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Positron Emission Tomography Assessments of Phosphodiesterase 10A in Patients With Schizophrenia

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***Background and hypothesis*: Phosphodiesterase 10A (PDE10A) is a highly expressed enzyme in the basal ganglia, where cortical glutamatergic and midbrain dopaminergic inputs are integrated. Therapeutic PDE10A inhibition effects on schizophrenia have been reported previously, but the status of this molecule in the living patients with schizophrenia remains elusive. Therefore, this study aimed to investigate the central PDE10A status in patients with schizophrenia and examine its relationship with psychopathology, cognition, and corticostriatal glutamate levels. *Study design*: This study included 27 patients with schizophrenia, with 5 antipsychotic-free cases, and 27 healthy controls. Positron emission tomography with [^{18}F]MNI-659, a specific PDE10A radioligand, was employed to quantify PDE10A availability by measuring non-displaceable binding potential (BP_{ND}) of the ligand in the limbic, executive, and sensorimotor striatal functional subregions, and in the pallidum. BP_{ND} estimates were compared between patients and controls while controlling for age and gender. BP_{ND} correlations were examined with behavioral and clinical measures, along with regional glutamate levels quantified by the magnetic resonance spectroscopy. *Study results*: Multivariate analysis of covariance demonstrated a significant main effect of diagnosis on BP_{ND} ($p = .03$). A posthoc test showed a trend-level higher sensorimotor striatal BP_{ND} in patients, although it did not survive multiple comparison corrections. BP_{ND} in controls in this subregion was significantly and negatively correlated with the Tower of London scores, a cognitive subtest. Striatal or dorsolateral prefrontal glutamate levels did not correlate significantly with BP_{ND} in either group. *Conclusions*: The results suggest altered striatal PDE10A availability and associated local neural dysfunctions in patients with schizophrenia.**

Key words: PET/MRS/PDE10A/striatum/cognition/glutamate

Introduction

Schizophrenia is a severe psychiatric disorder characterized by auditory hallucination, delusion, and impaired thought, affect, and cognition. Dopamine dysregulation is implicated in its pathophysiology, and positron emission tomography (PET) studies have demonstrated altered dopamine function in brain regions centered on the dorsal striatum in patients with schizophrenia.[1] Dopamine D_2 receptor antagonists have been widely used for the treatment of schizophrenia. However, their effects are found to be mostly limited to positive symptoms, including hallucination and delusion. As such, diverse symptom treatment in schizophrenia by targeting other brain molecules is a challenge that has yet to be realized.

One candidate target molecule for novel schizophrenia treatment is phosphodiesterase 10A (PDE10A), which is known to play an important role in intracellular signaling pathway regulation.[2] PDE10A is highly expressed in medium spiny neurons (MSNs) of the basal ganglia and hydrolyzes both cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP),

with higher cAMP affinity.[2,3] MSNs are divided into populations that mediate the "direct" output pathway that expresses dopamine D_1 receptors and the "indirect" output pathway that expresses D_2 receptors. Thereby, MSNs may be involved in behavioral responses by integrating cortical glutamatergic and midbrain dopaminergic inputs.[4,5] PDE10A inhibition activates cAMP/PKA signaling, thereby reinforcing dopamine D_1 receptor signaling in the direct pathway and provokes simultaneous adenosine A_{2A} receptor signaling potentiation and dopamine D_2 receptor signaling inhibition in the indirect pathway.[5]

