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ORIGINAL PAPER

The relationship between excitement symptom severity and extrastriatal dopamine $D_{2/3}$ receptor availability in patients with schizophrenia: a high-resolution PET study with [^{18}F] fallypride

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Abstract The purpose of this study was to investigate the relationship between specific symptom severity and $D_{2/3}$ receptor availability in extrastriatal regions in outpatients with schizophrenia to shed light on the role of extrastriatal dopaminergic neurotransmission in the pathophysiology of symptoms of schizophrenia. Sixteen schizophrenia patients receiving relatively low-dose maintenance atypical antipsychotics and seventeen healthy controls underwent 3-Tesla magnetic resonance imaging and high-resolution positron emission tomography with [^{18}F]fallypride. For $D_{2/3}$ receptor availability, the binding potential with respect to non-displaceable compartment (BP_{ND}) was derived using the simplified reference tissue model. The BP_{ND} values were lower in patients on antipsychotic treatment than in controls across all regions with large effect sizes (1.03–1.42). The regions with the largest effect size were the substantia nigra, amygdala, and insula. Symptoms of schizophrenia were assessed using a five-factor model of the Positive and Negative Syndrome Scale (PANSS). The region of interest-based analysis showed that PANSS excitement factor score had a significant positive correlation with the [^{18}F]fallypride BP_{ND} in the insula. The equivalent dose of antipsychotics was not significantly correlated with PANSS factor scores or regional BP_{ND} values. The voxel-based analysis also revealed a significant positive association between the PANSS excitement factor and the [^{18}F]fallypride BP_{ND} in the insula. The present study revealed a significant association between excitement symptom severity and $D_{2/3}$ receptor availability in the insula in schizophrenia, suggesting a possible important role of $D_{2/3}$ receptor-mediated neurotransmission in the insula and related limbic system in the pathophysiology of this specific symptom cluster.

Keywords Extrastriatal $D_{2/3}$ receptor · Excitement symptom · [^{18}F]fallypride · High-resolution PET · Insula · Schizophrenia

Introduction

Since the introduction of second generation antipsychotics, extrastriatal dopamine receptors have received much attention in schizophrenia research [1]. The development of high-affinity D_2-like receptor radiotracers has also allowed the exploration of D_2-like receptors in relatively low density regions including thalamus, temporal cortex, and limbic regions in recent years [2]. In particular, dopamine D_2-like receptors in extrastriatal regions have been implicated as the possible site of antipsychotic action, although a double-blind positron emission tomography (PET) study found no relationship between extrastriatal D_2-like receptor

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binding and treatment response but observed a significant relationship between striatal D_2-like receptor binding and antipsychotic response [3].

The investigation into extrastriatal dopamine receptors using high-affinity $D_{2/3}$ radiotracers such as [^{18}F]fallypride, a very high-affinity, specific radioligand for extrastriatal $D_{2/3}$ receptors [4, 5], is still an emerging field and more research is clearly required to better understand the role of extrastriatal $D_{2/3}$ receptor-mediated neurotransmission in schizophrenia. Previous studies in drug-naïve or drug-free patients with schizophrenia reported reduced $D_{2/3}$ receptor availability measured by [^{18}F]fallypride in the thalamus [4, 6, 7], temporal cortex [6, 7], prefrontal cortex [6], amygdala [7], uncus [8], and cingulate region [7]. Decreased thalamic binding was also reported in studies using [^{11}C]FLB, another PET tracer for extrastriatal $D_{2/3}$ receptor [9, 10]. In contrast, increased $D_{2/3}$ receptor availability assessed by [^{18}F]fallypride was also observed in the substantia nigra [4] and thalamus [8]. Although more research is clearly needed to reach conclusive evidence, the literature on extrastriatal $D_{2/3}$ receptors in schizophrenia shows a tendency toward reduced $D_{2/3}$ receptor availability in antipsychotic-free or antipsychotic-naïve patients with schizophrenia, which was reported in a recent meta-analysis [11]. The putative extrastriatal selectivity in the occupancy rate achieved by second generation antipsychotics has also been investigated using [^{18}F]fallypride [12–17]. However, previous studies were performed on antipsychotic-naïve or antipsychotic-free patients who were mainly admitted to research units. Few studies have been conducted to investigate $D_{2/3}$ receptor availability in clinically stable outpatients receiving maintenance antipsychotics and to quantify the level of extrastriatal $D_{2/3}$ receptors in those with maintenance treatment in a naturalistic clinical setting.

Moreover, while striatal $D_{2/3}$ receptor density in patients with schizophrenia has been extensively studied with molecular PET imaging and the clinical significance of striatal dopaminergic transmission is well documented [18–20], the clinical correlates of extrastriatal $D_{2/3}$ receptors are largely unknown [11]. In particular, only a few PET studies have reported the relationship between extrastriatal $D_{2/3}$ receptor availability and the psychopathology of schizophrenia, with the overall results being inconclusive [4, 6, 7, 10, 21]. Kessler et al. [4] found a significant positive correlation of positive symptom score with $D_{2/3}$ receptor availability in the right temporal cortex, while Lehrer et al. [6] and Buchsbaum et al. [7] reported significant negative correlations between the $D_{2/3}$ receptor availability in the thalamus and the psychotic symptom severity. Talvik et al. [21] reported a significant negative correlation between [^{11}C]raclopride binding potential in the right thalamus and grandiosity symptom score. In a single-photon emission computerized tomography (SPECT) study with [^{123}I]epidepride, a significant positive correlation between positive symptoms and cortical $D_{2/3}$ receptor binding was also reported [22]. Thus, further investigation into the relationship between extrastriatal $D_{2/3}$ receptor availability and the specific symptoms of schizophrenia is clearly warranted, considering that dopaminergic dysfunction may exist across the wide range of cortico-subcortical circuits in schizophrenia [2]. In addition, schizophrenia is a complex illness that is characterized by heterogeneous and multiple symptom domains beyond the dichotomous positive and negative symptoms [23–25].

