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Alterations of striatal phosphodiesterase 10 A and their association with recurrence rate in bipolar I disorder

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Phosphodiesterase 10 A (PDE10A), a pivotal element of the second messenger signaling downstream of the dopamine receptor stimulation, is conceived to be crucially involved in the mood instability of bipolar I disorder (BD-I) as a primary causal factor or in response to dysregulated dopaminergic tone. We aimed to determine whether striatal PDE10A availability is altered in patients with BD-I and assessed its relationship with the clinical characteristics of BD-I. This case-control study used positron emission tomography (PET) with 2-(2-(3-(4-(2-[18F]fluoroethoxy)phenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-4-isopropoxyisoindoline-1,3-dione ([18F]MNI-659), a radioligand that binds to PDE10A, to examine the alterations of the striatal PDE10A availability in the living brains of individuals with BD-I and their association with the clinical characteristics of BD-I. [18F]MNI-659 PET data were acquired from 25 patients with BD-I and 27 age- and sex-matched healthy controls. Patients with BD-I had significantly lower PDE10A availability than controls in the executive ($F = 8.86$; $P = 0.005$) and sensorimotor ($F = 6.13$; $P = 0.017$) subregions of the striatum. Lower PDE10A availability in the executive subregion was significantly associated with a higher frequency of mood episodes in patients with BD-I ($r = -0.546$; $P = 0.007$). This study provides the first evidence of altered PDE10A availability in patients with BD-I. Lower PDE10A availability in the executive subregion of the striatum is associated with an increased recurrence risk, suggesting that PDE10A may prevent BD-I relapse. Further studies are required to elucidate the role of PDE10A in BD-I pathophysiology and explore its potential as a treatment target.

INTRODUCTION

Bipolar I disorder (BD-I) is characterized by recurrent manic and depressive episodes [1]. BD-I is often associated with cognitive and functional impairments, which are more prevalent in patients with a higher number of manic and depressive episodes during their lifetime [2]. Therefore, the primary aim of BD-I treatment is to prevent the recurrence of manic and depressive episodes [3].

The pathomechanisms underlying the recurrence of mood episodes in BD-I have not been fully elucidated. However, the clinical efficacy of antipsychotics suggests that the dysregulation of dopamine neurotransmission may be associated with recurrent mood episodes in BD-I [4]. Supporting this view, several meta-analyses have reported that atypical antipsychotics significantly reduce the recurrence rate of manic and depressive episodes in patients with BD-I [5]. In addition, dopamine agonists such as levodopa and bromocriptine have been consistently reported to induce manic symptoms [6]. Several animal studies have indicated an association between dopaminergic signaling and mood regulation. A recent study using a mouse model of mania with *Clock*

mutation reported an increased dopaminergic firing rate in the ventral tegmental area of mutant mice [7]. Another optogenetics study using a mouse model of depression showed that dysregulation of the firing patterns of mesolimbic dopamine neurons resulted in social avoidance behaviors associated with depression [8].

Previous BD-I positron emission tomography (PET) studies measuring pre- and postsynaptic components of dopamine neurotransmission have suggested dysregulated dopamine signal transmission. However, consistent results have not been obtained. Lower dopamine transporter availability in the striatum relative to healthy controls (HCs) was reported in a previous PET study of unmedicated patients with BD-I in either the euthymic or depressed phase [9]. Another previous PET study on patients with BD-I and mania also showed decreased dopamine transporter availability in the striatum [10]. No significant differences in striatal dopamine synthesis capacity were demonstrated in a previous PET study in patients with nonpsychotic mania, but elevated striatal dopamine synthesis capacity was shown in another PET study in patients with bipolar psychosis [11, 12].

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Lower dopamine D1 receptor availability in the frontal cortex was reported in a previous PET study in patients with BD-I [13]. Elevated dopamine D2 receptor availability in the caudate was observed in a previous PET study of patients with BD-I bipolar psychosis. However, no significant differences in the dopamine D2 receptor availability were reported in another PET study of patients with nonpsychotic mania [14]. Despite the strong clinical association between the dopaminergic nervous system and BD-I, previous dopamine PET findings lack consistency, presumably due to the lack of information on the dopaminergic tone determined by the balance among these synaptic components. The second messenger signaling downstream of the dopamine receptor stimulation is conceived to be crucially involved in mood instability as a primary causal factor or the response to dysregulated dopaminergic tone [15].

