**Table 1.** Peak Coordinates (X Y Z) and Their *z*-Values of Cerebral Activation Under SEN-SND Contrast in One-Sample *t*-Test of Control Group (Left), in One-Sample *t*-Test of Patient Group (Center), and in Two-Sample *t*-test (Controls > Patients) (Right)

| Contrast | | | SEN-SND | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control Subjects | | | | | | | | Schizophrenia Patients | | | | | | | | Controls > Patients | | | | | | | |
| | | | L | | | | R | | | | L | | | | R | | | | L | | | | R | | | |
| Brain Regions | | | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value |
| Frontal Cortices | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MFG | | BA6/8 | −48, | 6, | 51 | 4.82 | | | | | −42, | 6, | 45 | 3.40 | | | | | −48, | 24, | 42 | 3.08 | | | | |
| IFG | Operculum | BA9/46 | −51, | 21, | 24 | 3.88 | | | | | −45, | 21, | 18 | 3.88 | | | | | −54, | 21, | 24 | 3.36 | | | | |
| IFG | Triangular | BA45/47 | −51, | 24, | −9 | 4.15 | | | | | −48, | 18, | −9 | 3.64 | | | | | −48, | 27, | −6 | 3.68 | | | | |
| Temporal Cortices | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Anterior | STS | BA38 | −52, | 0, | −9 | 4.32 | | | | | | | | | | | | | | | | | | | | |
| | MTG | BA21 | −57, | −3, | −21 | 6.22 | 60, | 6, | −15 | 4.64 | −57, | −12, | −12 | 4.41 | 63, | 0, | −15 | 3.94 | −54, | 3, | −12 | 3.41 | 57, | −3, | −15 | 3.98 |
| Posterior | STS/MTG | BA21/22 | −63, | −24, | 0 | 4.62 | | | | | | | | | | | | | −54, | −33, | −6 | 4.00 | 63, | −9, | −18 | 3.84 |
| | MTG | BA21 | −63, | −36, | −3 | 4.94 | 54, | −18, | −15 | 3.34 | −63, | −45, | −9 | 3.31 | 54, | −24, | −12 | 3.34 | −54, | −66, | 9 | 3.47 | 45, | −24, | −4 | 3.26 |
| Parietal Cortices | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Precuneus | | BA19 | −42, | −72, | 36 | 4.82 | | | | | | | | | | | | | −42, | −72, | 36 | 3.57 | | | | |
| Parahippocampus | | BA35 | −18, | −9, | −24 | 4.59 | | | | | −21, | −21, | −21 | 3.82 | | | | | −33, | 0, | −21 | 3.88 | | | | |
| Thalamus | | | −6, | −18, | 9 | 4.59 | | | | | | | | | | | | | −6, | −18, | 9 | 3.88 | | | | |
| Posterior Cingulate | | BA30 | −6, | −57, | 6 | 3.96 | | | | | | | | | | | | | −6, | −60, | 6 | 3.43 | | | | |
| Cerebellum | | | 3, | −75, | −33 | 3.84 | | | | | | | | | | | | | | | | | | | | |

Activation differences were considered significant at height threshold (one-sample *t*-test: $p < .001$, random effect model, uncorrected ($z = 3.31$)) and extent threshold ((50 voxels); two-sample *t*-test: $p < .005$, random effect model, uncorrected, $z = 2.89$). L, left hemisphere; R, right hemisphere; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; STS, superior temporal sulcus; MTG, middle temporal gyrus; BA, Brodmann's area; SEN, sentences; SND, identifiable non-vocal sounds.

