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•ORIGINAL RESEARCH ARTICLE•

Prefrontal Cortex GABA in Schizophrenia and Abnormal Glutamate Concentration: An in Vivo 1H-MRS Study

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Background: The etiology and pathomechanism of schizophrenia are unknown. The traditional dopamine (DA) hypothesis is unable to fully explain its pathology and therapeutics. The glutamate (Glu) and γ-aminobutyric acid (GABA) hypotheses suggest Glu or GABA concentrations are abnormal in the brains of patients with schizophrenia. Magnetic resonance spectroscopy (MRS) show glutamate level increases in the ventromedial prefrontal cortex (vmPFC) including the anterior cingulated cortex (ACC) in those with schizophrenia.

Aims: To investigate the function of the glutamate system (glutamate and γ-aminobutyric acid) in the etiology and pathomechanism of schizophrenia.

Methods: 24 drug naïve patients with schizophrenia and 24 healthy volunteers were matched by gender, age, and educational level. The Siemens 3T MRI system was used to collect the magnetic resonance spectroscopy (MRS) data of the subjects. The regions of interest included the left dorsolateral prefrontal cortex (lDLPFC), ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC). LCModel software was used to analyze the concentrations of γ-aminobutyric acid (GABA), glutamate (Glu), glutamine (Gln), N-acetylaspartate (NAA), and N-acetylaspartylglutamate (NAAG) in the region of interest. Meanwhile, the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Scale (CGI) were used to assess the mental symptoms and severity of the disease.

Results: The median GABA concentrations in the anterior cingulate cortex of the schizophrenia group and the healthy control group were 1.90 (Q1=1.55, Q3=2.09) and 2.16 (Q1=1.87, Q3=2.59) respectively; the mean (sd) Glu concentrations were 6.07 (2.48) and 6.54 (1.99); the median Gln concentrations were 0.36 (Q1=0.00, Q3=0.74) and 0.29 (Q1=0.00, Q3=0.59); the between-group difference of the GABA concentrations was statistically significant (Z=-2.95, p=0.003); the between-group difference of the GABA/(NAA+NAAG) was statistically significant (Z=-2.72, p=0.012); the between-group difference of Glu and Gln was not statistically significant. The age of the schizophrenia group was negatively correlated with the GABA concentration in the anterior cingulate (R=-0.494, p=0.014), and negatively correlated with GABA/ (NAA+NAAG) (R=-0.473, p=0.020). Yet there was no such correlation in the control group. After calibration, no significant correlation was found between the clinical symptoms and the concentrations of the metabolites.

Conclusions: The concentration of glutamate in the vemtromedial prefrontal cortex of patients with schizophrenia was abnormal, whereas the concentration of GABA in the anterior cingulate cortex decreased, supporting the hypothesis of abnormal glutamate -GABA in the brains of those individuals with schizophrenia. In patients with schizophrenia, the GABA in the anterior cingulate cortex had an accelerated decline with age. The clinical symptoms may be correlated to the metabolite concentration of the anterior cingulate cortex.

Key words: schizophrenia; magnetic resonance spectroscopy; γ-aminobutyric acid; glutamate

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1. Background

The etiology and pathomechanism of schizophrenia are unknown. The traditional Dopamine (DA) hypothesis also has a certain degree of limitation and is not able to fully explain the psychopathology and therapeutics of schizophrenia.[1] The glutamate (Glu) and γ-aminobutyric acid (GABA) hypotheses are important etiological hypotheses for schizophrenia, which posit that Glu or GABA concentrations are abnormal in the brains of those with schizophrenia.[2] Magnetic resonance spectroscopy (MRS) techniques can measure the in vivo metabolite concentration in the brain. Most studies have found that levels of glutamate in schizophrenia increase in the ventromedial prefrontal cortex (including the anterior cingulate cortex), however, there were no significant differences in other brain regions such as the parietal-occipital lobe, temporal lobe, hippocampus, and thalamus found, when compared with to those without schizophrenia.[3] In recent years, determination of the in vivo brain GABA concentration has become possible with the development of high-field-strength MRI technology and data analysis methods. Studies from other countries have revealed abnormal GABA concentration in the medial prefrontal lobe (cingulate gyrus or ventromedial prefrontal cortex) in schizophrenia. However, there are at least two limitations in the current GABA studies of schizophrenia: 1) the impact of antipsychotic drugs on the study outcome has not been completely excluded; 2) the positioning of the medial prefrontal lobe is often very vague or inaccurate. The ventromedial prefrontal cortex and anterior cingulate cortex are the critical brain areas of schizophrenia. However, the two areas have not been clearly differentiated in previous studies. This study measured the concentration of glutamate and GABA in the dorsolateral prefrontal cortex, ventromedial prefrontal cortex and anterior cingulated cortex in individuals with schizophrenia using high-field- strength MRS. The correlation between results and clinical symptoms was also studied.

2. Methods

2.1 Participants

2.1.1 Schizophrenia group

All participants in this study were outpatients or inpatients at the Shanghai Mental Health Center (Shanghai, China). Of these participants 50 did not take medication, 18 cases declined to participate in this study, and 4 cases met exclusion criteria upon collection of demographic data. In the end, 28 patients were enrolled and underwent magnetic resonance imaging. There were 3 cases that withdrew from the study due to inability to complete the magnetic resonance imaging and 1 case that was excluded because of excessive spontaneous head movements. The remaining 24 cases met the following criteria: 1) meet the diagnostic criteria for schizophrenia according to DSM-IV; 2) had not taken antipsychotic medication for at least two weeks; 3) aged 18 to 45 years; and 4) written informed consent provided by the patient and patient's family members. The exclusion criteria were the following: 1) severe physiological diseases, psychoactive substance or alcohol dependence, or mental retardation; 2) patients receiving MECT; 3) women who were pregnant or lactating; and 4) those who had abnormal brain structures as found by conventional MRI. There were 10 male cases and 14 female cases with a mean(sd) age of 28.8 (8.3) years and mean (sd) years of education of 13.5 (3.9) years. The number of episodes in patients was 1.58 (0.5), and the median (QR25, QR75) course of disease was 24 (2, 57) months. The Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Scale (CGI) were used to assess the mental symptoms and severity of the disease. The mean (sd) total PANSS score was 82.8 (11.6); the mean (sd) positive symptom score was 22.7 (5.8); the mean (sd) negative symptom score was 19.9 (5.6). The mean (sd) score of general psychopathology was 40.5 (5.6). The mean (sd) score for the severity of CGI disease was 4.8 (0.9).

