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SHORT COMMUNICATION

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In vivo gamma-aminobutyric acid -A/benzodiazepine receptor availability and genetic liability in asymptomatic individuals with high genetic loading of schizophrenia: A [11C]flumazenil positron emission tomography study

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Abstract

Objectives: Whilst reduced signalling and gene expression related to gamma-aminobutyric acid (GABA) play a role in the presumed pathophysiology of schizophrenia, its origin is unclear. Studying asymptomatic individuals with high genetic liability to schizophrenia (AIs) would provide insights. Therefore, this study aimed to investigate the role of genetic liability in GABAergic dysfunction of schizophrenia by exploring *in vivo* GABA-A/benzodiazepine receptor (GABAR) availability in AIs.

Methods: A total of 10 AIs with multiple relatives diagnosed as schizophrenia and 11 healthy controls underwent [11C]flumazenil positron emission tomography and neurocognitive function tests.

Results: There was no significant difference in [11C]flumazenil availability based on the groups. GABAR availability in caudate nuclei had positive correlations with genetic liability of AIs. GABAR availability in caudate nuclei and verbal memory measures of AIs revealed positive correlations. Only the correlation between right caudate and short-term verbal memory survived multiple-comparison correction ($p = 0.030$).

Conclusions: This study, for the first time, reports correlations between the genetic liability of schizophrenia and GABAR availability. Correlations between [11C]flumazenil binding in caudate of individuals with high genetic liability to schizophrenia suggests that the GABAergic dysfunction may arise from shared genetic factors and also that it may be responsible for cognitive impairment of AIs.

KEYWORDS
caudate nucleus, flumazenil, GABA, genetic liability, receptor, schizophrenia

1 | INTRODUCTION

Although relatively little is known about the aetiology of schizophrenia, extensive research has shown that reduced gamma-aminobutyric acid (GABA) signalling plays a substantial role (Lewis, Hashimoto, & Volk, 2005). Specifically, research indicates alteration of GABA receptors in schizophrenia. Postmortem studies showed that GABA or benzodiazepine (BZ) receptors may be up-regulated in response to downregulated GABAergic system (de Jonge, Vinkers, Hulshoff Pol, & Marsman, 2017). Yet, the source of observed GABA receptor alterations is unclear. Given high heritability of schizophrenia, attention was given to asymptomatic individuals with high genetic liability to schizophrenia (AIs) to specifically investigate the role of genetic liability in its pathophysiology. Opportunely, molecular imaging techniques such as positron emission tomography (PET) offer opportunities to assess target functions *in vivo*. The radioligand [11C] flumazenil specifically binds to the BZ allosteric binding site of GABA-A receptors which is responsible for most of the physiologic actions of GABA (Persson et al., 1985).

Up to now, two studies have used a similar radioligand, [18F] fluoro-flumazenil to examine in vivo GABA-A/BZ receptor (GABAR) availability in schizophrenia (Egerton, Modinos, Ferrera, & McGuire, 2017). Frankle et al. reported elevated baseline GABAR availability in the antipsychotics-naïve schizophrenia across the brain regions (Frankle et al., 2015), while Lee et al., 2013 found reduced GABAR availability in multiple cortices in medicated patients with schizophrenia. Interestingly, there has been a study reporting reduced GABAR availability in right caudate nucleus of individuals at clinical high risk for psychosis (CHR; Kang et al., 2014). However, to our best knowledge, there has been no study examining GABAR in AIs who share genetic liability of schizophrenia.

Therefore, in this study, to explore the trait difference and role of genetic liability in GABAR dysregulation in schizophrenia, we aimed to investigate whether *in vivo* GABAR availability is altered and associated with the genetic liability and neurocognitive functions in AIs using [11C]flumazenil PET. We hypothesised that GABAR availability would be elevated in AIs as in schizophrenia and would have negatively correlation with neurocognitive impairments.

2 | METHODS

2.1 | Participants

Ten AIs who have at least one first-degree relative and one or more other first-to third-degree relatives with schizophrenia were recruited from Seoul Youth Clinic (Kwon, Shim, Park, & Jang, 2010). Eleven healthy controls (HCs) were matched for age and sex. Exclulsion criteria were: <15 or >34 years old; intelligence quotient below 70; any history of psychiatric illnesses, substance use disorders or clinically significant medical or neurological disorders.

The study protocol was approved by the Institutional Review Board and all procedures followed recommendations of the Helsinki Declaration. All participants provided written informed consent.