Therefore, the purpose of the present study was to quantify $D_{2/3}$ receptor availability in extrastriatal and striatal regions in stable outpatients with schizophrenia receiving relatively low-dose maintenance treatment and to investigate the relationship between specific symptom severity and $D_{2/3}$ receptor availability to further shed light on the role of extrastriatal dopaminergic neurotransmission in the pathophysiology of symptoms of schizophrenia. In the present study, we used 3-Tesla magnetic resonance imaging (MRI) and high-resolution PET with [^{18}F]fallypride.

Materials and methods

Subjects

The study protocol was approved by the Institutional Review Board of the Gachon University Gil Medical Center, and all procedures used in the study were conducted in accordance with international ethical standard, Declaration of Helsinki. Patients were recruited from the outpatient clinic. Informed consent was obtained from all subjects after a full explanation of the study procedure. Sixteen patients (six men and ten women) were enrolled in the study (Table 1). All patients were diagnosed with schizophrenia by Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) [26], which was established by the Structured Clinical Interview for DSM-IV (SCID) [27], and they did not meet the diagnostic criteria for a psychiatric diagnosis other than schizophrenia. They also did not have a concurrent diagnosis of substance abuse/dependence or medical/neurological disorders. Patients had a mean [standard deviation (SD)] age of 36.9 (11.4) years and a mean (SD) duration of illness of 6.5 (3.7) years. The mean (SD) years of education were 10.4 (1.9) years. All patients were receiving at least 4 weeks of maintenance antipsychotic monotherapy without changes in the dosage of antipsychotics over the same period at the time of enrollment. Medication compliance was confirmed in weekly visits by reports from the patients and caregivers, i.e., family members, who were considered highly reliable by the investigator in providing support to the patient to

Table 1 Demographic characteristics and PET scan parameters

Variables	Patients with schizophrenia	Healthy control subjects	*t* value	*p* value
Age (year)	36.9 ± 11.4	32.3 ± 9.5	1.26	0.22
Gender (male/female)	6/10	8/9	$\chi^2 = 0.58$	0.73
Education (year)	13.5 ± 1.7	13.9 ± 1.7	−0.65	0.52
Duration of illness (year)	6.5 ± 3.7	NA		
PANSS total score	58.6 ± 17.8	NA		
Chlorpromazine equivalent dose (mg/day)	170.0 ± 102.8			
[^{18}F]fallypride PET scan				
Injected dose (MBq)	200.7 ± 24.9	196.1 ± 19.6	0.55	0.59
Specific activity (GBq/μmol)	92.0 ± 41.3	122.2 ± 65.8	−1.53	0.14

SD standard deviation, *PANSS* Positive and Negative Syndrome Scale, *PET* positron emission tomography

ensure compliance with the medication. The antipsychotics that patients were taking at the time of enrollment were paliperidone [$n = 5$, mean (SD) dose: 3.6 (1.3) mg/day], aripiprazole [$n = 3$, mean (SD) dose: 4.7 (4.6) mg/day], quetiapine [$n = 3$, mean (SD) dose: 410.9 (43.2) mg/day], olanzapine [$n = 2$, mean (SD) dose: 5.0 (3.5) mg/day], risperidone [$n = 2$, mean (SD) dose: 1.5 (0.7) mg/day], and ziprasidone ($n = 1$, dose: 100.0 mg/day). The chlorpromazine equivalent doses of antipsychotics were calculated based on the method proposed by Gardner et al. [28]. The mean (SD) chlorpromazine equivalent dose was 170.0 (102.8) mg/day. None of the patients were taking antidepressants or mood stabilizers. Seventeen healthy control subjects (eight men and nine women), who met the criteria of no current or past psychiatric, neurological, or medical illness and no current use of medications, were also recruited, provided written informed consent, and underwent the same MRI and PET protocols. All patients and control subjects performed urine tests for opiates and methamphetamines prior to PET scans to exclude substance abuse. For female participants, pregnancy was excluded using urine pregnancy tests before the PET scans. None of the participants showed any gross structural abnormalities on brain MRI, which was confirmed by a board-certified radiologist.

Clinical assessments

Symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS) [29]. The PANSS is a 30-item instrument that measures positive, negative, and general psychiatric symptoms. A five-factor model of the PANSS was used based on evidence from factor analysis studies [23–25]. The factors were positive, negative, cognitive/disorganization, excitement, and depression/anxiety. The global severity of schizophrenia was assessed using the Clinical Global Impression Scale of Severity (CGI-S) [30]. Antipsychotic-induced parkinsonism and akathisia were assessed using the Simpson-Angus Scale (SAS) [31] and the Barnes Akathisia Rating Scale (BARS) [32], respectively.

Scan protocol for high-resolution imaging

All participants were scanned using 3-Tesla MRI and High Resolution Research Tomograph (HRRT)-PET with [^{18}F]fallypride. The HRRT-PET is the high-resolution brain-dedicated PET scanner [33, 34]. The tracer [^{18}F]fallypride was synthesized, as previously described [35]. After a mean (SD) bolus injection of 198.5 (22.3) MBq [^{18}F]fallypride with a mean (SD) specific activity of 106.1 (55.3) GBq/μmol, an emission scan was conducted in a dynamic scan mode for 120 min. After the PET scan, 3-Tesla MRI scans were performed using a three-dimensional T1-weighted magnetization-prepared rapid gradient echo (3-D T1MPRAGE) sequence for structural brain imaging. The 3-D T1MPRAGE images were acquired with the following parameters: repetition time = 1900 ms, echo time = 3.3 ms, inversion time = 900 ms, flip angle = 9°, voxel size = 1.0 × 1.0 × 1.0 mm^3, and number of slices = 160.

