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ORIGINAL PAPER

# Extrastriatal dopamine $D_2$ receptor occupancy in olanzapine-treated patients with schizophrenia

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**Abstract** Olanzapine is described as a multi-acting receptor-targeted antipsychotic agent. Although regional differences of dopamine $D_2$ receptor occupancy, i.e., limbic selectivity, were reported for olanzapine, contradictory results were also reported. We measured dopamine $D_2$ receptor occupancy of olanzapine in extrastriatal regions in patients with schizophrenia using positron-emission tomography with [$^{11}$C]FLB457 and the plasma concentrations of olanzapine. Ten patients with schizophrenia taking 5–20 mg/day of olanzapine participated. Dopamine $D_2$ receptor occupancy in the temporal cortex ranged from 61.1 to 85.8%, and plasma concentration was from 12.7 to 115.4 ng/ml. The $ED_{50}$ value was 3.4 mg/day for dose and 10.5 ng/ml for plasma concentration. The $ED_{50}$ values obtained in this study were quite similar to those previously reported in the striatum. In conclusion, although the subjects and methods were different from previous striatal occupancy studies, these results suggest that limbic occupancy by olanzapine may not be so different from that in the striatum.

**Keywords** Dopamine $D_2$ receptor occupancy · Extrastriatum · Olanzapine · Positron-emission tomography · Schizophrenia

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## Introduction

Olanzapine is a second-generation antipsychotic drug that is widely used in the treatment of schizophrenia [7]. Most second-generation antipsychotic drugs, such as clozapine, risperidone, olanzapine and quetiapine, have high affinity for several kinds of neuroreceptors in addition to dopamine $D_2$ receptors [6]. Olanzapine has high affinity for dopamine $D_2$ receptors (Ki = 11 nM) as well as for other receptors, i.e., serotonin 5-$HT_{2A}$ (4 nM), 5-$HT_{2C}$ (11 nM), muscarine $m_1$–$m_5$ (1.9–25 nM), adrenaline $\alpha_1$ (19 nM) and histamine $H_1$ (7 nM) receptors [6]. The pharmacological profile is similar to that of clozapine, described as a multi-acting receptor-targeted antipsychotic agent. The difference in occupancy of dopamine $D_2$ receptors with clozapine between striatal and extrastriatal regions has been reported as 'limbic selectivity' [23]. This feature was considered one of the reasons for the low risk of extrapyramidal symptoms and a possible effect for negative symptoms [23].

Some animal studies reported greater effects on dopamine $D_2$ receptors by olanzapine in the extrastriatum than in the striatum [24, 27]. In human studies, higher occupancy in the temporal cortex than in the striatum was also reported for olanzapine [3, 34]. On the other hand, in another human study using olanzapine, no difference in dopamine $D_2$ receptor occupancies between the striatum and extrastriatum was also reported [16]. In those studies, occupancies in the striatum and extrastriatum were measured from the same data, despite their quite different receptor densities [15].

In the present study, dopamine $D_2$ receptor occupancy in extrastriatal regions by olanzapine was measured in patients with schizophrenia using positron-emission tomography (PET) with [$^{11}$C]FLB 457, an optimized

radiotracer for measuring extrastriatal dopamine $D_2$ receptors [10]. The receptor occupancy in the extrastriatum was compared with that in the striatum by olanzapine previously measured using [$^{11}$C]raclopride [13].

## Methods

### Subjects and study protocol

Ten patients, aged 23–47 years (36.2 ± 9.0, mean ± SD), diagnosed with schizophrenia according to DSM-IV criteria, participated in this study (Table 1). After complete explanation of the study, written informed consent was obtained from all patients. Exclusion criteria were current or past substance abuse, organic brain disease 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 olanzapine for more than 2 weeks before this study. Doses of olanzapine were 5 mg/day in two patients, 7.5 mg/day in two patients, 10 mg/day in three patients, 15 mg/day in one patient and 20 mg/day in two patients. The duration between PET scan and the last administration of olanzapine was between 2 and 20 h. Clinical symptoms were assessed by positive and negative symptom scale (PANSS). This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

### 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 then performed for 90 min after intravenous bolus injection of 197.0–238.0 MBq (217.5 ± 13.9 MBq, mean ± SD) of [$^{11}$C]FLB 457. The specific radioactivity of [$^{11}$C]FLB 457 was 85.8–339.9 MBq/nmol (188.0 ± 79.1 MBq/nmol, mean ± SD); the injected mass of FLB 457 was 0.24–0.90 μg (0.64 ± 0.20 μg, mean ± SD). Venous blood samples were taken before and after PET scanning to measure the plasma concentration of olanzapine. The average values of plasma concentration before and after PET scanning were used. The drug concentration of one patient (No. 8) could not be determined because of a technical error. Magnetic resonance images of the brain were acquired with 1.5 T MRI, Gyroscan NT (Philips Medical Systems, Best, Netherlands). T1-weighted images of 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 as for the extrastriatal region and cerebellar cortex [3, 34]. ROIs were drawn manually on PET images with reference to individual MR images. The values of ROIs for right and left sides were averaged. Binding potential ($BP_{ND}$) of dopamine $D_2$ receptor was calculated using a three-parameter simplified reference tissue model [18]. The cerebellum was used as reference tissue because of its negligible density of dopamine $D_2$ receptors [28].

Receptor occupancy of antipsychotic drug is expressed as follows: Occupancy (%) = $(BP_{base} - BP_{drug})/BP_{base} \times 100$, where $BP_{base}$ is $BP_{ND}$ in the drug-free state and $BP_{drug}$ is $BP_{ND}$ after administration of the drug. In this study,

**Table 1** Patient characteristics, plasma concentration of olanzapine, and dopamine $D_2$ receptor occupancy

| No. | Age (years) | Sex | Duration of illness (years) | PANSS | Dose (mg/day) | Duration of fixed dose (months) | Other medication | Plasma concentration (ng/ml) | Receptor occupancy (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 41 | M | 6.5 | 50 | 5 | 14 | – | 20.1 | 61.6 |
| 2 | 45 | M | 8 | 38 | 5 | 25 | BZ | 12.7 | 72.2 |
| 3 | 30 | F | 12 | 49 | 7.5 | 13 | – | 25.9 | 65.6 |
| 4 | 45 | F | 4 | 95 | 7.5 | 0.5 | BZ, AP | 25.5 | 76.9 |
| 5 | 23 | M | 0.8 | 50 | 10 | 7 | – | 48.5 | 69.7 |
| 6 | 41 | M | 17 | 44 | 10 | 30 | BZ | 21.8 | 61.1 |
| 7 | 47 | M | 27 | 92 | 10 | 3 | – | 44.5 | 81.8 |
| 8 | 32 | M | 17 | 75 | 15 | 16 | BZ | ND | 67.9 |
| 9 | 23 | M | 5 | 101 | 20 | 0.5 | BZ | 61.0 | 79.5 |
| 10 | 37 | F | 11 | 92 | 20 | 3 | BZ | 115.4 | 85.8 |

*BZ* benzodiazepine, *AP* anti-parkinsonian drug, *ND* not determined

mean $BP_{ND}$ of age-matched ten normal male subjects (age range 21–49; 36.2 ± 9.1 years, mean ± SD) measured by the same procedure as for the patients was used as $BP_{base}$ because of the lack of individual baseline $BP_{ND}$.

The relationship between receptor occupancy and dose (or plasma concentration) of antipsychotic drug can be expressed as follows:

$$\text{Occupancy}(\%) = D/(D + ED_{50}) \times 100,$$

where $D$ is the dose of olanzapine and $ED_{50}$ is the dose required to induce 50% occupancy [1, 13, 31]. In this study, maximum occupancy was fixed at 100%, the same as previous occupancy studies with olanzapine [13].

### Measurement of plasma concentration of olanzapine

Plasma concentrations of olanzapine were determined using a validated high-performance liquid chromatography (HPLC) method (JCL Bioassay Corporation., Hyogo, Japan).

### Statistical analysis

Correlations between dopamine $D_2$ receptor occupancy in the temporal cortex and daily dose, plasma concentration, age, duration of illness and PANSS (total or sub scores) were assessed using Pearson's correlation coefficient.

## Results

Dopamine $D_2$ receptor occupancy in the temporal cortex ranged from 61.1 to 85.8% (Table 1). Plasma concentration of olanzapine ranged from 12.7 to 115.4 ng/ml. $ED_{50}$ was 3.4 mg/day for the daily dose (Fig. 1) and 10.5 ng/ml for the plasma concentration (Fig. 2). The PANSS score ranged from 38 to 101. Average PANSS scores of all patients were 68.6 ± 24.7.

