別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
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前田貴記、加藤元一郎、鹿島晴雄	統合失調症の認知機能障害研究　—陽性症状の形成機構—	山内俊雄	精神疾患と認知機能	新興医学出版社	東京	2009	187-194

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Ⅳ. 研究成果の刊行物・別刷

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Regional dopamine synthesis in patients with schizophrenia using L-[β-^{11}C]DOPA PET

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ABSTRACT

The dopamine hypothesis has been the most widely known theory concerning schizophrenia. However, the exact mechanism including presynaptic dopaminergic activity and its relationship with symptom severity still remains to be revealed. We measured presynaptic dopamine synthesis using positron emission tomography (PET) with L-[β-^{11}C]DOPA in 18 patients with schizophrenia (14 drug-naïve and 4 drug-free patients) and 20 control participants. Dopamine synthesis rates, expressed as k_i values, were obtained using a graphical method, and the occipital cortex was used as reference region. Regions of interest were placed on the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. Psychopathology was assessed with the Positive and Negative Symptom Scale (PANSS). We found significantly higher k_i values in patients than in controls in the left caudate nucleus, but not in the other regions. The k_i values in the thalamus exhibited a significant positive correlation with the PANSS total scores. Furthermore, a significant positive correlation was observed between the PANSS positive subscale scores and k_i values in the right temporal cortex. Patients with schizophrenia showed higher dopamine synthesis in the left caudate nucleus, and dopaminergic transmission in the thalamus and right temporal cortex might be implicated in the expression of symptoms in schizophrenia.

1. Introduction

Positron emission tomography (PET) has allowed us to investigate the dopamine hypothesis in living human brain. Since there is no ideal animal model of schizophrenia, PET investigation is still the most useful method for investigating neurotransmission in patients. As for postsynaptic dopaminergic receptors, several studies have investigated striatal (Farde et al., 1990; Nordström et al., 1995; Wong et al., 1986) and extrastriatal (Suhara et al., 2002; Yasuno et al., 2004) D_2 receptor (D_2R) binding by the use of PET. Although studies investigating D_2R in the striatum in schizophrenia have reported inconsistent findings, those focusing on extrastriatal D_2R binding have repeatedly reported its reduction in the anterior cingulate cortex (Suhara et al., 2002) and the thalamus in schizophrenia (Talvik et al., 2003; Yasuno et al., 2004). Regarding intrasynaptic function, striatal dopamine release was reported to be enhanced in schizophrenia (Breier et al., 1997; Laruelle et al., 1996). On the other hand, many studies did not find any change in dopamine transporter binding in the striatum of schizophrenia (Laakso et al., 2000;

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Laruelle et al., 2000; Schmitt et al., 2005; Yang et al., 2004). These findings suggest that patients with schizophrenia may have elevated presynaptic dopamine synthesis, and investigations on presynaptic dopaminergic function in extrastriatal regions might be critical for providing an understanding of the pathophysiology of schizophrenia.

Radiolabeled L-DOPA, a precursor of dopamine, has been used to investigate presynaptic dopamine synthesis. L-DOPA is transported through the blood–brain barrier (BBB), taken up by presynaptic monoaminergic neurons, and metabolized to dopamine by aromatic amino acid decarboxylase (AADC). Previous studies on the dopamine synthesis of schizophrenia used 6-[^{18}F]fluoro-L-DOPA (Dao-Castellana et al., 1997; Elkashef et al., 2000; Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994;) or L-[β-^{11}C]DOPA (Gefvert et al., 2003; Lindström et al., 1999). The studies with 6-[^{18}F]fluoro-L-DOPA, which is widely used in schizophrenia research, indicated elevated dopamine synthesis (Hietala et al., 1995, 1999; Lindström et al., 1999; McGowan et al., 2004; Reith et al., 1994), elevated dopamine turnover (Kumakura et al., 2007), only higher variability (Dao-Castellana et al., 1997), and even reduced synthesis (Elkashef et al., 2000) in the striatum.

The 3-O-methyl metabolite of L-DOPA crossing the BBB can reportedly cause an error in quantification of the dopamine synthesis rate (Dhawan et al., 1996; Melega et al., 1990; Wahl et al., 1994). However, 3-O-methylation of L-[β-^{11}C]DOPA does not take place readily and rapidly when compared with 6-[^{18}F]fluoro-L-DOPA (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Recently, we evaluated the accuracy of quantitative analyses of L-[β-^{11}C]DOPA PET studies (Ito et al., 2006). In the current study, we investigated regional dopamine synthesis and its relationship with the severity of positive and negative symptoms in patients with schizophrenia using L-[β-^{11}C]DOPA.

2. Methods

2.1. Participants

Fourteen (8 males and 6 females) drug-naïve and 4 (2 males and 2 females) 3-month drug-free patients (35.6± 7.4 years, mean±SD) meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia or schizophreniform disorder were recruited from the outpatient units of university hospitals, their affiliated psychiatric hospitals, and a mental clinic. On the day of the PET study, the diagnosis was re-evaluated by 3 experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). The severity of psychotic symptoms was also evaluated by the same 3 psychiatrists with the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Igarashi et al., 1998). Each interview was conducted by 2 of 3 authors (S.N., F.Y., M.O.) and one other psychiatrist. Patients with schizophreniform disorder (2 males and 2 females) at the time of the PET study were followed up for at least 6 months from onset, confirming that they eventually met the criteria of schizophrenia. Twenty (10 males and 10 females) healthy volunteers (35.1±9.5 years) were recruited as controls through public notices. All the subjects were examined by physicians to obtain data concerning their educational background as well as current and past medical problems, and family history by unstructured interview and a general questionnaire. Handedness was assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971). The control subjects were matched with the patients for age, gender, education, and handedness. They were confirmed to have neither psychiatric nor neurological disorders, nor any first-degree relatives with neuropsychiatric disorders. The demographic characteristics of all participants are shown in Table 1. Exclusion criteria of patients and controls were as follows: (1) major brain anomaly or organic brain disease; (2) current or past substance abuse including alcohol; (3) previous episodes of mood disorder. One patient was excluded because of a large cyst in the cerebellum (data not shown).