The [^{18}F]fallypride PET images were reconstructed using the 3-dimensional ordinary Poisson ordered-subset expectation maximization (OP-OSEM) algorithm based on the symmetry and single-instruction multiple-data-based projection and backprojection [36]. The reconstructed PET images had a matrix of 256 × 256 × 207 and an iso-voxel resolution of 1.22 × 1.22 × 1.22 mm^3.

Image analysis

To calculate the [^{18}F]fallypride binding potential with respect to non-displaceable compartment (BP_{ND}), the emission data of [^{18}F]fallypride PET were reconstructed as 22 frames of increasing duration as follows: 4 × 30, 3 × 60,

2 × 150, 4 × 300, and 9 × 600 s (total 120 min). Attenuation, scatter, and decay time correction were estimated and applied for each frame.

The MRI scan of each subject was coregistered to his or her PET scan using statistical parameter mapping 8 (SPM8; Wellcome Trust Center for Neuroimaging, UK). The spatial normalization of the coregistered MRI images of each subject was performed on the Montreal Neurological Institute template using SPM8, and the estimated transform was applied to the corresponding PET images. Time-activity curves of [^{18}F]fallypride PET were generated from the dynamic PET images by averaging all the voxels within each region of interest (ROI) (Fig. 1), which were coregistered to the corresponding MRI images. For the estimation of $D_{2/3}$ receptor availability, [^{18}F]fallypride BP_{ND} was derived from each ROI using the simplified reference tissue model 2 (SRTM2) [37] with the cerebellar cortex devoid of $D_{2/3}$ receptors [38] as the reference region, based on the parameter estimation implemented in the PMOD software v3.2 (PMOD Technologies Ltd., Zürich, Switzerland). Representative examples of [^{18}F]fallypride BP_{ND}, HRRT-PET, and 3-Tesla MR images are shown (Fig. 2). The BP_{ND} values were obtained in the 18 predefined ROIs using the automated anatomical labeling (AAL) program [39]. The ROIs were the superior temporal cortex, thalamus, hippocampus, amygdala, insula, substantia nigra, caudate, putamen, and ventral striatum, and left and right regions were analyzed separately.

Statistical analysis

The mean [^{18}F]fallypride BP_{ND} values were compared between the groups using two-tailed *t* tests. Effect sizes (Cohen's d) were also calculated. Relationships between demographic variables and [^{18}F]fallypride BP_{ND} values were analyzed using Pearson's correlation analysis. The two-tailed *t* tests were performed to examine gender differences in regional [^{18}F]fallypride BP_{ND} values. To examine the possible effects of antipsychotic dosage on PANSS

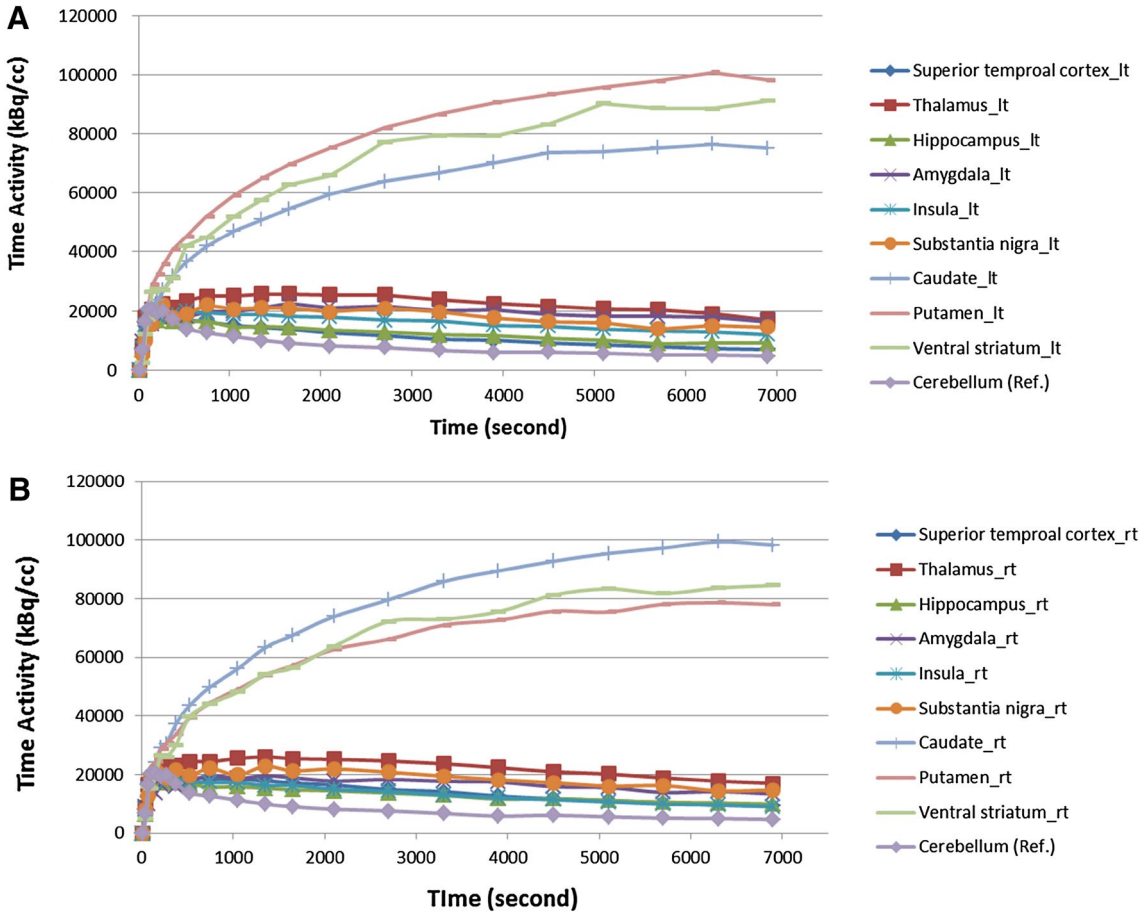

Fig. 1 Time activity curve of the [^{18}F]fallypride was extracted from the each *left* (**a**) and *right* (**b**) region of interest (ROI) of the PET image. The [^{18}F]fallypride BP_{ND} of each ROI was obtained from the time activity curve with the cerebellum as the reference region. *lt* left, *rt* right, BP_{ND} binding potential with respect to non-displaceable compartment