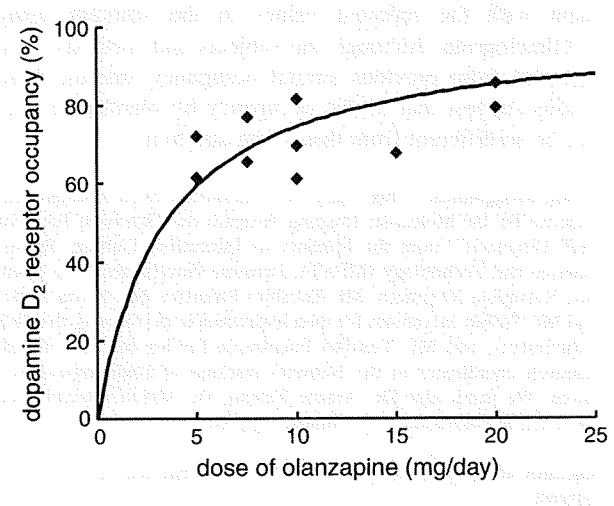


**Fig. 1** Relationship between dopamine $D_2$ receptor occupancy and daily dose of olanzapine

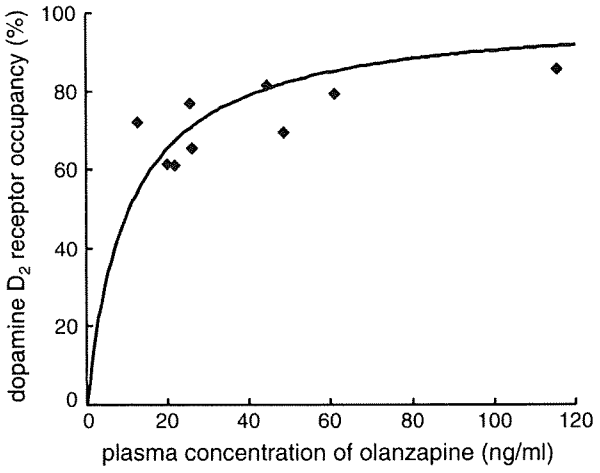


**Fig. 2** Relationship between dopamine $D_2$ receptor occupancy and plasma concentration of olanzapine

A positive correlation was observed between dopamine $D_2$ receptor occupancy in the temporal cortex and plasma concentration ($r = 0.72$, $P = 0.029$), but not daily dose within this dose range ($r = 0.57$, $P = 0.082$). A positive correlation was also observed with total PANSS scores ($r = 0.80$, $P = 0.0054$), positive scores ($r = 0.78$, $P = 0.0074$), negative scores ($r = 0.68$, $P = 0.032$), and general scores ($r = 0.78$, $P = 0.0072$). No correlations were observed between dopamine $D_2$ receptor occupancy in the temporal cortex and age ($P = 0.85$) or duration of illness ($P = 0.81$).

## Discussion

Although the measured occupancy value was above 50% with 5–20 mg/day of olanzapine, the calculated $ED_{50}$ value from the present result in the temporal cortex was 3.4 mg/day for the daily dose and 10.5 ng/ml for the plasma concentration. The previously reported $ED_{50}$ of olanzapine in the striatum was 4.5 mg/day for the daily dose and 10.3 ng/ml for the plasma concentration [13]. $ED_{50}$ of plasma concentration in the extrastriatum of the present study was similar to that reported in the striatum, meaning that there was no noteworthy regional difference in dopamine $D_2$ receptor occupancy by olanzapine between the striatum and extrastriatum. Based on 70–80% of dopamine $D_2$ receptor occupancy [8, 14, 20], the optimal daily dose of olanzapine would be about 8–14 mg/day. This estimated dose was in fairly good agreement with the current clinical dose (5–20 mg/day in Japan).

According to electrophysiological measurement, the effect of olanzapine was reported preferentially in the ventral tegmental area (A10) [27], and olanzapine was reported to increase c-fos expression to a greater degree in the nucleus accumbens than in the dorsolateral striatum [24]. These findings suggested that olanzapine had preferentially different regional effects for extrastriatal regions. The concept of 'limbic selectivity', i.e., differences in dopamine $D_2$ receptor occupancy between the striatum and extrastriatum, has been discussed. Although there are several reports about 'limbic selectivity' of second-generation antipsychotics, such as clozapine [9, 17, 23, 34], risperidone [5, 34], quetipaine [17, 26] and amisulpride [4, 34], it has also been reported that there is no limbic selectivity with second-generation antipsychotics such as clozapine [32] and risperidone (and paliperidone) [1, 11, 35].

Contradictory results of limbic selectivity have also been reported for olanzapine. Two studies showed higher occupancy in the temporal cortex than in the striatum using [$^{123}$I]epidepride SPECT (82.8 ± 4.2% in the temporal cortex and 41.3 ± 17.9% in the striatum) [3] and [$^{76}$Br]FLB 457 PET (83.6 ± 10.5% in the temporal cortex and 45.1 ± 20.9% in the striatum) [34]. On the other hand, no significant difference in occupancy between the temporal cortex (67.5 ± 7.1%) and striatum (70.9 ± 6.9%) was reported using [$^{18}$F]fallypride PET [16]. Regional differences in occupancies were calculated from the area under the time-activity curve ratio in [$^{123}$I]epidepride SPECT and [$^{76}$Br]FLB 457 PET [3, 34]. A previous study reported that the ratio method underestimated striatal occupancy using high-affinity radioligand such as [$^{123}$I]epidepride or [$^{11}$C]FLB 457 (probably also [$^{76}$Br]FLB 457) because radioligand bindings did not reach equilibrium due to the high density of dopamine $D_2$ receptors in the striatum [21]. In addition, because none of the studies concerning regional difference of occupancy by olanzapine presented plasma concentrations [3, 16, 34], $ED_{50}$ of the extrastriatum could not be compared with the present study.

Differences of occupancy or $EC_{50}$ values in the same brain region (e.g. striatum) were reported using different radioligands ("Discussion" in [19]). As commented above, this difference may be caused using different affinity radioligands at high-density receptor regions [21]. In this study, the dopamine $D_2$ receptor bindings in the temporal cortex were measured using [$^{11}$C]FLB 457 because the dopamine $D_2$ receptor density of the temporal cortex is very low compared with that of the striatum ($B_{max}$ = 0.4 and 16.6 pmol/g tissue, respectively) [15]. Recently, the absence of regional difference between striatal and extrastriatal occupancy of risperidone was reported using [$^{11}$C]raclopride and [$^{11}$C]FLB 457 by precise methods [11]. These results suggest that optimal radioligands are necessary for different brain regions with different receptor densities.

The significant positive correlation between temporal dopamine $D_2$ receptor occupancy and PANSS suggests that higher doses tend to be used for severe symptoms of schizophrenia. However, as this was an open study and the number of patients was limited, further studies (such as randomized controlled trials) are needed.

In the present study, the mean $BP_{ND}$ value of age-matched healthy subjects was used as value of the drug-free state. Although previous studies showed no difference in $BP_{ND}$ values of the temporal cortex between normal subjects and patients with schizophrenia [29, 33] or between the sexes [12], individual differences in $BP_{ND}$ values may lead to potential error in the estimation of dopamine $D_2$ receptor occupancy [8]. Moreover, there is a possibility of upregulation of dopamine $D_2$ receptor by neuroleptic treatment [25]. When $BP_{base}$ changes by ±15%, the estimated occupancy ranges from 41 to 57% for an assumed occupancy of 50%. The effect of displaceable binding of [$^{11}$C]FLB 457 in the cerebellum may also lead to an underestimation of receptor occupancy [2, 22].

Although the time point of the scan following the last drug administration was different among the scans, plasma concentration was measured and the reported time-course of occupancy of olanzapine fitted well with the occupancy simulated by plasma concentration [30].

In conclusion, dopamine $D_2$ receptor occupancy ranged from 61.1 to 85.8% in the temporal cortex of patients with schizophrenia taking 5–20 mg/day of olanzapine. The $ED_{50}$ values were 3.4 mg/day for dose and 10.5 ng/ml for plasma concentration of olanzapine, in fairly good agreement with the reported values in the striatum using [$^{11}$C]raclopride. Although the subjects and methods were different from previous striatal occupancy studies, these results suggest that limbic occupancy by olanzapine may not be so different from that in the striatum.