Previous preclinical studies have suggested that PDE10A inhibition exerts potential therapeutic effects on schizophrenia by modulating dopaminergic, as well as glutamatergic, signaling.[6] Indeed, pharmacological PDE10A inhibition has been shown to reduce conditioned avoidance responses in normal mice and rats and to alleviate prepulse inhibition deficits of the acoustic startle response in rats treated with an N-methyl-D-aspartate antagonist.[6,7] Furthermore, enhanced social interactions have been demonstrated in PDE10A2-deficient mice.[8] These nonclinical findings suggest that PDE10A inhibitors may offer symptomatic and functional improvements in patients with schizophrenia, considering that the amount and activity of PDE10A in these subjects could be altered as a neuromolecular basis of the disease. Accordingly, how these nonclinical findings could be applied to patients needs to be tested in a clinical setting. The benefits of PDE10A inhibitions and possible PDE10A abnormality contributions to symptoms in schizophrenia could be linked to modulation of the midbrain-striatal dopamine and corticostriatal glutamate systems by this enzyme based on previous findings of the dopamine–glutamate interactions within the circuit.[9–11] Therefore, investigating the PDE10A status in the living brains of schizophrenia patients would lead to a better understanding of the schizophrenia pathophysiology and improved disease treatments, although the PET radioligand availability may not directly reflect the enzymatic activity of its target molecule.

To date, several PET ligands for PDE10A have been developed and applied to the *in vivo* visualization of this molecule in humans,[12] including [^{11}C]IMA107, [^{11}C]Lu AE92686, and [^{18}F]MNI-659.[13] To the best of our knowledge, only two research groups have reported PDE10A availability in patients with schizophrenia compared to healthy subjects using these PET ligands. These results were deemed inconsistent,[14,15] as one group reported no significant differences in [^{11}C]IMA107 binding between patients and controls,[14] while the other group showed decreased [^{11}C]Lu AE92686 binding in patients,[15] and both were not in line with the above-mentioned nonclinical findings. However, drawing a decisive conclusion regarding this issue is challenging due to the small number of PDE10A PET studies of schizophrenia. In addition, anatomical (caudate, putamen, and nucleus accumbens) rather than functional subdivisions of the striatum were used for PDE10A availability quantification in those studies. Striatal dopamine dysfunction in schizophrenia has been reported as a characteristic of the dorsal parts of the functional striatal subregions[1]; therefore, the use of a striatal atlas based on its functional subdivisions[16–18] may provide more relevant PDE10A information on the aberrant dopaminergic signaling in schizophrenia.

In this study, we aimed to investigate the central PDE10A status in patients with schizophrenia by PET with [^{18}F]MNI-659. [^{18}F]MNI-659 has been utilized for studies of healthy subjects and patients with the neurodegenerative diseases[19] and provides a stable PDE10A availability measure in human brains. Based on the aforementioned nonclinical evidence, we hypothesized higher PDE10A availability within the dorsal striatal subregions in patients with schizophrenia than in controls. In addition, the association of PDE10A radioligand binding with clinical symptoms and cognitive functions and with glutamate (Glu) levels in the striatum and dorsolateral prefrontal cortex (DLPFC) was also examined by magnetic resonance spectroscopy (MRS). DLPFC was selected in addition to the striatum, because an association between DLPFC Glu levels and striatal dopamine has been documented in healthy subjects,[9] and alterations within the DLPFC circuitry were thought to be involved in the pathophysiology of schizophrenia.[20]

Methods

Participants

This study included 27 patients with schizophrenia, including 5 antipsychotic-free patients, from our affiliated hospitals and clinics. All the patients fulfilled the diagnostic criteria for schizophrenia based on the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). None of the patients were comorbid with other neuropsychiatric disorders or had a history of substance abuse. in addition, 27 healthy controls, who were matched to the patient group with respect to age and gender, were recruited by the National Institutes for Quantum Science and Technology, Chiba, Japan, for study participation. They were also evaluated with the Structural Clinical Interview for DSM-IV. None of the control participants had a history of psychiatric disease, substance abuse, or any first-degree relatives with a history of psychotic episodes. All patients and controls were physically healthy at the time of scanning. None had a history of neurological injury or disease or severe medical diseases that could affect brain function.

This study was approved by the Radiation Drug Safety Committee and the Institutional Review Board of the National Institutes for Quantum Science and Technology, Japan; moreover, this study was conducted in accordance with the Code of Ethics of the World

Medical Association. After a complete study description, written informed consent was obtained from all the participants.