Cyclic adenosine monophosphate (cAMP) is the primary mediator of postsynaptic dopamine signaling [16], and the intracellular signaling cascade mediated by cAMP plays a pivotal role in regulating dopamine signal transmission. Phosphodiesterase 10 A (PDE10A) is the major enzyme responsible for cAMP hydrolysis and is, therefore, the rate-limiting enzyme for intracellular dopamine neurotransmission [17]. A substantial body of evidence indicates an association between BD-I pathophysiology and PDE10A. Single nucleotide polymorphisms within the intron of *PDE10A* are associated with an elevated risk of BD-I by inhibiting the normal function of PDE10A [18]. cAMP-induced phosphorylation is increased in the platelets of patients with BD-I [19]. A mouse model of BD-I suggested that the cAMP/PDE10A pathway is correlated with a state of high or low locomotor activity [20]. Furthermore, *PDE10A* knockout mice display depression-like reduced spontaneous loco-motor activity [21]. However, no previous human PET studies have directly investigated the PDE10A status in BD-I.

We aimed to compare the PDE10A availability in the three striatal subregions (limbic, executive, and sensorimotor) of patients with BD-I and HCs, hypothesizing that the BD-I group would have lower PDE10A availability in the striatal subregions than the control group. PDE10A availability was quantified using 2-(2-(3-(4-(2-[^{18}F]fluoroethoxy)phenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl) ethyl)-4-isopropoxyisoindoline-1,3-dione ([^{18}F]MNI-659) [22]. [^{18}F]MNI-659 is a PET imaging biomarker with promising characteristics for assessing PDE10A, including high specificity, high signal-to-noise ratio, good test-retest reliability, low blood-brain barrier-penetrating radiometabolites, and accurate estimation of striatal binding potentials by a noninvasive method [23]. To elucidate the pathophysiological implications of PDE10A status in BD-I, the correlations between regional [^{18}F]MNI-659 radioligand binding and the clinical features of patients with BD-I were also examined.

MATERIALS AND METHODS
Participants
This case-control study included 25 patients with BD-I and 27 age- and sex-matched HCs. They were recruited from Tokyo and Chiba, Japan, through our affiliated hospitals and clinics. All the patients were outpatients or inpatients aged ≥20 years, of both sexes, who received continuous treatment for >1 year. They met the diagnostic criteria for BD-I at least 1 year before the PET scan based on all available clinical information, including the results of interviews using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) Axis I Disorders [24]. None of the patients had a history of alcohol or substance abuse. The HCs were recruited through advertisements at the National Institutes for Quantum Science and Technology, Chiba, Japan. The HCs were also evaluated using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders. None of the HCs had a history of neuropsychiatric disease or substance abuse or a first-degree relative with a history of psychotic episodes. All the participants were physically healthy at the time of scanning. None of the patients had a history of neurological injury, disease, or severe medical diseases that could affect brain function and received any drugs with the potential to interfere with [^{18}F]MNI-659 binding (e.g., papaverine). The participants also abstained from using any substances/medications with nonselective inhibitory effects on PDE10A (e.g., caffeine or theophylline) for at least 48 h before PET measurement.

The protocol and informed consent forms were approved by the Radiation Drug Safety Committee, Institutional Review Board of the National Institutes for Quantum Science and Technology, Chiba, Japan, and the Research Ethics Board of Keio University, Tokyo, Japan. Written informed consent was obtained from all the participants after receiving a complete description of the study.

PET and MRI acquisition and image analysis
All participants underwent PET using [^{18}F]MNI-659 to quantify PDE10A availability. Radiosynthesis of [^{18}F]MNI-659 was performed as previously described [25]. After an intravenous rapid bolus [^{18}F]MNI-659 injection, dynamic PET was performed for 90 min, as previously described [22]. PET was performed using a Biograph mCT flow system (Siemens Healthcare, Erlangen, Germany), which provided 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 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 head movement during PET measurements.

