidality and self-harm					0.788	
7.7 Dissociative symptoms					0.725	
7.2 Depression					0.591	
6.4 Subjective complaints of impaired autonomic functioning						0.796
7.5 Anxiety						0.651
7.6 Obsessive–compulsive symptoms						0.613
5.4 Aggression/dangerous behavior						
7.4 Mood swings/lability						
3.2 Observed blunter affect	0.493					

Extraction method: principal component analysis. Rotation method: Varimax with Kaiser normalization. All loadings greater than 0.45 are reported Explained variance (extraction sums of squared loadings): Whole sample: Total = 65% (factor 1 = 16.9%; factor 2 = 14.17%; factor 3 = 9.77%; factor 4 = 8.55%; factor 5 = 8.26%; factor 6 = 7.4%).

obtained from referral providers, i.e., general practitioners, child neuropsychiatry, psychology/adolescent centers, other mental health services, and school and college counselors).

Table 5 summarizes the results of the logistic regression analysis related to transition to psychosis as the outcome: Exp (B) is equivalent to the odds ratio (OR), a measure of a relationship's strength between the predictor and the binary outcome. We found that the second factor ("cognitive-disorganization") (hazard ratio = 1.282, 95% confidence interval = 1.022–1.607) and the third factor ("positive") (hazard ratio = 1.393, 95% confidence interval = 1.065–1.823) were positively associated with the risk of transition to psychosis, whereas the fifth factor ("affective factor") (hazard ratio = 0.661, 95% confidence interval = 0.476–0.918) was negatively associated with the outcome variable.

The association remained substantially unchanged (hazard ratio = 1.172, 95% confidence interval = 1.001–1.375 for factor 2; hazard ratio =1.294, 95% confidence interval =1.062–1.576 for factor 3; hazard ratio = 0.510, 95% confidence interval = 0.380–0.685 for factor 5) after controlling for age and gender.

The Nagelkerke R^2 value (i.e., R^2 = 0.754) demonstrates the model's good prediction performance: these three predictors would explain more than 75% of the risk of transition to psychosis when controlling for age and gender.

Factors 1, 4, and 6 were not significantly associated with transition.

TABLE 4 Spearman correlations between CAARMS factors and baseline demographic, behavioral, and functioning variables.

	CAARMS factors					
	1	2	3	4	5	6
Age	−0.212 (0.033)				−0.382 (<0.001)	−0.416 (<0.001)
Education					−0.465 (<0.001)	−0.355 (<0.001)
HoNOS behavior					0.232 (0.019)	−0.225 (0.023)
HoNOS cognitive, physical problems		0.280 (0.004)	0.205 (0.039)			
HoNOS symptoms		0.296 (0.002)	0.577 (<0.001)	0.214 (0.031)		
HoNOS environment			0.270 (0.006)			
HoNOS total	0.228 (0.021)	0.369 (−0.001)	0.433 (−0.001)			
SOFAS	−0.256 (0.009)	−0.297 (0.002)	−0.442 (<0.001)	−0.316 (0.001)		

p-value < 0.01. HoNOS, Health of the Nation Outcome Scales; SOFAS, Social and Occupational Functioning Assessment Scale.

4 Discussion

In the present study, we aimed to explore the dimensional structure of the CAARMS, in order to verify whether types of UHR symptoms, as assessed by means of the CAARMS, co-occur in a sample of help-seeking individuals on suspicion of psychosis risk, and whether these "groupings" of symptoms at baseline were associated with subsequent transition to a full-blown psychosis.

Several key findings emerged from our research.

First, the internal consistency of the scale was good, as the Cronbach's alpha coefficients for the CAARMS total score and the coefficients for single item were acceptable (above 0.5).

Second, item distributions within this sample reveal that most patients received low ratings on most symptoms. Individual item means typically fell below scale midpoints, with subjects exhibiting mild symptom presentations and most subjects rated as entirely normal on several symptoms. Moreover, we found that some symptoms are inherently multifactorial, i.e., disorganized behavior sometimes loads on both negative and disorganized factors, and unusual thought content loads on both cognitive/disorganized and positive factors.

Third, factor analysis of the CAARMS extracted six factors in our sample. Previously, factor analytic studies on the CAARMS revealed three underlying factors (negative-interpersonal, communicational-cognitive-behavioral disorganization, and perceptual-affective instability component) (17) and five factors (negative, anxiety, disorganization/cognitive, self-harm, and manic dimension) (18, 20). Other studies conducted on a conceptually similar instrument, the Scale of Prodromal Symptoms (SOPS), have found a three-model solution (31, 32).