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**Conflict of interest statement** All authors reported no conflict of interest.

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# Marked Improvement of Psychotic Symptoms After Electroconvulsive Therapy in Parkinson Disease

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**Objectives:** Psychosis is common and often medically intractable in Parkinson disease (PD). Sometimes, its management is essential for the determination of the prognosis of PD. There have been several lines of studies demonstrating the effectiveness of electroconvulsive therapy (ECT) for depression in PD but very few for psychosis. The purpose of this retrospective study was to examine the effects of acute ECT on PD-associated psychosis.

**Methods:** The subjects were 5 elderly PD patients (duration, 2–10 years); 4 of whom were diagnosed as "other substance (antiparkinsonian medications)–induced psychotic disorder, with hallucinations," and as 1 "psychotic disorder due to PD, with hallucinations," according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Two patients had comorbidity of major depressive disorder, single episode. The psychosis, being refractory to antipsychotics, was treated with a course of acute ECT. Psychiatric conditions were evaluated using the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression Rating Scale (HDRS), and the Global Assessment of Functioning (GAF) scale. Motor function was assessed using the Hoehn and Yahr staging.

**Results:** The total BPRS and GAF scores after ECT improved significantly compared with those just before ECT. The Hoehn and Yahr staging also showed significant improvement. No marked adverse effects were seen. Duration of the improvement was between 5 and 30 weeks in followed-up patients.

**Conclusions:** Acute ECT was effective for medically refractory psychosis in patients with PD regardless of the comorbidity of depression. Our results suggest a possible indication of acute ECT for refractory psychosis in patients with PD.

**Key Words:** parkinsonism, psychosis, hallucination, delusion, antipsychotics

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Psychotic episodes such as hallucinations and delusions are common in Parkinson disease (PD). They can occur in patients treated with L-dopa or any antiparkinsonian drugs and are termed *antiparkinsonian drug–induced psychosis*. In some fewer cases, the psychosis is intrinsic.[1] Visual hallucinations (VHs) are the most common, auditory hallucinations (AHs) are second, and delusions are also common. Other hallucinations such as somatic, presence, tactile, or olfactory in nature, although considerably less common, have also been reported.[2,3] These psychotic symptoms are often resistant to antipsychotics, and PD patients easily become intolerant to them. Thus, psychosis is an essential determinant of PD prognosis, and its management is one of the most important issues in the treatment of PD.

It has been pointed out that in the treatment of advanced PD, electroconvulsive therapy (ECT) is effective for both psychiatric symptoms, especially depression, and motor symptoms.[4,5] However, fewer cases have been reported regarding the use of acute ECT for psychosis in PD[6,7] in comparison to for depression.[5,8] Although there has been a report on the successful use of the combined therapy of atypical antipsychotics and ECT,[9] the effect of ECT on psychosis in PD has not been confirmed.

We performed a retrospective study of 5 elderly PD patients to examine the effectiveness of acute ECT for medically refractory psychosis in PD.

## METHODS

### Subjects

The subjects of this study were 5 patients (2 men and 3 women; mean age, 73.8 [6.1] years; range, 65–82 years) with a PD duration range of 2 to 10 years. They had been exhibiting prominent hallucinations and delusions and were admitted to Tokyo Metropolitan Tama Geriatric Hospital (case 1) or Tokyo Metropolitan Geriatric Hospital (cases 2–5) between 1999 and 2006. Antiparkinsonian drugs including L-dopa, amantadine, and dopamine agonists had been given to all patients except 1 (case 4) since just after PD presentation. The dosage of L-dopa ranged from 200 to 600 mg/d. The psychotic symptoms included VHs, AHs, somatic hallucinations (SHs), delusions of persecution, and excitement. Visual hallucinations, SHs, and delusions of persecution were observed in all cases with hallucinations predominating. Excitement and refusal of food and medication were observed in several cases. Mean duration of psychotic symptoms was 7.0 (5.3) months (range, 2–16 months). Diagnoses were other substance (antiparkinsonian medications)–induced psychotic disorder, with hallucinations, coded as 292.12 for cases 1, 2, 3, and 5 and psychotic disorder due to PD, with hallucinations coded as 293.82 for case 4 according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-R*).[10] Two patients (cases 1 and 2) had the comorbidity of major depressive disorder, single episode coded as 296.2 according to *DSM-IV-TR*. All the patients had a diagnosis of PD by neurologists not associated with this study and did not have a diagnosis of dementia. Other organic brain diseases were ruled out on admission based on full blood tests, magnetic resonance imaging or computed tomography, and electroencephalography.

After admission, antiparkinsonian drugs in 4 patients (cases 1–3, 5) were gradually reduced, but psychotic symptoms remained unchanged. Then, a small dosage of antipsychotics such as quetiapine, olanzapine, and tiapride was given to 4 patients (cases 2–5). These medications were, however, ineffective or poorly tolerated, with motor symptoms worsening, and 2 patients developed aspiration pneumonia or urinary tract infection. Because

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**TABLE 1.** Clinical Characteristics of the Study Patients Before ECT (N = 5)

| | |
|---|---|
| Sex ratio (men:women) | 2:3 |
| Age, yr | 73.8 (6.1) [65–82] |
| Duration of Parkinson disease, yr | 5.3 (3.1) [2–10] |
| Duration of psychotic episode, mo | 7.0 (5.3) [2–16] |
| L-Dopa dose (quantity to be administered at one time), mg/d | 270 (193) [0–600] |
| Hoehn and Yahr staging just before ECT | 4.4 (0.8) [3–5] |

Mean (SD) [range] values are shown.

patients were considered resistant or intolerant to antipsychotic medication, the administration of ECT was decided.

Patient characteristics are listed in Tables 1 and 2.

## Clinical Evaluation

The psychiatric conditions of the patients were evaluated using the Brief Psychiatric Rating Scale (BPRS),[11] the 17-item Hamilton Depression Rating Scale (HDRS), and the Global Assessment of Functioning (GAF) scale. Motor function was assessed using the Hoehn and Yahr staging. These assessments were performed by the attending psychiatrists who had been observing the study patients since their admission. The outcome in each case was determined by comparing the total BPRS, total HDRS, and GAF scores and Hoehn and Yahr staging obtained just before and approximately 1 week after ECT. Moreover, the condition after ECT was clinically observed as long as follow-up was possible.

Adverse cognitive function resulting from ECT was assessed on the basis of the Mini–Mental State Examination (MMSE) or the Revised Hasegawa Dementia Scale (HDS-R)[12]: a higher score, with a maximum score of 30 points, indicates normal intellectual function, and the cutoff for excluding dementia is 24 points in MMSE and 21 points in HDS-R. The HDS-R is reported to have the capability of screening dementia nearly equivalent to MMSE.[13] Because MMSE includes the task of drawing and writing and 4 patients (cases 1–4) had great difficulty in handwriting due to strong muscle rigidity, HDR-S was used for their evaluation. The MMSE was used in 1 patient (case 5). The assessments were performed just before and approximately 1 week after the ECT course unless it was not possible because of the patient's excitement or refusal. Any adverse physical effects resulting from ECT were evaluated at the same time.

Differences in total BPRS, total HDRS, and GAF scores and Hoehn and Yahr staging between before and after ECT were statistically analyzed by paired $t$ test. Bonferroni correlation was used to avoid errors from multiple testing. A $P < 0.05/4 = 0.0125$ was accepted as statistically significant.

## Acute ECT Procedures

Only modified ECT was applied in the treatment sessions. Thiamylal (2.5–5.0 mg/kg) was intravenously given as an anesthetic agent and succinylcholine (0.8–1.0 mg/kg) as a muscle relaxant. Acute ECT was performed with a CS-1 sine-wave apparatus (Sakai Medical Corp, Tokyo, Japan) or a Thymatron System IV brief-pulse square-wave apparatus (Somatics, LLC, Lake Bluff, Ill). The brief-pulse square-wave apparatus was approved in 2002 in Japan and was adopted into our hospital in 2004. The sine-wave apparatus was only used until then in the present study, although using the brief-pulse square-wave apparatus is now considered standard. Electrodes were placed in a bilateral frontotemporal manner. Only one adequate seizure, defined as the occurrence of not only a cerebral seizure exceeding 20 seconds but also a greater postictal suppression, both monitored electroencephalographically, was required for each ECT session. Stimulation with the CS-1 apparatus was done with an alternating current of 95 to 105 V at 50 Hz for 3 to 5 seconds. With the Thymatron System IV, an initial stimulus dose ranging between 40% (201.6 millicoulombs) and 100% (504.0 millicoulombs) was decided according to the half-age strategy.[14] If a missed or abortive seizure occurred with either apparatus, the patient was restimulated after a pause at an increased dose in the same session. The dose increments were 5 to 10 V with the CS-1 apparatus and 50% to 100% with the Thymatron System IV apparatus. When a seizure was induced but was inadequate, the stimulus dose was raised in the following session at a required increment to obtain an adequate seizure. The increments were 5 to 10 V with the CS-1 apparatus and approximately 50% with the Thymatron System IV apparatus. Electroconvulsive therapy was administered twice a week. When the attending psychiatrists considered the symptoms of the patient to have clinically remitted, the ECT course was terminated.