To determine the regions of interest (ROIs) (SA1), three-dimensional volumetric T1-weighted images (MAGNETOM Verio 3.0 Tesla magnetic resonance scanner [Siemens, Germany], with a 32-channel head coil) were obtained using a magnetization-prepared rapid acquisition with gradient echo sequence (repetition time, 2.3 s; echo time, 1.95 ms; inversion time, 900 ms; flip angle, 9°; FOV, 250 mm; matrix size, 256×256; voxel size, 1×1×1 mm). All images were visually assessed for scanner artifacts and anatomical anomalies. The PDE10A availabilities in the three striatal subregions (limbic, executive, sensorimotor) were quantified as the binding potentials relative to the non-displaceable tissue (BP_{ND}) of [^{18}F]MNI-659 (Fig. 1). BP_{ND} was calculated using the three-parameter simplified reference tissue model (SRTM) method [26] with the cerebellar cortex as the reference tissue, as in previous studies using [^{18}F]MNI-659 [22]. This quantification method has been validated in a previous study which demonstrated excellent correlation between BP_{ND} values determined by SRTM and total distribution volume (V_T) values calculated by kinetic analysis with arterial input function [23]. PET analyses were performed using PMOD 4.1 (PMOD Technologies Ltd., Zurich, Switzerland).

Clinical assessments
The cognitive function of the patients with BD-I and HCs was assessed using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS) consisting of six cognitive domain tasks to assess subtle cognitive changes: (1) verbal learning (verbal memory), (2) working memory (digit sequencing), (3) motor speed (token motor), (4) verbal fluency (verbal fluency), (5) processing speed (symbol coding), and (6) planning (tower of London) [27]. For each subtest of the BACS, we used the scores adjusted for age and sex (z-scores) in our analysis [28]. The test battery was administered in a silent room without distractions. The BACS could not be performed for four patients (one with euthymia and three with mania) because of fatigue.

Board-certified psychiatrists assessed the severity of the psychiatric symptoms of the patients using the 21-item version of the Hamilton Depression Rating Scale [29], Montgomery–Åsberg Depression Rating Scale (MADRS) [30], Young Mania Rating Scale (YMRS) [31], and Positive and Negative Syndrome Scale (PANSS) [32]. Manic or depressive episodes were defined using the DSM-IV-TR criteria. Additional demographic (age, sex, years of education) and clinical (age at illness onset, illness duration, number of mood episodes experienced during the 12 months before the PET scan, and psychotropic medications) information was obtained from clinical charts and direct patient interviews [33]. When possible, attempts were made to verify these data using third-party reports (e.g., medical records and family interviews) [34]. The antipsychotic medication status of the patients was evaluated by calculating the chlorpromazine-equivalent daily doses [35].

All clinical assessments were performed by six board-certified psychiatrists (Y. S., Y. Y., K. T., K. M., M. K., and S. K.) who received several training sessions on the BACS and PANSS before this study. Two trained psychiatrists administered the BACS and PANSS to each participant, and a consensus was reached in terms of the scoring to ensure consistency in the evaluations among raters.
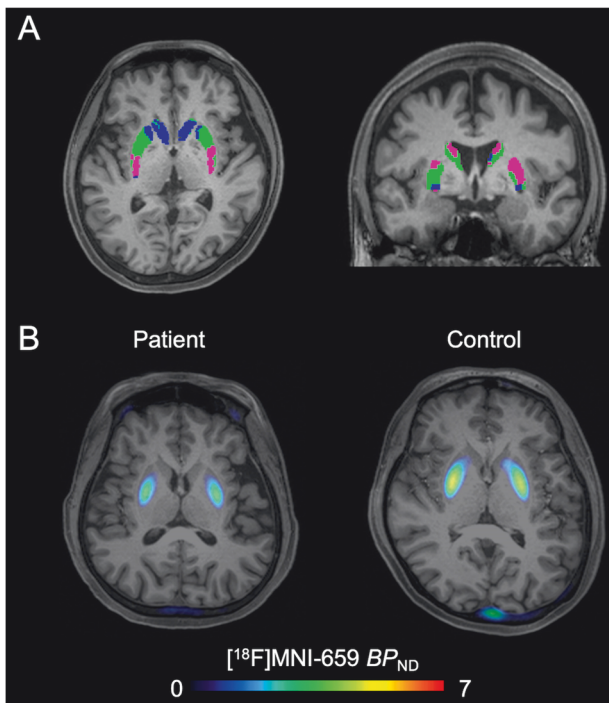
Fig. 1 Representative [^{18}F]MNI-659 BP_{ND} parametric and ROI images. A An example of ROIs placed on T1-weighted images. Limbic striatum ROI is shown in blue, executive striatum ROI in green, and sensorimotor striatum ROI in magenta. **B** Representative [^{18}F]MNI-659 BP_{ND} parametric images of patients and controls created for illustrative purposes. The parametric BP_{ND} images are overlaid on individual T1-weighted images. Abbreviations: BP_{ND}, binding potential of the target region relative to non-displaceable tissue; [^{18}F]MNI-659, 2-(2-(3-(4-(2-[^{18}F]fluoroethoxy)phenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-4-isopropoxyisoindoline-1,3-dione.