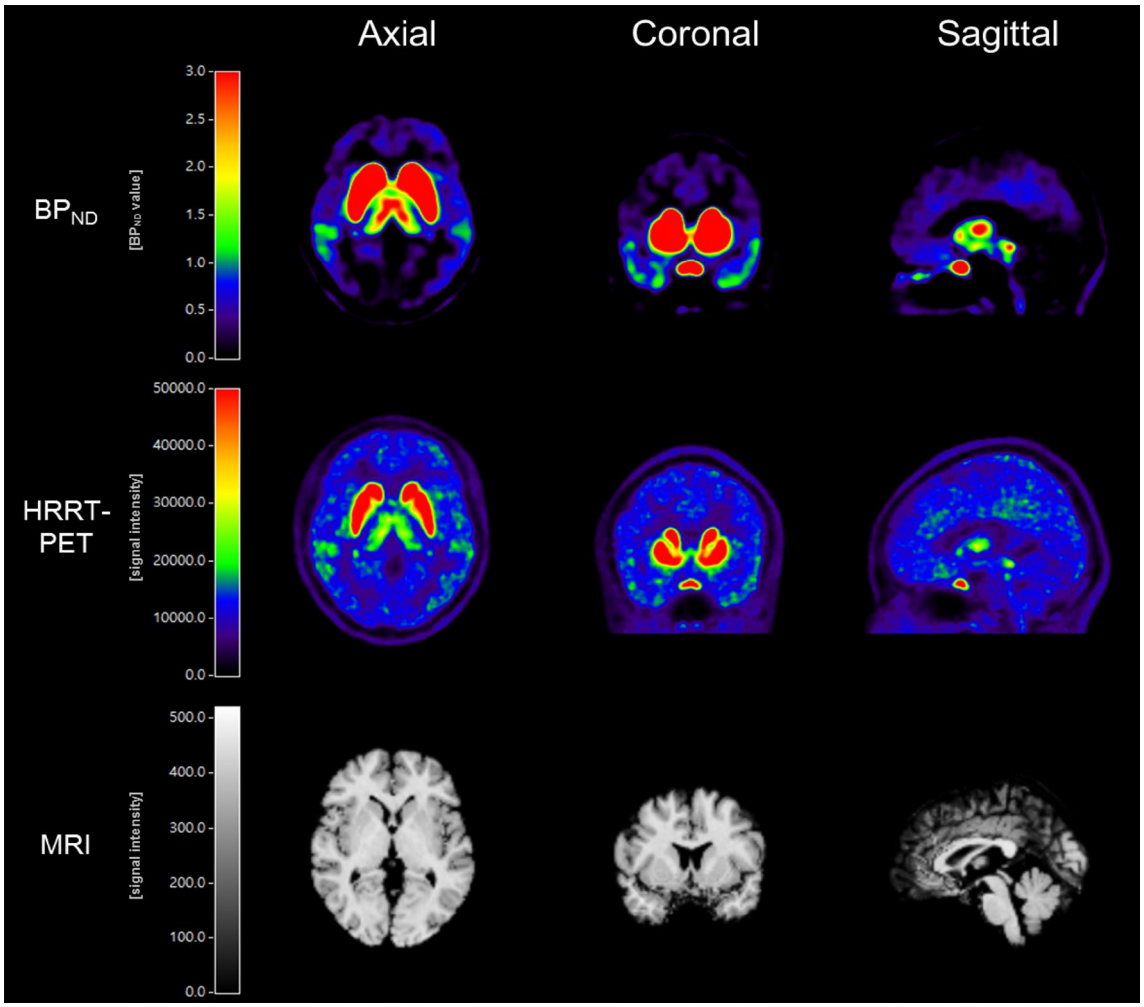

Fig. 2 Representative examples of [^{18}F]fallypride BP_{ND}, HRRT-PET, and 3-Tesla MR images of a subject. Each voxel value of the HRRT-PET image is an average of total dynamic images for 22 frames

scores and $D_{2/3}$ receptor availability, the relationship of chlorpromazine equivalents with PANSS factor scores and [^{18}F]fallypride BP_{ND} was evaluated using Pearson's correlation analysis.

The relationship between the [^{18}F]fallypride BP_{ND} values and the severity of clinical symptoms as measured by the PANSS factor scores was analyzed using ROI-based and voxel-based approaches. In the ROI-based analysis, the relationship was analyzed using Pearson's product–moment correlations. Age-adjusted correlation coefficients were also obtained using partial correlation analysis. We performed the Bonferroni correction for multiple correlations in the ROI-based analysis. The Bonferroni-corrected p value for multiple correlations (18 regions and 5 PANSS factors) is 0.00055 (0.05/90). Therefore, statistical significance was determined by a two-tailed $p < 0.0005$. The level of $p < 0.005$ was considered a statistical tendency.

To supplement and confirm the ROI-based results, a voxel-based analysis was also conducted for the same data. The voxelwise linear regression analysis was conducted using spatially normalized BP_{ND} images with the PANSS factor scores as regressors. In the voxel-based analysis, the significance was set at $p < 0.05$, with a false discovery rate (FDR) correction for multiple correlations. However, in view of the supplementary and exploratory nature of the voxel-based analysis in our study, when no significant associations were found at the FDR-corrected threshold, the correlations were further examined using less restrictive criteria and regions surviving an uncorrected $p < 0.0001$ with an extent threshold of 20 voxels were considered to be significant. The height threshold was set to as low as 0.0001 to reduce the chance of false-positive findings and the extent threshold was set to 20 voxels, which was reported to be acceptable in previous PET imaging studies [40–43].

