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Striatal GABA level is associated with sensory integration ability in individuals with low levels of negative schizotypy

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Abstract

Recent studies suggest that altered gamma-aminobutyric acidergic (GABAergic) function may result in multisensory integration deficits in schizophrenia. However, it is unclear whether the GABA level is abnormal in individuals with high levels of schizotypal traits and how it would correlate with sensory integration ability in these individuals. This study aimed to compare the GABA level between individuals with high and low levels of negative schizotypy, and examine the relationship between GABA levels and sensory integration ability in each group. In vivo GABA+ and *N*-acetylaspartate (NAA) levels in the striatum were measured using proton magnetic resonance imaging in 19 participants with high levels of negative schizotypy and 21 participants with low levels of negative schizotypy. The Sensory Integration subscale of the abridged version of the Cambridge Neurological Inventory was used. We examined the group differences in GABA+/NAA levels, and the correlation between striatal GABA +/NAA levels and sensory integration ability in each group. The two groups showed comparable levels of in-vivo GABA+/NAA. In-vivo GABA+/NAA levels were negatively correlated with sensory integration score in participants with low levels of negative schizotypy, but not in participants with high levels of negative schizotypy. Our findings indicate that the increased GABA level is correlated with better sensory integration ability in individuals with low levels of negative schizotypy, implicating the role of GABAergic function in multisensory integration. Unlike schizophrenia patients, individuals with high levels of schizotypy do not exhibit any abnormality in their GABAergic system and sensory integration ability.

KEYWORDS
GABA, multisensory integration, proton magnetic resonance spectroscopy, schizotypal traits

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Evidence from postmortem and animal studies suggests that GABA plays an important role in the pathophysiology of schizophrenia (Fatemi et al., 2011; Sargeant et al., 2012). Nowadays, sophisticated neuroimaging techniques, such as proton magnetic resonance spectroscopy (^{1}H-MRS), can measure in-vivo GABA levels in a noninvasive way. However, previous studies examining GABA levels in schizophrenia patients have yielded controversial results (Egerton et al., 2017; Kelemen et al., 2013; Kumar et al., 2021; Reddy-Thootkur et al., 2020; Reid et al., 2019; Rowland et al., 2013; Tayoshi et al., 2010). Moreover, previous studies also reported inconsistent findings in individuals at risk of developing psychosis (Da Silva et al., 2019; de la Fuente-Sandoval et al., 2015; Modinos et al., 2018). These inconsistent findings might have been confounded by antipsychotic medications that have direct and indirect effects on the GABAergic system (de la Fuente-Sandoval et al., 2018; Goto et al., 2010; Tayoshi et al., 2010). Meanwhile, heterogeneity of the

clinical variables in patients with schizophrenia, such as different illness stages or responsiveness to antipsychotics, further increases the difficulties in examining the potential abnormalities in neuronal metabolites for schizophrenia (Kumar et al., 2020; Merritt et al., 2021; Whitehurst et al., 2020).

The GABAergic system is essential in generating and modulating neural oscillations (Moran & Hong, 2011; Wyss et al., 2017), which have been implicated in multisensory integration (Kaiser et al., 2019; Roa Romero et al., 2015). Empirical evidence from healthy individuals and animal studies also supports the role of GABA in sensory integration (Balz, Keil, et al., 2016a; Gogolla et al., 2014; Iurilli et al., 2012). Deficits in sensory integration have been consistently demonstrated in schizophrenia patients (Tseng et al., 2015; Zhou et al., 2018). Ketamine-treated rats (the animal model of schizophrenia) showed that decreased GABAergic function was linked to impaired performance in a multisensory task (Cloke et al., 2016), suggesting that abnormal GABAergic function could lead to deficits in sensory integration. However, it remains unclear whether GABAergic function in schizophrenia patients is related to deficits in sensory integration or not.