Statistical analysis

Independent sample t-tests were used to examine the differences in clinical measures between the patients with BD-I and HCs. The statistical significance threshold was defined as $P < 0.05$ (two-tailed) with Bonferroni correction. All data were analyzed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA).

The main analyses compared the [^{18}F]MNI-659 BP_{ND} values of the patients with BD-I and HCs using multiple analyses of covariance (MANCOVA). The dependent variables were the [^{18}F]MNI-659 BP_{ND} values in three ROIs (the limbic, executive, and sensorimotor subregions of the striatum). The fixed factor was the diagnosis (BD-I = 1 and HCs = 0). The nuisance covariates were age and sex because of their potential influence on the PDE10A status of the brain [36]. When the diagnosis had a significant effect on the BP_{ND} values, a post-hoc univariate analysis with Wilk's lambda test was performed to examine the effect of the diagnosis on BP_{ND} values in each ROI. The threshold for statistical significance was set at $P < 0.05$ (two-tailed) with Bonferroni correction for the three PET ROIs.

The correlations between the regional [^{18}F]MNI-659 BP_{ND} values and clinical features of patients with BD-I (YMRS, MADRS, and PANSS scores; z-scores of BACS subtests; number of mood episodes experienced during the 12 months before PET scan; illness duration; and antipsychotic medications) were assessed using partial correlation analyses. Age and sex were used as control variables.

To investigate the effects of lithium on PDE10A availability, we conducted t-tests of [^{18}F]MNI-659 BP_{ND} values between lithium-taking versus non-lithium-taking patients.

RESULTS
Demographic data and group comparisons on behavioral measures

In total, 52 participants (mean [standard deviation {SD}] age, 51.3 [11.7] years), 25 patients with BD-I (mean [SD] age, 53.9 [12.8]

years; 12 [48%] women and 13 men [52%]), and 27 HCs (mean [SD] age, 48.9 [9.9] years; 13 [48%] women and 14 men [52%]) were included in the study (Table 1). Of the 25 patients, 20 had euthymia, four had mania, and one had depression. One patient was hospitalized. The mean YMRS score was 4.6 (SD = 7.2). Five patients met the criteria of rapid-cycling bipolar disorder (≥ 4 episodes/12 months) in DSM-IV-TR, and all of them experienced both depressive and manic episodes. The mean dose of antipsychotic medication was 105.9 mg (SD = 199.2) in chlorpromazine-equivalent daily doses. Only 2 of the 25 BD-I patients were taking antidepressants: one was taking 40 mg/day of duloxetine and the other was on 50 mg/day of sertraline. Among mood stabilizers, lithium was taken by 10 patients (mean [SD] dose, 490 [202] mg), lamotrigine by 3 (mean [SD] dose, 200 [82] mg), and valproic acid by 2 (dose, 400 and 600 mg) (Table S1). There were no significant differences between the BD-I and HC groups related to age, sex, or the proportion of smokers. Compared with the HCs, the patients with BD-I euthymia scored significantly lower on the BACS subtests of verbal memory, token motor, and symbol coding ($P < 0.05$).