Results

The mean values of [^{18}F]fallypride BP_{ND} for ROIs are shown in Table 2. As expected, the [^{18}F]fallypride BP_{ND} values were significantly lower in the patient group than in the control group across all regions with large effect sizes (Cohen's $d = 1.03–1.42$, $p < 0.01$), reflecting $D_{2/3}$ receptor antagonism by antipsychotics in the patient group. The regions with the largest effect size were the left substantia nigra, both amygdala, and right insula. The percentage difference of BP_{ND} values between the groups across all measured regions was 32.0–53.6%. Regarding the relationship between demographic variables and $D_{2/3}$ receptor availability, Pearson's correlation analysis revealed that age was negatively correlated with the [^{18}F]fallypride BP_{ND} values in the superior temporal cortex (left: $r = -0.61$, $p = 0.01$; right: $r = -0.60$, $p = 0.02$), thalamus (left: $r = -0.53$, $p = 0.04$; right: $r = -0.54$, $p = 0.03$), hippocampus (left: $r = -0.57$, $p = 0.02$; right: $r = -0.59$, $p = 0.02$), amygdala (left: $r = -0.55$, $p = 0.03$; right: $r = -0.60$, $p = 0.01$), and insula (left: $r = -0.56$, $p = 0.03$; right: $r = -0.61$, $p = 0.01$) in the patient group. In healthy control subjects, a decline of [18F]fallypride BP_{ND} values with age was observed in the left amygdala ($r = -0.49$, $p < 0.05$), left insula ($r = -0.49$, $p = 0.04$), and left caudate ($r = -0.48$, $p < 0.05$). No significant gender differences were found in regional [^{18}F]fallypride BP_{ND} values in either the patient group ($t = 0.19–1.58$, $p > 0.01$) or the control group ($t = -1.41$ to 0.54, $p > 0.01$). The [^{18}F]fallypride BP_{ND} values had no significant correlations with years of education (patients: $r = -0.15$ to 0.22, $p > 0.05$; controls: $r = -0.32$ to 0.27, $p > 0.05$). In addition, no significant correlation was found between illness duration and regional $D_{2/3}$ receptor availability ($r = -0.12$ to 0.16, $p > 0.05$). There were no significant correlations between chlorpromazine equivalent doses and [^{18}F]fallypride BP_{ND} values in any region ($r = -0.41$ to -0.20, $p > 0.05$).

The mean (SD) PANSS scores of the patient group were as follows: PANSS total score, 58.6 (17.8) (median 59.5, range 31–88); PANSS positive symptom score, 8.0 (2.9) (median 8.0, range 4–14); PANSS negative symptom, 15.1 (5.3) (median 15.5, range 7–25); PANSS cognitive/disorganization symptom score, 13.3 (4.1) (median 15.0, range 7–19); PANSS excitement symptom score, 8.8 (3.7) (median 7.5, range 5–18); and PANSS depression/anxiety symptom score, 7.9 (3.2) (median 7.5, range 4–15). The mean (SD) CGI-S score of the patients was 3.0 (0.7) (median 3.0, range 2–4). The mean (SD) SAS and BARS scores of the patients were 1.0 (3.0) (median 0, range 0–10) and 0.2 (0.5) (median 0, range 0–1), respectively.

Table 2 Dopamine $D_{2/3}$ receptor availability as measured by [^{18}F]fallypride BP_{ND} in regions of interest

Regions of interest	Patients with schizophrenia	Healthy control subjects	Percentage difference (%)	Effect size (Cohen's d)	*P* value
Superior temporal cortex (lt)	0.27 ± 0.31	0.53 ± 0.18	49.1	1.03	0.007
Superior temporal cortex (rt)	0.28 ± 0.33	0.60 ± 0.21	53.3	1.16	0.003
Thalamus (lt)	1.13 ± 1.04	2.12 ± 0.40	46.7	1.26	0.001
Thalamus (rt)	1.09 ± 1.01	2.07 ± 0.39	47.3	1.28	0.001
Hippocampus (lt)	0.27 ± 0.30	0.58 ± 0.14	53.4	1.32	0.001
Hippocampus (rt)	0.38 ± 0.38	0.76 ± 0.20	50.0	1.25	0.001
Amygdala (lt)	1.02 ± 0.87	1.93 ± 0.29	47.2	1.40	<0.001
Amygdala (rt)	0.86 ± 0.76	1.65 ± 0.26	47.9	1.39	<0.001
Insula (lt)	0.89 ± 0.81	1.67 ± 0.66	46.7	1.06	0.005
Insula (rt)	0.32 ± 0.33	0.69 ± 0.18	53.6	1.39	<0.001
Substantia nigra (lt)	1.07 ± 0.55	1.68 ± 0.26	36.3	1.42	<0.001
Substantia nigra (rt)	1.00 ± 0.44	1.47 ± 0.26	32.0	1.30	0.001
Caudate (lt)	9.40 ± 7.13	15.53 ± 4.39	39.5	1.04	0.005
Caudate (rt)	11.43 ± 8.51	18.62 ± 4.95	38.6	1.03	0.005
Putamen (lt)	12.48 ± 8.39	19.72 ± 4.79	36.7	1.06	0.004
Putamen (rt)	10.59 ± 7.58	17.83 ± 5.19	40.6	1.11	0.003
Ventral striatum (lt)	12.72 ± 8.97	20.78 ± 5.25	38.8	1.10	0.003
Ventral striatum (rt)	11.85 ± 8.36	19.34 ± 5.07	38.7	1.08	0.004

BP_{ND} binding potential with respect to non-displaceable compartment, *SD* standard deviation, *lt* left; *rt* right

One patient presented with antipsychotic-induced parkinsonism, and none of the patients had akathisia. There were no significant correlations between chlorpromazine equivalent doses and PANSS factor scores ($r = -0.35$ to -0.03, $p > 0.05$). In addition, no significant correlation was found between equivalent dose and CGI-S score ($r = 0.11$, $p = 0.70$).