Behavioral Measures

The cognitive abilities of all participants were assessed using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS),[21,22] which includes the following six subtests: Verbal Memory, Digit Sequencing, Token Motor, Verbal Fluency, Symbol Coding, and Tower of London. For each subtest, the *z*-score was calculated based on the published healthy control mean and standard deviation data[22] and was used in our analysis.

The psychopathology of patients was assessed using the Positive and Negative Syndrome Scale (PANSS).[23]

Supplementary methods and supplementary table S1 present detailed information on behavioral and clinical assessments and antipsychotic patient treatments, respectively.

Imaging Acquisition Procedures

Radiosynthesis of [^{18}F]MNI-659 was conducted as described elsewhere.[24] After intravenous rapid bolus [^{18}F]MNI-659 injection, three-dimensional dynamic images were acquired on a PET camera for 90 min with 29 frames of increasing duration from 30 s to 5 min (30 s × 6, 1 min × 4, 2 min × 4, and 5 min × 15). All PET scans were conducted using a Biograph mCT flow system (Siemens Healthcare, Erlangen, Germany), which provides 109 sections with an axial field of view (FOV) of 21.8 cm. Images were reconstructed using a filtered back-projection algorithm with a Hanning filter (4.0 mm full-width at half-maximum). All the PET images were corrected for attenuation based on the computed tomography images, randoms using the delayed coincidence counting method, and scatter using the single-scatter simulation method. A head fixation device was used to minimize the subject's head movement during the PET measurements.

Structural T1-weighted images were acquired with a 3-T MR imaging (MRI) scanner (MAGNETOM Verio, Siemens, Germany) with a 32-channel receiving head coil to obtain an MRI. Three-dimensional (3D) volumetric acquisition of a T1-weighted gradient-echo sequence produced a gapless series of thin sagittal sections (echo time/repetition time [TE/TR]: 1.95/2300 ms; TI: 900 ms; flip angle: 9°; FOV: 250 mm; acquisition matrix: 256 × 256; voxel size: 1 × 1 × 1 mm^3). T1-weighted MRI was obtained from an affiliated hospital for one patient due to technical reasons, with a 1.5-T Signa system (General Electric, Milwaukee, WI) and with the following parameters: 124 contiguous axial slices; 3D spoiled Grass sequence; slice thickness: 1.5 mm; TE: 9 ms; TR: 22 ms; flip angle: 30°; matrix: 256 × 192; FOV 25 × 25 cm.

Data Processing

Motion-corrected PET images were co-registered to the corresponding individual T1-weighted MR images using PMOD® software ver. 3.8 (PMOD Technologies Ltd., Zurich, Switzerland). Volumetric segmentation was performed with FreeSurfer tools (version 6.0.0; https://surfer.nmr.mgh.harvard.edu/fswiki) for each T1-weighted image.

Region of Interest (ROI) Definition and PET Quantification

The cerebellar cortex and pallidum ROIs were defined in each individual's MR space by a subcortical atlas implemented in FreeSurfer for ROI definition in our PET analysis.[25] A connectivity-based probabilistic atlas[17] defined in a standard anatomic orientation (MNI standard space; Montreal Neurological Institute, Montreal, QC, Canada) was used for striatum ROIs. The limbic, executive, and sensorimotor subregions of the striatum in the atlas were transformed into individual MR spaces with transformation matrixes calculated using Statistical Parametric Mapping software (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) and the CAT12 toolbox (https://neuro-jena.github.io/cat/), and then FreeSurfer's anatomical segmentation was used to exclude voxels that were outside the striatum.

The PDE10A availabilities in these three striatal subregions and the pallidum were quantified as binding potentials relative to non-displaceable tissue (BP_{ND}) of [^{18}F]MNI-659. BP_{ND} was calculated for each target ROI with a three-parameter simplified reference tissue model[26] using the cerebellar cortex as reference, as in previous studies with [^{18}F]MNI-659 PET.[13] PET analyses were performed using PMOD® software.