2.1.2 Healthy control group

30 healthy volunteers were recruited from the community. Several persons were excluded for the following reasons: 3 persons were younger than 18 or older than 45, 2 persons had a history of substance abuse, and 1 person had a family history of psychosis. None of the remaining 24 cases met the diagnostic criteria for any mental disorder as assessed by the Mini-International Neuropsychiatric Interview (MINI6.0). Patients with a family history of psychosis and severe physiological diseases, pregnant or lactating women, and those with abnormal brain structures as found by conventional MRI were also excluded. All participants gave consent to take part in this study. In this group there were 10 males and 14 females with a mean (sd) age of 26.6 (4.7) years and a mean(sd) years of education of 14.1 (2.6) years. The differences of age, educational level, and gender between the two groups were not statistically significant.

2.2 Methods

2.2.1 Scale assessment

PANSS[10, 11] and CGI[12] were used to assess the symptom severity of the patients with schizophrenia. The MINI.6.0[13] was used to interview and screen all participants. All scale assessments were conducted by a psychiatrist who had been trained in use of these scales.

2.2.2 MRI scan

Siemens MRI 3.0 (Magnetom Verio syngo MR B17) 32-channel coil was used to conduct the MRI. First, the magnetization-prepared rapid gradient-echo (MPRAGE) sequence was used to acquire the T1 structural image

of the subjects. Subsequently, the MEshcher-GArwood Point RESolved Spectroscopy sequence (MEGA-PRESS) was used to collect the MRS data of the subjects.[8,14] The areas of interest included: the left dorsolateral prefrontal cortex (lDLPFC), ventromedial prefrontal cortex, and anterior cingulate cortex. The sizes of the corresponding areas of interest were 35mm×25mm×30mm of the left dorsolateral prefrontal cortex (lDLPFC), 20mm×40mm×30mm of the ventromedial prefrontal cortex, and 40mm×20mm×20mm of the anterior cingulate cortex. Figures 2 to 4 show the location and sizes of the areas of interest. The dorsolateral prefrontal cortex voxel frame makes the upper edge be roughly parallel to the skull in coronal position, include the cerebral cortex, but avoid overlapping with the skull, in addition to coinciding with the upper inner edge and the superior frontal sulcus. Voxels included the middle frontal gyrus. The ventromedial prefrontal voxel frame on the horizontal axis took the longitudinal fissure of the brain as the midpoint extending 20mm to both sides and its trailing edge was located in the anterior cingulate cortex of the genu of corpus callosum in the sagittal plane, while trying not to include the anterior cingulate cortex. The lower edge was located in the upper part of the orbital gyrus. The anterior cingulate cortex: the voxel frame was symmetrical on the right and left sides taking the longitudinal fissure of the brain as the section; the anterior margin arose from the upper part of the genu of the corpus callosum; the lower edge along the upper region of the corpus callosum was out of shape; the upper and lower edges were approximately parallel to the corpus callosum. The MRS scan parameter was: TR=1500ms; TE=68ms; the number of acquisition was 164 times; the acquisition time of each area of interest was about 6 minutes. The MRI scan was calibrated before running. Manual shimming made the full width at half maximum of the water peak lower than 15 Hz. [15,16] At the same time, the chemical shift imaging stimulated by the radio-frequency pulse (PF pulse) underwent water content suppression. The water suppression rate (WS rate) was larger than 98%. Afterwards, the water suppression rates were collected with the same voxel at the same location (4 acquisition times).