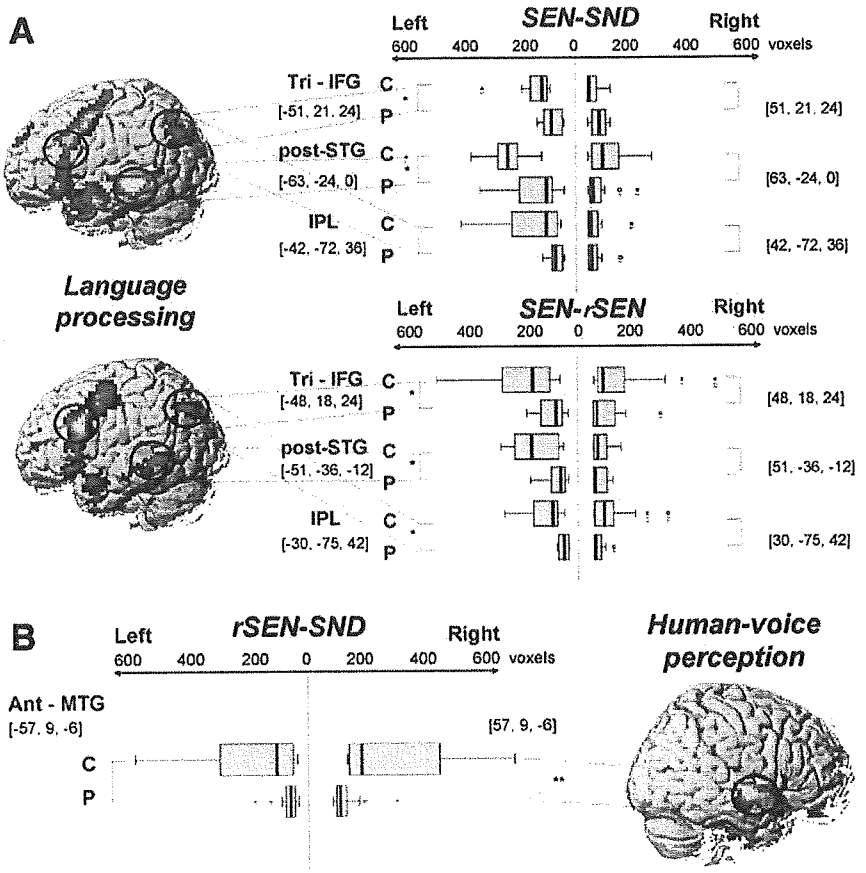


**Figure 3.** Distribution of the activated voxel numbers under the SEN-SND and SEN-rSEN contrasts in the fronto-tempo-parietal lobe **(A)**, and under rSEN-SND contrast in the temporal lobe **(B)** (threshold: $p = .001$, random effect model, uncorrected). From the center line (0 voxel), the left direction shows the left hemispheric-activated voxel numbers, while the right direction shows the right hemispheric-activated voxel numbers. The central coordinates of each ROI are shown on the left and right side of each graph. Each bar shows the 10th and 90th percentiles of distribution from the maximum voxel numbers. Each box shows the 25th, 50th, and 75th percentiles of distribution. The three pictures indicate the results of activation under each contrast in the control group. L, left hemisphere; R, right hemisphere; C, controls; P, schizophrenia patients; tri-IFG, triangular portion of inferior frontal gyrus; aMTG, anterior middle temporal gyrus; pSTG, posterior superior temporal gyrus; IPL, inferior parietal lobe; rSEN, reverse sentences; SEN, sentences; SND, identifiable non-vocal sounds. * $p < .05/6$; ** $p < .05/2$; Bonferroni's multiple comparison.

contrast, and Table 1 Schizophrenia patients: group analysis, random effect model, $p = .001$ uncorrected, extent threshold 50 voxels, $z = 3.31$). In the two-sample $t$-test between the control and patient groups, the patients with schizophrenia showed less activation than the control group in the IFG, posterior MTG, IPL, thalamus, hippocampus, and cingulate in the left hemisphere, but they showed no significantly greater activation in any region (Figure 2, right column of the SEN-SND contrast, and Table 1 Controls > Patients: group analysis, random effect model, $p = .005$ uncorrected, $z = 2.89$).

In the control group, cerebral activation under the SEN-rSEN contrast was observed at the left fronto-tempo-parietal region, and it was similar to that under the SEN-SND contrast. The patient group also showed less activation under the SEN-rSEN contrast, similar to under the SEN-SND contrast. The two-sample $t$ test revealed that the patient group showed less activation than the control group in the left fronto-tempo-parietal region (Figure 2).

Figure 3A (SEN-SND and SEN-rSEN) shows the results of ROI analysis in the tri-IFG, pSTG, and IPL. Table 3 shows the mean ± SD of the activated voxel numbers of the bilateral three regions in the control and patient groups under the SEN-SND and SEN-rSEN contrasts. The volume of the activated area in control subjects was significantly greater than that in schizophrenia patients in the left tri-IFG ($t$-test: $p = .008$ [SEN-SND and SEN-rSEN] $< .05/6$; Bonferroni's multiple comparison), left pSTG ($t$-test: $p = .008$ [SEN-SND], $p = .006$ [SEN-rSEN] $< .05/6$). In the left IPL, patients showed significantly less activation than controls under the SEN-rSEN contrast ($t$-test: $p = .008 < .05/6$), but under the SEN-SND contrast, a significant group difference was not observed ($t$-test: $p = .01 > .05/6$). On the other hand, there was no significant difference between control subjects and schizophrenia patients in the tri-IFG, pSTG, and IPL in the right hemisphere. Figure 4 shows the distribution of laterality index (LI) in the tri-IFG, pSTG, and IPL under the SEN-SND and SEN-rSEN contrasts. The LIs of patients were significantly greater than those of controls in the tri-IFG under the SEN-SND contrast ($t$-test: $p < .001$ ($< .05/6$); Bonferroni's multiple comparison) but not in the other areas ($t$-test: $p > .05/6$).

**Reverse SEN-SND Contrast.** Using the one-sample $t$-test for the rSEN-SND contrast, the control group showed right-lateralized activation in the STS and MTG and bilateral activation in the anterior and posterior cingulate (Figure 2, upper row of the rSEN-SND contrast, and Table 2 Control subjects: group analysis, random effect model, $p = .001$ uncorrected, extent threshold 50 voxels, $z = 3.31$). In contrast, cerebral activation of the patient group was revealed in the bilateral temporal lobe and in the anterior cingulate (Figure 2, middle row of the rSEN-SND contrast, and Table 2 Schizophrenia patients: group analysis, random effect model, $p = .001$ uncorrected, extent threshold 50 voxels, $z = 3.31$). In the two-sample $t$-test between the control and patient groups, the patients demonstrated less right-lateralized activation in the STS and the posterior cingulate than the control group, but they showed no significantly greater activation in any region (Figure 2, lower row of the rSEN-SND contrast, and Table 2 Controls > Patients: group analysis, random effect model, $p = .005$ uncorrected, $z = 2.89$). Figure 3 (rSEN-SND) shows the results of ROI analysis in the aMTG. Table 3 (rSEN-SND) shows the mean ± SD voxel numbers of the control and patient groups in the aMTG. The