2.2 | Assessments

Psychiatric symptoms in AIs were assessed with Positive and Negative Syndrome Scale (PANSS), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A) and Global Assessment of Functioning (GAF). The genetic liability to schizophrenia of AIs was quantified with the genetic liability score (GLS), a quantitative measure of genetic liability derived from pedigrees of the families as reported by Lawrie et al. (2001).

Intelligence was assessed with Korean Wechsler Adult Intelligence Scale (K-WAIS). Also, California Verbal Learning Test (CVLT), categorical verbal fluency test, Controlled Oral Word Association Test (COWAT), K-WAIS digit span test, Trail Making Test (TMT) and Wisconsin Card Sorting Test (WCST) were conducted to assess neurocognitive functions which are reported to be impaired in relatives of schizophrenia patients (Bora et al., 2014).

2.3 | PET and MRI acquisitions

Each participant underwent an [11C]flumazenil PET scan using a Siemens Biograph mMR PET/MRI scanner. The emission data of PET scans were acquired for 60 min after intravenous bolus injection of the radiotracer (454.7 $\pm$ 46.8 MBq with mean specific activity of 117.50 $\pm$ 59.13 GBq/μmol). Then [11C]flumazenil data were reconstructed into PET images (image matrix: 344 $\times$ 344 $\times$ 127; voxel: 1.04 $\times$ 1.04 $\times$ 2.03 mm3) using filtered back projection algorithm. All routine corrections for physical effects, such as radioactive decay, scatter and attenuation were incorporated in the reconstruction of every dynamic frame.

MR images were acquired simultaneously using (1) ultrashort echo time sequence (repetition time (TR): 11.9 ms; echo time (TE): 0.07 and 2.46 ms; field of view (FOV): 300 $\times$ 300 mm^2; flip angle: 10°; image matrix: 192 $\times$ 192 $\times$ 192; voxel: 1.56 $\times$ 1.56 $\times$ 1.56 mm^3) for PET attenuation correction and (2) 3D magnetization prepared rapid gradient echo sequence (TR: 1670 ms; TE: 1.89 ms; FOV: 250 $\times$ 250 mm^2; flip angle: 9°; image matrix: 256 $\times$ 256 $\times$ 208; voxel: 0.98 $\times$ 0.98 $\times$ 1 mm^3) for delineation of the following predetermined regions-of-

TABLE 1 Demographic and clinical information

	Unaffected relatives of schizophrenia patients ($n = 10$)	Healthy controls ($n = 11$)	Statistics[a]
Age (years)	25.3 (3.5)	25.4 (2.2)	$U = 57.5$, $p = 0.863$
Sex (M/F)	7/3	7/4	$p = 1.000$
Handedness (R/L)	9/1	9/2	$p = 1.000$
Education (years)	14.7 (1.8)	15.6 (0.7)	$U = 34.0$, $p = 0.152$
Positive and negative Syndrome Scale			
Positive	7.4 (0.7)	–	–
Negative	7.8 (1.3)	–	–
General psychopathology	17.9 (2.2)	–	–
Hamilton Depression Rating Scale	2.5 (2.3)	–	–
Hamilton Anxiety Rating Scale	2.8 (2.7)	–	–
Global assessment of functioning	85.5 (7.0)	–	–
Genetic liability score	0.274 (0.223)	–	–

Note: Values are presented as mean (SD).

[a]Mann–Whitney *U*-test used for continuous variables; Fisher's exact test used for categorical variables.

interest (ROIs): thalamus, caudate nucleus, putamen, pallidum and hippocampus.

2.4 | Data analysis

The ratio of specifically bound radioligand to that of non-displaceable radioligand, that is, BP_{ND}, was estimated from each ROI time-activity curve (TAC) using the simplified reference tissue model (SRTM). The reference-tissue input was obtained from the pons. Then, BP_{ND} maps of [11C]flumazenil were generated from the native-space dynamic images using a TLS-based linearization of SRTM (Seo et al., 2015), which is robust to high-level noise in voxel TACs.

3 | RESULTS

3.1 | Between-group comparisons

3.1.1 | Demographic and clinical characteristics

No statistically significant difference was found on demographic variables between AIs and HCs (Table 1). The scores of PANSS, HAM-D, HAM-A and GAF of AIs altogether indicated absence of significant psychiatric symptoms in AIs. The mean genetic liability of AIs quantified with GLS was 0.274 ± 0.223.