After giving explanation of the study, written informed consent was obtained from all patients and control subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

2.2. PET study

All the participants were instructed to fast for 4 h before PET scan in order to avoid the influence of the plasma concentration of neutral amino acid (NAA) on the L-[β-^{11}C]DOPA uptake rate. A PET scanner (ECAT EXACT HR, CTI-Siemens, Knoxville, TN), providing 63 planes with an axial field of view of 15.5-cm, was used. A head fixation device (Fixster, Stockholm Sweden) was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source. Data acquisition was performed in 3-dimensional mode with the interplane septa retracted. A bolus of 331.5 to 401.8 MBq (373.0±14.1 MBq, mean±SD) of L-[β-^{11}C]DOPA with specific radioactivities (9.9–156.4 GBq/μmol) was injected intravenously via the antecubital vein and flushed rapidly with 20 mL of saline. Dynamic scans were performed for 64 min immediately after the injection. The scanning sequence consisted of seven 1-min frames, five 2-min frames, four 3-min frames, and seven 5-min frames. All emission scan data were reconstructed with a Hanning filter with a cutoff frequency of 0.4 (final in-plane resolution: 7.5 mm full width at half maximum).

Table 1
Demographic and clinical characteristics of patients with schizophrenia and normal controls

	Controls (n=20)	Patients (n=18)
Gender, M/F	10/10	10/8
Age, y, mean±SD	35.1±9.5	35.6±7.4
Range	20–55	20–52
Medication, no. naïve (M/F)/free (M/F)		14 (8/6)/4 (2/2)
Handedness, no. right/left	20/0	18/0
Education, y, mean (range)	15.1 (12–9)	14.1 (9–16)
No. of smokers (M/F)	4 (4/0)	6 (4/2)
Duration of illness, mo, mean (range)		26.4 (1–120)
PANSS		
Whole score		
Mean±SD		79.2±21.4
Range		46–124
Subscales		
Positive (mean±SD)		22.6±7.3
Negative (mean±SD)		17.1±6.5
General psycho (mean±SD)		39.6±11.0

Table 2
k_i values of each ROI in patients with schizophrenia and normal controls

Region	L/R	Controls	Patients	ANCOVA#	
		(n=20)	(n=18)	F	p
Parahippocampus	L	4.54±1.13	4.91±1.45	0.704	0.407
	R	4.76±1.11	4.47±1.29	0.528	0.472
Temporal cortex	L	1.92±0.99	1.98±0.81	0.041	0.842
	R	1.86±0.83	1.92±0.87	0.037	0.849
Prefrontal cortex	L	1.31±0.73	1.22±0.64	0.324	0.573
	R	1.35±0.73	1.35±0.57	0	1.000
Thalamus	L	3.55±1.60	3.19±1.72	0.549	0.463
	R	3.11±1.45	3.09±1.54	0.001	0.970
Putamen	L	15.52±2.04	15.76±2.14	0.139	0.711
	R	15.39±2.31	14.90±3.01	0.329	0.570
Caudate	L	12.89±2.68	14.66±2.38	4.409	0.043*
	R	13.71±2.74	13.59±2.09	0.026	0.872
Anterior cingulate	L	2.74±1.33	3.05±1.50	0.445	0.509
	R	3.24±1.73	3.00±1.13	0.288	0.595

Dopamine synthesis rates, expressed as $k_i \times 1000$, were presented as mean± standard deviation.
#: Analysis of covariance with age as covariate (df= 1, 35).
L indicates left and R indicates right. The symbol * represents $p<0.05$.

2.3. Magnetic resonance images

For each participant, a structure magnetic resonance (MR) image was obtained. All MR imaging studies were performed with a 1.5-Tesla MR scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (echo time, TE: 9.2 ms; repetition time, TR: 21 ms; flip angle: 30°; field of view: 256 mm; acquisition matrix: 256×256; slice thickness: 1 mm).

2.4. Data analysis

All MR images were coregistered to the PET summation images of all frames using statistical parametric mapping 2 (SPM2; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Regions of interest (ROIs) were drawn on the coregistered MR images, referring to the human brain atlas (Mai et al., 1997), and then transferred to the PET images. ROIs were defined for the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. The ROIs were set on both left and right sides of the brain and those values were independently evaluated. To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time.

The overall uptake rate constant k_i of L-[β-^{11}C]DOPA, which indicates the net dopamine synthesis rate, was determined for each ROI by the graphical plot analysis method developed by Gjedde and Patlak (Gjedde, 1982; Ito et al., 2006; Patlak and Blasberg, 1985). k_i values can be estimated by simple linear least-squares fitting as follows:

$$\frac{C_i(t)}{C_i'(t)} = k_i \frac{\int_0^t C_i'(\tau)d\tau}{C_i'(t)} + F_{t>t^*}$$

where C_i is the total radioactivity concentration in a brain region that can be measured by PET, C_i' is the total radioactivity concentration in the reference brain region with no irreversible compartments, and t^* is the equilibrium time of the compartment for unchanged radioligand in the brain tissue. Plotting $C_i(t)/C_i'(t)$ versus $\int_0^t C_i'(\tau)d\tau/C_i'(t)$, after the time t^*, yields a straight line with the slope k_i and intercept F. In the present study, the occipital cortex was used as reference region (Ito et al., 2006). A range of equilibrium time t^* of 31.5 to 61.5 min was used.

ROI analyses were independently performed by 3 researchers who were blinded to the diagnoses. The intraclass correlation coefficient across all ROIs was 0.976 (McGraw and Wong, 1996), considered as excellent. In order to reduce variance, the k_i values by one researcher that most frequently showed medium values among those obtained by the 3 researchers were used for the following analyses.

2.5. Statistical analysis

Demographic variables were compared by independent sample t-test or chi-square test. Differences in the k_i values for each of the 7 × 2 brain regions between patients and controls were evaluated by one-way univariate analyses of covariance with age as a covariate, since an effect of age on k_i values has been reported (Ota et al., 2006). Pearson's correlation coefficients were calculated between the PANSS scores and k_i values. A significance level of $p<0.05$ (two-tailed) was used both in the comparison analyses between groups and in the correlation analyses.