**Table 2.** Peaks Coordinates (X Y Z) and Their z-Values of Cerebral Activation Under rSEN-SND Contrast in One-Sample *t*-Test of Control Group (Left), in One-Sample *t*-Test of Patient Group (Center), and in Two-Sample *t*-Test (Controls > Patients) (Right)

| Contrast | | | rSEN-SND | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control Subjects | | | | | | | Schizophrenia Patients | | | | | | | Controls > Patients | | | | | |
| | | | L | | | | R | | | L | | | | R | | | L | | | R | | |
| Brain Regions | | | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value | X, | Y, | Z | *z*-value |
| Temporal Cortices | | | | | | | | | | | | | | | | | | | | | | |
| Anterior | STS | BA38 | | | | | 57, | 9, | −6 | 3.66 | | | | | | | | | | | | |
| | MTG | BA21 | | | | | 60, | 3, | −12 | 5.36 | | | | | | | | | 54, | 6, | −21 | 3.63 |
| Middle | STS | BA22 | −60, | 0, | −3 | 3.63 | | | | | | | | | | | | | | | | |
| | MTG | BA21 | −57, | −3, | −9 | 3.36 | 60, | −3, | −6 | 3.41 | −60, | 0, | −12 | 3.32 | 57, | 0, | −9 | 3.46 | 60, | −3, | −18 | 3.16 |
| Posterior | STS | BA22 | −54, | −24, | 0 | 3.36 | | | | | | | | | | | | | | | | |
| | MTG | BA21 | | | | | 57, | −21, | −6 | 3.36 | | | | | | | | | −52, | −30, | −3 | 3.02 |
| Cingulate | | | | | | | | | | | | | | | | | | | | | | |
| Anterior Cingulate | | | −3, | 48, | −9 | 4.75 | | | | | | | | | 9, | 42, | −9 | 4.82 | | | | |
| Posterior Cingulate | | BA 31 | 0, | −57, | 27 | 3.62 | | | | | | | | | | | | | −6, | −57, | 24 | 3.34 |

Activation differences were considered significant at height threshold (one-sample *t*-test: $p < .001$, random effect model, uncorrected ($z = 3.31$)) and extent threshold ((50 voxels); two-sample *t*-test: $p < .005$, random effect model, uncorrected, $z = 2.89$). STS, superior temporal sulcus; MTG, middle temporal gyrus; BA, Brodmann's area; rSEN, reverse sentences; SEN, sentences; SND, identifiable non-vocal sounds.

**Table 3.** Mean ± SD of the Activated Voxel Numbers in Regions of Interest (ROIs)

| Contrast | SEN-SND | | |
|---|---|---|---|
| Region | Left | Right | LI |
| tri-IFG | | | |
| Controls | 99.8 ± 63.3[a] | 19.3 ± 28.0 | 75.2 ± 29.2[a] |
| Patients | 42.8 ± 35.8[a] | 36.2 ± 24.8 | −1.2 ± 61.2[a] |
| pSTG | | | |
| Controls | 219.8 ± 118.8[a] | 67.1 ± 67.0 | 57.7 ± 33.5 |
| Patients | 103.6 ± 89.9[a] | 34.5 ± 46.5 | 37.4 ± 62.9 |
| IPL | | | |
| Controls | 110.8 ± 105.2 | 29.6 ± 49.6 | 64.1 ± 47.7 |
| Patients | 30.6 ± 23.4 | 19.8 ± 28.6 | 26.2 ± 74.3 |
| Contrast | SEN-rSEN | | |
| Region | Left | Right | LI |
| tri-IFG | | | |
| Controls | 218.9 ± 171.5[a] | 116.8 ± 162.9 | 47.0 ± 37.8 |
| Patients | 77.8 ± 61.9[a] | 52.3 ± 81.5 | 36.9 ± 63.9 |
| pSTG | | | |
| Controls | 152.6 ± 102.7[a] | 33.1 ± 36.7 | 69.3 ± 28.8 |
| Patients | 58.9 ± 54.8[a] | 27.2 ± 31.9 | 39.6 ± 58.9 |
| IPL | | | |
| Controls | 109.4 ± 79.8[a] | 75.7 ± 96.8 | 39.2 ± 52.7 |
| Patients | 28.5 ± 25.1[a] | 18.6 ± 24.6 | 32.9 ± 69.5 |
| Contrast | rSEN-SND | | |
| Region | Left | Right | LI |
| aMTG | | | |
| Controls | 158.4 ± 179.7 | 210.7 ± 196.2[b] | −25.6 ± 39.0 |
| Patients | 43.7 ± 44.7 | 46.6 ± 62.1[b] | 7.5 ± 56.0 |

L, left hemisphere; R, right hemisphere; LI, Laterality Index; tri-IFG, triangular portion of inferior frontal gyrus; pSTG, posterior superior temporal gyrus; IPL, inferior parietal lobe; aMTG, anterior middle temporal gyrus.

[a] $p < .05/6$, Bonferroni's multiple comparison.