3.1.2 | Neurocognitive functions

Ten AIs and 8 HCs, except for 3 HCs who only participated in clinical assessments and PET scans, completed neurocognitive function tests. Intelligence and WAIS digit span test score were significantly lower in AIs compared to HCs (Table 2).

3.1.3 | GABA-A/BZR availability

Multivariate analysis of variance revealed no statistically significant difference based on the groups (F (10,10) $= 0.806$, $p = 0.630$; Wilks' $\Lambda = 0.554$, partial $\eta^2 = 0.446$) although [11C]flumazenil binding potential (BP_{ND}) values tended to be higher in AIs (Figure 1).

3.2 | Correlations between BP_{ND} and clinical characteristics in AIs

3.2.1 | Genetic liability

GABAR BP_{ND} in left and right caudate nuclei showed positive correlations with genetic liability in AIs (Spearman's $\rho = 0.661$, $p = 0.038$ and Spearman's $\rho = 0.697$, $p = 0.025$, respectively; Figure 2), although they did not reach statistical significance after adjusting for false discovery rate (FDR; FDR-adjusted $p = 0.150$ and 0.150, respectively). A trend towards positive correlations between genetic liability and GABAR availability in other ROIs such as left and right putamen and hippocampi was also observed (Table 3).

3.2.2 | Neurocognitive function measures

Consequently, correlations between GABAR BP_{ND} in left and right caudate nuclei neurocognitive functions were analysed and verbal memory had significant positive correlations (Spearman's $\rho = 0.755$

TABLE 2 Summary of neurocognitive function measures by groups

	Unaffected relatives of schizophrenia patients ($n = 10$)	Healthy controls ($n = 8$)	Statistics
IQ	110.6 (10.0)	127.0 (9.5)	$U = 10.0$, $p = 0.006$[a]
WAIS digit span test	12.4 (1.5)	14.5 (1.9)	$U = 13.0$, $p = 0.016$[a]
CVLT short	12.0 (2.8)	13.6 (1.2)	$U = 26.5$, $p = 0.237$
CVLT long	12.6 (2.4)	14.4 (1.2)	$U = 20.0$, $p = 0.083$
Category fluency	37.7 (6.4)	41.6 (3.9)	$U = 23.5$, $p = 0.146$
COWAT letter fluency	42.4 (8.8)	46.3 (11.9)	$U = 32.5$, $p = 0.515$
TMT A	24.4 (7.6)	24.1 (11.2)	$U = 44.5$, $p = 0.696$
TMT B	65.9 (30.8)	56.8 (14.9)	$U = 45.0$, $p = 0.696$
WCST perseverative errors	8.6 (3.2)	10.4 (4.8)	$U = 32.5$, $p = 0.515$
WCST categories completed	5.8 (0.6)	5.8 (0.7)	$U = 41.0$, $p = 1.000$

Note: Values are presented as mean (SD).

Abbreviations: CVLT, California Verbal Learning Test; COWAT, Controlled Oral Word Association Test; IQ, Intelligence Quotient; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

[a]This p value is statistically significant.

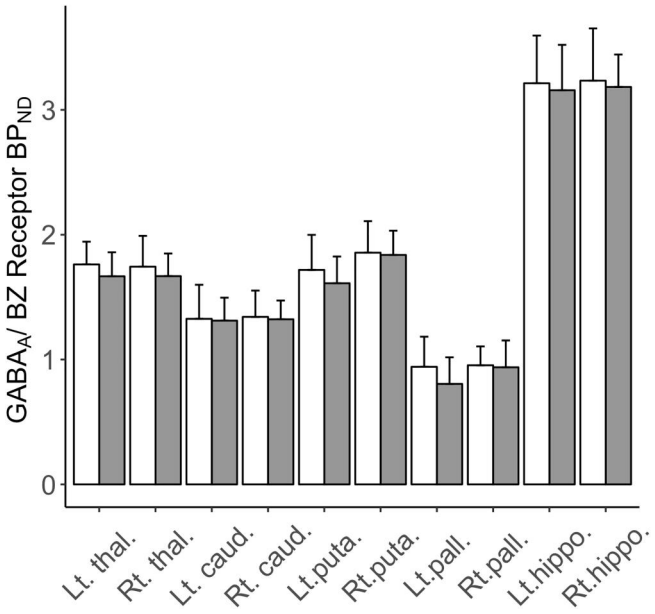

FIGURE 1 Mean and SD of gamma-aminobutyric acid (GABA)-A/benzodiazepine (BZ) receptor binding potential (BP_{ND}) in asymptomatic relatives of schizophrenia patients (white box) and healthy controls (grey box) in regions of interest (caud, caudate nucleus; hippo, hippocampus; puta, putamen; pall, pallidum; thal, thalamus)

