

Relationships between dorsolateral prefrontal cortex metabolic change and cognitive impairment in first-episode neuroleptic-naive schizophrenia patients

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Abstract

The present study aimed to explore the possible associations between the dorsolateral prefrontal cortex (DLPFC) metabolites and the cognitive function in first-episode schizophrenia (FES).

This study included 58 patients with FES (29 males and 29 females; mean age, 22.66 ± 7.64 years) recruited from the First Affiliated Hospital, College of Medicine, Zhejiang University, and 43 locally recruited healthy controls (16 males and 27 females; mean age, 23.07 ± 7.49 years). The single-voxel proton magnetic resonance spectroscopy was used to measure the levels of N-acetylaspartate (NAA); complex of glutamate, glutamine, and γ -aminobutyric acid (Glx); choline-containing compounds; and myo-inositol in the DLPFC. The ratios of metabolites to creatine (Cr) were calculated. The cognitive function was assessed by Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB). Correlation analysis was used to assess the relationships between the DLPFC metabolites and the cognitive function. Compared with the healthy controls, the patients with FES showed significantly reduced scores in each part of the MCCB, significantly reduced NAA/Cr, and significantly increased Glx/Cr in the left DLPFC. Poor performance in verbal learning and visual learning was correlated to the reduced NAA/Cr ratio in the left DLPFC.

These findings suggest that a lower NAA/Cr ratio in the left DLPFC is associated with the cognitive deficits in patients with FES, and may be an early biochemical marker for the cognitive impairment in schizophrenia.

Abbreviations: Cr = creatine, DLPFC = dorsolateral prefrontal cortex, FES = first-episode schizophrenia, Glx = complex of glutamate, glutamine, and γ -aminobutyric acid, MCCB = measurement and treatment research to improve cognition in Schizophrenia consensus cognitive battery, m-Ino = myo-inositol, NAA = N-acetylaspartate.

Keywords: ¹H-MRS, cognition, dorsolateral prefrontal cortex, first-episode schizophrenia, MCCB

1. Introduction

Several previous studies consistently demonstrated cognitive deficits in schizophrenia patients, which might be a predictor of functional outcomes in early psychosis.^[1–4] The first-episode schizophrenia (FES) showed a large generalized cognitive deficit and likely preceded the onset of illness in an attenuated form.^[5–10] The FES neuroleptic naive is perfect objects while

study brain metabolites in schizophrenia patient, because drug could be affect the neurochemical metabolites.^[11–14] Furthermore, schizophrenia patients showed significant cognitive deficits compared with healthy controls and they also assumed that cognitive dysfunction might relate to specific brain region in previous studies.^[13–16] The dorsolateral prefrontal cortex (DLPFC) plays an important role in the executive, verbal working memory, and visual-spatial working memory.^[17–20]

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This study was approved by the Zhejiang University Ethics Committee and consent form was obtained.

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FES, the early stage of schizophrenia, showed that the cognitive deficits associated with the dysfunction of DLPFC.^[15,21,22]

The Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB) contains 7 cognitive domains, including the speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning/problem solving, and social cognition.^[23] The MCCB has been used to evaluate the cognitive function in patients with early and chronic schizophrenia.^[12,23–25] Moreover, the MCCB is associated with the functional outcome and broad intellectual ability, and is therefore considered as a sensitive measurement index of the cognitive impairments in patients with schizophrenia.^[23]

The proton magnetic resonance spectroscopy (¹H-MRS) studies have demonstrated abnormal levels of N-acetylaspartate (NAA) and complex of glutamate, glutamine, and γ -aminobutyric acid (Glx) in the DLPFC of patients with schizophrenia.^[26–28] Previous studies have reported a reduction in NAA in the DLPFC of patients with neuroleptic-naïve FES.^[29–31] However, a study reported that chronic schizophrenia patients had significantly lower levels of NAA compared with healthy controls, but no significant difference between FES patients and healthy controls.^[32] The Glx was also reported as a marker of cognitive impairment in patients with schizophrenia.^[33] However, no significant differences were found in Glx levels between patients with schizophrenia and healthy controls.^[27] Other studies were attempted to link brain metabolites with the cognition impairment, and a correlation was found between the NAA change and cognitive deficits in patients with FES, but no significant differences were found in the NAA ratio between patients with FES and healthy controls.^[12,15,26] Changes in brain metabolites were frequently reported. However, the relationship between brain metabolic changes in the dorsolateral prefrontal cortex (DLPFC) and cognitive impairment in the FES has not been well studied.