3. Results

3.1. Demographic data

The demographic data of schizophrenia patients and controls are shown in Table 1. There were no significant differences between patients and controls in terms of age, gender, education, handedness, and the injected dose and

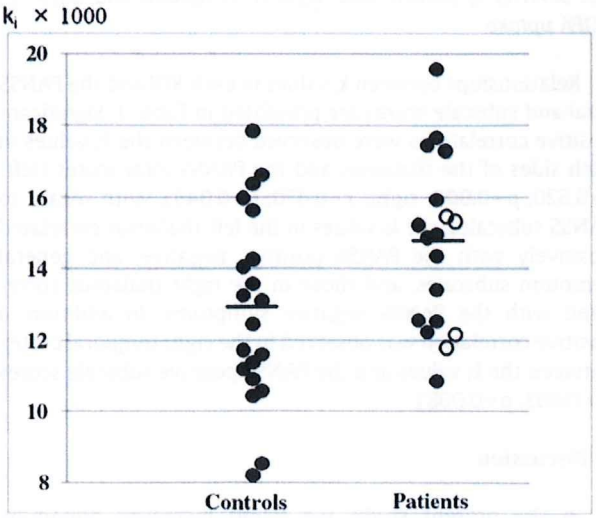

Fig. 1. Comparison of k_i values between patients with schizophrenia and control subjects in the left caudate nucleus. Horizontal lines represent mean values of the groups. Among patients, the closed circles indicate the values of antipsychotic drug-naïve patients, whereas the open circles indicate those of drug-free patients.

Table 3
Correlations between k_i values of each ROI and PANSS scores in schizophrenia

Region	L/R	Total scores		Positive symptoms		Negative symptoms		General symptoms	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Parahippocampus	L	−0.003	0.992	0.045	0.859	0.080	0.752	−0.083	0.745
	R	0.284	0.253	0.288	0.246	0.197	0.434	0.245	0.328
Temporal cortex	L	−0.088	0.728	0.133	0.598	−0.049	0.848	−0.232	0.355
	R	0.465	0.052	0.603	0.008*	0.242	0.334	0.361	0.141
Prefrontal cortex	L	0.380	0.120	0.288	0.246	0.339	0.168	0.346	0.160
	R	0.407	0.094	0.302	0.082	0.457	0.057	0.320	0.196
Thalamus	L	0.620	0.006*	0.490	0.039*	0.504	0.033*	0.589	0.010*
	R	0.470	0.049*	0.378	0.122	0.492	0.038*	0.372	0.129
Putamen	L	0.247	0.323	0.177	0.482	0.342	0.165	0.160	0.525
	R	0.359	0.143	0.327	0.186	0.407	0.094	0.240	0.338
Caudate	L	0.287	0.323	0.294	0.236	0.319	0.197	0.174	0.490
	R	−0.183	0.468	−0.223	0.375	0.021	0.935	−0.220	0.380
Anterior cingulate	L	−0.270	0.120	0.202	0.421	−0.418	0.085	−0.412	0.089
	R	0.355	0.149	0.421	0.082	0.303	0.222	0.231	0.357

L indicates left and R indicates right.
The symbol * represents $p<0.05$.

specific radioactivity of L-[β-^{11}C]DOPA. The duration of illness and the PANSS scores are also shown in Table 1.

3.2. Regional L-[β-^{11}C]DOPA uptake in schizophrenia and control subjects

Univariate analysis of covariance revealed no significant interaction between group and age in any of the regions, and a significant group difference in k_i values only for the left caudate between normal controls and schizophrenia patients was observed (df= 1, 35, F=4.409, p=0.043; Table 2 and Fig. 1). In addition, no significant difference was observed in the k_i values between antipsychotic drug-naïve and drug-free patients in any of the regions.

Furthermore, there was no significant correlation between the k_i values in any ROIs and the duration of illness in patients.

3.3. Severity of positive and negative symptoms and L-[β-^{11}C] DOPA uptake

Relationships between k_i values in each ROI and the PANSS total and subscale scores are presented in Table 3. Significant positive correlations were observed between the k_i values in both sides of the thalamus and the PANSS total scores (left: r=0.620, p=0.006; right: r=0.470, p=0.049). With regard to PANSS subscales, the k_i values in the left thalamus correlated positively with the PANSS positive, negative, and general symptom subscales, and those in the right thalamus correlated with the PANSS negative symptoms. In addition, a positive correlation was observed in the right temporal cortex between the k_i values and the PANSS positive subscale scores (r=0.603, p=0.008).

4. Discussion

In the present study, we found increased dopamine synthesis in the left caudate nucleus in patients with schizophrenia compared to normal controls. In addition, we observed a significant correlation between regional dopamine synthesis in the thalamus as well as in the right temporal cortex and symptom severity in patients.

Most of the previous studies with 6-[^{18}F]fluoro-L-DOPA have reported elevated dopamine synthesis mainly in the striatum of patients with schizophrenia (Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994), whereas decreased (Elkashef et al., 2000) or only greater variability (Dao-Castellana et al., 1997) have also been reported in this region. There are some plausible explanations for these inconsistent results. First, the participants with schizophrenia in these studies were not homogeneous. For example, one study investigated heterogeneous patients with psychosis (Reith et al., 1994), while the other studies included patients with schizoaffective disorder (Hietala et al., 1995, 1999). Furthermore, schizophrenia patients on antipsychotic medication participated in two of the PET studies (Elkashef et al., 2000; McGowan et al., 2004). Interestingly, a study on only unmedicated schizophrenia patients showed only greater variability in k_i values compared with normal controls (Dao-Castellana et al., 1997). Second, the differences between 6-[^{18}F]fluoro-L-DOPA and L-[β-^{11}C]DOPA in terms of 3-O-methyl metabolite of L-DOPA crossing the BBB might also result in such inconsistency (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Kumakura et al. reported a method to reduce this problem with metabolites and demonstrated that catabolism and elimination of 6-[^{18}F]fluoro-L-DOPA was elevated nearly 2-fold in the striatum in 8 patients with schizophrenia as compared to that in 15 age-matched control subjects. They concluded that not only the synthesis but also the turnover of radiolabeled dopamine was increased in patients with schizophrenia (Kumakura et al., 2007).