Group comparisons on [^{18}F]MNI-659 BP_{ND}

Representative [^{18}F]MNI-659 BP_{ND} parametric images of patients and controls are shown in Fig. 1B. MANCOVA showed a statistically significant effect of diagnosis (BD-I or HC) on [^{18}F]MNI-659 BP_{ND} values ($F = 6.31$; $P = 0.001$; Wilks' $\lambda = 0.708$) (Fig. 2). The post-hoc analysis with univariate tests showed significantly lower BP_{ND} values for the executive ($F = 8.86$; $P = 0.005$; $t = 2.976$; mean [SD] coefficient, 0.394 [0.132]; 95% confidence interval [CI], 0.128–0.661) and sensorimotor ($F = 6.13$; $P = 0.017$; $t = 2.477$; mean [SD] coefficient, 0.531 [0.214]; 95% CI, 0.100–0.962) subregions of the striatum in patients with BD-I than those in the HCs. In addition, t-tests of [^{18}F]MNI-659 BP_{ND} values between lithium-taking versus non-lithium-taking patients showed no significant differences (limbic, $P = 0.248$; executive, $P = 0.400$; sensorimotor, $P = 0.500$).

Correlation between [^{18}F]MNI-659 BP_{ND} and clinical features of patients with BD-I

Partial correlation analysis revealed a significant negative correlation between the [^{18}F]MNI-659 BP_{ND} values in the executive subregion of the striatum and the number of mood episodes in the 12 months before the PET scan (mean [SD] r, –0.546 [0.122]; 95% CI, –0.275 to –0.770; $P = 0.007$) (Fig. 3). The regional [^{18}F]MNI-659 BP_{ND} values were not significantly correlated with the YMRS, MADRS, or PANSS scores, z-scores of BACS subtests, illness duration, or daily dose of antipsychotic medications.

DISCUSSION

To the best of our knowledge, this is the first PET study to assess the central PDE10A status of patients with BD-I. The results showed that the [^{18}F]MNI-659 BP_{ND} values were significantly altered for the patients with BD-I than for the HCs. The patients with BD-I showed significantly lower PDE10A availability than the HCs; this was prominent in the executive subregion of the striatum. Moreover, lower [^{18}F]MNI-659 BP_{ND} values in the executive subregion of the striatum were correlated with a higher frequency of mood episodes. These findings have important implications for understanding BD-I pathophysiology and developing clinical interventions to prevent BD-I relapse.

The key strength of the present study is that we included only patients with BD-I in our BD patient group. We excluded patients with bipolar II disorder to avoid conflating the potentially distinct characteristics of the two major subtypes of bipolar disorder. Additionally, we minimized the potential confounding influence of mood status on the investigated variables by prioritizing patients with euthymia. Therefore, our approach ensures homogeneity that

Table 1. Characteristics of the participants included in this study.

		Patients			Controls			Statistics	
		N	Mean	SD	N	Mean	SD	t/chi-squared	P
Age (years)		25	54	13	27	49	11	1.560	0.125
Sex (male/female)		25	13/12		27	14/13		0.001	0.992
Smoking (yes/no)		25	19/6		27	20/7		0.157	0.876
Onset of illness (years)		25	28.4	10.3					
Duration of illness (years)		25	25.5	13.6					
Mood state at PET scan									
	Euthymic	20							
	Manic	4							
	Depressed	1							
Number of manic and depressive episodes experienced during the 12 months		25	2.1	1.8					
YMRS		25	4.6	10.7					
MADRS		25	2.6	6.0					
HDRS-21		25	2.4	4.9					
PANSS		25							
	Positive		6.0	3.8					
	Negative		6.4	3.8					
	General		13.5	7.9					
Antipsychotic medication		25	105.9	199.2					
BACS-J (z-score)		21			27				
	Verbal memory		−1.23	0.94		−0.62	0.92	2.761	0.008
	Digit sequencing		−0.68	1.12		−0.13	0.97	1.855	0.071
	Token motor		−0.88	0.79		−0.13	0.76	3.286	0.002
	Verbal fluency		−0.77	0.85		−0.67	0.98	0.733	0.468
	Symbol coding		−0.26	0.83		0.89	1.05	3.636	0.001
	Tower of London		−0.01	1.10		0.42	0.50	1.766	0.085
Size of ROI (cm³)		25			27				
	Limbic		2.92	0.37		3.13	0.42	2.070	0.130
	Executive		7.20	0.78		7.66	0.91	2.256	0.086
	Sensorimotor		2.92	0.36		3.06	0.45	1.759	0.254
Injected radioactivity (MBq)		25	190.0	5.0	27	189.2	5.0	0.616	0.540
Molar activity (GBq/µmol)		25	308.3	156.0	27	273.4	99.4	0.950	0.347