Figure 1. Flowchart of the study

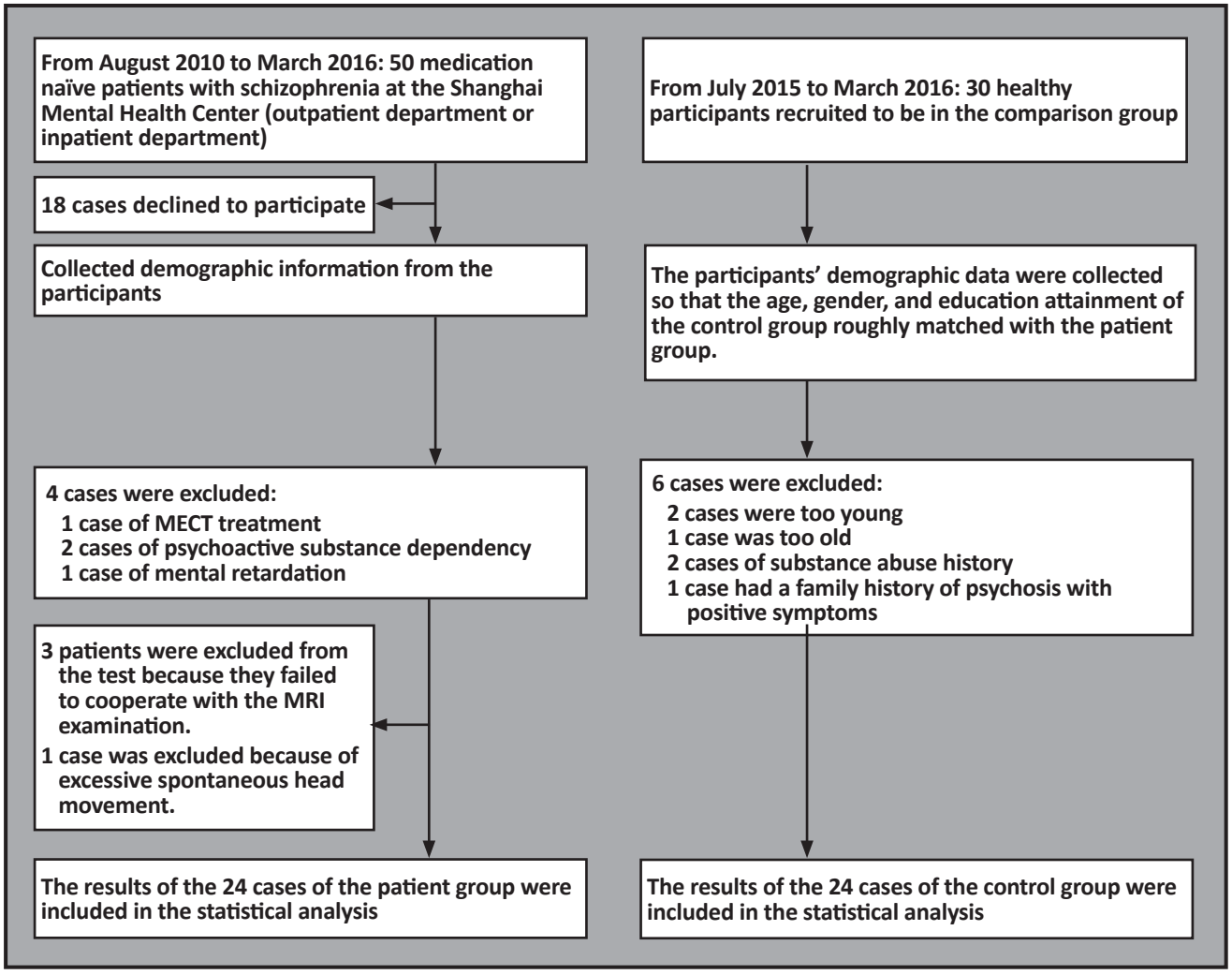


Figure 2. Size and location of the region of interest of the left dorsolateral prefrontal cortex (lDLPFC); the volume is 35mm X 25mm X 30mm

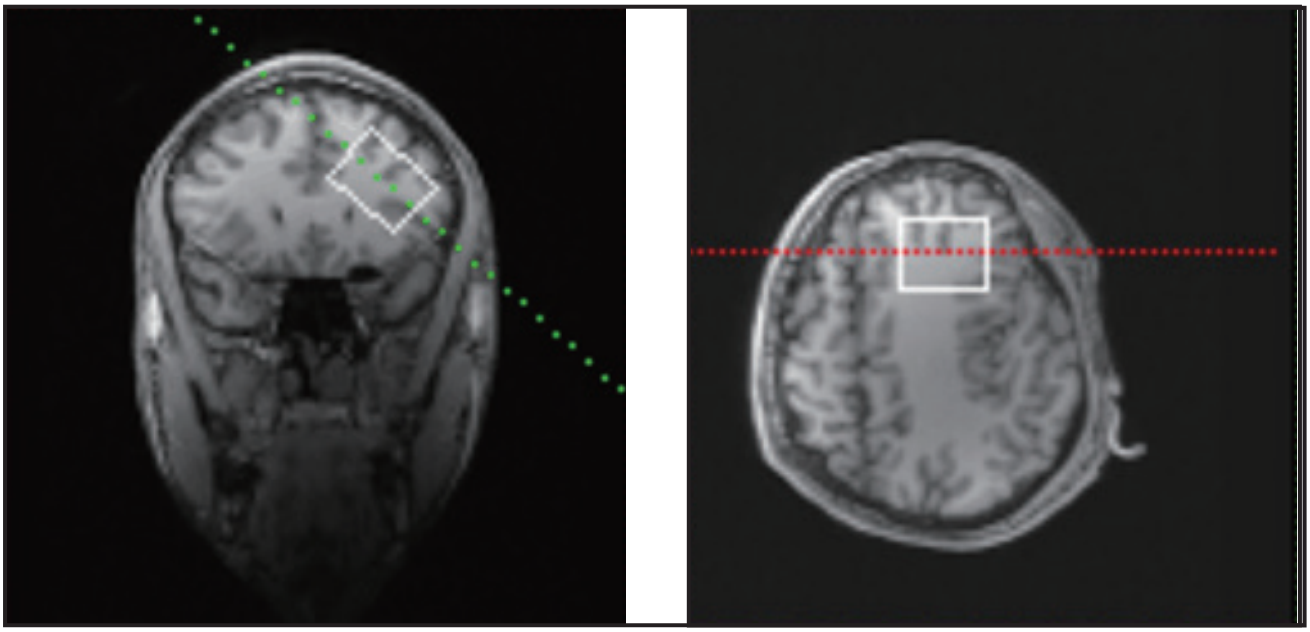
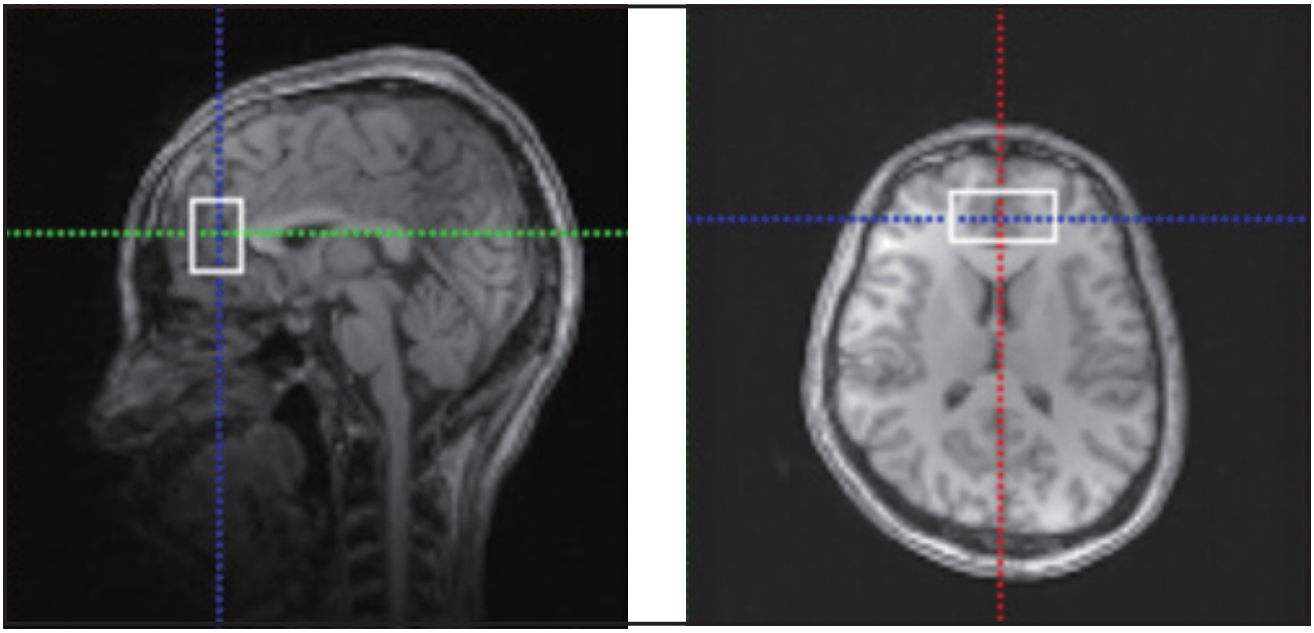