[b] $p < .05/2$, Bonferroni's multiple comparison.

ROI volume in controls was significantly greater than that in patients in the right aMTG (right aMTG: *t*-test: $p = .004 < .05/2$; Bonferroni's multiple comparison), but not in the left aMTG (left aMTG: *t*-test: $p > .05/2$). The LI distribution was not significantly different between controls and patients in the aMTG (*t*-test: $p > .05/2$, Figure 4).

### Correlation Analysis

We investigated the correlation between cerebral activation of local areas and symptoms of schizophrenia (total score of BPRS, positive symptoms and negative symptoms). However, no significant correlation was observed in any area (Spearman's correlation coefficient: $p > .05$). In addition, significant correlations were not seen between LI and the BPRS score in any area (Spearman's correlation coefficient: $p > .05$).

## Discussion

To clarify the cerebral function of language processing in patients with schizophrenia by considering cerebral activation of human voice perception, we investigated the difference of cerebral activation between right-handed control subjects and right-handed schizophrenia patients while they were listening to SEN, rSEN, and SND. Under the SEN-SND and SEN-rSEN contrasts, including language processing, the patients demonstrated less cerebral activation

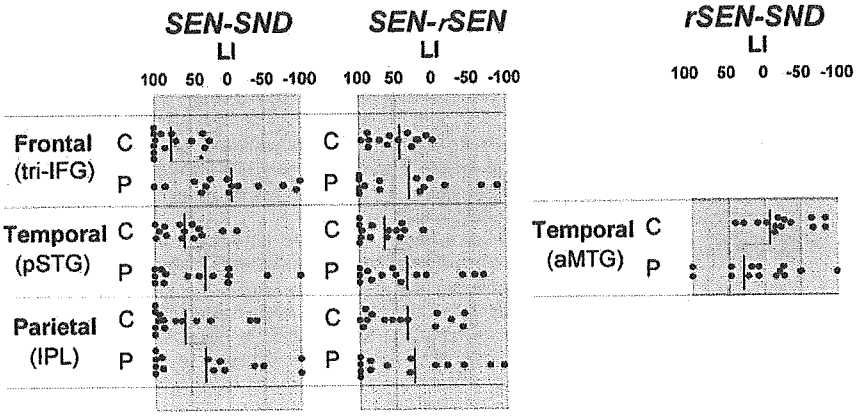


**Figure 4.** Distribution of the Laterality Index (LI) in individual subjects under the three contrasts. Each bar shows the mean of individual LIs. C, controls; P, schizophrenia patients; tri-IFG, triangular portion of inferior frontal gyrus; aMTG, anterior middle temporal gyrus; pSTG, posterior superior temporal gyrus; IPL inferior parietal lobe; rSEN, reverse sentences; SEN, sentences; SND, identifiable non-vocal sounds. * $p < .05/6$; Bonferroni's multiple comparison.

than the controls in the fronto-tempo-parietal region, hippocampus, thalamus and cingulate in the left hemisphere. Further, under the rSEN-SND contrast, which includes human voice perception, the patients demonstrated less activation than controls in the right STS, right MTG, and bilateral posterior cingulate.

### Language Processing in Schizophrenia

The results of fMRI studies of schizophrenia have demonstrated two patterns of cerebral activation for language processing. One is reduced left hemispheric activation (Gaillard et al 2002; Kiehl and Liddle 2001; Kircher et al 2001; Lehericy et al 2000; Schlosser et al 1998), and the other is the reversal of normal language dominance (Crow 2000; Dollfus et al 2005; Menon et al 2001; Ngan et al 2003; Sommer et al 2001, 2003; Woodruff et al 1997). In accordance with the former, our patient group showed less activation of the left hemisphere for language processing than the control group in the fronto-tempo-parietal region, thalamus, and cingulate. Numerous fMRI studies of normal subjects have demonstrated that the left tri-IFG, left pSTG, and left IPL were activated by lexical-semantic processing while listening to speech (Binder et al 1997; Price 2000; Schlosser et al 1999). Reduced activation of the left hemisphere in schizophrenia patients compared with control subjects could be considered to represent dysfunction of the semantic network in the fronto-tempo-parietal cortex associated with language processing.

Although our ROI analysis demonstrated significantly lower LI in the tri-IFG under the SEN-SND contrast in patients than in controls, we did not observe hyper-activation in the right hemisphere. Thus, the lower frontal LI in schizophrenia patients could be attributed to left hemispheric hypo-activation during language processing (Figure 3, Figure 4, Table 3).

### Human Voice Perception of Schizophrenia

We confirmed that reverse sentences were perceived as 'human voice' and 'non-semantic information' in a separate preliminary study. All subjects of the preliminary study recognized the sound as a human voice although they could not understand the contents. Therefore, we adopted the rSEN-SND contrast as a condition of human voice perception without semantic processing.