Discrepancies in findings between studies may be due to several factors that may affect the homogeneity of the sample, its representativeness of the help-seekers population, and the components extracted by factor analyses. Some of these factors are referral pathways and settings [international research protocol on the first episode prodrome (31) vs. early intervention in psychosis program (32) vs. public mental health service for youth (17, 18)], recruitment [four sites located in USA and Canada (29) vs. community-based catchment area (17, 18, 32)], and sample size [94 (31) vs. 30 (32) vs. 122 (18) vs. 223 (17)].

Factor 1, labeled "negative-interpersonal" factor accounting for almost 17% of the variance, included items describing a general reduction in the ability to engage with the environment with vitality (anhedonia and avolition-apathy) and maintain good social and role performance (impaired role function and social isolation) and daily situational affective coping (impaired tolerance to normal stress). Symptoms loading on this factor, and not elsewhere, are clearly primarily negative in nature. This factor resembles the negative factor identified by Raballo et al. (17) and Demjaha et al. (18) (negative-interpersonal component and negative dimension, respectively). However, unlike Demjaha et al. (18), avolition, blunted affect, social isolation, and anhedonia did not load together with depression on the same dimension, suggesting that in this sample, negative symptoms should be considered an "independent" dimension, clearly distinct from depression (that loads prominently on a separate factor, the fifth), and probably "primary" (not a cooccurrence of depression). These discrepant findings from the literature may reflect some methodological differences between the studies such as the use of different rating scales, definitions for depression and negative

TABLE 5 Multivariable logistic regression analysis with multicollinearity measures for the three factors significantly associated (predictor variables) to transition to psychosis (dependent variable) over a 6-month period of observation.

	beta	SE	*p*	Exp (*B*)	95% CI per Exp (*B*)	VIF	Tolerance
Factor 2	1.59	0.082	0.051	1.172	0.999–1.375	1.193	0.838
Factor 3	0.258	0.101	0.011	1.294	1.062–1.576	1.013	0.987
Factor 5	−0.673	0.150	<0.001	0.510	0.380–0.685	1.208	0.828

Nagelkerke R^2 = 0.754; VIF, variance inflation factor.

symptoms, sampling strategies, and definitions of the populations to be sampled. Moreover, as the data from the CAARMS in the present study were collected cross-sectionally, it is early to draw firm conclusions that the negative symptoms in our sample are of primary nature until these findings are further explored and replicated in future studies. These results suggest that the negative dimension is the most prominent help-seekers' characteristic, and is consistent with findings from a prodromal sample using another psychopathological instrument for prodromal symptoms, the SOPS (31, 32).

Factor 2, named the "cognitive-disorganized" component, representing the second contributor (14.17%) to the total variance, included items that comprised a broad range of subtle disturbances affecting subjective and objective cognitive changes and disorganized speech and behavior. In the CAARMS, Cognitive Change is a subscale comprising impaired attention, thought block, and racing thoughts, whereas Disorganized Speech includes two additional aspects of formal thought disorder: circumstantiality and tangentiality. Thus, our "cognitive-disorganized" factor manifests some resemblance to the "communication-attention and concentration problems" and "disorganization/cognitive" dimension found in one of the SOPS studies (32), in the other CAARMS studies (18, 20), and also the disorganization dimension identified in studies of patients with established psychosis, which typically comprises formal thought disorder and attentional impairment (43). Indeed, the two symptoms most consistently related to disorganization in established schizophrenia —"odd or bizarre behavior" and "conceptual disorganization" (thought disorder)—load with the cognitive symptoms (subjective and objective cognitive change) in this sample, supporting the notion of a unique factor, i.e., the cognitive/disorganized factor.

Factor 3, named "positive" component and explaining almost 10% of the total variance, comprised positive symptoms—reality distortion dimension (perceptual abnormalities, unusual thought content, and non-bizarre ideas), similar to psychotic positive factor in other studies, i.e., "unusual thought content-perceptual abnormalities" in Hawkins (31) and "unusual thought content-suspiciousness" in Lemos et al. (32). Consistent with the evidence of heterogeneity of the positive symptoms, a cardinal symptom of its domain, unusual thought content, also loads on the cognitive/disorganization factor, although our findings suggested that the psychotic and disorganization dimensions should be considered independent domains of psychopathology (44).

Interestingly, besides positive symptoms, one basic symptom (BS) (subjective complaints of impaired bodily sensations) was found to load on this factor. Unlike objectively observed and operationally defined positive and negative signs and symptoms, the BS items of the CAARMS (45, 46) assess subtle disturbances in drive, affect, thought, language, perception, motor and vegetative function, and stress tolerance from the subjective perspective reported by the help-seeker (47). Because BSs appear in the earliest prodromal stage, recognizing these symptoms promotes early detection and intervention (46). In this context, it is noteworthy that the factor consisting of BS was extracted, corroborating the recommendation that BS should be an important axis in evaluating prodromal individuals (46).