Lindström et al. (1999) investigated unmedicated schizophrenia patients using L-[β-^{11}C]DOPA and found increased dopamine synthesis in the striatum and medial prefrontal cortex, while we observed elevated dopamine synthesis only in the left caudate. As for differences between the two studies, however, the patients in the study of Lindström et al. had relatively more severe psychotic symptoms (Clinical Global Impression ≥4) than our patients. In addition, our patients were mostly outpatients, and thus, such a difference in the demographic of patients might be responsible for the difference in results. In addition, the caudate nucleus might be more important than the putamen in the pathophysiology

of schizophrenia because the caudate has extensive interconnections from the limbic and cortical areas, which play crucial roles in the regulation of cognition and emotion compared to the putamen (Parent, 1990). Further, lateralization to the left of the caudate is consistent with the reports by Hietala et al. (1995, 1999).

With regard to the relationships with symptoms, in our patients, presynaptic dopamine synthesis in the thalamus was positively correlated with overall symptom severity, although that in the right thalamus was correlated only with PANSS negative scores, besides the PANSS total scores; in addition, dopamine synthesis in the right temporal cortex was positively correlated with positive symptoms. The thalamus has been repeatedly reported to be engaged in the pathophysiology of schizophrenia (Clinton and Meador-Woodruff, 2004; Takahashi et al., 2006). Previous neuroimaging studies have shown altered thalamic perfusion and metabolism (Andreasen et al., 1997; Buchsbaum et al., 1996; Clark et al., 2001; Hazlett et al., 1999, 2004; Kim et al., 2000; Mitelman et al., 2005; Resnick et al., 1988) and decreased dopamine D_2 receptor availability in the thalamus in patients with schizophrenia (Buchsbaum et al., 2006; Talvik et al., 2003, 2006; Yasuno et al., 2004). The thalamus is reported to have a pivotal role in the processing and integrating of sensory information related to emotional and cognitive functions (Clinton and Meador-Woodruff, 2004), and it has also been suggested to have sensory gating function (Carlsson et al., 2000; Takahashi et al., 2006). Further, elevated dopamine transmission in the thalamus was reported to disrupt sensory gating function (Young et al., 1995). Impaired gating function could contribute to both positive and negative symptoms by the inability to automatically "gate out" much redundant and unessential information, leading to irrelevant thought and fragmentation of mind and behavior in schizophrenia (Braff et al., 1999). Additionally, one study with 6-[^{18}F]fluoro-L-DOPA examined before and after 5 weeks of haloperidol treatment for schizophrenia demonstrated that the thalamus was the only structure in which the change of dopamine synthesis was related to improvement in negative symptoms (Gründer et al., 2003). Thus, dopaminergic regulation in the thalamus might be associated with positive and negative symptoms in schizophrenia. However, the contribution of different roles of each side of the thalamus to diverse symptom dimensions remains unclear.

In terms of the correlation between dopamine synthesis in the right temporal cortex and the PANSS scale, our data suggested that higher dopamine synthesis in the right temporal cortex might be associated with the expression of positive symptoms in patients with schizophrenia. Previous functional MRI studies have demonstrated the involvement of the right temporal cortex in some of the positive symptoms such as auditory hallucination (Shergill et al., 2000; Woodruff et al., 1997) and formal thought disorder (Kircher et al., 2002) in schizophrenia. On the other hand, although previous PET (Buchsbaum et al., 2006) and SPECT (Tuppurainen et al., 2003) studies have suggested decreased dopamine D_2R binding in the right temporal cortex, no significant correlation was found between the binding and positive symptoms. Furthermore, no study has demonstrated the relationship between presynaptic dopamine synthesis in the right temporal cortex and positive symptoms.

There are several limitations in the present study. First, smoking is regarded as a confounding factor in the estimation of k_i values (Salokangas et al., 2000), and some of our participants were smokers, although the smoking rate of the patients was only slightly higher than that of the normal controls (33% for patients and 20% for controls). Second, our patients consisted of both males and females, although we selected age- and gender-matched control subjects. Laakso et al. (2002) indicated gender differences in striatal dopamine synthesis with the use of 6-[^{18}F]fluoro-L-DOPA PET. However, we did not find such differences in our subjects (data not shown). Nonetheless, since gender differences have been suggested in schizophrenia (Salem and Kring, 1998), this issue should be addressed in future studies. Finally, although our sample size is hitherto the largest among reported studies on dopamine synthesis in schizophrenia, the current study may still not have enough power. Our results of both comparison and correlation analyses were significant only when uncorrected for multiple comparisons, and the failure to observe significant correlations with symptoms in other regions might be due to a type II error. Therefore, further investigations using still larger samples are required.

5. Conclusion

We measured the dopamine synthesis rate in patients with schizophrenia and normal control subjects by using PET with L-[β-^{11}C]DOPA. Patients had higher dopamine synthesis in the left caudate nucleus than controls, which was in line with the results of most previous studies that indicated an increase in dopamine synthesis in the striatum. Moreover, correlation analyses between k_i values and symptoms suggested that dopamine synthesis in the thalamus and right temporal cortex might be implicated in the pathophysiology of schizophrenia. There is little evidence concerning extrastriatal presynaptic dopaminergic functions of schizophrenia in vivo. Further studies are required to better understand the presynaptic dopaminergic functions of schizophrenia.

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Contributors

S. Nozaki, F. Yasuno, A. Takano, and T. Suhara designed the study and wrote the protocol. S. Nozaki, M. Kato, F. Yasuno, M. Ota, A. Otsuka, and Y. Okubo recruited the patients and made psychiatric evaluations. S. Nozaki, H. Takano, M. Okumura, R. Arakawa, R. Matsumoto, and Y. Fujimura participated in the data analysis. S. Nozaki wrote the first draft of the manuscript. S. Nozaki, M. Kato, H. Takano, H. Takahashi, H. Ito, H. Kashima and T. Suhara had discussions and corrected the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors have no conflict of interest.