Regarding the associations between $D_{2/3}$ receptor availability and clinical symptoms, the ROI-based analysis showed that the PANSS excitement factor score had significant positive correlations with the [^{18}F]fallypride BP_{ND} in the right insula ($r = 0.78$, $p = 0.0004$, age-adjusted $r = 0.72$, $p = 0.002$) and left insula ($r = 0.81$, $p = 0.0001$, age-adjusted $r = 0.77$, $p = 0.001$) at the level of $p < 0.0005$ (Fig. 3). There was a positive correlation with a statistical tendency between the PANSS excitement factor score and the [^{18}F]fallypride BP_{ND} in the right amygdala at the level of $p < 0.005$ ($r = 0.68$, $p = 0.004$, age-adjusted $r = 0.59$, $p = 0.021$) (Fig. 3). No other significant or trend-level correlations were observed between $D_{2/3}$ receptor availability and other symptoms measured by the PANSS at the threshold of $p < 0.005$ (positive factor score: $r = 0.42$–0.62; negative factor score: $r = 0.35$–0.61; cognitive/disorganization factor score: $r = 0.27$–0.42; depression/anxiety factor score: $r = 0.39$–0.62) (Supplementary Table). No significant or trend-level correlations were found between the BP_{ND} values in the striatal regions and the PANSS factor scores ($r = 0.31$–0.61, $p > 0.005$) (Supplementary Table). There were no significant correlations between $D_{2/3}$ receptor availability and CGI-S score ($r = 0.18$–0.42, $p > 0.05$). In addition, no significant correlations were found between $D_{2/3}$ receptor availability and side effect scores (SAS: $r = -0.13$ to 0.30, $p > 0.05$; BARS: $r = -0.10$ to 0.09, $p > 0.05$).

To confirm ROI-based findings, a voxel-based analysis was also conducted for the same data. The voxel-based analysis using SPM8 revealed a significant positive correlation between the PANSS excitement factor score and the [^{18}F]fallypride BP_{ND} in the right insula (MNI coordinate: $x = 38$, $y = 0$, $z = -2$; cluster size: 96; z equivalent: 4.47,

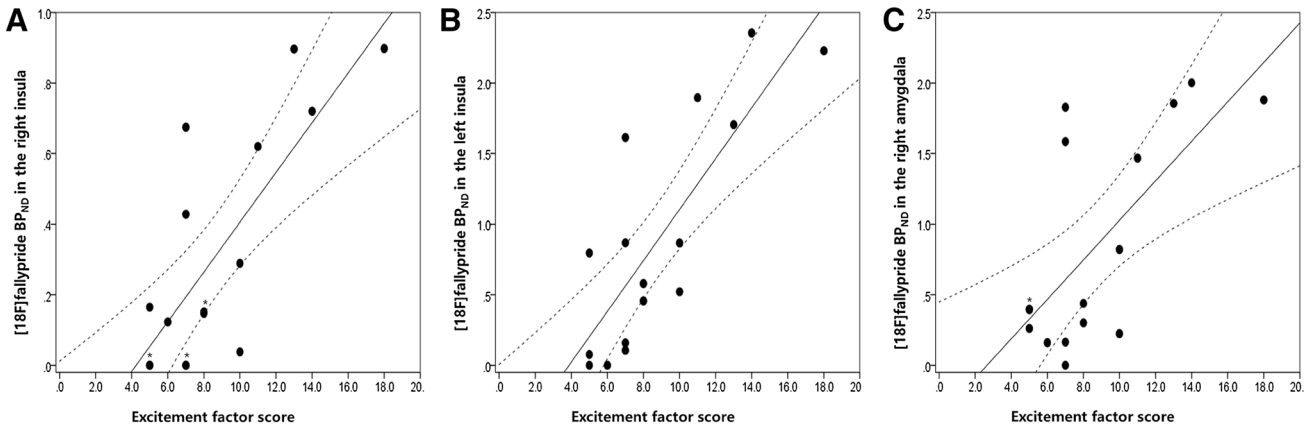

Fig. 3 Excitement factor score had significant or trend-level positive correlations with the [^{18}F]fallypride BP_{ND} in the right insula ($r = 0.78$, $p = 0.0004$) (**a**), left insula ($r = 0.81$, $p = 0.0001$) (**b**) and right amygdala ($r = 0.68$, $p = 0.004$) (**c**). The *asterisk*, *solid line*, and *dotted line* indicate the superposition of different subjects, regression line, and 95% confidence line, respectively. BP_{ND} binding potential with respect to non-displaceable compartment

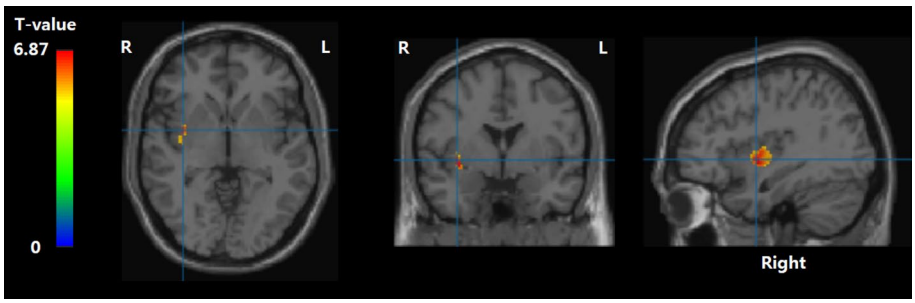

Fig. 4 Voxel-based analysis using SPM8 showed a significant positive correlation between the excitement factor score and the [^{18}F] fallypride BP_{ND} in the right insula (MNI coordinate: $x = 38$, $y = 0$, $z = -2$; cluster size 96; z equivalent 4.47, $p < 0.0001$ uncorrected at a cluster level of 20 voxels). *SPM8* statistical parameter mapping 8, BP_{ND} binding potential with respect to non-displaceable compartment

$p < 0.0001$ uncorrected) (Fig. 4), which did not survive FDR correction for multiple correlations (FDR-corrected $p = 0.357$).