Therefore, the aim of this study was to use ¹H-MRS to explore the metabolite change in the DLPFC and its correlations with the cognitive impairment in patients with FES using the MCCB, which a standardized battery for use with patient with schizophrenia.

2. Methods

The present study is an observational cross-sectional study, evaluating dorsolateral prefrontal cortex metabolic change and cognitive impairment alterations in first-episode neuroleptic-naïve schizophrenia patients. The study was approved by the ethics committee of the First Affiliated Hospital of Medical School of Zhejiang University. All patients participated voluntarily and were informed of the purposes, methods, and potential risks. All subjects provided written informed consent before participating in the study. The trial was conducted in accordance with the ethical principles included in the Declaration of Helsinki consistent with Good Clinical Practices and applicable regulatory requirements. All subjects were informed that they could quit the study at any time with an additional examination and further therapy support. The clinical trial number of the study is ChiCTR-COC-14005302.

2.1. Patients

A total of 58 patients with FES (29 males and 29 females; mean age, 22.66 \pm 7.64 years) were recruited from the First Affiliated Hospital, College of Medicine, Zhejiang University, and 43 healthy controls (16 males and 27 females; mean age, 23.07 \pm 7.49 years)

who were age, sex, and education status matched to the patients with FES were recruited from the local community via advertisement in this study. None of the controls had a family history of mental disorder. Inclusion criteria for patients with FES were as follows: age between 13 and 35 years old; met the diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10 F20)^[34], experiencing their first episode; being antipsychotic drug naïve; both male and females; and ethnicity of Han origin. The ICD-10 diagnosis in all studies was verified by the Mini-International Neuropsychiatric Interview.^[35]

The exclusion criteria for both patients and healthy people were as follows: with a primary active ICD-10 diagnosis other than schizophrenia at screening or an ICD-10 diagnosis of active substance dependence within 3 months before screening (except nicotine and caffeine); with a diagnosis of past psychiatric or central nervous system disorders; any contraindications to MRS scanning (e.g., claustrophobia or metallic implants); with a diagnosis of serious disease of the heart, liver, kidney, internal secretion, blood system, or any other disease that might disturb the outcome of the study; with a diagnosis of organic mental disorders or mental retardation; and pregnancy.

2.2. Neuropsychological and clinical assessments

The tests were completed for all subjects by fully trained psychiatrists with consistent training courses in the First Affiliated Hospital of Medical School of Zhejiang University. The trained psychiatrists evaluated the patients and healthy controls using the MCCB tests within 1 week before the magnetic resonance imaging (MRI) examination.^[36] The raw measurement scores were converted to normalize T-scores. Then, each domain T-score of MCCB and the total T-score were recorded. The patients and healthy controls were required to finish the MCCB tests. The PANSS was used to assess the clinical characteristics in 58 patients with FES in the time of the neuropsychological tests.

2.3. Spectroscopic imaging ¹H-MRS

All MRI and MRS examinations were performed on a 3.0-Tesla MR scanner (Achieva 3.0T; Philips Medical Systems, Eindhoven, the Netherlands). Spectroscopy data were acquired from a single-voxel using a chemical shift-selecting saturation (CHESS, for water suppression) stimulated echo pulse with the following acquisition parameters: echo time=9.2 ms, repetition time=2000 ms, mixing time=16 ms, volume of interest (VOI)=15 \times 15 \times 15 mm³, number of signal average=128, and sample=1024.

The VOI was placed on the left DLPFC based on the structural MRI as shown in Figure 1. A 3-plane localizer MRI was first acquired to define the spatial position of the brain. Three oblique localizer MRIs were then obtained with T1 FLAIR: an axial/oblique slices were parallel to the Sylvian fissure, a coronal/oblique slices were perpendicular to the axial/oblique planes, and sagittal/oblique slices were oriented parallel to the interhemispheric fissure (Fig. 1).