Patients with schizophrenia have a dysfunction in the ability to discriminate between their own voice and another person's voice (Allen et al 2004). Functional MRI studies of normal subjects demonstrated that the human voice-specific area was located in the STS, dominantly in the right hemisphere (Belin and Zatorre 2003; Belin et al 2000, 2002; von Kriegstein et al 2003; Zatorre et al 2004). However, there are few studies to investigate cerebral response specifically to human voice. One psychological study has indicated that voice recognition, including emotion, is impaired in subjects with schizophrenia (Morrison and Wells 2003). Another fMRI study suggested that the normal right-lateralized response due to emotional prosody is reversed when schizophrenia patients recognize emotional prosody of sentences (Mitchell et al 2004). Since schizophrenia patients showed increased cerebral activation in the temporal cortex during auditory hallucination (Bentaleb et al 2002; Dierks et al 1999; Woodruff et al 1997), we supposed that cerebral activation in such patients would be greater than that in control subjects. However, contrary to our expectations, cerebral activation under the rSEN-SND contrast in patients showed less activation than controls in the right STS, right MTG, and posterior cingulate, although the mean of the performance ratio to human voice was not significantly different. Our present finding of less activation indicates that cerebral activation to human voice was disturbed in schizophrenia patients, suggesting that patients have impairment of broader bilateral cortical and subcortical regions, accompanied by dysfunction of both the semantic network in the left hemisphere and the voice-specific network in the right hemisphere.

Our present study has limitations. First, most of the patients were taking neuroleptic medications, possibly affecting neural activation. They were, however, taking atypical neuroleptics at relatively low doses. To our knowledge, there have been no previous studies on the effect of neuroleptics on the BOLD response of language processing and human voice perception. Atypical neuroleptics have shown less influence on BOLD contrast in the motor cortex or the thalamus during a finger-tapping procedure as compared to typical neuroleptics (Braus et al 1999; Muller and Klein 2000). Second, we could not demonstrate any correlation between signal changes and BPRS scores in patients, possibly due to a lack of dispersion in the psychopathology of the patients, most of them being outpatients with mild psychiatric symptoms. Third, recent fMRI studies discussed gender differences of cerebral activation in language processing (Gur et al 2000; Kansaku et al 2000; Shaywitz et al 1995; Sommer et al 2003). These studies demonstrated reduced language dominance in normal female groups in comparison with normal male groups. We could not evaluate the influence of gender differences in our study, because only two of the fourteen patients were female. Since there have been few studies concerning the influence of gender differences on language dominance in schizophrenia, this point would need to be investigated in the future.

When cerebral function in language processing was investigated, cerebral activation of right-handed patients with schizo-

phrenia was less than controls in the broader language-associated areas, including the left IFG, left posterior MTG, left IPL, left thalamus, left hippocampus, and bilateral posterior cingulate. The patient group did not show greater activation than the control group in any language-associated area. Furthermore, in cerebral activation of human voice perception, the patient group demonstrated less activation than the control group in the right STS, right MTG, and bilateral cingulate. These findings indicate that right-handed schizophrenia patients have a disturbance of both left hemispheric function for language processing and right hemispheric function for human voice perception.

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## Appendix 1.

We used the following sentences in the task.

1. Ms. Keiko Ueda, who lives in Kitakyushu City and works as a licensed cook at a company cafeteria, notified the police near the station that 56,000 yen were stolen when she was mugged at Odouri last night.
2. Last night, when Mr. Ichiro Sato was driving a 10-ton truck full of eggs along the road to Yokohama, near the mouth of the Tama River the axle of the truck broke, and the truck slipped off the road and was buried in a ditch.
3. These days "Casual Day" during which businessmen work in plain clothes with no tie has been established, but the apparel business has developed and is marketing a "Dressed Up Monday Campaign" that advertises "Let's be smartly dressed in a suit every Monday."
4. Today, the designs of Northern Europe have become increasingly popular, and a cultural event showing a collection of Swedish designs, music and images, etc., called 'Swedish style 2001,' will be held at various locations in Tokyo.

## Appendix 2.

### Questionnaire

Please answer the following question after listening to two sounds.

1. **As what did you recognize these sounds? Please circle the appropriate one.**

(1) Human voice
(2) Animal sound
(3) Machine sound
(4) Environmental sound

2. **If you circled No. (1), please answer these questions.**

As what did you recognize the first sound?

(1) Male voice
(2) Female voice

As what did you recognize the second sound?

(1) Male voice
(2) Female voice

3. **Did you recognize these sounds as having intonation?**

Yes No

4. **Did you recognize a message from these sounds?**

Yes No

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ARTICLE

# The antipsychotic sultopride is overdosed – a PET study of drug-induced receptor occupancy in comparison with sulpiride

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**Abstract**

Conventional antipsychotics tend to elicit extrapyramidal symptoms at clinical doses, but dose optimization could reduce the risk of such side-effects. In-vivo receptor-binding studies have suggested that 70–80% of dopamine $D_2$ receptor occupancy provides the desired antipsychotic effects without extrapyramidal symptoms. In terms of dose optimization based on the occupancy, there has not been enough supporting data regarding the clinical doses of the respective antipsychotics. In this study, we measured dopamine $D_2$ receptor occupancy of two conventional benzamide antipsychotics, sulpiride and sultopride, using positron emission tomography, to investigate the rationale of their clinical dose. Although they are prescribed at similar doses (300–1200 mg), the doses required to obtain similar receptor occupancy (70–80%) were quite different: 1010–1730 mg for sulpiride but 20–35 mg for sultopride. In terms of dose, sultopride has about 50 times greater potency than sulpiride based on dopamine $D_2$ receptor occupancy. Evidence for the optimal doses of conventional antipsychotics based on dopamine $D_2$ receptor occupancy would be helpful for rational antipsychotic therapy.