PET positron emission tomography, *YMRS* Young Mania Rating Scale, *MADRS* Montgomery–Åsberg Depression Rating Scale, *HDRS*-21 Hamilton Depression Rating Scale, 21-item version, *PANSS* Positive and Negative Syndrome Scale, *BACS-J* Japanese version of the Brief Assessment of Cognition in Schizophrenia, *SD* standard deviation.

optimizes our analysis, which enhances the internal and external validity of our study. The robustness of the present study is further amplified by the inclusion of a significant proportion of participants with early-onset and extended illness durations. This feature ensures a representative and enriched sample of BD-I experiences, thereby increasing the applicability of the findings.

The present study revealed significantly lower PDE10A availability in the striatum in patients with BD-I, suggesting that it is a promising imaging biomarker. The following points support an association between decreased [18F]MNI-659 binding in BD-I and altered PDE10A availability. First, preclinical studies have suggested that dopaminergic modulation may affect [18F]MNI-659 measurements [37]; however, our correlation analysis did not show a significant effect of antipsychotics on [18F]MNI-659 binding. Second, age matching and covariate inclusion in the MANCOVA minimized the potential effect of aging. Third, the exclusion of patients using papaverine and theophylline

strengthens the association with altered PDE10A availability. Therefore, our results raise the possibility that PDE10A-dependent dysregulation of corticostriatal signaling may be related to BD-1 pathophysiology. Furthermore, our post-hoc analysis showed significantly lower BP_{ND} values in the executive and sensorimotor subregions of the striatum in patients with BD-I than in the HCs but not in the limbic subregion of the striatum. This suggests that the contribution of altered striatal PDE10A density to BD-1 pathophysiology differs in functional subregions of the striatum. PDE10A dysfunction in the executive subregion of the striatum may be involved in several cognitive functions reported to be impaired in bipolar disorder in past neuropsychological studies, including working memory and inhibitory control [38, 39]. In addition, there was no significant correlation between [18F]MNI-659 BP_{ND} values and illness duration. However, a larger number of early-course cases need to undergo imaging to assess the initial changes in PDE10A availability in bipolar disorder.
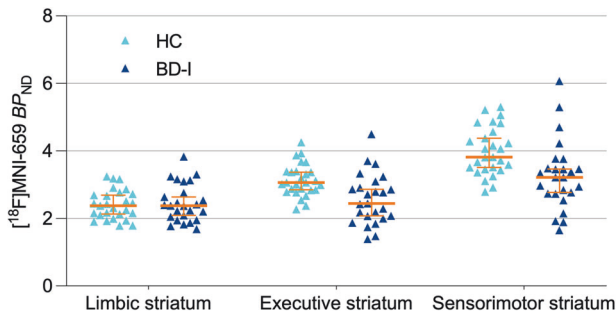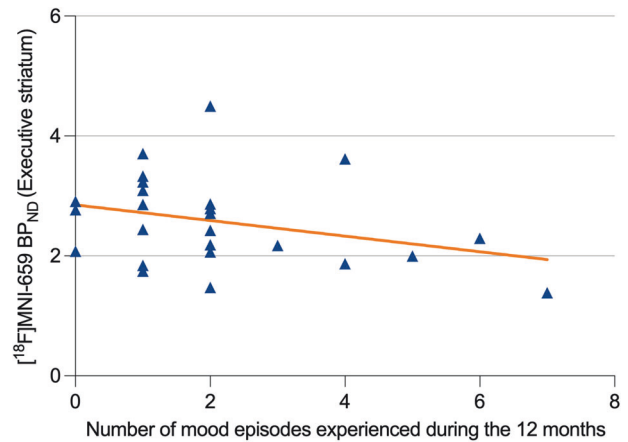
Fig. 2 [^{18}F]MNI-659 BP_{ND} in the striatal subregions of patients with BD-I and healthy controls. Plots represent the regional [^{18}F]-MNI-659 BP_{ND} values in the three striatal subregions in the two groups. Horizontal orange lines indicate group means, and orange error bars indicate standard deviation. After correcting for the potential effects of age and sex, multiple analyses of covariance demonstrated a significant effect of diagnosis on [^{18}F]-MNI-659 BP_{ND} values in the three striatal subregions ($F = 5.03$, $P = 0.005$). The post-hoc analysis with univariate tests showed significantly lower BP_{ND} values in the executive ($F = 8.86$; $P = 0.005$; $t = 2.976$; mean [SD] coefficient, 0.394 [0.132]; 95% confidence interval [CI], 0.128–0.661) and sensorimotor ($F = 6.13$; $P = 0.017$; $t = 2.477$; mean [SD] coefficient, 0.531 [0.214]; 95% CI, 0.100–0.962) subregions of the striatum in patients with BD-I than in healthy individuals ($F = 6.70$, $P = 0.013$). Abbreviations: HC, healthy control; BD-I, bipolar I disorder; BP_{ND}, binding potential of the target region relative to non-displaceable tissue; [^{18}F]MNI-659, 2-(2-(3-(4-(2-[^{18}F]fluoroethoxy)phenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-4-isopropoxyisoindoline-1,3-dione.