Figure 3. Size and location of the region of interest of the ventromedial prefrontal cortex (vmPFC); the volume is 20mm X 40mm X 30mm



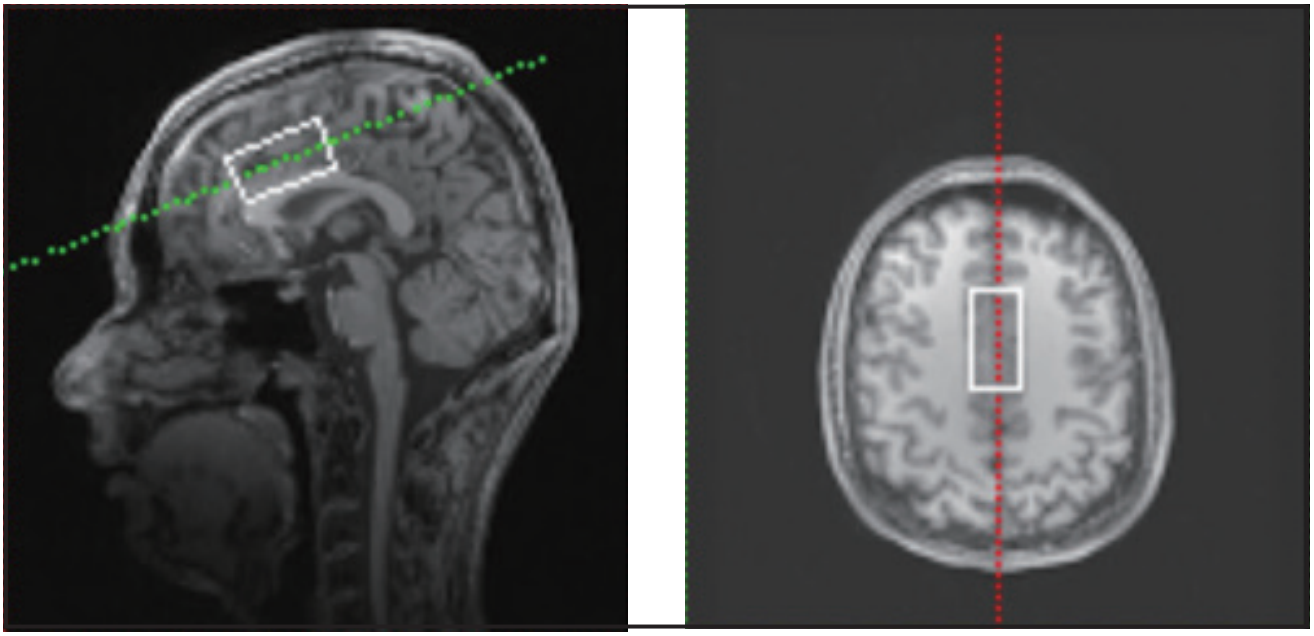
2.2.3 Image post-processing and data collection

The LCModel software from the Shanghai Jiao Tong University School of Biomedical Engineering workstation was used to process data. The editing frequency of the spectrum was 1.9ppm; the delta frequency was -1.7ppm; the editing bandwidth was 45Hz. Water was used as the internal reference to separately calculate the concentrations of the γ-aminobutyric acid (GABA), glutamate (Glu), glutamine (Gln), N-acetylaspartate (NAA), and N-acetylaspartylglutamate (NAAG) in the areas of interest and the ratios of GABA, Glu, and Gln to (NAA+NAAG).

2.3 Statistical processing

SPSS 19.0 statistical software package was used for statistical analysis. The metabolite concentration was expressed using mean (standard deviation). The data

Figure 4. Size and location of the region of interest of the anterior cingulate cortex (ACC); the volume is 40mm X 20mm X 20mm



from the non-normal distribution were expressed using median (quartiles). The between-group differences of the schizophrenia and healthy comparison groups were analyzed by two independent samples t-tests. T-test was used when the variance was heterogenous. Non-normal distribution data were checked using the Mann-Whitney U test. The age structure ratio in the general data was analyzed using chi-squared. Pearson correlation analysis was used to examine correlations. Spearman correlation analysis was used to analyze non-normal distribution data.

3. Results

3.1 Comparison of the GABA and glutamate concentrations

Table 1 lists the comparisons of the metabolite concentrations such as GABA and glutamate in the three regions of interest.

3.1.1 Left dorsolateral prefrontal cortex

Table 1 shows that the between-group differences of the GABA, Glu, and Gln concentrations and the GABA/ (NAA+NAAG), Glu/ (NAA+NAAG), Gln/ (NAA+NAAG) concentration ratios between the schizophrenia group and comparsion group were not statistically significant.

3.1.2 Ventromedial prefrontal cortex

The mean (sd) concentrations of GABA of the schizophrenia group and the comparison group were 2.50 (1.53) and 1.83 (0.63) respectively; the mean (sd) concentrations of Glu were 5.13 (2.44) and 3.49 (1.91); the mean (sd) concentrations of Gln were 2.46 (1.66) and 4.36 (1.90). The between-group differences for Glu (t=2.60, p=0.013) and Gln (t=-3.68, p=0.001) were statistically significant, suggesting an elevated Glu concentration and a reduced Gln concentration in schizophrenia. The Glu and Gln concentrations were negatively correlated (R=-0.86, p<0.001). The between-group differences of the GABA concentrations was not statistically significant (t= 1.97, p=0.058). Further ratio analysis suggested that the between-group difference of Glu/ (NAA+NAAG) was statistically significant (z= -2.18, p=0.030) and the between-group difference of Gln/ (NAA+NAAG) was statistically significant (z= -3.01, p=0.004).