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**Key words**: Antipsychotics, dopamine $D_2$ receptor, dose settings, occupancy, PET.

## Introduction

Conventional antipsychotics have been regarded as drugs with more frequent extrapyramidal side-effects (EPS) compared with second-generation antipsychotics (Gerlach and Peacock, 1995; Waddington et al., 1997). However, a recent meta-analysis suggested that low-potency conventional antipsychotics at optimal doses might in fact not induce more EPS than second-generation antipsychotics (Leucht et al., 2003), and another meta-analysis reported that second-generation antipsychotics were found not to have greater efficacy than high-potency conventional antipsychotics at lower dose (Geddes et al., 2000). Discussion on the scientific evidence for clinical doses of conventional antipsychotics has been inconclusive, and opposing results were also reported in a meta-analysis (Davis et al., 2003). Although antipsychotics are classified in several ways, in the present article, the term 'second-generation antipsychotics' refers to clozapine and all the novel antipsychotics introduced in the 1990s, and 'conventional antipsychotics' refer to older antipsychotics. The advent of positron emission tomography (PET) has made it possible to measure the receptor occupancy of antipsychotics in the living human brain (Farde et al., 1988). PET studies have suggested that a range of 70–80% of dopamine $D_2$ receptor occupancy provides the desired antipsychotic effects without EPS (Farde et al., 1992; Kapur et al., 2000). It was also suggested that one advantage of the use of second-generation

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antipsychotics might be better explained by the determination of appropriate clinical dose settings (Kapur and Mamo, 2003). Amisulpiride, a benzamide antipsychotic drug, was reported to show fewer EPS and has been regarded as a second-generation antipsychotic drug; its clinical doses were reported to show appropriate dopamine $D_2$ receptor occupancy (Martinot et al., 1996). On the other hand, sulpiride and sultopride, other benzamide antipsychotics, were considered as conventional antipsychotics. Despite their similar registered clinical doses (sulpiride 300–600 mg, max 1200 mg; sultopride 300–600 mg, max 1800 mg in Japan) and the fact that the equivalency of clinical potency was reported (2 mg haloperidol is equivalent to 200 mg sulpiride or 200 mg sultopride) (Inagaki et al., 1999), sultopride has been reported to induce more EPS than sulpiride (Peselow and Stanley, 1982). The relationship between the dose/plasma concentration and dopamine $D_2$ receptor occupancy by the two drugs has not been fully explored. Since they are relatively selective dopamine $D_2$ receptor antagonists (Peselow and Stanley, 1982), their dopamine $D_2$ receptor occupancy in the living human brain can be expected to provide us with the criteria to decide the appropriate doses. In this study we measured dopamine $D_2$ receptor occupancy of the two conventional substitute benzamide antipsychotics, sulpiride and sultopride, to investigate the rationale for their dose settings.

## Materials and methods

### *Subjects*

Twenty-one male healthy volunteers ($26.6 \pm 5.7$ yr) were enrolled in this study. None had a history of psychiatric or neurological illness, chronic somatic illness or substance abuse. None was receiving any medication, and none had a close relative with a known psychiatric illness.

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

### *Radioligand*

The precursors of [$^{11}$C]FLB 457 were kindly supplied by Astra Arcus (Sodertaje, Sweden). [$^{11}$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 (Halldin et al., 1995; Suzuki et al., 1999). The radiochemical purities were more than 95%.

### *PET procedure*

Dynamic scans were performed for 90 min using ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA) immediately after a bolus injection of $220 \pm 16$ MBq of [$^{11}$C]FLB 457 with high specific radioactivities ($141 \pm 34$ GBq/$\mu$mol).

MRIs were acquired on Gyroscan NT (Philips Medical System, Best, The Netherlands) (1.5 T) to obtain T1-weighted images of the brain.

Two PET scans were performed, one before antipsychotics administration, and the second at the possible peak time of plasma concentration of the drugs, 3 h after a single dose of sulpiride (200–800 mg; 3 subjects at 200 mg, 3 at 400 mg, 3 at 600 mg, 2 at 800 mg) and 2 h after a single dose of sultopride (10–200 mg; 3 subjects at 10 mg, 3 at 25 mg, 2 at 50 mg, 1 at 100 mg, 1 at 200 mg). Three subjects with sultopride (50, 100, and 200 mg respectively) did not complete the 90-min PET scans due to akathisia and EPS, with PET data of 60 min being used for the subject receiving 200 mg and 70 min for the two subjects receiving 50 mg and 100 mg sultopride respectively. Blood samples were taken just before each PET scan for concentration measurements of sulpiride or sultopride.

The subjects were examined for EPS, akathisia, and other adverse effects after the PET scans by two psychiatrists who were aware of the dosage of the antipsychotics.