The standard spectroscopic phantom was used to determine reliability before the spectrum scanning. The line width was <4 Hz and water suppression level at least 99% in the prescan for patients. The data postprocessing (including signal-to-noise ratio assessment and baseline adjustment) and quantification steps were automated by the spectral view. The quantitative data of NAA and Glx (major metabolites), choline-containing

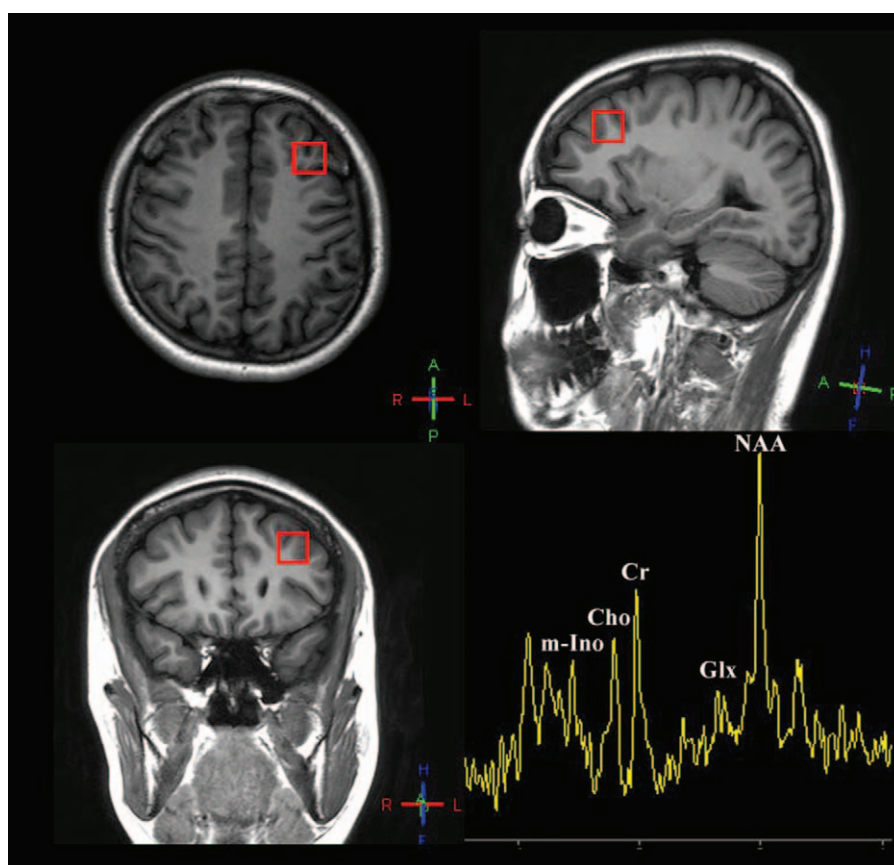


Figure 1. Anatomical localization of a left sample volume. Cho=choline, Cr=creatine, Glx=glutamine plus glutamate, m-Ino=myo-inositol, NAA=N-acetylaspartate.

compounds,^[5] and myo-inositol (minor metabolites) were calculated with the spectral view.

2.4. Statistical analyses

The statistical analysis was performed using SPSS version 17.0 (SPSS, Chicago, IL). All data were presented as means ± standard deviation. Group differences in clinical characteristics, demographic data, metabolite levels, and MCCB scores were evaluated using independent-samples *t* tests or chi-squared tests. Correlations between the DLPFC metabolites and the clinical characteristics were assessed using the Person correlation analysis. All the results were quoted as 2-tailed *P* values, and *P* < .05 was considered statistically significant.

3. Result

3.1. Demographic characteristics

Table 1 presents the demographic and clinical characteristics of the 58 patients (22.66 ± 7.64 years; 29 males and 29 females) and 43 healthy controls (23.07 ± 7.49 years; 16 males and 27 females). We found no significantly different in terms of age, gender, and education years between the patients with FES and healthy controls.

3.2. Cognitive impairments in FES

FES showed significant cognitive deficits compared with healthy controls in each of the MCCB domain scores and total score

(*P* < .001), those cognitive domains including the speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning/problem solving, and social cognition. The details are presented in Table 2.

