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SHORT COMMUNICATION

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Glutamate correlates negatively with cognitive theory of mind in schizotypy

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Abstract

This study showed a negative correlation between the glutamate level in the anterior cingulate cortex and cognitive theory of mind in individuals with high level of schizotypy but not in non-schizotypy individuals.

KEYWORDS
glutamate, magnetic resonance spectroscopy (MRS), schizotypy, social cognition, theory of mind

The glutamate (Glu) hypothesis of schizophrenia suggests that dysfunctions of glutamatergic N-methyl-D-aspartate (NMDA) receptors could result in psychopathology and cognitive deficits (Reddy-Thootkur et al., 2020). Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive measure for *in vivo* Glu levels. A few MRS studies had been conducted to explore the correlation between Glu levels and cognitions in schizophrenia, including social cognitive functions such as empathy and theory of mind (Reddy-Thootkur et al., 2020). Previous findings were heterogeneous, and exposure to antipsychotic medications may be a confounder. Schizotypy is a multidimensional personality organization distributed in the general population, reflecting the liability to schizophrenia (Kwapil & Barrantes-Vidal, 2015). Individuals with high level of schizotypy exhibit attenuated psychopathology resembling symptoms of schizophrenia, and also show milder cognitive impairments than schizophrenia patients (Kwapil & Barrantes-Vidal, 2015). The study of schizotypy provides a viable method to minimize the confounding effects of antipsychotic medication, course of disease, and institutionalization.

This study aimed to investigate the relationship between Glu levels and social cognitions in people with high level of schizotypy. Participants were recruited from a pool of 1127 college students in Shanghai, China, based on their ratings ($Mean = 11.40$, $SD = 6.55$) on the Chinese versions of the Revised Social Anhedonia Scale (CSAS; Chan et al., 2012). Participants with a CSAS score of above 19 (the top 10%) were classified as the high-schizotypy group, whilst those with a CSAS score of below 12 (the mean score) were classified as the non-schizotypy group. Twenty-six high-schizotypy participants (seven males, $Mean_{age} \pm SD = 21.15 \pm 2.32$, $Mean_{length\ of\ education} \pm SD = 14.85 \pm 1.74$, $Mean_{IQ} \pm SD = 123.73 \pm 8.25$, $Mean_{CSAS\ score} \pm SD = 24.42 \pm 3.99$) and 29 non-schizotypy participants (eight males, $Mean_{age} \pm SD = 21.41 \pm 2.31$, $Mean_{length\ of\ education} \pm SD = 15.17 \pm 1.89$, $Mean_{IQ} \pm SD = 119.93 \pm 11.16$, $Mean_{CSAS\ score} \pm SD = 6.14 \pm 2.47$) were recruited. The two groups did not differ in sex, age, education, and estimated IQ. The ratio of Glu to creatine total (creatine + phosphocreatine, Cr) in the anterior cingulate cortex (ACC; with a voxel size of $20 \times 18 \times 30$ mm^3) was measured in a 3T Siemens Prisma scanner using point-resolved spectroscopy

(PRESS) sequence (repetition time, TR = 2000 ms, echo time, TE = 35 ms, 32 averages). A TE-averaging quantification method was used for the collection of spectra with the TE ranging from 35 ms with 6 ms increments for 32 spectra. The Glu/Cr levels of six participants (three high-schizotypy and three non-schizotypy) were excluded, because the Cramer–Rao lower bound (CRLB) estimate was above 20%. Participants completed the Chinese version of the Questionnaire of Cognitive and Affective Empathy (QCAE; Liang et al., 2019) and the computerized Yoni Task (Shamay-Tsoory & Aharon-Peretz, 2007). The Ethics Committee of the Institute of Psychology of the Chinese Academy of Sciences approved this study. All participants provided written informed consent.

Independent sample *t* tests found that the two groups had comparable Glu/Cr levels, theory of mind performance, and QCAE cognitive empathy scores. The QCAE affective empathy score in the high-schizotypy group was significantly lower than that in the non-schizotypy group ($Mean_{\text{high-schizotypy}} \pm SD$ = 28.54 ± 5.22, $Mean_{\text{non-schizotypy}} \pm SD$: 32.28 ± 3.30, $t_{[53]} = -3.21$, $p < .002$, Cohen' s $d = -.87$). These results remained unchanged when participants with CRLB estimates above 20% were included.

Pearson's correlation analysis found that the Glu/Cr level in the high-schizotypy group was negatively correlated with cognitive theory of mind performance in the second-order condition of the Yoni Task ($r_{21} = -.443$, $p = .034$; see Figure 1). Such correlation remained significant after controlling for sex, age, education, and IQ ($r_{17} = -.632$, $p = .004$). No significant correlations were found between Glu/Cr level and empathy or other theory of mind performances. In the non-schizotypy group, no significant correlations were found between Glu/Cr level and all social cognitive measurements. These results remained unchanged when participants with CRLB estimates above 20% were retained in the sample (CRLB estimates included as a covariate).