### *Data analysis*

All emission scans were reconstructed with a Hanning filter cut-off of 0.4. Regions of interest (ROIs) (prefrontal cortex, temporal cortex, thalamus, cerebellum) were drawn on PET/MRI images by a template-based method (Yasuno et al., 2002). The average values of right and left ROIs were used to increase the signal-to-noise ratio for the calculations. Quantification of PET data was performed using a three-parameter simplified reference tissue model to estimate binding potential (BP) (Lammertsma and Hume, 1996). The cerebellum was used as the reference tissue because of its negligible density of dopamine $D_2$ receptors for calculation (Suhara et al., 1999). This model allows the estimation of BP, which was defined as the ratio of receptor density ($B_{max}$) to dissociation constant ($K_d$). Dopamine $D_2$ receptor

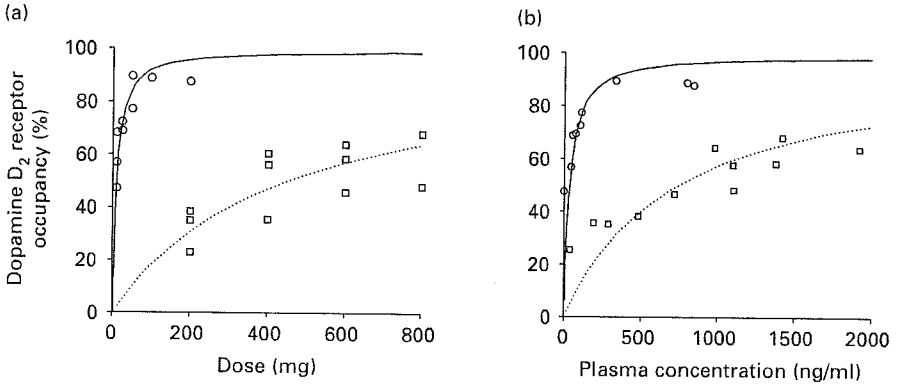


**Figure 1.** Relationship between dopamine $D_2$ receptor occupancy and doses of sulpiride and sultopride (a), and between dopamine $D_2$ receptor occupancy and plasma concentrations of sulpiride and sultopride (b). Mean dopamine $D_2$ receptor occupancy of three regions (prefrontal cortex, temporal cortex, and thalamus) was shown as dopamine $D_2$ receptor occupancy. Open squares indicate sulpiride, and open circles indicate sultopride. The dotted regression curve was fitted to the sulpiride data, and the solid regression curve was fitted to the sultopride data.

occupancy by antipsychotics was calculated using the following equation:

$$Occu = (BP_{baseline} - BP_{drug}) \times 100/BP_{baseline},$$

where Occu is receptor occupancy, $BP_{baseline}$ is BP in the drug-free state, and $BP_{drug}$ is BP of the subject on the drug.

The relationship between dopamine $D_2$ receptor occupancy and dose/plasma concentration of antipsychotics was fitted to the following equation:

$$D_{2,occu} = 100 \times D/(ED_{50} + D),$$

where $D_{2,occu}$ is dopamine $D_2$ receptor occupancy, $ED_{50}$ is the dose/concentration to induce 50% occupancy, and $D$ is the dose/concentration of the drug (Fitzgerald et al., 2000; Kapur and Remington, 1996).

### *The measurement of plasma concentrations of sulpiride and sultopride*

The plasma concentration of sulpiride was measured according to a previous report (Tokunaga et al., 1997) with the following modification. The HPLC column was a Waters Xterra RP18, a 150 × 3.9 mm i.d. with a mobile phase of 10% $CH_3CN$ in 0.1 M phosphate buffer (pH 2.0) at a flow rate of 1.0 ml/min. A UV detector was set at 235 nm.

The plasma concentration of sultopride was measured according to a previous report (Kobari et al., 1985) with the following modification. The HPLC column was Waters Xterra RP18, a 150 × 3.9 mm i.d. with a mobile phase of 12% $CH_3CN$ in 0.1 M phosphate buffer (pH 2.0) at a flow rate of 1.0 ml/min. A UV detector was set at 235 nm.

## Results

The mean dopamine $D_2$ receptor occupancy in the three regions (prefrontal cortex, temporal cortex, and thalamus) ranged from 25.3% to 68.3% on doses of 200–800 mg sulpiride and from 47.4% to 89.4% on doses of 10–200 mg sultopride. Occupancy values of the three subjects taking sultopride and not completing the 90-min PET scans due to EPS or akathisia were more than 87%. No subjects taking sulpiride showed akathisia or EPS. None of the 21 subjects showed any other adverse effects. For both sulpiride and sultopride, mean dopamine $D_2$ receptor occupancy increased as the dose and plasma concentration increased (Figure 1a,b). There were no obvious differences in occupancy among the three regions. The S.D. of dopamine $D_2$ receptor occupancy among the three regions ranged from 0.9% to 10.2% (mean ± S.D., 5.1 ± 3.0%) for sulpiride and from 0.8% to 6.5% (4.3 ± 1.9%) for sultopride. The $ED_{50}$ value of sulpiride was 433 mg ($r = 0.69$) for dose and 740 ng/ml ($r = 0.71$) for plasma concentration, while that of sultopride was 8.7 mg ($r = 0.85$) for dose and 32 ng/ml ($r = 0.66$) for plasma concentration.