Factor 4, named the "motor-physical changes" component, explaining 8.55% of the total variance, included subjective (subjective complaints of impaired motor functioning) and objective impairment in motor functioning (observed changes in motor functioning) and one disorganized symptom ("observed inappropriate affect").

It is apparently a quite heterogeneous factor; however, as both the items "subjective complaints of impaired motor functioning" and "observed changes in motor functioning" could be viewed as antecedents of "odd/stigmatizing behavior" (a disorganized symptom), we can hypothesize that these two symptoms loaded with another disorganized symptom ("observed inappropriate affect") into a factor more homogeneous as appeared at first sight. Furthermore, the observed appropriateness of the affect is a direct manifestation of the subject's vocal expressiveness, body language, and facial expressions in response to certain emotional stimuli. Therefore, impaired motor control might convey to the observer inappropriate affect that would be the result of a discrepancy between the affect experienced by the help-seeker and that which he or she is then actually able to express.

Factor 5, named the "mood-affective-emotional" factor, explaining 8.26% of the total variance, was exclusively made up of three symptoms, i.e., depression, self-harm/suicidality, and dissociative symptoms. Depressive symptoms are relatively common in the ARMS (48) and the nonspecificity of depression in our sample might reflect distress secondary to the recent onset of dissociative symptoms. Both depression and dissociative symptoms may trigger self-harm behavior. However, as our data were cross-sectional, we can only conclude that depression loaded together with self-harm and dissociative symptoms.

Factor 6, explaining 7.4% of the total variance, is more heterogeneous and includes one basic symptom (consisting of subjective complaints of impaired autonomic functioning) and two psychopathological symptoms (anxiety and obsessive–compulsive symptoms). Again, the cross-sectional design of the study does not allow us to ascertain if anxiety (free-floating and somatic and obsessive somatic ruminations) is a consequence of worry (and focalization) about impaired automatic functioning or if they simply occur together, loading on the same factor.

Fourth, cognitive-disorganization and positive factors presented similar patterns of correlations, with the latter manifesting the strongest association with impairment related to cognitive and physical problems (as indexed by HoNOS cognitive and physical problems) and problems related to symptoms (as described by HoNOS symptoms), besides HoNOS and SOFAS total score. It is not surprising, given that cognitive-disorganized and positive factors included items that can have an impact on the HoNOS and SOFAS total score. Cornblatt et al. (49) suggested that a sustained attentional impairment in CHR subjects might negatively affect social information processing, thus leading to an impairment in social interactions and the emergence of social difficulties and isolation. Poor global functioning has also previously been independently associated with the transition to psychosis in ARMS subjects (50). Therefore, the link between the severity of positive and disorganization/cognitive factors and poor global functioning and the evidence that all these may predict the subsequent onset of psychosis sustain both the clinical relevance of the factors extracted from this study and the hypothesis that they

may each be a prodromal phenomenon of a common underlying process that increases the risk of developing a psychotic disorder (18).

Moreover, there was also a significant but less prominent correlation between the mood-affective-emotional dimension and HoNOS behavior. It is not surprising that subjects with higher levels of depression, dissociative symptoms, and self-harms are more likely, *ipso facto*, to exhibit higher impairment in behavior.

Fifth, the rate of psychosis among help-seeking subjects in our sample (i.e., approximately 30% within 6 months) is two to three (51) and two orders of magnitude higher than in the same at-risk age group in the general population or in help-seeking in specialized early intervention settings (10.1%–17.9% at 6 months) (15, 50), respectively. This suggests that in our early detection and intervention program, we evaluate subjects at risk in prodromic phases that are somewhat closer to frank psychosis than desired.

Sixth, in line with previous studies (17, 18, 21, 49, 52), we found that both the disorganization/cognitive and positive factors were positively associated with subsequent transition to psychosis. It is possible that these symptoms, generally considered core psychopathological features of schizophrenia, are the phenomenological expression of an underlying neurodevelopmental perturbation that confers a particularly high risk for the disorder (53). On the other hand, the mood-affective-emotional factor, characterized by mild to moderate levels of depression and mild level of self-harm, showed a negative association with the longitudinal outcome of transition to psychosis, probably identifying a different psychopathological trajectory.

There are several limitations in this study that researchers must consider in the interpretation of our findings: first, the relatively small sample size to assess the psychometric properties of the CAARMS, especially the factor structure; second, the examination of CAARMS scores only at baseline, and not longitudinally, with an experimental design that could allow mapping the fluctuations of both CAARMS components and clinical symptoms over time; third, the need for contextualization concerning the setting and referral pathway, which may be different from other UHR services; fourth, the recruitment of voluntary subjects who provided informed consent to participate in this research study, i.e., a selection bias in favor of participants with higher cooperativeness and/or more intense help-seeking.