MRS Acquisition

In 24 patients and 17 controls, MRS scans were conducted using a short TE spin-echo full-intensity-acquired localized single voxel spectroscopy (SPECIAL) sequence[27] in the same session following the T1-weighted image acquisition with the 3-T MRI scanner with the following parameters: TE: 8.5 ms, TR: 3000 ms, and 128 averages. The volumes of interest (VOIs) were localized at the left striatum (20 × 20 × 20 mm^3) and the left DLPFC (30 × 15 × 20 mm^3). After performing 3D Shim (syngo MR version for B17, Siemens, Erlangen, Germany), manual shimming was performed for the linewidth of the water spectrum in magnitude mode to become smaller than 20 Hz.

MRS Quantification

A weighted combination of receiver channels was then processed before signal averaging and data analysis using the FID-A toolkit running on MATLAB R2019a.

Motion-corrupted average removal, frequency and phase drift correction spectral registration, and subspectra alignment before subtraction were performed.

We analyzed MRS data by LCModel software (ver. 6.3-1L, Stephen Provencher Inc., Oakville, Ontario, Canada) for a linear combination of model spectra provided in a basis set. This current study assessed the Glu level. Tissue composition inside the VOIs was calculated based on the T1-weighted image segmentation using Gannet 3.0.[28] Water concentrations were calculated based on the volume fractions of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF), assuming their water concentrations as 35,880 mM, 43,300 mM, and 55,556 mM, respectively. Metabolite concentrations (μmol/g) were then divided by the WM and GM fractions to correct for CSF inside the VOI.

For details of MRS quantification including information concerning metabolites other than Glu, see supplementary materials.

Statistical Analysis

Group Comparisons as Regards Behavioral Measures and Glu Levels. Independent sample *t*-tests were applied to examine differences in behavioral measures, as well as in the striatal and DLPFC Glu levels, between the patient and control groups. The statistical significance threshold was defined as $p < .05$ (two-tailed).

Group Comparisons of [^{18}F]MNI-659 BP_{ND}. Multiple analysis of covariance (MANCOVA) was performed to examine differences in [^{18}F]MNI-659 BP_{ND} values between the groups. Dependent variables are [^{18}F]MNI-659 BP_{ND} values in the four ROIs (limbic, executive, and sensorimotor subregions of the striatum, and the pallidum). A fixed factor was the diagnosis (patients = 1, controls = 0). Nuisance covariates were defined as age and gender because they might potentially influence the PDE10A status in the brain.[29] A posthoc analysis was conducted to investigate the diagnostic effects on BP_{ND} in each ROI in case of a significant effect of diagnosis on the BP_{ND} values. The statistical significance threshold was defined as $p < .05$.

Correlational Analyses. First, we performed correlational analyses between BP_{ND} values and *z*-scores of BACS subtests in each group and between BP_{ND} values and clinical variables in patients (positive, negative, and general psychopathology subscale scores of PANSS, onset of illness, and amount of antipsychotic medication intake calculated by daily doses of chlorpromazine equivalent). Statistical thresholds were set at $p < .05$ (two-tailed) with Bonferroni correction for the four PET ROIs (three striatal subregions and pallidum: $p < .05/4$).

Next, correlational analyses were performed in patients and controls, respectively, between BP_{ND} values in each ROI and Glu levels in the striatal and DLPFC VOIs. Statistical thresholds were set at $p < .05$ (two-tailed) with the Bonferroni correction for the four PET ROIs ($p < .05/4$).

A partial correlational analysis was performed while controlling for age, gender, smoking status, or medication intake (in the patient group only), with a statistical significance of $p < .05$, in case of a significant correlation in these analyses.

All the statistical analyses were conducted using Statistical Package for the Social Sciences version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic Data and Group Comparisons of Behavioral Measures and Glu Levels

Participant demographics are shown in table 1. Patients and controls did not significantly differ in terms of age, gender, predicted intelligence quotient, or proportion of smokers. Patients showed significantly lower scores for all six BACS subtests compared to controls. The proportion of participants who underwent PET and MRI scans on the same day was significantly smaller in the patients than in the controls. Glu levels in either the striatum or DLPFC were not significantly different between the groups, and this finding was retained in the analysis for subjects who underwent PET and MRS scans on the same day.