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Increase in thalamic binding of [^{11}C]PE2I in patients with schizophrenia: A positron emission tomography study of dopamine transporter

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ABSTRACT

Previous *in vivo* imaging studies reported no difference in dopamine transporter (DAT) bindings in the striatum between control subjects and patients with schizophrenia. However, as the signals of radioligands with moderate affinity were insufficient for allowing the evaluation of small amounts of DAT, DAT binding in extrastriatal regions has not been determined. Positron emission tomography scanning using [^{11}C]PE2I was performed on eight patients with schizophrenia and twelve normal control subjects. Binding potential (BP_{ND}) for DAT in the caudate, putamen, thalamus and substantia nigra was calculated, using the cerebellum as reference region. In patients with schizophrenia, clinical symptoms were evaluated by Positive and Negative Syndrome Scale (PANSS). BP_{ND} in the thalamus of patients with schizophrenia was significantly higher than in control subjects ($P = 0.044$). In patients with schizophrenia, there were significantly positive correlations between BP_{ND} in the thalamus and total ($r = 0.75$), positive ($r = 0.78$) and negative PANSS scores ($r = 0.82$). Altered DAT in the thalamus might be related to the pathophysiology and clinical symptoms of schizophrenia.

1. Introduction

One of the most accepted hypotheses concerning the pathophysiology of schizophrenia are the hyperactivity of dopaminergic neurotransmission. This 'dopamine hypothesis' is supported by the facts that antipsychotic effects are mainly related to dopamine D_2 receptor antagonism and that dopamine stimulating agents can cause psychotic symptoms such as hallucination or delusion. Dopamine transporter (DAT) plays a role in the reuptake of dopamine into pre-synaptic nerves and regulates dopaminergic transmission in the synaptic cleft. DAT inhibitors such as cocaine increase dopamine concentration in the synaptic cleft (Schlaepfer et al., 1997) and worsen the clinical course of schizophrenia, e.g., exacerbating positive and negative symptoms, increasing the risk of relapse, or hospitalization (Green, 2005).

Previous *in vivo* imaging studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) reported no difference in DAT bindings between control subjects and patients with schizophrenia (Hsiao et al., 2003; Laakso et al., 2000; Laruelle et al., 2000; Lavalaye et al., 2001; Schmitt et al., 2005, 2006, 2008; Yang et al., 2004) except for one study reporting lower binding in patients with schizophrenia as compared with controls (Mateos et al., 2007). However, those studies evaluated DAT binding only in the striatum, as DAT density in extrastriatal regions is very low (in a postmortem human study, [^{125}I]PE2I binding in the thalamus was reported to be 15% of that in the striatum and negligible in the cortex) (Hall et al., 1999). The recent development of [^{11}C]PE2I, which has high affinity ($K_i = 17$ nM) and selectivity (more than 30-fold for other monoamine transporters) for DAT, allows the evaluation of extrastriatal DAT bindings (Halldin et al., 2003; Hirvonen et al., 2008; Jucaite et al., 2006). In this study, we evaluated DAT binding in the striatal and extrastriatal regions of patients with schizophrenia using [^{11}C]PE2I.

2. Materials and methods

2.1. Subjects

Eight patients (age range 25–52 yr, mean ± SD: 36.5 ± 9.5 yr) diagnosed with schizophrenia or schizophreniform disorder according to DSM-IV criteria participated in this study. Four patients with schizophreniform disorder met the criteria for schizophrenia at six month follow-up. Exclusion criteria were current

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Table 1
Demographic and clinical characteristics.

	Controls	Patients
N	12	8
Age (years)	33.2 ± 12.0	36.5 ± 9.5
Gender (M/F)	10/2	6/2
Naïve/free		6/2
Duration of illness (months)		32.1 ± 42.8
PANSS (total)		77.8 ± 18.8
Positive		17.8 ± 4.8
Negative		18.9 ± 6.5
General		41.1 ± 10.8

Values are mean ± SD.

or past substance abuse, organic brain disease, or epilepsy. Demographic and clinical data are shown in Table 1. Six of the patients were antipsychotic naïve and two had been antipsychotic-free for at least six months before the PET scan. Three patients had taken benzodiazepines the night before the PET scan.

Psychopathological symptoms were assessed by three experienced psychiatrists on the same day as the PET scans using the Positive and Negative Syndrome Scale (PANSS), and consensus ratings were used. PANSS scores used were total score and subscores for positive symptom, negative symptom and general symptom.

Twelve normal control subjects (age range 23–56 yr, mean ± SD: 33.2 ± 12.0 yr) also participated. None of them had a history of psychiatric or neurological disorders, brain injury, chronic somatic illness, or substance abuse. None had taken any drugs within two weeks before the PET scan.

After complete description of this study, written informed consent was obtained from all subjects. The study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. Data were collected from 4/2003 to 8/2006.

2.2. PET procedure

A PET scanner system, ECAT EXACT HR+(CTI-Siemens, Knoxville, TN, USA), was used for all measurements. A head fixation device was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source before each scan. A dynamic PET scan was performed for 90 min (20 s × 9, 1 min × 5, 2 min × 4, 4 min × 11, 5 min × 6) after intravenous bolus injection of 214.7 ± 13.7 MBq (mean ± SD) of [^{11}C]PE2I. The specific radioactivity of [^{11}C]PE2I was 344.5 ± 355.3 MBq/nmol. Injected dose and specific radioactivity between the control and patient groups were not significantly different (two-tailed *t*-test; $P = 0.15$ and $P = 0.16$, respectively). Since two previous quantitative studies of [^{11}C]PE2I had reported good reliability with scan times of 63 and 69 min, the scan time of 90 min was considered sufficient for estimation of DAT bindings especially in extrastriatal regions (Hirvonen et al., 2008; Jucaite et al., 2006). Magnetic resonance (MR) images of the brain were acquired with a 1.5 Tesla MR imaging system, Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images were obtained at 1 mm slices. All subjects were free of organic brain lesions.