5 Conclusions

The aim of this study was to depict the clinical manifestations of help-seeking individuals at the time of their referral to our service by adopting a dimensional approach (along continuous coordinates) instead of a categorical one (such as UHR criteria). We found the CAARMS to have an underlying six-factor structure. It can be observed that factors 1, 2, and 3 are relatively homogeneous.

Moreover, our observation that disorganized/cognitive dimension is associated with transition to psychosis suggests that, in addition to attenuated positive symptoms, more attention should be paid to these features, especially when pronounced at first contact/referral. The relevance of those subclinical psychopathological dimensions as targets for intervention is also highlighted by their strong association with global functioning. It is thus crucial to recognize the type and severity of psychopathology in help-seeking individuals in order to design specific care pathways, intensive clinical monitoring of subclinical psychopathology risk profiles, and interventions suitable for this group, as suggested by the ITAlian partnership for psychosis prevention (ITAPP) (54), which highlights the necessity to provide multidisciplinary interventions tailored to meet individual needs. These interventions should be standardized across centers and for follow-up periods to be extended, as a different longitudinal risk of psychosis onset has been observed across the CHR clinical academic centers.

Implementing early and personalized interventions presents a challenge due to clinicians' limited understanding of mental risk states and the scarce resources. For the future, it would be desirable to promote training to equip teams to identify and assess individuals in prodromal phases; raise awareness among the population regarding mental health; increase the implementation of psychosocial interventions in services; and advocate for a multidisciplinary and personalized approach for the individual.

Indeed, beyond identifying at-risk individuals, the implementation of personalized early interventions tailored to subclinical psychopathological dimensions is crucial. This proactive approach fosters more effective clinical management strategies.

The Canadian Treatment Guidelines for Individuals at Clinical High Risk of Psychosis recommended psychosocial interventions as the first-line treatment for CHR individuals (55). Specifically, psychoeducation and cognitive behavioral therapy (CBT) for ultra-high-risk subjects not only help improve subclinical psychotic symptoms and psychosocial functioning but also reduce the risk of progression to psychosis (56). Psychoeducation has gained prominence as a preferred therapeutic approach, with individuals expressing greater readiness to engage in it compared to alternative interventions (57).

Data availability statement

The datasets presented in this article are not readily available because the full datasets contain identifying information, and data sharing is subject to facility guidelines. Requests to access the datasets should be directed to cristiana.montemagni@unito.it. and paola.rocca@unito.it.

Ethics statement

The studies involving humans were approved by Research Ethics Committee AOU Città della Salute e della Scienza di Torino. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed

consent for participation in this study was provided by the participants or participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

CM: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. AC: Data curation, Methodology, Writing – original draft, Writing – review & editing. CB: Supervision, Writing – original draft, Writing – review & editing. FV: Investigation, Resources, Writing – review & editing. PR: Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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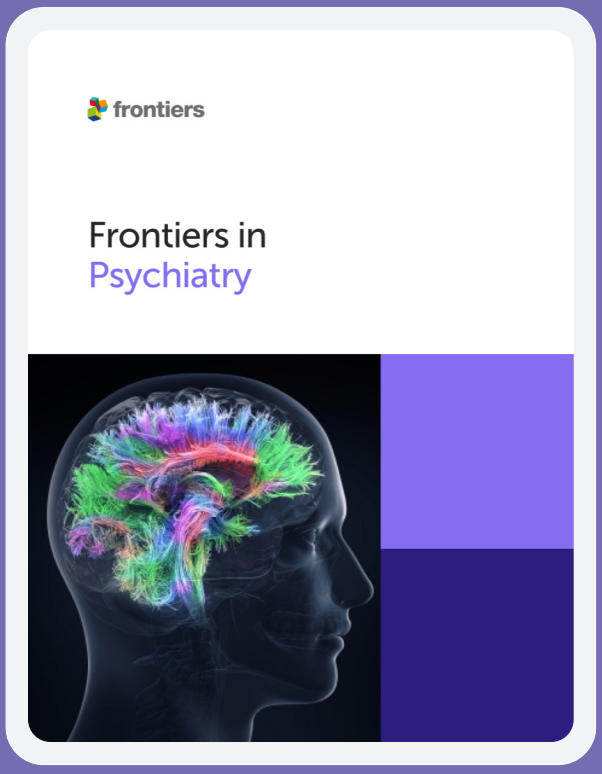

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