3.1.3 Anterior cingulated cortex

Since the GABA concentrations of the schizophrenia group and the comparison group were non-normally distributed, and were expressed as medians 1.90 (Q1=1.55, Q3=2.09) and 2.16 (Q1=1.87, Q3=2.59) respectively; the medians of Gln concentrations were 0.36 (Q1=0.00, Q3=0.74) and 0.29 (Q1=0.00, Q3=0.59); the mean Glu concentrations were 6.07 (2.48) and 6.54 (1.99); the between-group difference of the GABA concentrations was statistically significant (z=-2.95, p=0.003); the between-group difference of Glu and Gln was not statistically significant; further ratio analysis suggested that the between-group difference of the GABA/(NAA+NAAG) was statistically significant (z=-2.72, p=0.012).

Table 1. Comparison of the metabolite concentrations such as GABA and glutamine

	Schizophrenia group (n=24)	Comparison group (n=24)	Statistics *t* / *z*	Degrees of freedom d.f.	*p*
Dorsalateral prefrontal cortex					
GABA	1.37 (1.18)	1.13 (0.93)	*t*=0.77	46	0.446
□Gln	1.95 (0.25,6.44)	3.12 (0.00,5.15)	*z*=-0.59	46	0.554
□Glu	1.03 (0.58,3.31)	1.05 (0.21,2.58)	*z* =-0.34	46	0.733
△GABA/NAA+NAAG)	0.18 (0.03,0.25)	0.11 (0.00,0.21)	*z* =-0.99	46	0.324
△Gln/NAA+NAAG）	0.27 (0.04,0.54)	0.36 (0.00,0.47)	*z* =-0.34	46	0.732
□Glu (NAA+NAAG)	0.15 (0.38,0.48)	0.15 (0.02,0.34)	*z* =-0.44	46	0.657
Ventromedial prefrontal cortex					
GABA	2.50 (1.53)	1.83 (0.63)	*t* =1.97	30.44	0.058
Gln	2.46 (1.66)	4.36 (1.90)	*t* =-3.68	46	0.001*
Glu	5.13 (2.44)	3.49 (1.91)	*t* =2.60	46	0.013*
△GABA/NAA+NAAG)	0.27 (0.21,0.45)	0.24 (0.22,0.33)	*z* =-1.10	46	0.270
Gln/NAA+NAAG)	0.37 (0.26)	0.74 (0.58)	*t* =-3.01	46	0.004*
△Glu/NAA+NAAG)	0.66 (0.51,0.92)	0.46 (0.37,0.63)	z=-2.18	46	0.030*
Anterior cingulate cortex					
□GABA	1.90 (1.55,2.09)	2.16 (1.87,2.59)	z=-2.95	46	0.003*
□Gln	0.36 (0.00,0.74)	0.29 (0.00,0.59)	*z* =-0.83	46	0.410
Glu	6.07 (2.48)	6.54 (1.99)	*t* =-0.74	46	0.464
GABA/NAA+NAAG)	0.26 (0.07)	0.43 (0.30)	*t* =-2.72	25.85	0.012*
Gln/NAA+NAAG)	0.06 (0.00,0.11)	0.05 (0.00,0.99)	*z* =-0.80	46	0.423
Glu/NAA+NAAG)	0.84 (0.20)	1.05 (0.53)	*t* =-1.88	46	0.066

**p*<0.05 statistical significance
□ The concentration of the skewed distribution is the median (P25, P75); The rest is the mean (standard deviation).

3.2 Correlation of GABA and glutamate concentration with the demographic characteristics and clinical symptoms

The correlation between education level and duration of disease and GABA, glutamate, and the ratio of each area of interest was not statistically significant. Table 2 shows that age was negatively correlated with the concentration of GABA in the anterior cingulate cortex (r=-0.494, *p*=0.014); age was negatively correlated with the GABA/ (NAA+NAAG) in the anterior cingulated cortex (r=-0.473, *p*=0.020) and was negatively correlated with Glu/ (NAA+NAAG) of the anterior cingulated cortex (r=-0.459, *p*=0.024). However, only the negative correlation of age and the GABA concentration in the anterior cingulate cortex was statistically significant after the Bonferroni correction was used (p value should than 0.017). In the comparison group, there was no such correlation. The positive symptom scores of the PANSS scale were negatively correlated with the Gln concentration in the anterior cingulate cortex (r=-0.406, *p*=0.049) and was negatively correlated with Gln/ (NAA+NAAG) in the same area (r=-0.419, *p*=0.042). The negative symptom scores of the PANSS scale were positively correlated with the GABA in the anterior cingulate cortex (r=-0.417, *p*=0.043). None of the correlations above was statistically significant after the Bonferroni correction was applied (p value should be less than 0.017). There was a lack of correlation between the GABA concentrations and glutamate in other areas of interest and clinical symptoms.

4. Discussion

4.1 Main findings

Regarding glutamates in the prefrontal cortex, our study was consistent with most of the results from previous studies that there was no change in the left dorsolateral prefrontal cortex and an increase of Glu concentration in the ventromedial prefrontal cortex. The concentration of GABA in the prefrontal cortex corresponded to the concentration of Glu; there was no change in the left dorsolateral prefrontal cortex. There was a rising trend

Table 2. The correlation of GABA in the anterior cingulate cortex and glutamine in schizophrenia with other clinical data