2.3. Data analysis

All MR images were coregistered to the PET images using the statistical parametric mapping (SPM2) system. MR images were transformed into the standard brain size and shape by SPM2 (anatomic standardization). All PET images were also transformed into the standard brain size and shape using the same parameters as the MR image standardization. Thus, brain images of all subjects had the same anatomic format (Ito et al., 2008). Motion corrections were not made.

Regions of interest (ROIs) were drawn on all anatomically standardized PET images with reference to the T1-weighted MR images. ROIs were defined for the cerebellar cortex, caudate head, putamen, substantia nigra and thalamus (Fig. 1).

Binding potential (BP_{ND}) was calculated by the simplified reference tissue model (SRTM) method. The cerebellum was used as reference region because of its negligible density of DAT (Hall et al., 1999). In this study, the software package PMOD (PMOD Technologies, Zurich, Switzerland) was used to calculate BP_{ND}.

2.4. Statistics

Statistical analysis concerning the difference of BP_{ND} for each ROI between patients and controls was performed by two-tailed *t*-test. Correlations between BP_{ND} of patients with schizophrenia and age, duration of illness, and PANSS scores were evaluated using Pearson's correlation coefficient. In all analyses, $P < 0.05$ was considered significant.

3. Results

The BP_{ND} values of control subjects and patients with schizophrenia are shown in Table 2. The BP_{ND} value in the thalamus was significant higher in patients with schizophrenia than in con-

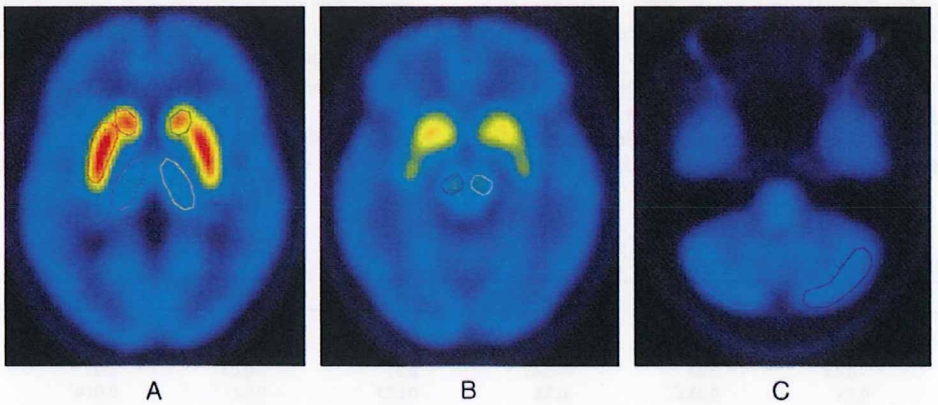

Fig. 1. Summated images of [^{11}C]PE2I with regions of interest. Average normalized images of twelve control subjects are shown at the level of caudate, putamen and thalamus (A), substantia nigra (B) and cerebellum (C).

Table 2
BP_{ND} in all regions.

	BP_{ND}[a]				*t*-test	
Region	Controls	Patients	% Change[b]	Effect size	*t*	*P*
Caudate	7.54 ± 1.22	8.21 ± 1.38	8.9 ± 18.4 (−6.5–24.2)%	0.55	1.14	0.27
Putamen	7.54 ± 1.25	8.23 ± 0.71	9.2 ± 9.4 (1.3–17.0)%	0.55	1.41	0.18
Thalamus	0.28 ± 0.08	0.36 ± 0.07	27.9 ± 25.8 (6.3–49.5)%	1.0	2.16	0.044*
Substantia nigra	1.09 ± 0.16	1.13 ± 0.12	4.1 ± 11.3 (−5.3–13.6)%	0.25	0.66	0.52

[a] Values are mean ± SD.
[b] Values are mean ± SD and 95% confidence interval.
* $P < 0.05$.

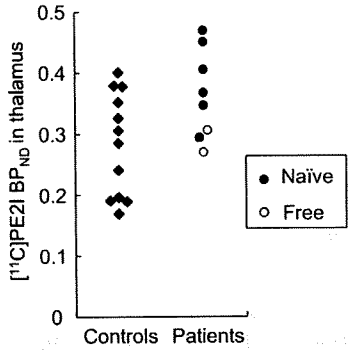

Fig. 2. BP_{ND} in the thalamus of normal controls and patients with schizophrenia. BP_{ND} of patients with schizophrenia was significantly higher than that of the control group (df = 18, $t = 2.16$, $P = 0.044$).

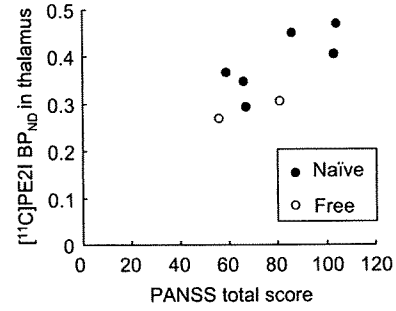

Fig. 3. Relationship between BP_{ND} in the thalamus of patients with schizophrenia and total PANSS score. There were significantly positive correlations between BP_{ND} and total PANSS score ($r = 0.75$, $P = 0.032$).

trols (df = 18, $t = 2.16$, $P = 0.044$) (Table 2, Fig. 2). There were no significant differences in BP_{ND} between the two groups in the caudate, putamen or substantia nigra. In patients with schizophrenia, there were significant positive correlations between BP_{ND} in the thalamus and total PANSS score ($r = 0.75$, $P = 0.032$), positive ($r = 0.78$, $P = 0.023$) and negative PANSS scores ($r = 0.82$, $P = 0.014$), but no correlation was observed with the general PANSS score (Table 3, Fig. 3). There was no significant correlation between BP_{ND} in other regions and clinical symptoms. There was also no significant correlation between BP_{ND} in each region and age or duration of illness.