3.3. Metabolite levels

As shown in Table 3, FES showed significantly reduced ratios of NAA/creatine (Cr) (*t* = -3.030, *P* = .003) and significantly increased ratios of Glx/Cr (*t* = 2.036, *P* = .045) compared with the

Table 1
Demographic characteristics between FES and HCs.

Measures	FES (N=58)	HC (N=43)	<i>t</i> / χ^2	<i>P</i>
Age, mean ± SD, y	22.66 ± 7.64	23.07 ± 7.49	-0.273 ^a	.786
Gender (male/female)	29/29	16/27	0.635 ^b	.201
Nationality, Han/other, n	58/0	43/0		
Education years	11.41 ± 2.73	12.65 ± 3.81	-1.903 ^a	.060
Course of illness, mo	15.14 ± 25.01			
Age of first onset, y	21.29 ± 6.96			
PANSS total scores	80.93 ± 18.27			
PANSS P scores	21.53 ± 4.98			
PANSS N scores	18.67 ± 8.10			
PANSS G scores	40.72 ± 9.49			

Data are presented as mean ± SD.
FES = first-episode schizophrenia, HC = healthy control, SD = standard deviation.
^a *t* test.
^b χ^2 test.
^c *P* < .05.

Table 2**MCCB domain scores between FES and HCs.**

Measures	FES (N=58)	HC (N=43)	t	P
SP	35.27 ± 11.51	53.90 ± 8.12	-9.064	<.001*
AV	35.41 ± 12.2	50.14 ± 9.48	-6.777	<.001*
WM	44.02 ± 13.22	54.09 ± 7.17	-4.453	<.001*
VeL	39.10 ± 9.26	48.74 ± 6.93	-5.412	<.001*
ViL	42.62 ± 12.46	53.35 ± 7.94	-4.944	<.001*
RPS	41.84 ± 9.53	49.49 ± 7.40	-4.535	<.001*
SC	30.33 ± 11.41	42.07 ± 6.61	-6.033	<.001*
OC	38.43 ± 7.50	50.25 ± 4.11	-9.332	<.001*

Data are presented as mean ± standard deviation.

AV=attention/vigilance, FES=first-episode schizophrenia, HC=healthy control, MCCB=measurement and treatment research to improve cognition in Schizophrenia consensus cognitive battery, OC=overall composite, RPS=reasoning/problem solving, SC=social cognition, SP=speed of processing, VeL=verbal learning, ViL=visual learning, WM=working memory.

*P<.05.

healthy controls in the left DLPFC. However, other indexes did not show any significant differences between groups.

3.4. Relationships between metabolites and clinical characteristics

In the patients with FES, no significant correlations were found between the major metabolites (NAA and Glx) in the DLPFC and the scores of PANSS.

3.5. Relationships between metabolites and cognitive function

In the left DLPFC, the NAA/Cr showed significantly positive correlations of FES, with the verbal learning (VeL) ($r=0.265$, $P=.045$) and the visual learning (ViL) ($r=0.281$, $P=.033$) (Fig. 2A and B). In the left DLPFC of the controls, the NAA/Cr showed no significant correlations with the VeL ($r=0.185$, $P=.242$) and the ViL ($r=0.063$, $P=.692$). Other significant correlations were not found.

4. Discussion

The present study compared the differences in metabolite levels of the bilateral DLPFC between the FES patients and the healthy controls, and assessed the correlations of the metabolite levels of

Table 3**Comparison of metabolites between FES and HCs.**

Position	FES (N=58)	HC (N=43)	t	P
Left dorsolateral prefrontal cortex				
NAA/Cr	1.95 ± 0.53	2.37 ± 0.83	-3.030	.003*
Glx/Cr	1.74 ± 1.16	1.37 ± 0.67	2.036	.045*
Cho/Cr	1.03 ± 0.59	1.23 ± 0.64	-1.577	.118
m-Ino/Cr	0.80 ± 0.81	0.75 ± 0.52	0.341	.734
Right dorsolateral prefrontal cortex				
NAA/Cr	1.89 ± 0.53	2.02 ± 0.59	-1.191	.237
Glx/Cr	1.45 ± 0.87	1.24 ± 0.71	-1.304	.195
Cho/Cr	0.96 ± 0.41	1.08 ± 0.64	-1.054	.294
m-Ino/Cr	1.42 ± 1.78	1.63 ± 1.85	-0.588	.558

Data are presented as mean ± standard deviation.