Written informed consent for ECT was obtained from each patient or guardian before the initial ECT session.

# RESULTS

The mean number of ECT sessions was 8 (2) [range, 5–12 sessions]. In cases 1 to 3, acute ECT was administered with the CS-1 sine-wave apparatus, with adequate seizure in every session. In case 4, the Thymatron System IV brief-pulse square-wave apparatus was used in the initial 4 sessions, but no seizure at maximum stimulus intensity was induced. The CS-1 apparatus was used in the following 8 sessions, each with adequate seizure. Case 5 received 7 sessions with the Thymatron System IV apparatus, which induced no seizure in the first session and adequate seizures in all the following sessions at increased intensity up to a maximum.

After the ECT treatments, the psychotic symptoms almost completely disappeared and the motor symptoms were relieved in all cases. The mean scores of total BPRS significantly improved after ECT (from 40.6 [4.8] just before ECT to 4.4 [3.3] after ECT; $P < 0.01$). The mean scores of GAF also improved significantly (from 24.2 [6.7] to 70.6 [9.0]; $P < 0.01$). The mean scores of total HDRS decreased, but the difference was not statistically significant (from 14.8 [8.6] to 2.4 [1.1]; $P = 0.04$). Furthermore, the mean scores of Hoehn and Yahr staging showed significant improvement as well (from 4.4 [0.8] to 3.4 [0.8]; $P < 0.01$). The improvement in motor function enabled the patients to reduce daily L-dopa doses in all cases except case 4, who did not take L-dopa. These scores are shown in Tables 2 and 3. Moreover, clinically observational follow-up showed that the improvement lasted, without a starting or increased dose of antipsychotics, for 30 weeks in case 1 and 8 weeks in case 2 with both psychotic and motor symptoms and 5 weeks with psychotic and 25 weeks with motor symptoms in case 4. Cases 3 and 5 could not be followed up.

The HDS-R score of case 4 did not change (25 points) between before and after ECT, and the score of case 5 increased after ECT (to 27 points from 25 points). Although cases 1 to 3 could not be examined with HDS-R before ECT owing to excitement or refusal, the scores obtained after ECT were fairly good (24, 24, and 21 points, respectively). No other obvious adverse effects in cognitive function were detected. No delirium

**TABLE 2.** Clinical Characteristics of Each Case in the Study

| Case/Age, yr/Sex | 1/78/Woman | 2/65/Man | 3/69/Woman | 4/82/Woman | 5/75/Man |
|---|---|---|---|---|---|
| Duration of PD, yr | 2.5 | 8 | 10 | 2 | 4 |
| L-Dopa dose (quantity to be administered at one time) on admission, mg/d | 200 | 300 | 600 | 0 | 250 |
| Other APD besides L-dopa | Amantadine, DA (talipexole) | DA (cabergoline) | DA (bromocriptine) | None | DA (pramipexole) |
| Duration of psychotic episode before ECT, mo | 4 | 2 | 7 | 16 | 6 |
| *DSM-IV-TR* diagnosis at ECT (comorbidity) | Other substance (APD)–induced psychotic disorder (MDD) | Other substance (APD)–induced psychotic disorder (MDD) | Other substance (APD)–induced psychotic disorder | Psychotic disorder due to PD | Other substance (APD)–induced psychotic disorder |
| Main psychiatric symptoms | VH, SH, and DP<br>Excitement and refusal of food and medication | VH, AH, SH, and DP<br>Excitement, refusal of food and suicide attempt | VH, AH, and DP<br>Excitement, refusal of food and medication | VH, SH, and DP | VH, AH, and DP<br>Delusion of jealousy |
| APC before ECT | None | 50- to 25-mg QTP followed by 2.5-mg OLZ | 50- to 25-mg QTP | 37.5-mg QTP followed by 25-mg TPD | 100-mg QTP |
| Reason for administering ECT | High risk of AP due to reduced APD and inanition | Intolerance to APC: worsening of AP and high risk of suffocation | Intolerance to APC: high risk of UTS and inanition | Intolerance to APC: high risk of neck dystonia | Intolerance and resistance to APC |
| Total No. ECT sessions | 5 | 10 | 6 | 12 | 7 |
| Hoehn and Yahr staging | | | | | |
| Just before ECT | 4 | 5 | 5 | 5 | 3 |
| 1 wk after ECT | 3 | 4 | 4 | 4 | 2 |
| BPRS score | | | | | |
| Just before ECT | 47 | 44 | 39 | 38 | 35 |
| 1 wk after ECT | 2 | 3 | 5 | 2 | 10 |
| GAF score | | | | | |
| Just before ECT | 25 | 20 | 15 | 30 | 31 |
| 1 wk after ECT | 85 | 71 | 71 | 65 | 61 |
| HDRS score | | | | | |
| Just before ECT | 23 | 25 | 9 | 11 | 6 |
| 1 wk after ECT | 2 | 1 | 3 | 4 | 2 |
| MMSE or HDS-R score | | | | | |
| Just before ECT | Could not take | Could not take | Could not take | 25 | 25 |
| 1 wk after ECT | 24 | 24 | 21 | 25 | 27 |
| Duration of improvement, wk | | | | | |
| Psychotic symptoms | 30 | 8 | Unknown | 5 | Unknown |
| Motor symptoms | 30 | 8 | Unknown | 25 | Unknown |

AP indicates aspiration pneumonia; APC, antipsychotics; APD, antiparkinsonian drug; DA, dopamine agonist; DP, delusion of persecution; MDD, major depressive disorder; OLZ, olanzapine; QTP, quetiapine; TPD, tiapride; UTS, urinary tract sepsis.

**TABLE 3.** Scores of BPRS, HDRS, GAF, and Hoehn and Yahr Staging Before and After ECT (N = 5)

| | Just Before ECT | After ECT |
|---|---|---|
| Total BPRS score | 40.6 (4.8) [35–47] | 4.4 (3.3) [2–10]* |
| Total HDRS score | 14.8 (8.6) [6–25] | 2.4 (1.1) [1–4] |
| GAF score | 24.2 (6.7) [15–31] | 70.6 (9.0) [61–85]* |
| Hoehn and Yahr staging | 4.4 (0.8) [3–5] | 3.4 (0.8) [2–4]* |

Mean (SD) [range] are shown.
*$P < 0.01$.

or confusion after ECT was observed. No adverse physical effects of ECT were seen in any of the cases.

## DISCUSSION

Hallucinations and delusions are common and often medically refractory in PD. These psychotic symptoms are usually induced by increased doses of antiparkinsonian drugs, but they also sometimes occur intrinsically.[1] The psychotic symptoms in our study were considered antiparkinsonian drug induced in cases 1, 2, 3, and 5 and intrinsic in case 4. Although psychoses in PD sometimes occur as part of a delirium,[4] all of the study cases were considered to be in a clear sensorium, not in a delirium. This was based on the fact that the psychotic states were persistent, with little fluctuation, and also that the electroencephalographic evaluation results suggested no obvious delirium.

Psychotic symptoms are important determinants of prognosis and mortality in PD.[4,9] These symptoms usually force physicians to reduce the dosage of antiparkinsonian drugs, but this often leads to worsening motor symptoms. In most cases, prescribed antipsychotic agents also can result in a worsening of their motor symptoms, whereas they have only a partial effect on psychoses. Even atypical antipsychotics can actually often lead to a deterioration of parkinsonism in elderly patients at advanced PD stages. The American Academy of Neurology[15] recommends clozapine as the best pharmacological option and quetiapine as the second best for psychosis in PD, but clozapine is not available in our country. Moreover, in the present study, psychosis was resistant to treatment. Dosage reduction of antiparkinsonian drugs had no effect on the psychotic symptoms. A smaller dosage of quetiapine prescribed in 4 cases worsened their parkinsonism, and subsequently, in 2 cases, infectious disease occurred, together with continued refusal to eat. Efficacious treatment was urgently needed for the high risk of suffocation, sepsis, severe extrapyramidal symptoms, or inanition.