One possible way to avoid these confounding effects is to utilize subclinical samples exhibiting high levels of schizotypy. Schizotypy is conceptualized as a phenotype carrying vulnerability to develop schizophrenia (Fonseca-Pedrero et al., 2018; Meehl, 1962; Meehl, 1990). The construct of schizotypy comprises different dimensions, such as positive and negative schizotypy (Ettinger et al., 2015; Raine, 2006). Previous studies have found that higher glutamate/GABA ratio in the right superior temporal cortex was correlated with higher levels of negative schizotypy (Ford et al., 2017). Moreover, the glutamate/GABA ratio in the left primary auditory cortex was found to be correlated with audio-tactile multisensory integration and schizotypy (Ferri et al., 2017), indicating the potential role of the GABAergic system in sensory integration in individuals with high levels of schizotypy. However, previous studies (Ferri et al., 2017; Ford et al., 2017) mainly investigated the imbalance between the excitatory and inhibitory neurotransmitter systems, instead of the GABAergic system per se, and did not compare individuals with high and low levels of schizotypy.

In this study, we compared the GABA levels between individuals with high and low levels of negative schizotypy and examined the relationship between GABA level and sensory integration ability. Since the striatum integrates sensory information from multiple cortical areas and modalities (Reig & Silberberg, 2014) and striatal GABAergic interneurons have been demonstrated to be important for sensory integration (Ramanathan et al., 2002), we specifically measured striatal GABA levels and defined the striatum as a region of interest (ROI) for MRS. Sensory integration ability was assessed using a subscale of the abridged version of the Cambridge Neurological Inventory (CNI; Chan et al., 2009; Chen et al., 1995).

Based on previous findings that antipsychotic-naive participants at clinical high risk for psychosis had increased striatal GABA levels (de la Fuente-Sandoval et al., 2015) and individuals with high levels of schizotypy have a higher risk of developing psychosis (Rawlings et al., 2008), we hypothesized that individuals with high levels of negative schizotypy would have increased striatal GABA levels, relative to individuals with low levels of negative schizotypy.

Since sensory integration processing involves the functioning of striatal GABAergic interneurons (Ramanathan et al., 2002), there would be an association between striatal GABA levels and sensory integration ability. Evidence also suggests that higher levels of schizotypy are related with poorer sensory integration ability (Di Cosmo et al., 2021; Ferri et al., 2017), and increased GABA level is correlated with better sensory integration ability (Balz, Keil, et al., 2016a; Cloke et al., 2016). Therefore, there would be a relationship between levels of schizotypy, GABA levels, and sensory integration ability. In view of the previous evidence, we hypothesized that individuals with low levels of negative schizotypy would show a correlation between higher GABA levels and better sensory integration ability while individuals with high levels of negative schizotypy would show a different pattern.

MATERIALS AND METHODS

Participants

The revised Chinese version of the Chapman Social Anhedonia Scale (CSAS; Chan et al., 2012; Chapman et al., 1976) was disseminated online. A total of 570 university students in Shanghai completed the online questionnaire (M_{CSAS} = 15.91, SD = 3.71). The CSAS has been widely used to measure negative schizotypy (Cai et al., 2019; Chan et al., 2015; Wang et al., 2016). Based on the cut-offs of the CSAS recommended in earlier studies (Cai et al., 2019; Chan et al., 2015; Wang et al., 2016), we recruited individuals who scored greater than 17 on the CSAS as participants with high levels of negative schizotypy, and those who scored lower than 8 as participants with low levels of negative schizotypy. The exclusion criteria were as follows: (1) active substance abuse; (2) a history of brain injury; and (3) known history of any psychiatric disorders, neurological disorders or physical illness. We also ascertained that none of the participants had any contraindications for MRI scanning, such as metallic dentures or pacemakers. Students who met the eligibility criteria were invited to participate in this study.

Participants were then interviewed using the MINI-International Neuropsychiatric Interview (Sheehan et al., 1998) by a trained experimenter to ascertain the absence of psychiatric disorders. Finally, 40 participants were recruited; 19 of them had high levels of negative schizotypy and 21 had low levels of negative schizotypy. This study was approved by the Ethics Committee of the Institute of Psychology of the Chinese Academy of Sciences. All participants gave written informed consent.

Self-report questionnaires and behavioral assessment

The Chinese version of the CSAS was used to assess negative schizotypy. The CSAS consists of 40 items with *true/false* answers. Higher scores indicate less pleasure experience from social or interpersonal activities. The Chinese version of the CSAS has been found to possess good validity and reliability (Chan et al., 2012).