	Age (years) (n=24)	PANSS P score (n=24)	PANSS N score (n=24)
□*GABA*	R=-0.494, *p*=0.014*	R=0.008, *p* =0.971	R=0.417, *p* =0.043*
□*Gln*	R=0.045, *p*=0.834	R=-0.406, *p* =0.049*	R=-0.017, *p* =0.939
Glu	R=-0.386, *p*=0.063	R=0.256, *p* =0.226	R=0.223, *p* =0.294
GABA/NAA+NAAG）	R=-0.473, *p*=0.020*	R=-0.158, *p* =0.460	R=0.210, *p* =0.325
Gln/NAA+NAAG）	R=0.112, *p* =0.603	R=-0.419, *p* =0.042*	R=-0.002, *p* =0.992
Glu/NAA+NAAG）	R=-0.459, *p* =0.024*	R=-0.166, *p* =0.438	R=0.097, *p* =0.650

* *p* <0.05 means statistical significance in correlation
□ are the results of Spearman correlation analysis. The rest are the results Pearson correlation analysis

in the ventromedial prefrontal cortex. The results of studies from Kegeles and colleagues (2012), Fuente-Sandoval and colleagues (2015), and Zhilei Yang and colleagues (2015)[4,14,17] tended to show that: the GABA concentration in the ventromedial prefrontal cortex was elevated in the early stage of the disease. The ketamine challenge experiment found that ketamine selectively acted on the NMDA receptor that caused an elevation of Glu in the vmPFC resulting in positive symptoms, negative symptoms, and cognitive impairment in healthy people. In addition, they found that glutamine was converted back to glutamate as the release of glutamate increased. This was completely in line with results we saw from patients in this study.

The anterior cingulate cortex is an important component of the limbic system, and is related to cognitive attention. Animal and neurobiology experiments have shown that schizophrenia is associated with genetic defects that involve changes of GABA-ergic neurons in the early stages of ontogeny.[18] Yu Zhe and colleagues (2013) found that, in a schizophrenia animal model of GABA transporter 1 deficiency caused by GAT1, knockout rats with a decline in GABA showed would show a variety of schizophrenia-like symptoms such as positive symptoms, negative symptoms, and cognitive deficits.[19] The neurons of the cingulate gyrus were closely related to the prefrontal cortex. The pyramidal neurons of the cerebral cortex and hippocampus were densely distributed with the anterior synapses of GABA neurons. There were feed-forward and feedback loops of neurons between the GABA neurons and Glu pyramidal neurons.[20] Our study found a decrease in GABA concentration in the anterior cingulate cortex; therefore, the GABA- glutamate hypothesis speculated that Fast-spiking parvalbumin positive interneurons released less GABA in the course of schizophrenia. The projection to the prefrontal cortex could free Glu from inhibited release, in which the increased Glu could give feedback inducing GABA to go up again.

Previous studies have shown that NAA increased in the caudate nucleus and cerebellum in patients with first-episode schizophrenia.[21] Additionally, studies have found that NAAG was higher in younger patients with schizophrenia than in healthy controls.[9] Other studies have found progressive loss of brain tissues in schizophrenia and reduction of neuronal density decreased in the prefrontal cortex, as well as (NAA+NAAG) representative neuronal density and activity gradually decreased with the development of disease.[22,23] Due to the production of NAGG from the combination of NAA and Glu, this may be one of the compensatory regulation mechanisms for the change of Glu levels in patients with schizophrenia. This experiment concurrently compared the concentrations of various metabolites, and their ratio to (NAA+NAAG). The ratio was corrected for the differences of the neuronal density in individual brain tissues and deducted the part of compensation that could better reflect the Glu and GABA function of the patients with schizophrenia, not the structural abnormality. In this study, the between-group difference of the GABA concentration in the ventromedial prefrontal cortex between the schizophrenia group and comparison group neared statistical significance. Yet, its ratio with (NAA+NAAG) has no between-group difference and may possibly reflect the change of GABA concentration as a kind of compensatory result.

The reason for the abnormality of Glu among patients with schizophrenia is not certain. Genetics suggests the possibility of an allelic variation in GRM3 that affected the Gln-Glu cycle, resulting in Glu translocation disorder.[23] Gln is converted to Glu by the glutaminase in presynaptic neurons. Glu, released into the synaptic gap, is reabsorbed by astrocytes and regenerated into Gln by glutamine synthetase. This study observed an increase of Glu concentrations in the same area of interest and a decrease of the Gln level and Gln/ (NAA+NAAG). Moreover, the higher the Glu concentration, the lower the Gln concentration was. This may be due to an increase in the release of Glu that was freed from inhibition, resulting in an increase of Gln consumption. It may also be due to the metabolic impairment of Glu, resulting in reduced Gln production

without colloid cells resorption. Or it could be the result of the interaction between these two reasons.[24]

In healthy human brains, Glu and GABA decrease with age.[24] In this study, GABA of the patients with schizophrenia decreased with age. Nevertheless, there was no similar trend in the comparison group. This may be related to the general lack of elderly persons in this study. Rowland and colleagues (2016) also found that GABA was significantly reduced in the older segment of a schizophrenia group (over 35 years) compared to the younger segment (under 35 years). However, there is no such difference in the control group. This resembles the results of this study. These results reflect a gradual decline of GABA in the anterior cingulate cortex in patients with schizophrenia, that is earlier and more pronounced compared with the normal population.

Egerton and colleagues (2012) suggest that glutamate /Cr in the anterior cingulate cortex is positively related to negative symptoms.[27] Reid and colleagues (2012) found that the severity of negative symptoms was negatively related to the Glx level.[22] However, Poels and colleagues (2013) mentioned in a systematic review, most studies have not found the correlation between the metabolites and clinical symptoms.[3] The underlying cause of these different results deserves further investigation. Most previous studies coherently agreed that presynaptic DA in striatum and prefrontal cortex increased, triggering psychotic positive symptoms.[28] The Glu system and the DA system have the intersection point. Therefore, we hypothesized that the concentration of Glu/Gln and the positive symptoms are correlated. Moreover, Stone and colleagues (2012) have shown in the normal population that the elevated Glu concentration in the anterior cingulate cortex and the degree of positive symptoms induced by ketamine were related to each other.[29] However, this study found that the correlation between metabolite concentration after calibration and symptoms was not statistically significant. Therefore, a study with a larger sample size is needed to further validate this hypothesis.