After the acute ECT sessions, total BPRS and GAF scores were significantly improved, and the Hoehn and Yahr staging also showed significant improvement. There were no marked adverse cognitive or physical effects in the treatment course. Furthermore, the duration of improvement in 3 cases, ranging from 5 to 30 weeks, suggests that the beneficial effect of ECT is short lived. However, it may keep PD patients with uncontrollable symptoms from critical conditions and would be considered persistent enough to introduce continuation and maintenance ECT, if necessary. Thus, these findings indicate the effectiveness of acute ECT for the treatment of psychosis in PD.

The treatment also showed an antidepressant effect of ECT in our patients with PD, as was often reported in previous literature.[5,8] Cases 1 and 2 were considered to have the comorbidity of severe major depression, with higher total HDRS scores of 23 and 25 points, respectively, before ECT. However, considering that the other 3 patients did not show this comorbidity, acute ECT in the study was considered an effective treatment approach for psychosis in PD regardless of whether it was associated with a depressive state or not.

As for the effectiveness of ECT on motor function in PD, there have been a number of reports,[5,7,8] including a controlled double-blind study.[16] Nevertheless, the American Academy of Neurology[15] has not made any recommendations that included ECT as a nonpharmacological treatment of PD with depression, not to mention the psychosis in PD. On the other hand, in the guidelines of ECT published by the American Psychiatric Association,[17] the effects of ECT on motor symptoms in PD are suggested. Although the mechanism of action of ECT on motor symptoms remains unclear, it has been proposed that ECT may enhance the dopaminergic neurotransmission, involved with changes in presynaptic and postsynaptic receptor responsiveness.[6,16]

Our study had several limitations. These were the major use of the sine-wave apparatus, the very small number of subjects, and the fact that it was retrospective. It also showed only the short-term effect of acute ECT, and the duration of effectiveness remains obscure.[9,18] There have, however, been only a few reports of success with acute ECT for psychosis in PD,[6,7,9] as most reports were concerned with depression.

In summary, acute ECT was effective and safe for medically refractory psychosis in 5 patients with PD, regardless of the presence or absence of the comorbidity of depression. Our results suggest a possible indication of acute ECT for refractory psychosis in patients with PD. An effect of acute ECT on motor symptoms in PD was also suggested. Prospective studies on a larger scale are warranted.

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# Electroconvulsive Therapy Decreases Dopamine $D_2$ Receptor Binding in the Anterior Cingulate in Patients With Depression: A Controlled Study Using Positron Emission Tomography With Radioligand [$^{11}$C]FLB 457

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***Objective:*** Electroconvulsive therapy (ECT) has been confirmed as one of the most effective treatments in drug-resistant major depression. However, the mechanism of ECT is still poorly understood. Although several lines of studies have focused on its effect on dopamine neurotransmission, the effects of ECT on dopamine $D_2$ receptors in a living human brain have not been investigated. Using positron emission tomography (PET) scans with the radioligand [$^{11}$C]FLB 457, we aimed to evaluate the effect of ECT on extrastriatal $D_2$ receptor binding in medicated patients with major depressive disorder (MDD).

***Method:*** Seven patients with a *DSM-IV* diagnosis of MDD underwent PET scans before and after a series of 6–7 treatments with bilateral ECT. Eleven healthy controls were scanned for comparison. All participants were scanned at the National Institute of Radiological Sciences, Chiba, Japan, between November 2000 and September 2005. The parametric images of [$^{11}$C]FLB 457 binding were generated on the basis of a simplified reference tissue model. Voxel-based methods were used to assess the effect of ECT on $D_2$ receptor binding.

***Results:*** There were no significant differences in $D_2$ receptor binding between patients with MDD and controls. All 7 patients showed clinical improvements in response to ECT treatment ($P<.001$). Significant changes in $D_2$ receptor binding, a mean of 25.2% reduction, were found in the right rostral anterior cingulate (AC) following ECT ($P<.001$).

***Conclusions:*** Electroconvulsive therapy decreased $D_2$ receptor binding in the rostral AC in MDD patients responding to ECT. Our finding suggests that one of the biologic mechanisms of ECT could be related to dopaminergic alteration in the rostral AC.

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Electroconvulsive therapy (ECT) has been confirmed as one of the most effective treatments in drug-resistant major depression.[1] Among several neurotransmitter systems, such as the serotonergic, noradrenergic, and GABAergic neurotransmitter systems, on which ECT has been reported to have an effect,[2,3] it has also been suggested that the dramatic and early improvements of severe psychomotor retardation and appetite loss after ECT were related to the dopaminergic effect.[4] In addition, ECT has been widely used, with documented efficacy, in the treatment of different mental disorders involving dopaminergic dysregulation, such as mania, schizophrenia, and catatonia, and it has also led to prolonged improvement in some patients with Parkinson's disease and effectively treated neuroleptic malignant syndrome.[1] Such clinical effects suggest that dopamine neurotransmission plays a crucial role in the mechanism of the action of ECT.

Several lines of studies have focused on the effect of ECT on dopamine neurotransmission. Both animal and human studies[5,6] have suggested that repeated ECT enhances dopamine-mediated behaviors. Some animal studies[7,8] have indicated that both acute and chronic electroconvulsive shock (ECS) at the head increases dopamine release in the frontal cortex and the striatum. A human study[9] also demonstrated increases in the concentrations of homovanillic acid in cerebrospinal fluid after ECT.

Animal behavioral studies[10,11] have demonstrated that ECS stimulates dopamine $D_2$ receptor functions. However, only a few animal studies have investigated $D_2$ receptor binding after ECS, and the results have not been consistent.[12,13] In addition, the effects of ECT on $D_2$ receptors in humans have not been investigated.

Recently, a positron emission tomography (PET) study[14] using [$^{18}$F]setoperone revealed that chronic ECS decreases serotonin 5-$HT_2$ receptors in nonhuman primates. In a human PET study,[15] decreased regional cerebral glucose metabolism was reported after ECT, but the effect on specific neurotransmitter systems has not been studied.

Common symptoms of depression, such as anhedonia and amotivation, can be viewed as impairment in the

Table 1. Clinical Characteristics of Patients

| Patient | Age, y[a] | Sex | Drug | Dose, mg/d | Length of Treatment, wk | No. of Episodes | Duration of Illness, mo | Length of Current Episode, mo | Current Clinical Features | GAF Score at Pre-ECT | HDRS Score | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Pre-ECT[b] | Post-ECT[c] |
| 1 | 32 | M | Paroxetine hydrochloride | 40 | 8 | 3 | 8 | 2 | Melancholia | 51 | 16 | 4 |
| 2 | 53 | M | Fluvoxamine | 125 | 8 | 3 | 56 | 2 | Melancholia | 40 | 17 | 3 |
| 3 | 36 | F | Fluvoxamine | 100 | 20 | 3 | 31 | 5 | Melancholia | 35 | 28 | 13 |
| 4 | 35 | F | Fluvoxamine | 150 | 16 | 2 | 11 | 4 | Melancholia | 55 | 12 | 5 |
| 5 | 52 | M | Paroxetine hydrochloride | 40 | 70 | 3 | 21 | 1 | Melancholia | 31 | 26 | 11 |
| 6 | 58 | M | Paroxetine hydrochloride | 40 | 31 | 1 | 9 | 9 | Melancholia | 35 | 21 | 14 |
| 7 | 33 | M | Paroxetine hydrochloride | 40 | 47 | 2 | 20 | 2 | Melancholia | 45 | 16 | 2 |

[a]Mean (SD) age was 42.7 (11.1) years.
[b]Mean (SD) pre-ECT HDRS score was 19.43 (5.83).
[c]Mean (SD) post-ECT HDRS score was 7.43 (5.06).
Abbreviations: ECT = electroconvulsive therapy; F = female; GAF = Global Assessment of Functioning; HDRS = 21-item Hamilton Depression Rating Scale, Japanese version; M = male.

control of dopaminergic reward and motivational systems.[16] Those systems are reportedly closely connected with the dopamine mesolimbic-cortical pathway functionally and anatomically.[17]

The radioligand [$^{11}$C]FLB 457 is a well-known dopamine $D_2/D_3$ antagonist that has picomolar in vitro affinity to both $D_2$ and $D_3$ receptors and has proven useful for the quantification of extrastriatal $D_2$ receptors in the human brain.[18] We have previously demonstrated that the measurements of cortical $D_2$ receptor binding with [$^{11}$C]FLB 457 are reproducible and reliable.[19] In the present study, using [$^{11}$C] FLB 457, we measured $D_2$ receptors in patients with major depressive disorder (MDD) before and after ECT to clarify the effect of ECT on the dopaminergic role in MDD.