The short form (the Information, Similarities, Arithmetic and Digit Span subtests) of the Chinese version of the Wechsler Adult Intelligence Scale (WAIS_R; Gong, 1992) were administered to estimate the IQs of the participants.

The abridged version of the CNI was used to assess neurological soft signs (Chan et al., 2009; Chen et al., 1995). The CNI comprises three subscales: Motor Coordination, Sensory Integration, and Disinhibition. A trained experimenter rated each item on a dichotomized scale with "0" for *absence* and "1" for *presence* of neurological soft signs. A higher score on the CNI indicates more severe neurological soft signs. High intraclass correlation coefficients have been found for the three subscales and the full scale (Chan et al., 2009). In this study, only the Sensory Integration subscale was used to assess sensory integration ability.

Image acquisition and analysis

All participants were scanned in a 3T MR imaging system (Magnetom Trio Tim, Siemens Healthcare, Erlangen, Germany) for acquisition of T1-weighted structural imaging data and proton MRS data at the East China Normal University, Shanghai, China.

T1-weighted structural imaging data were acquired using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence, with the following parameters: TR = 2530 ms, TE = 2.34 ms, voxel size = $1 \times 1 \times 1$ mm^3, matrix size = 256×256, FOV = 256 mm, flip angle = 7°, and slice thickness = 1 mm.

MRS data were acquired using a single-voxel Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) J-difference editing sequence, with the following parameters: TR = 2000 ms, TE = 68 ms, 128 water-suppressed averages, and 8 unsuppressed-water averages. As shown in Figure 1, ROI ($40 \times 20 \times 25$ mm^3) was prescribed to include the ventral striatum.

All spectra were analyzed using the jMRUI software (http://www.jmrui.eu). Prior to fitting in the jMRUI, zero Filling added 1,024 zeros to the loaded signals. Phase adjustment and frequency alignment were performed according to the position of the residual water peaks (Arrubla et al., 2014; Donahue et al., 2010). Hankel Lanczos singular value decomposition (HLSVD) filter was selected to suppress the residual water peak. An apodization function for Gaussian 2 Hz was used for the spectra. As the MEGA-PRESS sequence without macromolecule suppression (Donahue et al., 2010; Near et al., 2011) was used in this study, the notation GABA + (GABA plus macromolecule measurements) was employed to indicate GABA levels. After preprocessing, the relative concentration of GABA+ levels was calculated using the Advanced Method for Accurate, Robust, and Efficient Spectral fitting (AMARES) quantitation algorithms (Vanhamme et al., 2001). The relative concentration of GABA+ levels was expressed as a ratio of the amplitude of the GABA+ peak to the amplitude of the NAA peak (GABA+/NAA). Because the NAA peak was acquired simultaneously as the GABA+ peak, the potential drifts during scanning were optimized (Stagg et al., 2014). GABA+ and NAA were respectively modeled as paired and inversely single Lorentzian peaks with the same linewidth (Figure 1B; Donahue et al., 2010). Spectral quality parameters, including the signal-to-noise ratio (SNR) and the Cramer-Rao lower bounds (CRLB) of GABA+ and NAA, were obtained for each participant (Table 1). The CRLB of GABA+ and NAA for all participants were lower than 15%. A high signal-to-noise ratio (SNR) and a low CRLB were obtained in this study, indicating excellent quality of the MRS data. No participant was excluded from the subsequent analysis based on SNR