Group Comparisons of [^{18}F]MNI-659 BP_{ND}

Group comparison results are shown in table 2 and figure 1. MANCOVA demonstrated a significant main effect of diagnosis on [^{18}F]MNI-659 BP_{ND} ($F_{4, 47} = 2.94$, $p = .03$). The posthoc analysis via univariate test showed a trend-level higher BP_{ND} value in the sensorimotor subregion of the striatum in patients ($F_{1, 50} = 6.02$, $p = .02$); however, it did not survive correction for multiple comparisons of the four ROIs.

To investigate BP_{ND} values in antipsychotic-free patients, we additionally performed the same analysis by including five antipsychotic-free patients and 27 controls, while excluding 22 patients who were taking antipsychotics. In this analysis, main effect of diagnosis did not reach statistical significance ($F_{4, 25} = 1.65$, $p = .19$), possibly due to the small sample size of the antipsychotic-free group.

Correlations Between [^{18}F]MNI-659 BP_{ND} and Behavioral Measures

A significant negative correlation was found between [^{18}F]MNI-659 BP_{ND} in the sensorimotor subregion of the striatum and BACS Tower of London task scores in controls (Pearson's $r = -0.58$, $p = .001$). We performed partial correlational analyses between BP_{ND} in

Table 1. Characteristics of Subjects Included in This Study

	Patients			Controls			Statistics	
	N	Mean	SD	*N*	Mean	SD	*t*/chi-square	*p*
Age (years)	27	41.8	9.5	27	42.3	8.0	−0.19	0.85
Gender (male/female)	27	15/12		27	14/13		0.07[a]	0.78
Predicted IQ[b]	27	103.1	11.0	27	107.4	7.8	−1.65	0.10
Smoking (yes/no)	27	8/19		27	6/21		0.39[a]	0.53
Onset of illness	27	27.0	7.9					
Duration of illness	27	14.8	8.1					
PANSS positive	27	12.0	4.7					
PANSS negative	27	14.7	5.7					
PANSS general	27	25.4	7.5					
Antipsychotic medication[c]	27	564.1	457.9					
BACS-J (*z*-score)								
Verbal memory	27	−1.51	1.03	27	−0.62	0.90	−3.39	0.001[d]
Digit sequencing	27	−0.85	1.21	27	0.10	0.85	−3.31	0.002[d]
Token motor	27	−1.23	1.08	27	−0.30	0.69	−3.75	<0.001[d]
Verbal fluency	27	−1.33	0.87	27	−0.65	1.00	−2.66	0.01[d]
Symbol coding	27	−0.70	1.01	27	0.78	0.96	−5.52	<0.001[d]
Tower of London	27	−0.28	0.83	27	0.43	0.38	−4.03	<0.001[d]
Glu levels (μmol/g)								
Left striatum	24	6.60	0.57	17	6.76	0.84	−0.72	0.48
Left DLPFC	24	7.51	1.02	17	7.12	0.68	1.39	0.17
Injected radioactivity (MBq)	27	190.7	5.2	27	190.5	5.2	0.13	0.89
Molar activity (GBq/mmol)	27	333.9	200.2	27	262.9	100.5	1.65	0.11
Subjects who underwent PET and MRI on the same day/different days[e]	27	17/10		27	24/3		4.96[a]	0.03[d]
(MRS, PET, and MRI on the same day/different days)	(24)	(14/10)		(17)	(14/3)			

Note: BACS, Brief Assessment of Cognition in Schizophrenia; DLPFC, dorsolateral prefrontal cortex; Glu, glutamate; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation, PET, positron emission tomography; MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging.
[a]Chi-square.
[b]Predicted IQ was measured using a Japanese version of the National Adult Reading Test (JART).
[c]Expressed as chlorpromazine equivalent daily doses. For calculation of chlorpromazine equivalence for each antipsychotic, see supplementary methods. In total, 22 patients had been taking antipsychotics regularly without change in the type or dosage for at least 3 months prior to their participation. Overall, 5 patients were antipsychotic-free, with an average duration of 2.3 years (range, 0.5–5 years).
[d]$p < .05$.
[e]The scan intervals were 12.0 ± 15.8 days (mean ± sd) for subjects who underwent PET and MRI scans on different days.