## METHOD

### Subjects

Seven inpatients (mean age = 42.7 years, SD = 11.1 years; 5 men and 2 women; all right-handed) with MDD who had consented to ECT for clinical reasons, such as poor medication response and patient's own preference, at Nippon Medical School, Tokyo, or at Asai Hospital, Togane, Japan, and 11 age-matched healthy volunteers (mean age = 40.5 years, SD = 11.3 years; all men; all right-handed) participated in this study (Table 1).

The 7 patients met *DSM-IV* criteria for MDD. Based on conventional unstructured interviews and medical histories, we excluded patients with psychiatric disorders other than MDD, such as schizophrenia, substance abuse, anxiety disorder, and personality disorder. All patients were being treated with selective serotonin reuptake inhibitors (SSRIs), and their daily doses remained unchanged throughout the study (Table 1). Their median duration of treatment before ECT was 20 weeks (range, 8–70 weeks). Their medications for anxiety and sleep disturbances included lorazepam (1.5 mg/d) and flunitrazepam (1–2 mg/d).

The severity of symptoms was assessed using the Japanese version of the 21-item Hamilton Depression Rating Scale (HDRS)[20] on the same day as each PET scan. The HDRS was evaluated by 3 trained psychiatrists. The ratings were reviewed after the interviews; disagreements were resolved by consensus, and the consensus ratings were then used in this study. Each patient's Global Assessment of Functioning[21] score was assessed by the treating physicians on the day before the patient's first ECT session.

The healthy volunteers were recruited from the surrounding community. Based on unstructured psychiatric screening interviews, they were free of current and past psychiatric or major medical disease and had no relatives with neuropsychiatric disorders.

This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan; the Ethics Committee of Nippon Medical School, Tokyo, Japan; and the Ethics Committee of Asai Hospital, Togane, Japan. After we provided complete explanation of the study, written informed consent was obtained from all patients and healthy volunteers.

### Electroconvulsive Therapy Procedure

The patients received a series of 6–7 bilateral ECT sessions, 2–3 per week. Electroconvulsive therapy was administered with a square-wave, brief-pulse, constant-current device (Thymatron DGX; Somatics Inc, Lake Bluff, Illinois). Before the stimulus, subjects received atropine (0.4 mg), propofol (2.0 mg/kg), and succinylcholine (0.75 mg/kg), with dose adjustment as needed. Standard bifrontotemporal placement of electrodes was used for the treatment. Stimulus intensity was determined as a function of age, initially, and was increased until an adequate electroencephalographic seizure activity of 25 seconds or longer was obtained. Treatment was terminated when patients were judged by the treating physicians to have shown adequate symptom response.

### Positron Emission Tomography Procedure

Patients underwent baseline PET scans with [$^{11}$C]FLB 457 on the day before their first ECT session. Follow-up PET studies were performed on the day after the last ECT session. Healthy volunteers were scanned once for comparison. All PET scans were conducted at the National Institute of Radiological Sciences, Chiba, Japan, between November 2000 and September 2005. Patients and healthy volunteers were placed in a supine position with eyes closed, and head-fixation devices (Fixter Instruments, Stockholm, Sweden) with thermoplastic attachments made to fit the individuals were used.

Radioligand [$^{11}$C]FLB 457 was synthesized by O-methylation of the corresponding precursors with [$^{11}$C] methyliodide with high specific radioactivity, which was obtained by a reduction of [$^{11}$C]$CO_2$ with $LiAlH_4$ in an inert atmosphere with specially designed equipment.[22] The radiochemical purities were higher than 95%.

After a transmission scan with a $^{68}$Ge-$^{68}$Ga source, a bolus of 81.4–248.0 MBq of [$^{11}$C]FLB 457 was injected into the antecubital vein with a 20-mL saline flush. Specific radioactivity of [$^{11}$C]FLB 457 was 44.5–393.6 GBq/μmol at the time of injection. Dynamic PET data were acquired for 90 minutes using CTI-Siemens ECAT EXACT HR+ (CTI-Siemens, Knoxville, Tennessee) in 3D mode without arterial sampling.

T1-weighted magnetic resonance imaging (MRI), by Philips Intera, 1.5 Tesla (Philips Medical Systems, Best, The Netherlands), was acquired from all patients and healthy volunteers. The scan parameters were 1-mm-thick 3D T1 images with a transverse plane (TR/TE 21/9.2 ms, flip angle 30°, matrix 256 × 256 mm).

### Data Analysis

All emission scans were reconstructed with a Hanning filter cut-off frequency of 0.4 (full width at half maximum [FWHM] = 7.5 mm).

The parametric images of [$^{11}$C]FLB 457 binding were generated on the basis of a 3-parameter simplified reference tissue model.[23,24] This model gives parametric images of $R_1$ (relative delivery of radioligand normalized to the cerebellum) and binding potential ($BP_{ND} = f_{ND}B_{avail}/K_D$), in which $f_{ND}$ is the free fraction in the nondisplaceable compartment, $B_{avail}$ is the density of receptors available to bind radioligand in vivo, and $K_D$ is the dissociation constant for the radioligand.[25] The cerebellum was used as the reference region because of its negligible $D_2$ receptor density for calculation.[26] The cerebellar tissue concentration of radioactivity was obtained from regions of interest for the cerebellum, which were manually delineated on the individual MRIs coregistered to the PET summated images for 90 minutes using SPM2 (Wellcome Department of Cognitive Neurology, London, United Kingdom).

Analysis of parametric images of $BP_{ND}$ and $R_1$ was undertaken using SPM2 to investigate differences in the brain.[27] A ligand-specific template image[28] was used to define the stereotactic transformation parameters for the $BP_{ND}$ and $R_1$ images of [$^{11}$C]FLB 457. Normalized $BP_{ND}$ and $R_1$ images were smoothed with a Gaussian filter to 8-mm full-width half-maximum.

### Group Comparisons and Correlation

Statistical analyses of the $BP_{ND}$ and $R_1$ data were performed with SPM2 using voxel-based paired or unpaired *t* tests. The $BP_{ND}$ and $R_1$ differences were estimated for the following 3 contrasts: (1) patients before and after ECT, (2) healthy volunteers versus patients before ECT, and (3) healthy volunteers versus patients after ECT. For those analyses, the significant voxel level threshold was set at $P < .001$, uncorrected, with a minimal cluster size of > 100 voxels. The resulting *t* values were converted to *z* scores, with brain locations reported as x, y, and z coordinates in Montreal Neurological Institute space with approximate Brodmann areas identified by mathematical transformation of SPM2 coordinates into Talairach space.[29,30]

For significant regions, relation to the clinical effect was investigated. The percent changes in $BP_{ND}$ values in significant clusters after ECT and the correlation between changes in $BP_{ND}$ values and those of HDRS scores were evaluated. The following procedures were performed in SPM2: (1) the detected significant cluster was extracted as a volume of interest (VOI) and (2) individual mean $BP_{ND}$ values in the VOI were acquired by applying the detected significant cluster extracted as a VOI to each of the normalized $BP_{ND}$ images. The Spearman correlation method was used to examine the relationship between changes in $BP_{ND}$ variables and changes in HDRS scores. We also investigated individual mean $BP_{ND}$ values for controls and $R_1$ values for patients before and after ECT in the above VOI by applying the detected significant cluster extracted as a VOI to each of the normalized $BP_{ND}$ images of controls and the normalized $R_1$ images of patients, respectively.

### Statistical Analysis of Clinical Data

The paired *t* test was used to statistically analyze the difference between HDRS scores 1 day before the first session and 1 day after the last session of ECT. Values of $P < .05$ were considered significant.

## RESULTS

All patients showed clinical improvement in response to ECT (Table 1). The baseline HDRS score was reduced from a mean ± SD of 19.43 ± 5.83 to 7.43 ± 5.06 (paired *t* test: $t_6 = 8.92$, $P < .001$).