4. Discussion

The *in vivo* evaluation of thalamic DAT had not been previously performed in detail due to its very low density as compared to that in the striatum (Hall et al., 1999). [^{11}C]PE2I allows the estimation of specific binding in low density regions because of its high affinity and selectivity for DAT (Halldin et al., 2003; Hirvonen et al., 2008; Jucaite et al., 2006). In this study, BP_{ND} in the thalamus of patients with schizophrenia was significantly higher than that of control subjects and was positively correlated with clinical symptoms. There was no significant difference in the area under the time activity curves of the cerebellum between controls and the patient group (two-tailed *t*-test; $P = 0.37$), suggesting that the higher DAT bindings were not due to cerebellar difference. An effect of endogenous dopamine on [^{11}C]PE2I binding has not been reported. However, as [^{11}C]PE2I is a high-affinity radioligand ($K_i = 17$ nM), it is reasonable to expect such an effect based on the result from a high-affinity ralioligand for serotonin transporter, [^{11}C]DASB ($K_i = 1.1$ nM) (Wilson et al., 2000). [^{11}C]DASB binding did not change by manipulation of endogenous serotonin in human brain (Praschak-Rieder et al., 2005; Talbot et al., 2005). Although these results may not apply directly to [^{11}C]PE2I binding, high [^{11}C]PE2I binding can nevertheless be interpreted as high DAT density.

The thalamus has been considered as the key brain structure of processing or integrating sensory information related to emotional or cognitive functions (Clinton and Meador-Woodruff, 2004). Several studies have reported morphological abnormalities of the thalamus in patients with schizophrenia using MR imaging or postmortem studies (Clinton and Meador-Woodruff, 2004). Regarding dopaminergic transmission, increased dopamine concentrations in the thalamus of patients with schizophrenia were reported in a postmortem study (Oke and Adams, 1987). The distribution of dopaminergic innervation in the thalamus was reported recently using immunohistochemistry in monkey (Melchitzky and Lewis, 2001) and human brain (Garcia-Cabezas et al., 2007). These studies reported that thalamic dopamine or DAT was relatively higher in the midline and mediodorsal nuclei. In patients

Table 3
Correlation between regional BP_{ND} and PANSS scores.

	Total		Positive		Negative		General	
Region	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Caudate	−0.04	0.93	0.03	0.95	0.10	0.81	−0.14	0.74
Putamen	−0.44	0.28	−0.42	0.31	−0.03	0.93	−0.55	0.15
Thalamus	0.75	0.032*	0.78	0.023*	0.82	0.014*	0.47	0.24
Substantia nigra	0.04	0.93	0.26	0.53	0.03	0.94	−0.07	0.86

* $P < 0.05$.

with schizophrenia, lower dopamine D_2 receptor binding was observed in the thalamus using PET with [^{11}C]FLB457 (Buchsbaum et al., 2006; Talvik et al., 2003; Yasuno et al., 2004) and [^{11}C]raclopride (Talvik et al., 2006). Significant differences in calcyon and spinophilin, dopamine receptor-associated intracellular proteins, and no difference in vesicular monoamine transporter (VMAT) binding of the thalamus were reported in a postmortem study of patients with schizophrenia and controls (Clinton et al., 2005). Assuming that low dopamine D_2 receptor binding is related to the disruption of the feedback system of dopamine release mediated by GABA interneuron (Takahashi et al., 2006), a high turnover of dopamine at the synapse would exist as a hyper-dopaminergic state. Although the function of DAT in the thalamus has remained unclear, high DAT bindings may suggest a hyper-dopaminergic state of pre-synaptic dopamine function in patients with schizophrenia.

Most of the previous PET and SPECT studies reported that DAT binding in the striatum did not differ between subjects and patients with schizophrenia (Hsiao et al., 2003; Laakso et al., 2000; Laruelle et al., 2000; Lavalaye et al., 2001; Schmitt et al., 2005, 2006, 2008; Yang et al., 2004), and our present results were in line with these reports. DAT binding in the substantia nigra also showed no difference between control subjects and patients with schizophrenia. However, BP_{ND} in the striatum using SRTM can be underestimated as compared to the values by kinetic model analyses with arterial blood sampling (Hirvonen et al., 2008; Jucaite et al., 2006). This might affect the results in the striatum.

In this study, the number of subjects was small, and in the statistical analysis we did not perform multiple comparisons regarding group differences of BP_{ND} between patients and controls to avoid type II error. Moreover, two of the eight patients were in a drug-free state, not drug-naïve state. Nonetheless, even when the two drug-free patients were excluded, the group difference of BP_{ND} in the thalamus was still observed (two-tailed t-test; $P = 0.018$). Further study with larger numbers of subjects in a drug-naïve state will be needed.

In conclusion, [^{11}C]PE2I binding in the thalamus of patients with schizophrenia was significantly higher than in control subjects and was correlated with clinical symptoms. Altered DAT in the thalamus might be related to the pathophysiology and clinical symptoms of schizophrenia.

Conflict of interest

All authors have no conflicts of interest.

Contributors

R. Arakawa, T. Ichimiya, A. Takano, F. Yasuno, and T. Suhara designed the study and wrote the protocol. R. Arakawa, T. Ichimiya, A. Takano, M. Okumura, H. Takahashi, H. Takano, F. Yasuno, M. Kato, and Y. Okubo recruited the patients and made psychiatric evaluations. R. Arakawa, H. Ito, M. Okumura, H. Takahashi, and H. Takano participated in the data analysis. R. Arakawa wrote the first draft of the manuscript. R. Arakawa, H. Ito, H. Takahashi, H. Takano, M. Kato, Y. Okubo, and T. Suhara had discussions and corrected the manuscript. All authors contributed to and have approved the final manuscript.