and 0.086, $p = 0.007$ and 0.003 for CVLT immediate free recall score (Figure 3); and Spearman's $\rho = 0.605$, $p = 0.049$ and Spearman's $\rho = 0.693$, $p = 0.018$ with CVLT delayed free recall score, respectively). Correlations between the GABA-A/BZ receptor BPND in left and right caudate nucleus and the scores of COWAT, Digit Span test, TMT and WCST were not significantly significant. When adjusted for FDR across the tests, the correlation of right caudate remained statistically significant (FDR-adjusted $p = 0.030$).

4 | DISCUSSION

The main findings of this study are (1) comparable GABAR availability in AIs to HCs and (2) positive correlations of GABAR availability with genetic liability to schizophrenia and with neurocognitive functions in AIs.

To our knowledge, this is the first report on correlations of GABAR availability with the genetic liability to schizophrenia and with neurocognitive functions. In particular, the result shows GABAR alteration only in caudate: GABAergic neurons comprise up to 95% of all neurons in striatum and regulate its activity (Tepper, Tecuapetla, Koos, & Ibanez-Sandoval, 2010). Structural imaging studies also showed caudate volume reduction and GABAergic neuronal loss especially in antipsychotics-naïve schizophrenia (Keshavan, Rosenberg, Sweeney, & Pettegrew, 1998). Notably, dopamine synthesis capacity in striatum was also increased in drug-naïve schizophrenia (McCutcheon, Beck, Jauhar, & Howes, 2018) and in their twin siblings (Stokes et al., 2013).

In schizophrenia, increased GABAR availability was argued to be a compensatory response for a deficit in GABAergic transmission (Frankle et al., 2015), and our finding of positive correlations between GABAR availability and the genetic liability, although not significant after FDR corrections, implicates that the same might be the case for AIs, too. However, interestingly, a reduction in GABAR availability in caudate of CHRs was reported (Kang et al., 2014). These contrasting findings in CHR were replicated in previous studies using magnetic resonance spectroscopy: reduced striatal

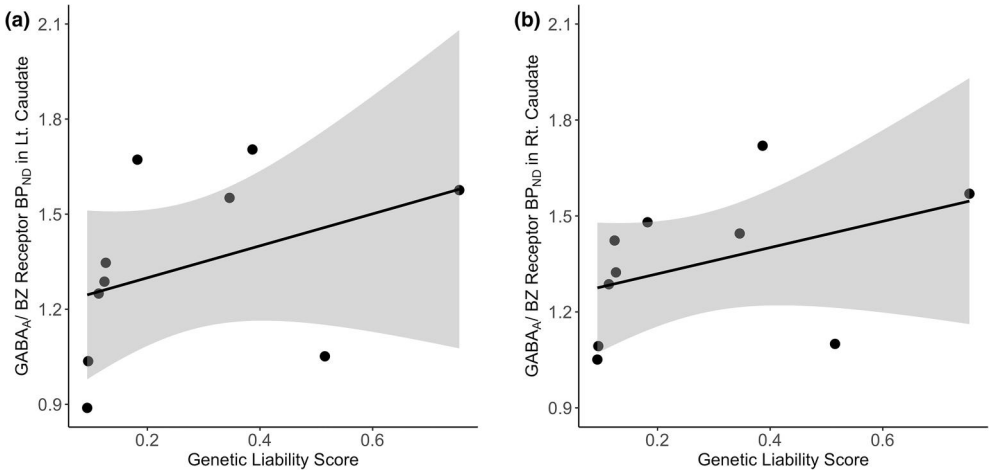

FIGURE 2 Correlations between genetic liability score and gamma-aminobutyric acid (GABA)-A/benzodiazepine (BZ) receptor binding potential (BP_{ND}) in asymptomatic relatives of schizophrenia patients. (a) Left caudate nucleus (Spearman's $\rho = 0.661$, $p = 0.038$). (b) Right caudate nucleus (Spearman's $\rho = 0.697$, $p = 0.025$)