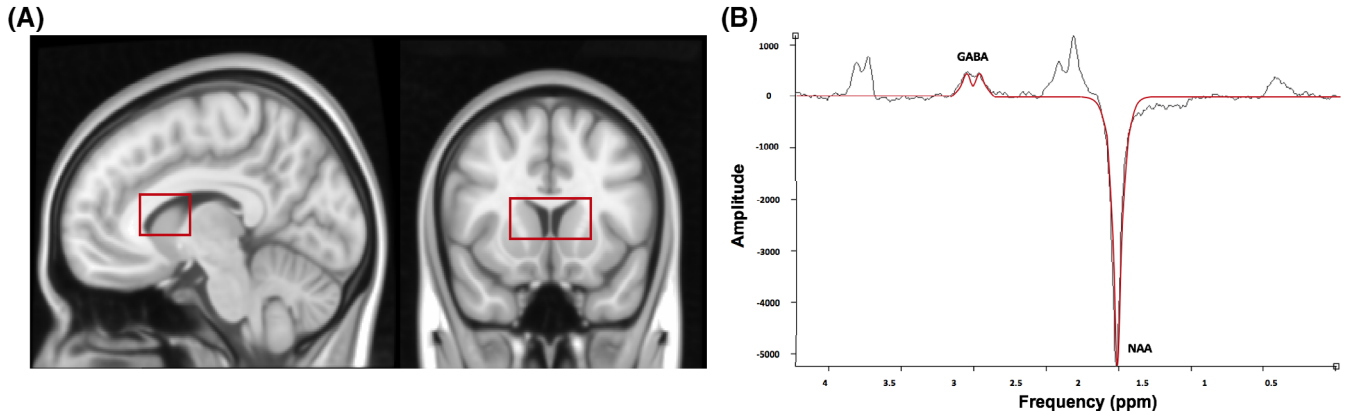

FIGURE 1 (A) Representative T1-weighted images of the location of voxel in the ventral striatum. (B) Spectrum fitting from the ventral striatum using AMARES in JMRUI. GABA = gamma-aminobutyric acidergic; NAA = N-acetylaspartate

TABLE 1 Demographics and MRS quality parameters of participants

	Low levels of negative schizotypy ($n = 21$) mean (*SD*)	High levels of negative schizotypy ($n = 19$) mean (*SD*)	*t* test		
			t/χ^2	*p*	Cohen's d
Demographics					
Age (years)	21.19 (2.14)	19.89 (1.60)	$t_{38} = 2.16^{*}$	**.038**	0.690
Gender (male/female)	2/19	1/18	0.26	.609	
Estimated IQ	125.76 (10.29)	124.53 (8.95)	$t_{38} = 0.40$	.689	0.128
Education (years)	15.05 (1.88)	13.74 (1.33)	$t_{38} = 2.52^{*}$	**.016**	0.804
CSAS	4.67 (1.83)	19.53 (1.81)	$t_{38} = -25.84^{**}$	**<.001**	−8.165
CNI sensory integration	1.57 (0.98)	1.37 (0.83)	$t_{38} = 0.70$	.486	0.220
MRS quality parameters					
GM proportion	0.42 (0.06)	0.40 (0.11)	$t_{38} = 0.74$	.467	0.226
WM proportion	0.44 (0.15)	0.48 (0.13)	$t_{38} = -0.78$	.441	−0.285
CSF proportion	0.12 (0.12)	0.13 (0.08)	$t_{38} = -0.06$	.954	−0.098
SNR	21.62 (3.83)	21.69 (4.39)	$t_{38} = -0.05$	.963	−0.017
CRLB of GABA+ (%)	0.93 (0.50)	0.81 (0.12)	$t_{38} = 0.99$	.327	0.330
CRLB of NAA (%)	0.90 (0.49)	0.79 (0.12)	$t_{38} = 0.99$	.329	0.308

Note: $^{*}p < .05$, $^{**}p < .001$.

Abbreviations: CNI = abridged version of the Cambridge Neurological Inventory; CRLB = the Cramer-Rao lower bounds; CSAS = Chinese version of the Chapman Social Anhedonia Scale; CSF = cerebrospinal fluid; GABA = gamma-aminobutyric acid; GM = gray matter; NAA = *N*-acetylaspartate; SNR = signal-to-noise ratio; WM = white matter.

and CRLB. The Statistical Parameter Mapping (SPM) software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12) was used to segment the T1-weighted image into gray matter (GM), water matter (WM) and cerebrospinal fluid (CSF).

Statistical analysis

Group differences in age, education level, estimated IQ, scores on the CSAS, the CPQ and the Sensory Integration subscale of the CNI, as well as the SNR, GM ratio, WM ratio, and CSF ratio were examined using independent sample *t*-tests. Chi-square tests were performed to compare gender ratio between groups. The normality of the neurometabolite data was tested by the Shapiro–Wilk test. Given the small sample and skewed distribution of GABA+/NAA levels, Mann–Whitney *U* test was used to compare the group difference. As the two groups differed significantly in age, Quade's rank analysis of covariance was used to examine the group differences in GABA+/NAA levels with age as a covariate. The two groups also had significantly different education level, so we further included education level as another covariate to test group differences.