Discussion

In the present study, we have quantitatively analyzed $D_{2/3}$ receptor availability in extrastriatal as well as striatal regions using [^{18}F]fallypride PET and investigated the relationship between the specific symptom severity and the $D_{2/3}$ receptor availability in patients with schizophrenia. We found that the PANSS excitement factor score had significant positive correlations with the $D_{2/3}$ receptor availability as measured by the [^{18}F]fallypride BP_{ND} in the right and left insula. The voxel-based analysis confirmed a significant positive correlation between the PANSS excitement factor score and the [^{18}F]fallypride BP_{ND} in the right insula. To our knowledge, this is the first report on the association of excitement symptom severity with dopamine $D_{2/3}$ receptor availability in extrastriatal regions in clinically stable patients with schizophrenia receiving maintenance treatment.

A previous study using fluorodeoxyglucose (FDG) PET reported that patients with a history of violence showed decreased FDG uptake in the anterior inferior temporal regions [44]. Our high-resolution PET study extends the earlier investigation by showing that dopaminergic dysfunction within the limbic system, particularly the insula, underlies excitement symptoms. Our results are in line with previous suggestion that the neural circuit involving the insula and amygdala mediates impulsive aggression [45]. It has also been suggested that the insula and its associated neural circuit orchestrates necessary changes in behavioral response and that the functional integrity of the structures is associated with behavioral inhibition [45]. The insula is closely connected with the amygdala, hypothalamus, and periaqueductal gray matter, which together form a network that serves to appraise external stimuli and initiate autonomic responses [46]. In addition, the insula has been implicated as an important component of the neural circuits mediating impulsivity in schizophrenia [47]. A lack of cortico-subcortical limbic regulation may result in affective and behavioral dysregulation characterized by hostility, excitation, poor impulse control, and uncooperativeness.

The amygdala and insula were also suggested to be the main limbic regions of bottom-up drives associated with aggression [48]. Our results may support the notion that the imbalance between the top-down control system subserved by the frontal cortex and the bottom-up drives triggered by limbic regions including the insula and amygdala is implicated in the neurobiology of aggression in schizophrenia [48]. Coexisting cognitive impairments in patients with schizophrenia may further aggravate this imbalance [49]. The results of the present study along with previous findings on the significant relationship between striatal $D_{2/3}$ binding and antipsychotic response suggest that dopaminergic dysfunction in extrastriatal as well as striatal regions may underlie multiple symptom domains of schizophrenia. The present study also extends the findings of earlier studies on the importance of altered extrastriatal dopaminergic neurotransmission in schizophrenia [50, 51]. Interestingly, the right insula was one of the regions with the largest effect size, where the mean BP_{ND} was 53.6% lower in patients on antipsychotic treatment than in healthy controls. The result may further emphasize the role of the insula in the pathophysiology and treatment of symptoms of schizophrenia. However, due to the absence of antipsychotic-free baseline data, it is difficult to interpret this finding in relation to the significant correlation with the PANSS excitement factor. Prospective PET scans before and after treatment with antipsychotics in antipsychotic-free patients, as well as analysis of the correlations between changes in symptom severity and changes in BP_{ND} values are required to better understand the role of the insula in schizophrenia. It is possible that different antipsychotics may have differential effects on the excitement symptom dimension.

In addition, the excitement symptom dimension is not exclusively found in schizophrenia, but is frequently observed in various psychiatric disorders including affective disorders, anxiety disorders, and personality disorders. The excitement symptom domain is significantly associated with affective symptoms and a disinhibition of motor and language domains [52]. Therefore, it may well be that dopamine $D_{2/3}$ receptor availability in the insula and related limbic system may also contribute to excited or agitated behavior in healthy subjects or patients with non-psychotic psychiatric disorders, and may have no direct association with pathophysiology of schizophrenia. Future studies should employ various measures of excited behavior, impulsivity, and aggression in non-psychotic populations and in medication-naïve patients with schizophrenia to clarify the disease-specific, physiological and pharmacological causes of the relationship that was observed in the present study.

It should be noted that although previous studies have shown the utility of quantifying $D_{2/3}$ receptor availability in patients receiving stable antipsychotic treatment in evaluating the relationship with clinical characteristics [53–55], the present study has the limitation of being a cross-sectional study without a drug-free time point. Therefore, we could not calculate $D_{2/3}$ receptor occupancy by antipsychotics due to the absence of baseline (medication-free) PET data. The observed relationship between psychopathology and $D_{2/3}$ receptor availability might have been influenced by the antipsychotics that patients were taking at the time

of study enrollment. In our study, the daily chlorpromazine equivalent dose was not significantly correlated with the PANSS factor scores or the regional [^{18}F]fallypride BP_{ND} values. However, the chlorpromazine equivalent doses do not adequately represent differential bindings of various antipsychotics to $D_{2/3}$ receptors in extrastriatal and striatal regions. In addition, previous studies have shown that long-term antipsychotic treatment leads to differential changes in dopamine receptor availability depending on receptor subtypes, brain regions, and the types of antipsychotic medications [56, 57]. Moreover, the antipsychotics that patients were taking at the time of enrollment were not equal in terms of sedative effects, and excited patients may have received medications different from those that patients without excitement or agitation received. Therefore, the confounding effect of antipsychotic treatment can neither be corrected nor be ignored in the experimental design of the present study.