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ORIGINAL INVESTIGATION

Dopamine D_2 receptor occupancy by perospirone: a positron emission tomography study in patients with schizophrenia and healthy subjects

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Abstract
Rationale Perospirone is a novel second-generation antipsychotic drug with high affinity to dopamine D_2 receptor and short half-life of plasma concentration. There has been no investigation of dopamine D_2 receptor occupancy in patients with schizophrenia and the time course of occupancy by antipsychotics with perospirone-like properties.
Objective We investigated dopamine D_2 receptor occupancy by perospirone in patients with schizophrenia and the time course of occupancy in healthy subjects.
Materials and methods Six patients with schizophrenia taking 16–48 mg/day of perospirone participated. Positron emission tomography (PET) scans using [^{11}C]FLB457 were performed on each subject, and dopamine D_2 receptor occupancies were calculated. Moreover, baseline and three serial PET using [^{11}C]raclopride were performed at 1.5, 8, and 25.5 h after administration of a single dose of 16 mg of perospirone on four healthy male subjects, and occupancy was calculated for each scan.
Results Dopamine D_2 receptor occupancy in the temporal cortex of patients ranged from 39.6% to 83.8%. Especially, occupancy in two patients who took 16 mg of perospirone 2.5 h before PET was over 70%. Mean occupancy in the striatum of healthy subjects was 74.8% at 1.5 h, 60.1% at 8 h, and 31.9% at 25.5 h after administration.
Conclusion Sixteen milligrams of perospirone caused over 70% dopamine D_2 receptor occupancy near its peak level, and then occupancy dropped to about half after 22 h. The time courses of receptor occupancy and plasma concentration were quite different. This single dosage may be sufficient for the treatment of schizophrenia and might be useful as a new dosing schedule choice.

Keywords Dopamine D_2 receptor occupancy · Perospirone · Positron emission tomography · Schizophrenia · Time course

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Introduction

Perospirone is a novel second-generation antipsychotic drug used in Japan (Onrust and McClellan 2001). This drug shows high affinity to dopamine D_2 receptor (K_i= 1.77 nM) and serotonin 5-HT_2 receptor (K_i=0.06 nM; Takahashi et al. 1998), and its plasma concentration has a short half-life ($T_{1/2}$=1.9 h; Yasui-Furukori et al. 2004). A previous positron emission tomography (PET) study using [^{11}C]raclopride and [^{11}C]NMSP in healthy subjects with single 8 mg of perospirone showed blockage of both dopamine D_2 receptor and serotonin 5-HT_2 receptor (Sekine et al. 2006), but the optimal dose of perospirone in patients with schizophrenia has not been investigated.

Kapur et al. (2000b) reported that transient high dopamine D_2 receptor occupancy by quetiapine showed clinical effects for patients with schizophrenia. They suggested that this transient occupancy was related to "atypical" features of second-generation antipsychotics

with low affinity for dopamine D_2 receptor (Kapur and Seeman 2001). Plasma pharmacokinetics and affinity for receptor were considered to affect the time course of receptor occupancy (Kapur and Seeman 2001; Takano et al. 2004). However, the time course of receptor occupancy by antipsychotics with high affinity for dopamine D_2 receptor and a short half-life of plasma concentration has not been investigated.

In this study, we investigated dopamine D_2 receptor occupancy by several doses of perospirone in patients with schizophrenia. Moreover, we investigated the time course of dopamine D_2 receptor occupancy by perospirone with serial PET scanning in healthy subjects.

Materials and methods

This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. After complete explanation of this study, written informed consent was obtained from all subjects.

Patient study

Subjects and study protocol

Six patients aged 26–44 years (34.9±7.1, mean ± SD), diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders-IV criteria, participated in this study (Table 1). Exclusion criteria were current or past substance abuse, brain tumor or vascular disease, and history of severe head injury or epilepsy. Subjects with severe liver or renal dysfunction, or having undergone electroconvulsive therapy within 90 days prior to this study were also excluded. The patients had been taking fixed dosages of perospirone for more than 2 weeks before this study. Doses of perospirone were 16 mg/day in one patient, 24 mg/day in two patients, and 48 mg/day in three patients. The interval between the last administration of perospirone and PET scan was from 2.5 to 17.5 h. Clinical symptoms were assessed by positive and negative symptom scale (PANSS). Venous blood samples were taken before and after PET scanning to measure the plasma concentration of perospirone and ID-15036, an active metabolite of perospirone (hydroxyperospirone). The average values of pre- and post-PET scanning were used.

PET procedure

A PET scanner system, ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA), was used for all subjects. A head fixation device was used to minimize head movement. Before the dynamic scan, a transmission scan for attenuation correction was performed using a ^{68}Ge-^{68}Ga source. The dynamic PET scan was performed for 90 min after intravenous bolus injection of 204.0–225.0 MBq (218.5± 7.7 MBq, mean ± SD) of [^{11}C]FLB 457. The specific radioactivity of [^{11}C]FLB 457 was 129.6–219.4 MBq/nmol (175.4±34.3 MBq/nmol, mean ± SD). Magnetic resonance images of the brain were acquired with 1.5 Tesla magnetic resonance imaging (MRI), Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images at 1-mm slices were obtained.

Data analysis

All emission scan data were reconstructed with a Hanning filter. Regions-of-interest (ROIs) were defined for the temporal cortex and cerebellar cortex. ROIs were drawn manually on PET images with reference to the individual MR images. The values of ROIs for right and left sides were averaged. Binding potential (BP_{ND}), defined as the specific binding compared to nondisplaceable uptake, of dopamine D_2 receptor in the temporal cortex was calculated using a three-parameter simplified reference tissue model (SRTM; Innis et al. 2007; Lammertsma and Hume 1996). The cerebellum was used as reference tissue because of its negligible density of dopamine D_2 receptors (Suhara et al. 1999).

Table 1 Patient characteristics, plasma concentration, and dopamine D_2 receptor occupancy

Number	Age (year)	Sex	PANSS	Dose (mg/day)	Interval: last dose–PET (h)	Last dose (mg)	Plasma concentration		Receptor occupancy (%)
							Perospirone (ng/ml)	ID-15036 (ng/ml)	
1	38	M	59	16	2.5	16	4.5	23.3	83.8
2	30	F	69	24	7.5	8	0.6	3.05	61.8
3	44	F	62	24	9.0	8	0	0.75	39.6
4	26	M	81	48	2.5	8	1.25	8.45	60.8
5	30	F	46	48	2.5	16	0.25	8.35	70.1
6	42	F	80	48	17.5	32	0.85	2.1	65.0