Fig. 3 Partial correlation between [^{18}F]MNI-659 BP_{ND} and number of mood episodes experienced during the previous 12 months. [^{18}F]MNI-659 BP_{ND} values (Y-axis) and the number of mood episodes experienced during the previous 12 months (X-axis) are plotted. There was a negative correlation between [^{18}F]MNI-659 BP_{ND} values in the executive subregion of the striatum and the number of mood episodes experienced during the 12 months before the PET scan (r, –0.546; 95% confidence interval, –0.275 to –0.770; $P = 0.007$). Abbreviations: BP_{ND}, binding potential of the target region relative to non-displaceable tissue; PET, positron emission tomography; [^{18}F]MNI-659, 2-(2-(3-(4-(2-[^{18}F]fluoroethoxy)phenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-4-isopropoxyisoindoline-1,3-dione. Abbreviations: PET, positron emission tomography; YMRS, Young Mania Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; HDRS-21, Hamilton Depression Rating Scale, 21-item version; PANSS, Positive and Negative Syndrome Scale; BACS-J, Japanese version of the Brief Assessment of Cognition in Schizophrenia; SD, standard deviation.

A substantial body of evidence indicates an association between the pathophysiology of bipolar disorder and PDE10A. PDE10A is the major enzyme responsible for cAMP hydrolysis and is, therefore, the rate-limiting enzyme for intracellular dopamine neurotransmission [17]. A mouse model of BD-I suggested that the cAMP/PDE10A pathway is correlated with high or low locomotor activity [20]. Further, a past animal study showed that PDE10A knockout mice develop depressive behaviors [21]. These findings from animal studies and the association between PDE10A availability and mood instability observed in the present study suggest that reduced PDE10A binding could lead to PDE10A-dependent dysregulation of dopamine second messenger system, possibly leading to mood instability in bipolar disorder.

Our results showed that lower [^{18}F]MNI-659 BP_{ND} values in the striatum were correlated with a higher rate of mood episodes. This correlation suggests that patients with BD-I with lower PDE10A availability in the striatum tend to show increased recurrence. This association between PDE10A-dependent dysregulation of corticostriatal signaling and the risk of BD-I recurrence indicates that PDE10A can be a therapeutic target for preventing BD-I relapse. Supporting this notion, atypical antipsychotics reduce BD-I recurrence [40]. Conversely, PDE10A inhibition with TAK-063 (1-(2-fluoro-4-(1H-pyrazol-1yl)phenyl)-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-4(1H)-one) triggers mood instability, anxiety, and impaired processing speed in healthy individuals [41]. Therefore, a key clinical implication of our findings is that the stimulation of PDE10A activity can have therapeutic effects in reducing the recurrence rate of manic and depressive episodes in patients with BD-I.