This study was one of the few to explore the relationship between *in vivo* Glu level of the ACC and theory of mind performances in people with schizotypy. Our findings suggested a negative correlation between the ACC Glu/Cr level and cognitive theory of mind performance in high-schizotypy rather than non-schizotypy individuals, consistent with the Glu hypothesis (Merritt et al., 2021). Merritt et al. (2021)'s meta-analysis pooled data from 45 ^{1}H-MRS studies in schizophrenia, and concluded that the Glu/Cr level in the medial frontal cortex was positively correlated with positive symptoms but negatively correlated with global functioning, whereas the Glx (Glu + glutamine)/Cr level was positively correlated with negative symptoms in the medial temporal lobe. The ACC is an important region of the "social brain" and would have hypo-activation during engagements with the theory of mind tasks in schizophrenia patients (Kronbichler et al., 2017). Our findings of ACC Glu/Cr level having significant correlations with theory of mind may further indicate that hypo-activation could result from the excessive ACC Glu concentration and possible excitotoxicity to neurons (Merritt et al., 2021). Indeed, a previous study demonstrated that *in vivo* Glu level was positively correlated with gray matter volume reduction in the dorsal to posterior ACC in people with "at-risk mental state" (Stone et al., 2009). Although we did not find abnormal Glu levels within high-schizotypy individuals, we found correlations of Glu level with theory of mind in the high-schizotypy group. This negative correlation between Glu concentration and cognitive theory of mind further supported the role of the glutamatergic system in social cognition in schizophrenia.

This study has several limitations. First, the whole ACC rather than a smaller specific subregion was chosen as the region of interest. Second, empathy was measured using a self-reported questionnaire rather than a performance-based task. Lastly, our sample size was small. Replication of our findings

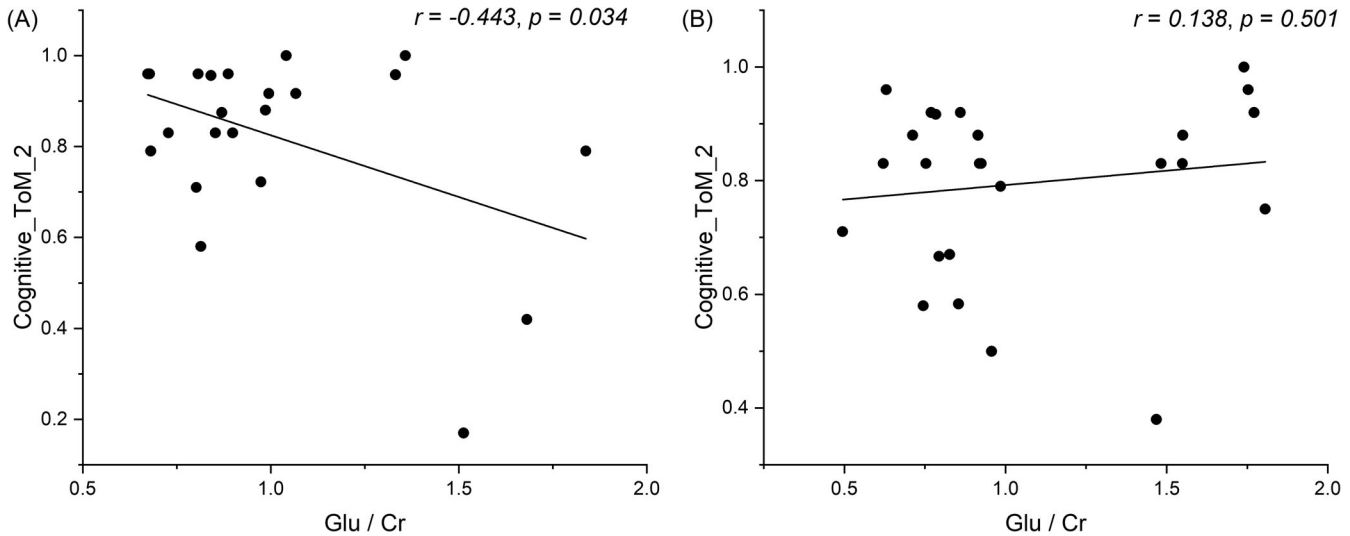

FIGURE 1 (a) The glutamate (Glu)/creatine total (creatine + phosphocreatine, Cr) level was negatively correlated with cognitive theory of mind scores in the second-order condition of the Yoni Task in individuals with high schizotypy. (b) The Glu/Cr level was not correlated with cognitive theory of mind scores in the second-order condition of the Yoni Task in the non-schizotypy group. Cognitive_ToM_2, cognitive theory of mind scores in the second-order condition

using a larger sample with comprehensive set of performance-based tasks of social cognition is needed.

In conclusion, our study found a negative correlation between the ACC Glu level and cognitive theory of mind in individuals with high level of schizotypy. Neurochemical understanding on glutamatergic dysfunctions underlying social cognitive impairments in schizotypy and schizophrenia may be useful for developing future interventions of social cognitive deficits.

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DISCLOSURE OF CONFLICT OF INTEREST

None to declare.

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