Table 2. Comparisons of [^{18}F]MNI-659 BP_{ND} Between Patient and Control Groups

	Patient Group (n = 27)		Control Group (n = 27)		Multivariate Tests (Effect of Diagnosis)		Between-Subject Effects	
BP_{ND}	Mean	SD	Mean	SD	F (df = 4, 47)	p	F (df = 1, 50)	p
Regions					2.94	0.03[a]		
Limbic striatum	2.13	0.43	2.20	0.39			0.48	0.49
Executive striatum	3.34	0.56	3.26	0.41			0.57	0.45
Sensorimotor striatum	4.69	0.73	4.33	0.60			6.02	0.02[ab]
Pallidum	3.46	0.57	3.39	0.50			0.24	0.62

Note: df, degree of freedom.
[a]$p < .05$.
[b]The p-value did not survive for correction of multiple comparisons for the 4 regions.

this region and BACS Tower of London task scores in controls while setting age, gender, or smoking status as a control variable. The correlation remained significant after controlling for age (p = .005), gender (p = .003), or smoking status (p = .001). In contrast, the patient group did not show a significant correlation between [^{18}F]MNI-659 BP_{ND} in this subregion and Tower of London scores. Scatter plots of BP_{ND} in this subregion against BACS

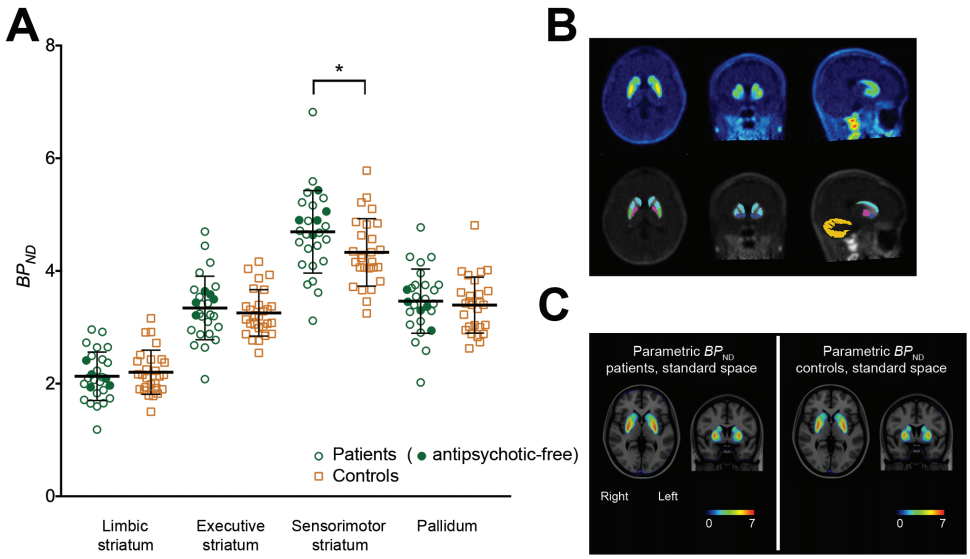

Fig. 1. Group comparisons of [^{18}F]MNI-659 BP_{ND}. (A) Group comparison results of [^{18}F]MNI-659 BP_{ND} in each region of interest (ROI). Error bars represent standard deviation. Multiple analysis of covariance (MANCOVA) demonstrated a significant main effect of diagnosis on [^{18}F]MNI-659 BP_{ND} (p = .03). (B) An example of ROIs placed on a summation (0–90 min after injection) of PET image in a single subject. (C) Averaged parametric [^{18}F]MNI-659 BP_{ND} images created for illustrative purposes. The parametric BP_{ND} images were normalized with SPM12 software using individual MR images and were separately averaged across patients and controls. Images are shown along with an MR template in the standard space. Patients: n = 27; controls: n = 27. Filled circles indicate patients who are antipsychotic-free. *p < .05 (posthoc analysis by univariate test). The p-value did not survive for correction of multiple comparisons for the 4 regions. *Note*: BP_{ND}, non-displaceable binding potential.