4.2 Limitations

This study is cross sectional in nature, therefore we did not conduct any follow up regarding changes in metabolite concentration and changes in clinical status. The sample size of this study was relatively small. This could lead to a false positive correlation between some metabolites and the patients' demographics and their degree of clinical symptoms such as cognitive impairment and so on. In this experiment, the metabolite concentration calculated by LCModel was not further corrected by partial volume correction. The proportion of gray matter, white matter, and cerebrospinal fluid was not compared between groups. Therefore, the tissue volume difference of the individuals and the effects of tissue components on each metabolite concentration cannot be confirmed.

4.3 Implications

This study differentiated the ventromedial prefrontal cortex from the anterior cingulate cortex. Excluding the effects of drugs, the metabolite concentrations were detected respectively by the MEGA-PRESS sequence and LCModel software using the 1H-MRS method. It was found that there were different changes in metabolite concentration in different regions of interest. The results supported the hypothesis of GABA- glutamate abnormalities in schizophrenia and found that the GABA in the anterior cingulate cortex in the patients with schizophrenia had a tendency to accelerate depletion. For future studies, we can start by increasing the sample size. Moreover, a comparative observation can be made before and after the intervention to the areas of interest with significant differences. Additionally, we can analyze the relationship between the metabolites and positive symptoms, negative symptoms, cognitive impairment and so forth, as well as further exploring the predictive effects of brain metabolites such as GABA and Glu on disease development and prognosis.

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Conflict of interest statement

The authors declare no conflict of interest related to this manuscript.

Informed consent

All the participants provided written informed consent.

Ethical approval

This study was approved by the ethics committee of Shanghai Mental Health Center

Authors' contributions

Study design: Dengtang Liu, Tianyi Chen
Data collection: Tianyi Chen, Yingchan Wang, Zhilei Yang
Acquisition of image data: Jianye Zhang
Quality control and clinical guidance: Zuowei Wang
Experimental data analysis: Tianyi Chen, Jiale Xu
Provision of the tools for analysis: Yao Li

精神分裂症患者前额叶的 GABA 及谷氨酸浓度异常 —— 活体 1H-MRS 研究

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背景：进食障碍是一种文化相关疾病，东西方患者的临床表现有所不同，新版 ICD-11 指南即将出版，其喂养和进食障碍部分在中国进食障碍患者中的适用性尚不明确。

目的：探索中国进食障碍患者的潜在类别结构，研究新版 ICD-11 指南中进食障碍相关部分在中国的跨文化适用性。

方法：采用自制问卷和进食障碍问卷量表对 379 名 2010-2016 年于上海市精神卫生中心就诊的进食障碍患者的症状进行评估，使用 SPSS20.0 录入数据、处理人口学资料，通过 Latent GOLD 4.5 进行潜在剖面分析。

结果：依据潜在剖面分析结果可以将进食障碍分成：极低体重限制进食组（23.17%），无怕胖暴食清除组（21.54%），低水平怕胖暴食组（19.27%），怕胖暴食组（19.27%），极低体重无怕胖组（16.76%）。在提取的临床症状表现中，BMI、有无暴食行为、有无催吐、有无服用导泻剂及怕胖观念存在显著性差异，而有无限制性进食并无显著性差异。

结论：中国的进食障碍患者根据症状可以分成五个潜类别，基本符合 ICD-11 喂养和进食障碍的诊断分类。但进食障碍患者的怕胖观念标准和中国人群的低体重标准有待进一步完善。

关键词：进食障碍；潜类别模型；ICD-11；神经性厌食

References

1. Bigliani V, Mulligan RS, Acton PD, Visvikis D, Ell PJ, Stephenson C, et al. In vivooccupancy of striatal and temporal cortical D2/D3 dopamine receptors by typical antipsychotic drugs. [123I]epidepride single photon emission tomography (SPET) study. *Br J Psychiatry.* 1999; **175**: 231-238. doi: https://doi.org/10.1192/bjp.175.3.231
2. Liu XH. [*Oxford psychiatric textbooks. Fifth Edition. Chinese version*]. Sichuan: Sichuan University Press; 2010. p. 324-325. Chinese
3. Poels EM, Kegeles LS, Kantrowitz JT, Slifstein M, Javitt DC, Lieberman JA, et al. Imaging glutamate in schizophrenia: review of findings and implications for drug discovery. *Mol Psychiatry.* 2013; **19**(1): 20-29. doi: https://doi.org/10.1038/mp.2013.136
4. Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, et al . Elevated prefrontal cortex γ-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. *Arch Gen Psychiatry.* 2012; **69**(5): 449. doi: https://doi.org/10.1001/archgenpsychiatry.2011.1519
5. Goto N, Yoshimura R, Moriya J, Kakeda S, Ueda N, Ikenouchi-Sugita A, et al. Reduction of brain γ-aminobutyric acid (GABA) concentrations in early-stage schizophreniapatients: 3T Proton MRS study. *Schizophr Res.* 2009. **112**(1-3): 192-193. doi: https://doi.org/10.1016/j.schres.2009.04.026
6. Tayoshi S, Nakataki M, Sumitani S, Taniguchi K, Shibuya-Tayoshi S, Numata S, et al. GABA concentration in schizophrenia patients and the effects of antipsychotic medication: A proton ma6netic resonance spectroscopy study. *Schizophr Res.* 2010; **117**(1): 83-91. doi: https://doi.org/10.1016/j.schres.2009.11.011
7. Yoon JH, Maddock RJ, Rokem A, Silver MA, Minzenberg MJ, Ragland JD, et al. GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *J Neurosci.* 2010; **30**(10): 3777-3781. doi: https://doi.org/10.1523/JNEUROSCI.6158-09.2010
8. Ongür D, Prescot AP, McCarthy J, Cohen BM, Renshaw PF, et al. Elevated gamma- aminobutyric acid levels in chronic schizophrenia. *Biol Psychiatry.* 2010; **68**(7): 667-670. doi: https://doi.org/10.1016/j.biopsych.2010.05.016
9. Rowland LM, Kontson K, West J, Edden RA, Zhu H, Wijtenburg SA, et al. In vivo measurements of glutamate, gaba, and naag in schizophrenia. *Schizophr Bull.* 2013; **39**(5): 1096-1104. doi: https://doi.org/10.1093/schbul/sbs092
10. Kay S R, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull.*1987; **13**(2): 261-276. doi: https://doi.org/10.1093/schbul/13.2.261
11. Si TM, Yang JZ, Shu L, Wang XL, Kong QM, Zhou M, et al. [The Reliability,Validity of PANSS and its Implication]. *Zhongguo Xin Li Wei Sheng Za Zhi*. 2004; **18**(1): 45-47. doi: http://dx.chinadoi.cn/10.3321/j.issn:1000-6729.2004.01.016. Chinese
12. Wu WY, Zhang MY. [Clinical Global Impression (CGI)]. *Shanghai Arch Psychiatry*. 1984; **2**(1): 76-77. Chinese
13. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E. The Mini- International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998; **59** (Suppl 20): 22-33
14. Fuente-Sandoval CDL, Reyesmadrigal F, Mao X, León-Ortiz P, Rodríguez-Mayoral O, Solís-Vivanco R, et al. Cortico-Striatal GABAergic and Glutamatergic Dysregulations in Subjects at Ultra-High Risk for Psychosis Investigated with Proton Magnetic Resonance Spectroscopy. *Int J Neuropsychopharmacol.* 2015; **19(**3): pyv105. doi: https://doi.org/10.1093/ijnp/pyv105
15. Bartha R. Effect of signal-to-noise ratio and spectral linewidth on metabolite quantification at 4 T. *NMR Biomed.* 2007; **20**(5): 512-521. doi: https://doi.org/10.1002/nbm.1122
16. Tan SH, Liang CH, Zheng JH, Xu L. [Effect of shimming on water suppression and metabolites concentrations of 3.0T proton spectrum]. *Zhongguo Yi Xue Ying Xiang Ji Shu*. 2010; **26**(2): 369-371. doi: http://dx.chinadoi.cn/10.13929/j.1003-3289.2010.02.009. Chinese
17. Yang ZL, Zhu YQ, Song ZH, Mei L, Zhang JY, Chen TY, et al. [Comparison of the density ofgamma-aminobutyric acid in the ventromedial prefrontal cortex of paitents with ifrst-episode psychosis and healthy controls]. *Shanghai Arch Psychiatry*. 2015; **27**(6): 341-347. doi: https://doi.org/10.11919/j.issn.1002-0829.215130