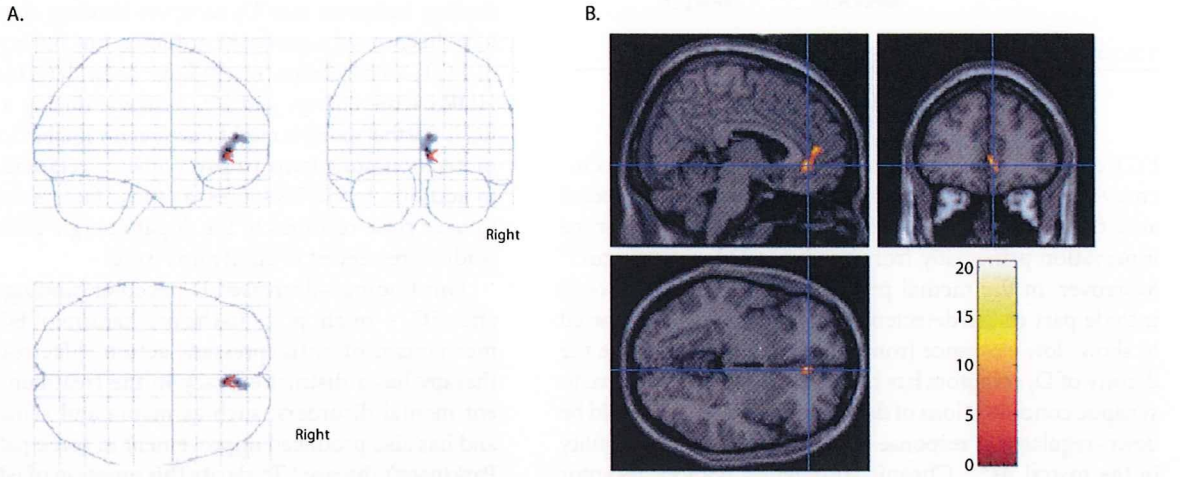
A voxel-based paired *t* test showed significant reduction of $BP_{ND}$ in patients after ECT compared with patients before ECT in the right anterior cingulate (AC) (area 24), which extended rostrally to mesial regions of area 32 and to some voxels in area 10 (Table 2 and Figure 1). In contrast,

Table 2. Effect of ECT on [$^{11}$C]FLB 457

| Region | Brodmann Area | Cluster Level P (corrected) | $K_E$ | Cluster Level P (uncorrected) | Voxel Level P (FWE-corrected) | Voxel Level P (FDR-corrected) | t | z | P (uncorrected) | MNI[a] x | MNI[a] y | MNI[a] z | Talairach[b] x | Talairach[b] y | Talairach[b] z |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rAC | 10/24/32 | <.001 | 109 | <.001 | .042 | .067 | 20.5 | 4.92 | <.001 | 6 | 40 | −4 | 5 | 35 | −3 |
| | | | | | .133 | .077 | 16.85 | 4.69 | <.001 | 6 | 48 | 10 | 5 | 44 | 8 |
| | | | | | .308 | .078 | 14.62 | 4.51 | <.001 | 4 | 42 | 0 | 3 | 38 | 0 |
| | | | | | 1 | .085 | 9.8 | 3.99 | <.001 | 8 | 54 | 8 | 7 | 49 | 6 |

[a]The MNI column contains spatial coordinates in MNI canonical magnetic resonance imaging.
[b]The Talairach column contains spatial coordinates in the Talairach atlas.[30]
Abbreviations: FDR = false detective rate, FWE = family-wise error, $K_E$ = number of voxels in the cluster, MNI = Montreal Neurological Institute, rAC = right anterior cingulate.

Figure 1. Map of *t* Values Showing the Voxels With Significant Decrease in [$^{11}$C]FLB 457 Binding Potential After Electroconvulsive Therapy (ECT)[a,b]




[a]$P < .001$, uncorrected.
[b]Detected areas exceed an uncorrected *P* value of .001 with 100 or more contiguous voxels. In the left panel, all clusters throughout the whole brain are demonstrated in the "glass brain" in SPM2. The red arrow indicates a significant cluster of 109 voxels in the right anterior cingulate. The right panel shows the *t* statistic for the effect of ECT superimposed on the SPM2 canonical single-subject T1 image. The color scale shows the *t* values.

no changes in $R_1$ were seen in the patients between pre-ECT and post-ECT scans. Significant increases of $BP_{ND}$ in patients after ECT compared with patients before ECT were not found.

Voxel-based unpaired *t* tests demonstrated no significant differences in $BP_{ND}$ either for healthy volunteers versus patients before ECT or for healthy volunteers versus patients after ECT.

In the post-ECT patients, there was a mean ± SD reduction in $D_2$ receptor binding of 25.2% ± 7.5% in the VOI compared with the pre-ECT patients (Figure 2). No significant correlations were observed between changes in $BP_{ND}$ values and changes in HDRS scores. The mean ± SD individual $BP_{ND}$ values for controls and for patients before and after ECT were 0.81 ± 0.26, 0.92 ± 0.28, and 0.70 ± 0.27, respectively.

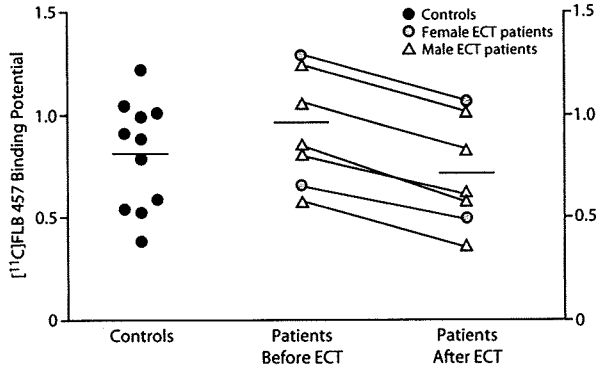
The mean ± SD individual $R_1$ values for patients before and after ECT were 0.81 ± 0.06 and 0.79 ± 0.04, respectively. The paired *t* test revealed that there were no changes in $R_1$ values in the right AC cluster in patients between the pre-ECT and post-ECT scans ($t_6 = 1.13$, $P = .302$).

## DISCUSSION

The major finding of this study was that ECT induced a mean ± SD significant decrease of 25.2% ± 7.5% in $D_2$ receptor binding in the right rostral (AC).

Our previous study[31] indicated that extrastriatal [$^{11}$C]FLB 457 was not sensitive to endogenous dopamine. In healthy volunteers, interindividual variance in $BP_{ND}$ has been suggested to be due mainly to variability in $B_{max}$ rather than $K_D$.[32] In clinical PET studies, $BP_{ND}$ is thus commonly used as an index of receptor density.[33] It is therefore reasonable to assume that the decreased [$^{11}$C]FLB 457 binding observed in this study reflects a reduction of $D_2$ receptor density in the anterior cingulate of patients with MDD after ECT. Providing that there was no neuronal cell loss after ECT,[34] the reduction of receptor density levels after

Figure 2. [$^{11}$C]FLB 457 Binding Potential of Right Anterior Cingulate in 11 Controls and 7 Depressed Patients Before and After 1 Course of Electroconvulsive Therapy (ECT)[a]




[a]Horizontal lines indicate means.

ECT could be attributable to mechanisms adaptive to increased dopamine levels in the synaptic cleft.[7,9] The detected area, the rostral region of the AC, receives dense dopamine innervation principally from the ventral tegmental area.[35] Moreover, in the medial prefrontal cortex, which would include part of the detected area, dopamine was reported to show slow clearance from the synaptic cleft.[36] Since the density of $D_2$ receptors has been reported to be sensitive to synaptic concentrations of dopamine, $D_2$ receptors could be down-regulated in response to higher dopamine availability in the rostral AC.[37] Chronic stimulation with $D_2$ receptor agonists can lead to down-regulation of $D_2$ receptors,[38] and repeated ECS is reported to sensitize $D_2$ receptors.[10,11] Taken together, our finding of decreased $D_2$ receptor binding in the rostral AC could be interpreted as a down-regulation of $D_2$ receptors after the ECT-induced dopamine release and $D_2$ receptor stimulation in the same area.

There has been only 1 animal study on $D_2$ receptors in the AC after ECS.[12] However, it was an autoradiographic study using [$^3$H]spiroperidol, demonstrating that ECS had no effect on $D_2$ receptor binding in the AC. The differences in the method of ECT administration, the species differences, and the ligand selectivity could explain the difference in results.