TABLE 3 Correlations between genetic liability score and GABA-A/benzodiazepine receptor BP_{ND} in unaffected relatives of schizophrenia patients

	Spearman's ρ	p value	FDR-adjusted p value
Left thalamus	0.273	0.446	0.584
Right thalamus	0.200	0.580	0.644
Left caudate	0.661	0.038	0.150
Right caudate	0.697	0.025	0.150
Left putamen	0.624	0.054	0.150
Right putamen	0.455	0.187	0.312
Left pallidum	0.152	0.676	0.676
Right pallidum	0.261	0.467	0.584
Left hippocampus	0.612	0.060	0.150
Right hippocampus	0.527	0.117	0.234

Abbreviations: BP_{ND}, binding potential; FDR, false discovery rate; GABA, gamma-aminobutyric acid.

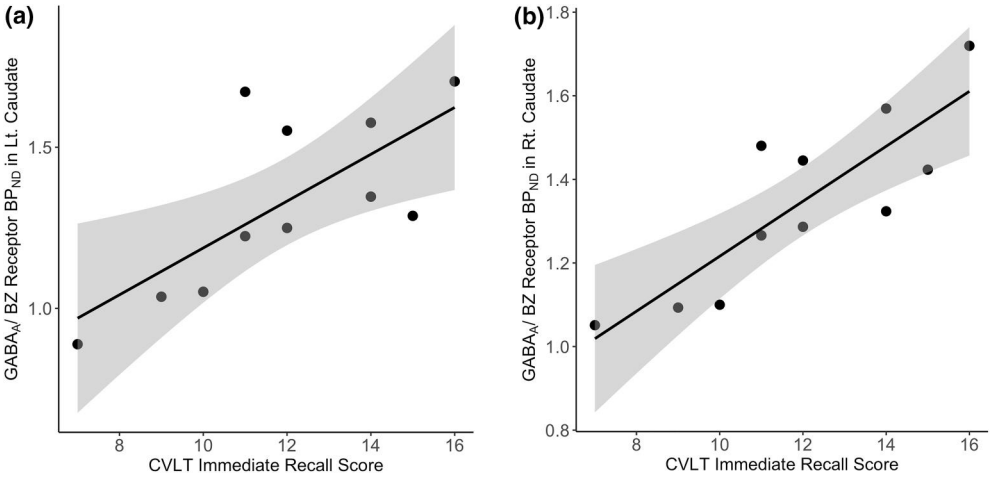

FIGURE 3 Correlations between immediate recall score of California Verbal Learning Test (CVLT) and gamma-aminobutyric acid (GABA)-A/benzodiazepine (BZ) receptor binding potential (BP_{ND}) in asymptomatic relatives of schizophrenia patients. (a) Left caudate nucleus (Spearman's $\rho = 0.755$, $p = 0.007$). (b) Right caudate nucleus (Spearman's $\rho = 0.806$, $p = 0.003$)

GABA concentration in schizophrenia and AIs (Thakkar et al., 2017), and increased in CHR (de la Fuente-Sandoval et al., 2015). This implicates a possibility of compensated GABAergic dysregulation in AIs and that its decompensation in CHR might lead to the emergence of attenuated psychotic symptoms and eventually psychotic conversion.

While Frankle et al. reported negative correlations between GABAR binding and visual memory in antipsychotics-naïve schizophrenia (Frankle et al., 2015), we found an opposite correlation with verbal memory. One possible explanation is that, in AIs, compensatory increase in GABAR availability recomposed cognitive impairments. This would also be supported by previous studies which showed compensatory increase in task-elicited brain activities in AIs (Choi et al., 2012).

The major limitation of this study is limited sample size. Trends towards positive correlations between GABAR availability and genetic liability were observed across regions such as caudate, hippocampi and putamen: However, most of them did not reach statistical significance after correction for multiple comparisons. Further study with larger samples is needed to validate these findings. Notwithstanding modest sample size, this study comes with several strengths. AIs were free from common confounding variables, which allowed relatively unbiased investigation of the genetic contribution. Also, using [11C]flumazenil radioligand enabled precise and specific measurement of *in vivo* GABAR availability.

In summary, our findings of correlations between [11C]flumazenil binding in caudate of individuals with high genetic liability to schizophrenia suggests that the GABAergic dysfunction might arise from shared genetic factors and also that it may be responsible for cognitive impairment in the relatives of patients with schizophrenia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are available upon request.

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