Cho=choline, Cr=creatine, FES=first-episode schizophrenia, Glx=glutamine plus glutamate, HC=healthy control, m-Ino=myo-inositol, NAA=N-acetylaspartate.

*P<.05.

the bilateral DLPFC with the clinical characteristics and the cognitive performance in the patients with drug-naïve FES. The results indicated that the patients with FES showed worse cognitive performances in the speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning/problem solving, social cognition, and overall composite score compared with the healthy controls, which is consistent with other studies.^[23,24]

This study found a decrease in the NAA/Cr ratios of the left DLPFC in the patients with FES compared with the healthy controls, which is consistent with previous studies.^[30,31] But some studies found that no significant differences in NAA levels were found between patients with FES and healthy controls.^[15,26] A lower NAA/Cr ratio might reflect the impaired functional integrity of the neurons and/or the mitochondrial metabolism dysfunction.^[13,26] However, the physiological role of NAA in the neurons has yet to be well elucidated.^[21,31] Furthermore, the study also found an increase in the Glx/Cr ratios of the left DLPFC in the patients with drug-naïve FES compared with the healthy controls.^[37] This finding was consistent with a review of neurobiology and treatment for FES; the Glx/Cr ratios increased in the patients with drug-naïve FES compared with the healthy controls.^[37] The increase in the Glx/Cr ratio may be related to the impairment of the glia–neuron interaction^[38] and may reflect the adaptation of the glutamatergic dysfunction of DLPFC in the patients with FES.^[39]

Previous study found that the NAA level of DLPFC to be significantly correlated with the behavioral performances in the verbal learning or poorer Wisconsin Card Sorting Test in patients with FES, but no significant differences in NAA levels were found between patients with FES and healthy controls,^[15,26] these result may be related to the lack of sample size. Furthermore, the DLPFC was strongly correlated with NAA/Cr ratios and was responsible for some neuropsychological deficits in patients with FES.^[18,19,21,26,30,40] The present study found a direct correlation between the NAA/Cr ratios of the left DLPFC with the verbal and visual learning (MCCB) in the patients with FES.^[15,41] Our study also found a significant alteration of the NAA/Cr ratios, and showed significant positive correlations with the cognitive deficits, it was speculated that the reduced NAA/Cr ratio might participate in the poor cognitive performances in the verbal and visual learning in early stage of schizophrenia. Therefore, NAA/Cr ratio might be a potential biochemical marker of cognitive deficits in the patients with FES.^[42]

According to the chemical shift position, the Glx was divided into Glx- α (3.75 ppm) and Glx- $\beta + \gamma$ (2.11 ppm). Some studies indicated that the N-methyl-D-aspartate receptor/glutamate system might be related to some cognitive function.^[43,44] In the present study, the Glx/Cr ratios had a tendency to show an inverse correlation with the MCCB overall composite score. Although no significant correlations were found between the increased Glx/Cr ratio and the cognitive function, the aforementioned finding may enhance the knowledge about the activity of the glutaminergic neurons and the pathogenesis of FES.

Reductions in NAA are seen in a variety of disorders such as neurodegenerative diseases, schizophrenia, epilepsy, and multiple sclerosis,^[45] if the cognitive deficit of FES occur secondary to neuroexcitatory degeneration, then the damage and resulting executive functioning impairments might irreversible, and neurocognitive deficits in schizophrenia tend to be present at the first episode and statically persist throughout the illness.^[46] Since our result supports that cognitive decline begins early in the illness trajectory. Therefore, it is important to timely capture the early-