The rostral AC, connecting reciprocally to both the dorsal AC and the subgenual AC,[39] is considered to act as a bridge between attention and emotion[40] and to consist of the limbic-cortical circuits that maintain homeostatic mood control against stress. The region has been postulated as being one of the distinct targets that different modes of treatment modulate, resulting in a variety of complementary chemical and molecular adaptations and homeostatic effects that establish a normal mood state.[41] In addition, anhedonia and amotivation, which are frequent symptoms of depression, have been hypothesized to be associated with a dysfunction of the subgenual prefrontal cortex (part of which is the rostral AC) to maintain tonic dopaminergic-dependent, reward-related activity.[42] According to these lines of thought, one of the most relevant factors of the mechanism of antidepressant action would be the amelioration of the function of this region to regulate mesolimbic-cortical dopamine neuron activity.

We found no significant correlation between the changes of $BP_{ND}$ in the rostral AC and the changes in HDRS score. The small sample size and the lack of diversity of patients made it difficult to investigate the correlation between ECT effects and clinical improvements. In a related study, Marano et al[43] reported that ECT increased brain-derived neurotrophic factor during a course of ECT and that the change was accompanied by a significant decrease in HDRS score. This finding indicates that $D_2$ receptor binding change might have been most significant not after, but during, a course of ECT; a correlation might have been detected between HDRS score change and $BP_{ND}$ change during a course of ECT. Furthermore, it might have been valuable to assess the motivation/anhedonia or psychomotor retardation scores, in addition to HDRS scores, as those factors are reported to have close relations to the dopaminergic effect. Further studies are needed to clarify this issue.

Our finding—decreased $D_2$ receptor binding in the AC after ECT—might point to the mechanism of ECT, not the mechanism of antidepressant action. Electroconvulsive therapy has a distinct efficacy in the treatment of different mental disorders, such as mania and schizophrenia, and has also produced improvement in some patients with Parkinson's disease.[1] To clarify this question of whether our finding might point to the mechanism of ECT or the mechanism of antidepressant action, investigations of the effect of ECT on $D_2$ receptors in patients with different mental disorders will be required.

Significant differences in [$^{11}$C]FLB 457 binding between patients with depression and control subjects were not detected in this study. Results of neuroimaging studies of striatal $D_2$ receptor binding in MDD have been inconsistent. For instance, increased dopamine $D_2$ receptor binding or sensitivity[16,44–46] has been found in depressive and/or suicidal patients. Meanwhile, no difference in $D_2$ receptor binding was found in 2 recent studies.[47,48] There had been, however, only 1 in vivo study measuring extrastriatal $D_2$ receptor binding of patients with MDD, and it demonstrated no difference in [$^{11}$C]FLB 457 binding between 7 people with depression and 7 healthy controls.[49] Our result was consistent with this study. Nevertheless, both studies may have been affected by methodological limitations, such as small sample size, differences in sex distribution of each group, and differences in medications. Further study is needed to clarify this issue.

In our study, the additional analysis of $BP_{ND}$ in the right AC of controls revealed relatively large interindividual variability of $BP_{ND}$ values (Figure 2). This result is supported by

a former study[50] that demonstrated a mean ± SD $BP_{ND}$ value in the AC of healthy volunteers of 0.79 ± 0.2 (N = 10; 7 men and 3 women; age, 22–38 y). In this respect, our finding that $D_2$ binding did not differ between patients with MDD and controls despite the fact that all $BP_{ND}$ values in the right AC of patients with MDD had decreased after ECT might be explained.

Several confounding factors need to be considered for the interpretation of the present results. Since our sample size was small, our data might not assume normality of distribution. Therefore, we conducted additional analysis using a nonparametric voxel-based approach (SnPM; Wellcome Department of Cognitive Neurology, London, United Kingdom) to confirm our result. Nonparametric voxel-based analysis also revealed significant reduction of $BP_{ND}$ in the right AC in patients after ECT compared with patients before ECT (Montreal Neurological Institute coordinates: x = 4, y = 44, z = 4; pseudo $t = 4.85$; $P = .008$).

Although ECT might alter blood flow,[51] we could not detect a change in $R_1$ values between patients before and after ECT, suggesting that altered blood flow was unlikely to be responsible for the decreases in $BP_{ND}$. Our method for quantification required the use of the cerebellum as a reference region for estimation of nonspecific binding and free ligand concentration. Functional or structural abnormality of the cerebellum in mood disorders might hamper its use as a reference.[52,53] There is also a possibility that ECT could induce differences in tracer kinetics for the cerebellum. In addition, a more recent study[54] with [$^{11}$C]FLB 457 in rodents has shown that it cannot be excluded that a small percentage of the activity in the cerebellum may represent specific binding to $D_2$ receptors. However, cerebellar time-activity curves normalized by injected radioactivity did not differ significantly between patients before and after ECT.

We found no main effect of ECT or ECT-by-time interaction using repeated-measures analysis of variance with Greenhouse-Geisser correction (ECT: $F_{1,12} = 0.03$, $P = .865$; ECT-by-time interaction: $F_{2.28,22.4} = 0.281$, $P = .784$). It should be noted that there was no significant difference between the patients before and after ECT with respect to the injected specific radioactivity and injected mass in [$^{11}$C]FLB 457 (radioactivity injected: $t_6 = -0.81$, $P = .449$; mass of [$^{11}$C]FLB 457 injected: $t_6 = 0.90$, $P = .402$). The mean ± SD values for injected mass for patients before and after ECT were 0.43 ± 0.17 μg and 0.49 ± 0.17 μg, respectively. Increased receptor occupancy of unlabeled radioligand could lead to lower $BP_{ND}$ values, constituting a possible source of error. In simulation studies, for $D_2$ receptor density of the AC, an injected mass of 0.5 μg has been shown to result in a radioligand occupancy of 5%, while an injected mass of 1.0 μg corresponded to 8% occupancy.[50] On the basis of this analysis, the reported difference of 0.43–0.49 should account for 1% or 2% difference in $BP_{ND}$.

Regarding the possible contribution of atropine, propofol, and succinylcholine to our findings, only the effects of atropine and propofol against $D_2$ receptors have so far been investigated. Atropine has been reported not to occupy striatal or nigral dopamine $D_2$ receptors.[55] Propofol has been reported not to interact strongly with $D_2$ receptors ($K_{50}$ values, affinity constant, for propofol binding to $D_2$ receptors > 150 μM).[56] Taken together, it is unlikely that these medications used with ECT contributed to decreased $D_2$ receptor binding in the AC.

In this study, all patients were established on SSRI (fluvoxamine or paroxetine) treatment and were defined as treatment nonresponders on the basis of the clinical judgment of the attending physicians. Among depressive patients receiving paroxetine (modal daily dose, 50 mg; range, 30–50 mg), an increase in $D_2$ receptor binding has been reported in the anterior cingulate gyrus in treatment responders but not in nonresponders.[57] Paroxetine has also been reported to improve social functioning in A1+ allelic patients with posttraumatic stress disorder to a greater extent than in A1− allelic patients with posttraumatic stress disorder.[58] In that study, A1+ allelic patients with lower $D_2$ receptor density of basal ganglia, relative to A1− allelic patients, were speculated to respond to paroxetine via up-regulation of $D_2$ receptors. Chronic treatment of depressed patients with fluvoxamine (daily dose, 300 mg) has been shown not to alter $D_2$ receptor binding in the basal ganglia.[59] For patients with obsessive-compulsive disorder, repeated administration of fluvoxamine (mean ± SD daily dose, 233 ± 50 mg) has been reported to increase $D_2$ receptor binding in the basal ganglia.[60] The relationship between the effect of fluvoxamine and changes in $D_2$ receptor binding in the AC has not been clarified. Taken together, although the effects of SSRIs cannot be ruled out completely, it is unlikely that SSRIs contributed to the reduction in $D_2$ receptor binding in the AC of treatment nonresponders in the present study.

In conclusion, using PET with [$^{11}$C]FLB 457, we measured $D_2$ receptors in patients with MDD before and after ECT and found that ECT decreased $D_2$ receptor binding significantly in the rostral region of the right AC. The present findings suggest that the down-regulation of brain $D_2$ receptors might be induced after ECT as a compensatory change secondary to the modulation of the dopamine system in the region. We provide evidence that one of the biologic mechanisms of ECT could be related to dopaminergic alteration in the rostral AC.

***Drug names:*** atropine (Atropen and others), fluvoxamine (Luvox and others), lorazepam (Ativan and others), paroxetine (Paxil, Pexeva, and others), propofol (Diprivan and others), succinylcholine (Quelicin and Anectine).

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