Glutamatergic dysfunction has been implicated in the pathogenesis of bipolar disorder. Our previous meta-analysis of proton magnetic resonance spectroscopy studies showed glutamatergic dysfunction in patients with BD-I [42]. Accumulating evidence from animal and human studies supports the association of striatal dopamine neurotransmission and cortical glutamate neurotransmission in the pathophysiology of various psychiatric disorders [43, 44]. Studies on dopamine-glutamate interactions suggested

that PDE10A regulates midbrain-striatal dopamine and cortical-striatal glutamate systems, which are involved in the pathogenesis of bipolar disorder [45]. Therefore, striatal PDE10A dysfunction might mediate cortical glutamatergic dysfunction in bipolar disorder.

Several meta-analyses have demonstrated strong associations between BD-I and cognitive deficits [46]. Compared with HCs, patients with BD-I were typically impaired for all cognitive domains. Most previous meta-analyses have included symptomatic patients, cognitive dysfunction in patients with BD-I has also been observed in the euthymic state [47]. The present study consistently described widespread cognitive impairment in patients with euthymic BD-I. Our findings cannot be explained by the effects of age, because the cognitive function test scores were adjusted for age. Furthermore, there was no correlation between the cognitive test scores and [^{18}F]MNI-659 binding potentials, suggesting that corticostriatal PDE10A-dependent dysregulation may not be associated with the pathophysiological basis of cognitive impairment in patients with BD-I.

[^{18}F]MNI-659 PET has been evaluated in studies on neurodegenerative diseases [48]. These studies have consistently shown decreased [^{18}F]MNI-659 binding in patients with Huntington's disease, identified [^{18}F]MNI-659 as a reliable PET radiotracer with a high signal-to-noise ratio and good test-retest reliability, and validated the noninvasive quantitative measurement of PDE10A. We recently reported that patients with schizophrenia demonstrated increased [^{18}F]MNI-659 binding [22], which contrasts with our findings of patients with BD-I. Further studies are required to thoroughly discuss these findings, but the differences between the [^{18}F]MNI-659 PET findings for BD-I and schizophrenia suggest a pathophysiological difference between BD-I and schizophrenia. It also indicates that [^{18}F]MNI-659 is a potential imaging biomarker to distinguish BD-I from schizophrenia.

Along with the strengths of our study, some limitations should be acknowledged. We could not clarify the association between PDE10A status and mood status because the number of patients in depressive and manic states was insufficient for rigorous statistical analyses. To clarify the changes in PDE10A availability associated with mood state, it is necessary to perform longitudinal imaging with [^{18}F]MNI-659 PET in the same participant in different mood states. Increasing the sample size to draw more conclusive evidence would be deemed desirable, given that the statistically significant effect of diagnosis (BD-I or HC) on [^{18}F]MNI-659 BP_{ND} values was observed even when patients with BD-I were restricted to 20 patients with euthymia ($F = 3.96$; $P = 0.016$; Wilks' $\lambda = 0.741$). However, our findings suggest that PDE10A status likely reflects the trait rather than the disorder status.

CONCLUSION
In summary, lower [^{18}F]MNI-659 BP_{ND} values were observed in the striatum of patients with BD-I. Moreover, lower [^{18}F]MNI-659 BP_{ND} values in the executive subregion of the striatum were associated with a higher rate of mood episodes, raising the possibility of corticostriatal PDE10A-dependent dysregulation in BD-I pathophysiology. Our data justifies future clinical trials to investigate the efficacy of PDE10A stimulators for reducing the recurrence rate of manic and depressive episodes in BD-I.

DATA AVAILABILITY
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS
Substantial contribution to conception and design: YS, YY, KT, MK, MH. Acquisition, analysis, or interpretation of data: YS, YY, KT, SM, MK, SK, KM, KT, HE, YT. Administrative, technical, or material support: BY, HS, RT, KN, HT, MM, KK, MRZ. Study supervision: HU, MM, MH. Drafting of the article: YS, YY, KT. Critical revision of the manuscript for important intellectual content: all authors. All authors contributed to the article and approved the final version of the manuscript.

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COMPETING INTERESTS
The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
All methods were performed in accordance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects. The study received approval from the Radiation Drug Safety Committee, Institutional Review Board of the National Institutes for Quantum Science and Technology, Chiba, Japan (number: 17-027), and the Research Ethics Board of Keio University, Tokyo, Japan (number: 20170199). Written informed consent was obtained from participants prior to any study procedures being performed.

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