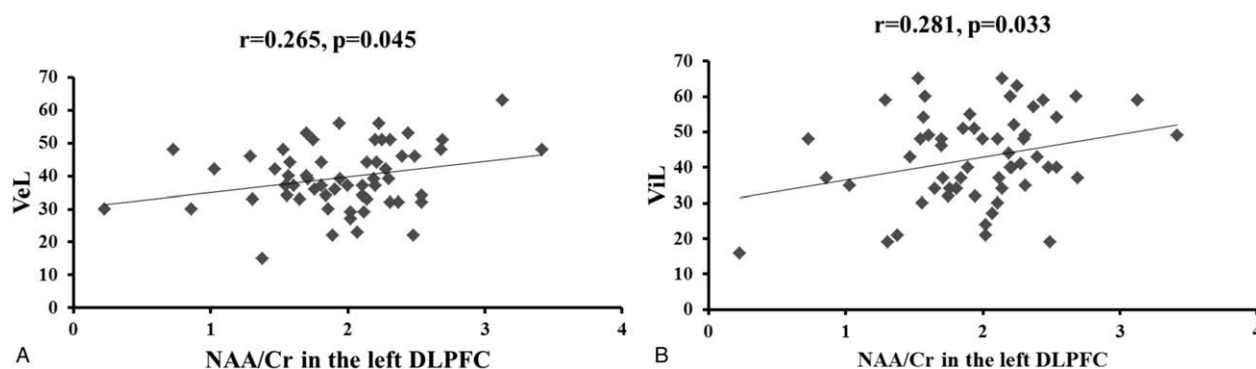


Figure 2. Correlation between left DLPFC metabolites and MCCB domains (N=58). (A) Left dorsolateral prefrontal cortex NAA/Cr shows a positive correlation ($r = 0.265$, $P = .045$) with VeL in first-episode schizophrenia patients. (B) Left dorsolateral prefrontal cortex NAA/Cr shows a positive correlation ($r = 0.281$, $P = .033$) with ViL in first-episode schizophrenia patients. Cr=creatine, DLPFC=dorsolateral prefrontal cortex, MCCB=measurement and treatment research to improve cognition in Schizophrenia consensus cognitive battery, NAA=N-acetylaspartate, VeL=verbal learning, ViL=visual learning.

phase schizophrenia and carried out an early intervention, to prevent patient from develop to severe cognitive impairment. Unfortunately, to date, there is no pharmacological agent that has been found to consistently improve cognitive deficits in schizophrenia, and this has been reported in a longitude study.^[47] Hence, our study attempts to provide some evidence in diagnosis of prodromal period of schizophrenia or the possible of neuropathological mechanisms in schizophrenia. Furthermore, there may be a potential pharmaceuticals in prevention of psychosis.

Besides that, a cross-sectional study could not illustrate the causal relationships between DLPFC metabolites change and cognitive deficits. In other study, they reported a relationship between NAA and cognition but not with symptomatology, and suggest that NAA reduction, although not disease specific, reflects an impaired functional state apparent early in the schizophrenia.^[48] Their result also supports that there are some link between brain metabolism and cognitive deficit in schizophrenia patient. Since abnormal brain metabolites reflect the dysfunction of neuron cells,^[49,50] so we suspect that brain metabolites occur before cognitive impairment, and somehow might be a role in cognitive deficit. To corroborate the hypothesis and the causal relationships, our study group will undergo a long-term following study to investigate the relationship between DLPFC metabolites and cognitive performance in patients before and after application of antipsychotic agents.

5. Limitation

The present study had several limitations that should be noted. First, the cross-sectional design of the study could not reveal causal relationships; hence, a longitudinal study should be performed in the future to interpret the correlations between the neural metabolism and the cognitive dysfunction. Second, other regions related to the cognitive function should be explored in future studies. Third, the participants in the present study were 13 to 35 years FES; a larger sample size should be considered in the future; and we should discuss the adolescent and adult schizophrenia separately. At last, because of a lack of a standard research fitting package like Linear combination model, the concentrations of metabolite could not be calculated in the spectra, as a consequence, only the ratios of metabolite divide creatine were chosen as the dependent variables. Although the results with a dependent variable of concentration or the ratio are reported to be the same in most studies and meta-

analysis,^[21,30,40,45,51] only taking the ratio to analysis may challenge the stability of outcomes of our study.

6. Conclusion

Our findings support the hypothesis that the neural metabolism of DLPFC, as measured by ¹H-MRS, is correlated with the cognitive function in patients with FES. The patients demonstrated abnormal NAA/Cr and Glx/Cr ratios in the early stage of the illness, and these metabolites in the DLPFC might be involved in the pathogenesis of FES. Moreover, the lower NAA/Cr ratio in the left DLPFC might be a potential marker for the cognitive impairment in the patients with FES.

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