18. Kim JY, Liu CY, Zhang F, Duan X, Wen Z, Song J, et al . Interplay between DISC1 and GABA Signaling Regulates Neurogenesis in Mice and Risk for Schizophrenia. *Cell.* 2012; **148**(5): 1051-1064. doi: https://doi.org/10.1016/j.cell.2011.12.037

19. Yu Z, Fang Q, Xiao X, Wang YZ, Cai YQ, Cao H, et al. GABA Transporter-1Deficiency Confers Schizophrenia-Like Behavioral Phenotypes. *PLoS ONE.* 2013; **8(**7): e69883. doi: https://doi.org/10.1371/journal.pone.0069883

20. Benes FM, Berretta S. GABAergic Interneurons: Implications for Understanding Schizophrenia and Bipolar Disorder. *Neuropsychopharmacology.* 2001; **25**(1): 1-27. doi: https://doi.org/10.1016/S0893-133X(01)00225-1

21. de la Fuente-Sandoval C, León-Ortiz P, Favila R, Stephano S, Mamo D, Ramírez- Bermúdez J, et al . Higher Levels of Glutamate in the Associative-Striatum of Subjects with Prodromal Symptoms of Schizophrenia and Patients with First-Episode Psychosis. *Neuropsychopharmacology.* 2011; **36**(9): 1781-1791. doi: https://doi.org/10.1038/npp.2011.65

22. Kraguljac NV, Reid M, White D, Jones R, den Hollander J, Lowman D, et al. Neurometabolites in schizophrenia and bipolar disorder — A systematic review and meta-analysis. *Psychiatry Research: Neuroimaging*. 2012; **203**(2-3): 111-125. doi: https://doi.org/10.1016/j.pscychresns.2012.02.003

23. Marsman A, van den Heuvel MP, Klomp DW, Kahn RS, Luijten PR, Hulshoff Pol HE, et al. Glutamate in Schizophrenia: A Focused Review and Meta-Analysis of 1H-MRS Studies. *Schizophr Bull.* 2012; **39**(1): 120-129. doi: https://doi.org/10.1093/schbul/sbr069

24. Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM. N-Acetylaspartate in the CNS: From Neurodiagnostics to Neurobiology. *Progress in Neurobiology*. 2007; **81**(2): 89-131. doi: https://doi.org/10.1016/j.pneurobio.2006.12.003

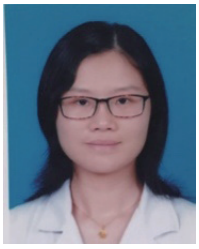
25. Gao F, Edden RA, Li M, Puts NA, Wang G, Liu C, et al . Edited magnetic resonance spectroscopy detects an age-related decline in brain GABA levels. *Neuroimage.* 2013; **78**(9): 75–82. doi: https://doi.org/10.1016/j.neuroimage.2013.04.012

26. Rowland LM, Krause BW, Wijtenburg SA，McMahon RP, Chiappelli J, Nugent KL, et al. Medial frontal GABA is lower in older schizophrenia: a MEGA-PRESS with macromolecule suppression study. *Molecular Psychiatry*. 2015; **21**(2): 198-204. doi: https://doi.org/10.1038/mp.2015.34

27. Egerton A, Brugger S, Raffin M, Barker GJ, Lythgoe DJ, McGuire PK, et al . Anterior Cingulate Glutamate Levels Related to Clinical Status Following Treatment in First-Episode Schizophrenia. *Neuropsychopharmacology.* 2012; **37**(11): 2515-2521. doi: https://doi.org/10.1038/npp.2012.113

28. Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci USA*. 2000; **97**(14): 8104-8109. doi: https://doi.org/10.1073/pnas.97.14.8104

29. Stone JM, Dietrich C, Edden R, Mehta MA, De Simoni S, Reed LJ, et al. Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. *Mol Psychiatry.* 2012; **17**(7): 664-665. doi: https://doi.org/10.1038/mp. 2011.171



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