Tower of London subtest scores in each group are shown in figure 2.

No other significant correlations between BP_{ND}s and BACS subtest scores were noted in either group. There were also no significant correlations between BP_{ND}s and PANSS subscale scores, onset of illness, or daily doses of chlorpromazine equivalent in the patient group (supplementary table S2).

Correlations Between [^{18}F]MNI-659 BP_{ND} and Glu Levels

No significant correlations were found between [^{18}F]MNI-659 BP_{ND} in each ROI and Glu levels in the striatum or DLPFC of either group.

The data obtained from selected subjects who underwent PET and MRS on the same day were also analyzed because of possible neurochemical status alterations in the interval between PET and MRS measurements. In these analyses, no significant correlations were found between [^{18}F]MNI-659 BP_{ND} in any of the ROIs and Glu levels in either group after corrections for multiple comparisons.

Results are shown in supplementary table S3 and supplementary figure S1.

Discussion

The current PET investigation revealed significantly altered [^{18}F]MNI-659 BP_{ND} values in patients with schizophrenia compared with the healthy controls, and there was a trend-level higher BP_{ND} value in the sensorimotor subregion of the striatum in patients. It is also noteworthy that [^{18}F]MNI-659 BP_{ND} in this subregion was significantly and negatively correlated with the BACS Tower of London subtest scores in controls but not in patients.

Our PDE10A ligand binding between-group comparisons indicate that PDE10A expression, density, or activity

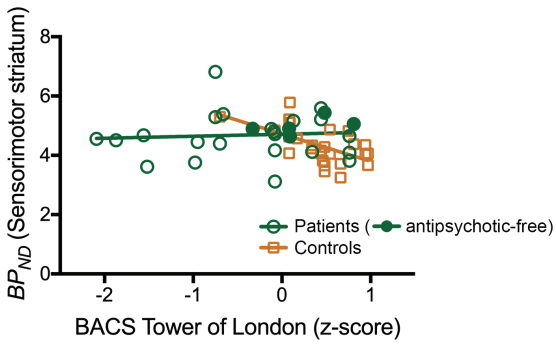

Fig. 2. Scatter plots of [^{18}F]MNI-659 BP_{ND} in the sensorimotor striatal subregion against z-scores of BACS Tower of London subtest in patients and controls. Patients: n = 27; controls: n = 27. Filled circles indicate patients who are antipsychotic-free. *Note*: BP_{ND}, non-displaceable binding potential; BACS, Brief Assessment of Cognition in Schizophrenia. A significant negative correlation was found between the BP_{ND} in this subregion and BACS Tower of London scores in controls only (Pearson's r = −0.58, p = .001).

may be increased in patients with schizophrenia, thereby rationalizing the therapeutic applications of a PDE10A inhibitor to the disease, as suggested by previous animal studies. A rodent study documented that repeated D-amphetamine administration, which has been used to generate animal models for schizophrenia, has increased PDE10A radioligand binding,[30] implying the attribution of potentiated PDE10A availability to augmented dopamine neurotransmission in the etiological disease process. At a clinical level, previous studies showed that patients with schizophrenia exhibited enhanced presynaptic dopamine function within the dorsal striatum[1] and that the conversion from clinical high risk to psychosis is likely to be primarily associated with a progressively increased dopamine synthesis capacity in the sensorimotor striatum.[31] Collectively with these findings and their indications, our results support the view that altered PDE10A availability is implicated in the pathophysiology of schizophrenia in association with increased presynaptic dopamine function. However, caution should be taken regarding the interpretation of our current results, as the PDE10A radioligand availability that we quantified with [^{18}F]MNI-659 PET does not necessarily reflect the enzymatic reaction rate or function of PDE10A.