Non-parametric correlations were calculated to examine the correlation between GABA+/NAA levels and scores on the Sensory Integration subscale of the CNI in each group independently, with age as a covariate. Furthermore, education level was also entered as a covariate in the non-parametric correlations. All statistical analysis was conducted using SPSS (Version 20, IBM).

RESULTS

Demographic and behavioral data

As shown in Table 1, the two groups did not differ in gender ratio and estimated IQ. However, participants with high levels of negative schizotypy were significantly younger, had significantly lower education level, and scored higher on the CSAS than participants with low levels of negative schizotypy. There was no significant difference in scores on the Sensory Integration subscale of the CNI between the two groups.

GABA+/NAA levels

The MRS data were of good quality, with jMRUI reporting a mean ± SD SNR of 21.65 ± 4.05, a GABA+'s CRLB (%) of 0.88 ± 0.37 and an NAA's CRLB (%) of 0.85 ± 0.36. As shown in Table 1, there was no significant group difference in the MRS-related variables. Therefore, the proportions of tissue volume, SNR, CRLB of GABA+ and GRLB of NAA were not included as covariates in the subsequent analysis in GABA+/NAA levels.

Shapiro–Wilk test showed a significant departure from normality for GABA+/NAA ($W_{40} = 0.872$, $p < .001$). Mann–Whitney U-test showed that there was no significant difference in striatal GABA+/NAA levels between the two groups (Figure 2; $p = .728$). After entering age as a covariate, the Quade's test did not find any significant group difference in striatal GABA+/NAA levels ($F_{[1,38]} = 0.014$, $p = .905$). The results remained unchanged after entering education level as a covariate ($F_{[1,38]} = 0.007$, $p = .933$).