Previous in vivo SPECT study showed that the correlation between psychopathology and striatal dopamine parameters such as $D_{2/3}$ receptor availability and dopamine transporter availability is different between drug-naïve patients and haloperidol-treated patients [58]. In addition, in the present study, the antipsychotics that patients were taking at the time of the study were heterogeneous. Previous studies have shown that $D_{2/3}$ occupancy by aripiprazole is high in extrastriatal and striatal regions [13, 14] and that quetiapine yields a low occupancy and has a preferential binding to extrastriatal $D_{2/3}$ receptors [17]. Therefore, we cannot rule out the possibility that the variation of BP_{ND} values might be ascribed to antipsychotic treatment rather than psychopathology itself. BP_{ND} represents a combined parameter of the concentration of receptors available to bind with radioligand and the affinity of the radioligand for the receptor. The higher $D_{2/3}$ receptor availability could result from either an increase in $D_{2/3}$ receptor density or greater affinity of the radiotracer for the $D_{2/3}$ receptor [2]. Further study is warranted to clarify the relationship between specific symptom severity and extrastriatal $D_{2/3}$ receptor availability in schizophrenia, such as longitudinal studies including drug-naïve or drug-free time points.

The results of our study are in line with those of the study by Mizrahi et al. [59], where a significant correlation was found between the extrastriatal $D_{2/3}$ BP_{ND} measured with [^{11}C]FLB 457 in the insula and the subjective well-being score in patients with schizophrenia after 2 weeks of continuous antipsychotic treatment. In the study by Mizrahi et al. [59], the higher the BP_{ND} value (i.e., lower occupancy by antipsychotics) in the insula, the higher the Subjective Well-Being Under Neuroleptics Scale score. Since the functional activity of the insula has been implicated in subjective awareness of inner feelings and emotionality [60], it may be speculated that the feeling of detachment from one's emotions that could be induced by dopamine receptor blockade in the insula is a common cause of lower subjective well-being and reduced excitement scores in antipsychotic-treated patients with schizophrenia.

It should be noted that the [^{18}F]fallypride scan duration in our study was shorter than that in previous studies, which might have led to an underestimation of BP_{ND} values. Although the optimal [^{18}F]fallypride scan duration is a matter of debate, Vernaleken et al. [61] reported that [^{18}F]fallypride scan durations of 180 min reliably reached equilibrium and that moderate reductions in scan durations only caused small changes to SRTM-derived BP_{ND} results even in $D_{2/3}$ receptor-rich regions. Vernaleken et al. [61] suggested that 180-min duration is adequate for [^{18}F]fallypride PET scanning.

In the present study, the mean BP_{ND} value of the left insula was substantially higher than that of the right insula. Previous studies have suggested the possibility of lateralization of the striatal dopaminergic system in the human brain [62]. A study using [^{18}F]desmethoxyfallypride PET by Vernaleken et al. [63] revealed a significant rightward lateralization in $D_{2/3}$ receptor availability in the caudate of healthy men, suggesting a functional asymmetry in the striatal dopamine neurotransmission system. However, the functional asymmetries of $D_{2/3}$ receptors in extrastriatal regions are largely unknown, although asymmetrical involvement of mesolimbic dopaminergic neurons in affective-perceptual processes was suggested [64]. Therefore, further in vivo imaging studies with a large sample size using high-affinity ligands, e.g., [^{123}I]epidepride, are required to examine possible asymmetries of $D_{2/3}$ receptor availability in extrastriatal regions with low receptor density such as the limbic and cortical regions.

The strengths of the present study include the use of high-resolution PET imaging techniques. Compared with conventional scanners, the HRRT-PET system that was used in the present study has been reported to improve the quantification of monoamine neurotransmission parameters owing to reduced partial volume effects [65, 66].

The interpretation of the results of the present study should be considered in light of limitations. The relatively small sample size may not have provided adequate power to detect small-to-moderate effect sizes of the correlation coefficients. The symptom dimensions might be differentially affected by different antipsychotic drugs that were used in the present study. The cross-sectional measures of $D_{2/3}$ receptor availability do not necessarily account for occupancy of the receptor by endogenous dopamine. The $D_{2/3}$ receptors are configured in interconvertible states of high- or low-affinity for agonists [67], and antagonists, such as [^{18}F]fallypride, bind with equal affinity to both states. In addition, most antipsychotic drugs exert their effects on D_2 and D_3 receptors. However, [^{18}F]fallypride has nearly equal affinity

for both D_2 and D_3 receptors [68, 69]. Therefore, further studies using both [^{18}F]fallypride and an agonist radiotracer such as [^{11}C]PHNO [70] are required to elucidate whether the relationship between specific symptom severity and dopamine receptor availability is selectively associated with the high- or low-affinity state of $D_{2/3}$ receptors and whether the relationship is specifically related to D_3 receptors.

In conclusion, the present study, which used high-resolution imaging techniques and [^{18}F]fallypride, revealed a significant association between excitement symptom severity and $D_{2/3}$ receptor availability in the insula in patients with schizophrenia. This suggests that $D_{2/3}$ receptor-mediated neurotransmission in the insula and its related limbic system may play an important role in the pathophysiology of this specific cluster of symptoms. Further studies including drug-naïve or drug-free patients are warranted to confirm the relationship and to elucidate the extent to which antipsychotic treatment affects it.

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Compliance with ethical standards

Informed consent The study protocol was approved by the institutional review board of the Gachon University Gil Medical Center, and all procedures used in the study were conducted in accordance with international ethical standard, Declaration of Helsinki. All participants gave their written informed consent prior to their inclusion in the study.

Conflict of interest The authors declare that they have no conflicts of interest.

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