Our results of group comparisons in PDE10A radioligand binding are not consistent with previous PDE10A PET studies in schizophrenia conducted by two research groups.[14,15] Along with distinct methodologies for the basal ganglia segmentation in PET assays, these differences might be due to small sample sizes and confounding factors. Marques et al. found no significant between-group differences in PDE10A radioligand binding by analyzing 12 patients and 12 controls.[14] Bodén et al. reported lower PDE10A radioligand binding in male patients with schizophrenia, based on PET measurements in 10 patients and 16 controls, and reported significantly higher average age in patients (mean: 39.5 years) than in controls (mean: 24 years).[15] Notably, 7 of the 10 patients in that study were treatment-resistant and were treated with clozapine, whereas there were no such subjects in our present work.

Only in controls, [^{18}F]MNI-659 BP_{ND} in the sensorimotor striatal subregion was negatively correlated with the BACS Tower of London task scores. The role of striatal dopamine function in cognition has been well documented in the literature.[32,33] The Tower of London task is thought to reflect executive function, problem-solving, and planning abilities.[34,35] Our results suggest that PDE10A in the sensorimotor striatum is associated with cognitive performance measured with the Tower of London task in healthy individuals, possibly through its dopamine modulatory function that involves corticostriatal activity. In contrast, the absence of these correlations in our patient group might be attributed to balanced D_1- and D_2-MSN activation dysregulation mediated by PDE10A in schizophrenia, which may contribute to cognitive dysfunction. Moreover, significant correlations were not found between [^{18}F]MNI-659 BP_{ND} and clinical variables, suggesting that the PDE10A status likely reflects trait rather than the disorder status.

The lack of significant group differences in striatal or DLPFC Glu levels in our MRS results is in line with previous MRS studies of patients with chronic schizophrenia.[36,37] As for the results of the correlational analyses, correlations between [^{18}F]MNI-659 BP_{ND} and Glu levels in neither the striatum nor the DLPFC reached statistical significance, even when the analysis was restricted to subjects who underwent PET and MRS scans on the same day. Possible reasons for lacking tight corrections between the striatal PDE10A binding and cortical or striatal Glu include (1) differences in the locations between striatal ROIs in PET based on functional subdivisions and striatal VOI in MRS and (2) differences in the spatial resolution between PET and MRS data in addition to the low statistical power stemming from the small sample size in our MRS analysis of selected subjects. The glutamatergic neurotransmissions and their associations with PDE10A in schizophrenia would also be assessable by PET imaging of group II metabotropic Glu receptors[38–40] along with PDE10A-PET, although dopaminergic and glutamatergic tone fluctuations between two PET scans should be considered.

Several limitations should be considered when interpreting the results of this current study. First, although we analyzed a larger number of controls and patients than in previous PDE10A PET research in schizophrenia,[14,15] expanding the sample size further to draw more conclusive evidence would be deemed desirable. Second, we cannot exclude possible confounding effects of medications on PDE10A. A previous rodent study reported increased PDE10A protein and mRNA expressions following chronic antipsychotic treatment,[41] while another report demonstrated no changes in the expression of this enzyme, along with unaltered PET radioligand binding in a similar rodent model.[42] Our analysis showed no clear differences in PDE10A availability between antipsychotic-free and -treated patients, suggesting an absence of apparent effects of antipsychotic medication on the PDE10A status (figures 1a and 2, S1). However, because of the limited sample size of antipsychotic-free patients in this study, future studies with larger numbers of drug-naïve and drug-free patients will be required to further clarify this issue.

In conclusion, these current findings indicate an altered status of central PDE10A and associated neural network dysfunctions related to cognition in patients with schizophrenia. Additional studies will be needed to further clarify the underlying mechanisms of PDE10A alterations in schizophrenia, including its relation to cognition and midbrain-striatal dopamine and corticostriatal glutamate neurotransmissions.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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