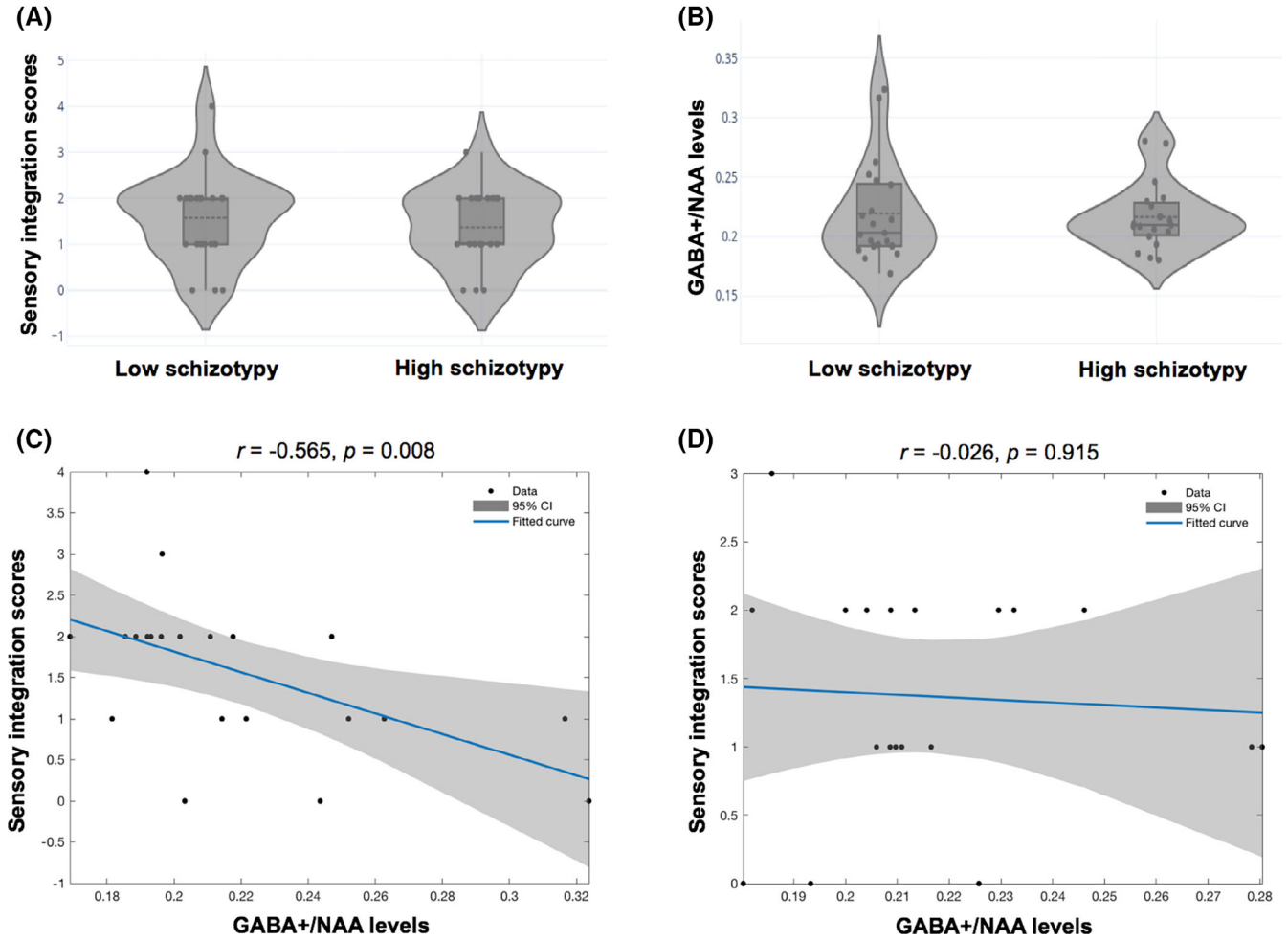

FIGURE 2 (A) Violin plot of sensory integration scores in participants with low levels of negative schizotypy and participants with high levels of negative schizotypy. (B) Violin plot of GABA+/NAA levels in participants with low levels of negative schizotypy and participants with high levels of negative schizotypy. (C) Scatterplot of the significant correlation between GABA+/NAA levels and scores of sensory integration in participant with low levels of negative schizotypy ($r = -.565$, $p = .008$). (D) Scatterplot of the nonsignificant correlation between GABA+/NAA levels and scores of sensory integration in participant with high levels of negative schizotypy ($r = -.026$, $p = .915$). GABA = gamma-aminobutyric acidergic; NAA = *N*-acetylaspartate

Overall, individuals with high and low levels of negative schizotypy did not differ significantly in GABA+/NAA levels in the striatum.

Relationship between GABA+/NAA levels and the CNI Sensory Integration subscale scores

Striatal GABA+/NAA levels were negatively correlated with scores on the Sensory Integration subscale of the CNI ($r = -.565$, $p = .008$) in participants with low levels of negative schizotypy (see Figure 2), indicating that higher GABA+/NAA levels were correlated with better sensory integration ability. There was no significant correlation between striatal GABA+/NAA levels and scores on the Sensory Integration subscale of the CNI in participants with high levels of negative schizotypy ($r = -.026$, $p = .915$). After controlling for age, these results remained unchanged (low levels of negative schizotypy: $r = -.590$, $p = .006$; high levels of negative schizotypy: $r = .066$, $p = .794$). After controlling for education level, these results remained unchanged (low levels of negative schizotypy: $r = -.626$, $p = .004$; high levels of negative schizotypy: $r = -.061$, $p = .817$).

DISCUSSION

The present study is the first study that investigates the correlation between in-vivo striatal GABA levels and sensory integration ability in individuals with high and low levels of negative schizotypy. Our findings suggest that individuals with high and low levels of negative schizotypy showed comparable striatal GABA+/NAA levels. We found that GABA+/NAA level was negatively correlated with scores on the Sensory Integration subscale of the CNI in individuals with low levels of negative schizotypy, indicating the increased GABA level was correlated with better sensory integration ability. But such correlation pattern was not observed in individuals with high levels of negative schizotypy. Our findings support the role of

GABAergic neurotransmission in sensory integration ability in individuals with low levels of negative schizotypy.

Previous studies on GABA levels have reported divergent results in individuals at different stages of schizophrenia. Thakkar et al. (2017) utilized an ultra-high magnetic field strength of 7 Tesla (T) to measure striatal GABA levels, and found that patients with chronic schizophrenia, their unaffected siblings and controls did not differ significantly (Thakkar et al., 2017). Tayoshi et al. (2010) also reported similar negative findings using patients with chronic schizophrenia and controls (Tayoshi et al., 2010). On the other hand, Goto et al. (2009) recruited patients with first-episode schizophrenia and found reduced GABA levels relative to controls (Goto et al., 2009). Furthermore, de la Fuente-Sandoval et al. (2018) recruited antipsychotic-naive first-episode psychosis patients and measured their GABA levels before and after antipsychotic treatment (de la Fuente-Sandoval et al., 2018). They found that antipsychotic-naive first-episode psychosis patients showed higher GABAergic neurometabolite levels relative to controls at baseline (i.e., before antipsychotic treatment), but such differences disappeared after 4 weeks of antipsychotic treatment. Taken together, these previous findings suggest that altered GABA levels may be found in psychosis patients early in the course of illness, but may normalize as the illness progresses or after treatment with antipsychotic medications. Importantly, studies in antipsychotic-naive individuals at risk of developing psychosis also found no significant difference when comparing their GABA levels with healthy controls (Da Silva et al., 2019; Modinos et al., 2018). Similarly, we also recruited antipsychotic-naive participants in this study. Our negative findings may suggest that the striatal GABAergic system is more likely to be affected at the onset of frank psychosis, rather than in those at risk of developing psychosis.

As the major inhibitory neurotransmitter system in the central nervous system, GABAergic neurons are widely distributed in the whole brain. Despite our negative findings, future studies investigating GABA levels in individuals with high levels of schizotypy should include more ROIs for MRS scanning. For example, previous studies have consistently shown reduced GABA levels in the occipital cortex (Kelemen et al., 2013; Thakkar et al., 2017; Yoon et al., 2020) and the prefrontal cortex (Marenco et al., 2016; Marsman et al., 2014) in schizophrenia patients compared with controls. It is possible that similar alterations in GABA levels in these brain regions may also be found in individuals with high levels of schizotypy.

Interestingly, we observed a significantly negative relationship between GABA+/NAA levels and scores on the Sensory Integration subscale of the CNI in individuals with low levels of negative schizotypy, indicating that higher GABA+/NAA levels may correlate with better sensory integration ability. Notably, Balz, Keil, et al. (2016a) conducted a study in the healthy population and found that GABA level was robustly correlated with sound-induced flash illusion rate (an indicator of multisensory integration ability) (Balz, Roa Romero, et al., 2016b). The findings from Balz, Roa Romero, et al. (2016b) and our study support the notion that the GABAergic neurotransmitter system plays a fundamental role in sensory integration in the healthy population. However, we did not find any significant correlation between GABA levels and sensory integration ability in individuals with high levels of negative schizotypy. These findings are inconsistent with evidence from animal models that showed that ketamine-treated rats with impaired sensory integration ability had reduced GABAergic current (Cloke et al., 2016). Regarding research in individuals with schizotypy, Ferri et al. (2017) found that those with high schizotypy were correlated with less efficient audio-tactile and tactile-proprioceptive integration, and the excitation/inhibition (EI) balance indexed by glutamate/GABA ratio was also correlated with such abnormal multisensory integration (Ferri et al., 2017).

This study has several limitations. Multisensory integration is a complex cognitive process involving many different brain regions. GABAergic neurons have extensive innervations throughout the brain. However, this study only measured GABA levels in a single voxel within the striatum. Multi-voxel MRS scanning techniques (Boer et al., 2012), which can acquire MRS data across several brain regions simultaneously, should be used in future studies. Second, we only used a 3T MRS machine. MRS with ultra-high magnetic field could yield a better SNR and higher spectral resolution, and is therefore more suitable to detect subtle alterations of GABA levels in subclinical populations (Puts & Edden, 2012). Third, our sample size was small. Larger samples are warranted in future studies. Lastly, this study only explored the dimension of negative schizotypy. Future studies in this area should include other dimensions of schizotypal traits, such as positive schizotypy.

CONCLUSION

In summary, we found that the higher striatal GABA level was correlated with better sensory integration ability in individuals with low levels of negative schizotypy, but not in individuals with high levels of negative schizotypy. Our findings suggest that the GABAergic neurotransmitter system plays a fundamental role in sensory integration.

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ETHICS STATEMENT

This study was approved by the Ethics Committee of the Institute of Psychology of the Chinese Academy of Sciences. All participants gave written informed consent.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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