## Discussion

Despite the similar registered clinical doses for sulpiride and sultopride (Inagaki et al., 1999), the $ED_{50}$ values measured by PET were quite different. Based

on the dopamine $D_2$ receptor occupancy, sultopride has approx. 20 times greater potency than sulpiride when viewing plasma concentration, and approx. 50 times greater potency in terms of dose. Calculating the optimal doses with this occupancy data, 1010–1730 mg sulpiride would be required to obtain 70–80% of dopamine $D_2$ receptor occupancy, while 20–35 mg sultopride would be sufficient. The calculated optimal dose range for sulpiride overlapped with the upper range of the registered clinical doses. On the other hand, the registered clinical doses of sultopride were approx. 10 times higher than the calculated optimal doses. Clinically, sultopride has been used for sedation rather than for the treatment of psychotic symptoms, and it was reported to have a high incidence of EPS (Peselow and Stanley, 1982). However, the present results suggest that a much lower dose of sultopride would be sufficient to treat psychotic symptoms. A future clinical trial would be required with such lower dose.

There are some pharmacological differences in the profiles of the two drugs. The affinity to dopamine $D_2$ receptor of sultopride ($IC_{50}$ value 18 nM) was higher than that of sulpiride (69 nM) (Mizuchi et al., 1982). In addition, the brain uptake from blood was much higher for sultopride compared to sulpiride (Mizuchi et al., 1983). As the log *p* value was 1.46 for sultopride and 0.42 for sulpiride, the difference in brain uptake was considered to be due to the higher lipophilicity of sultopride (Mizuchi et al., 1983). Since drug transport is regulated by efflux transporters such as P-glycoprotein at the blood–brain barrier (Wang et al., 2004), we investigated the possibility of a *substrate* of P-glycoprotein for both drugs. However, we could not obtain supportive data for any *substrate* (data not shown). The different receptor occupancy profiles of the two drugs could be attributed to differences in drug affinity and penetration into the brain.

Despite the pharmacological differences, the clinical doses of the two drugs were determined as equivalent (Inagaki et al., 1999). Several potential problems concerning the process of determining the clinical doses of antipsychotics at the stages of both animal and clinical studies seem to exist. In a series of animal experiments, the inhibition of apomorphine- or methamphetamine-induced stereotyped behaviour and the induction of catalepsy were evaluated for sulpiride and sultopride (Araki et al., 1986). In the inhibition of apomorphine-induced stereotyped behaviour, sultopride was approx. 100 times weaker than haloperidol. For catalepsy induction, sultopride was approx. 25 times weaker than haloperidol (Araki et al., 1986). Although a series of paradigms such as the inhibition of apomorphine- and methamphetamine-induced stereotyped behaviours was used for animal studies, psychiatric symptoms in human patients could not themselves be modelled as in animals. The optimal dose in any such model will certainly not represent the dose for humans, making it difficult to estimate optimal doses for humans from animal experiments. Doses chosen on the basis of an animal study were often unrepresentative of the clinical condition (Kapur et al., 2003), and the doses in a clinical study tended to be higher than the minimum optimal dose (Talvik et al., 2004). In clinical studies, several preliminary reports were published in the 1970s regarding the use of sultopride in psychiatric disorders (Genevieve and Couriol, 1976; Maurel and Pujol, 1975; Robert, 1978). However, the doses in those reports were diverse, from 200 mg to 4800 mg, and a variety of patients were included (Peselow and Stanley, 1982). In a double-blind comparative study of sultopride (800–1600 mg) with thioproperazine (8–16 mg), EPS emerged for both drugs, and no differences in EPS were reported between them (Sizaret and Moreau, 1977). In a double-blind comparative study of sultopride with haloperidol, the dose (300–1800 mg/d) was defined on the basis of an animal study, a phase-two study and preliminary clinical data (Kudo et al., 1987). In that study, antiparkinsonian medications were allowed to be prescribed, and it was concluded that sultopride was as efficacious as haloperidol. However, the co-administration with antiparkinsonian medications might have masked any possible overdose. In another double-blind study for comparison between sulpiride (300–1800 mg) and sultopride (300–1800 mg), antiparkinsonian medications were also allowed (Kudo et al., 1986), and the effectiveness of the two drugs was judged to be not significantly different. Again, EPS might have been masked by the antiparkinsonian medications. In clinical studies for antipsychotics, symptoms and side-effects of patients with schizophrenia would not be easy to evaluate if also using antiparkinsonian medications.

Since the clinical doses of amisulpride were reported to show appropriate dopamine $D_2$ receptor occupancy (Martinot et al., 1996), one advantage of the use of second-generation antipsychotics might be better explained by the application of appropriate clinical dose settings.

Although sulpiride was introduced in the clinical field in the 1970s and is classified as a conventional antipsychotic (Ago et al., 2005; Keltner and Johnson, 2002), some reports considered it as an 'atypical' antipsychotic due to its low EPS rate (Caley and Weber, 1995; Rummel et al., 2003). The present result

indicated that the clinical doses of sulpiride overlapped with the lower range of the optimal doses. If the proper setting of the clinical dose explains the low rate of EPS, sulpiride could be regarded as 'atypical'.

There are several confounding factors in this study. First, we measured occupancy with normal subjects after a single administration. Although it is unlikely that there is a marked difference in dopamine $D_2$ receptor occupancy between normal subjects and patients with schizophrenia, further occupancy studies in patients with schizophrenia and repeated administrations may provide useful information. Second, although most previous occupancy reports were based on striatal measurements, we measured extrastriatal regions with [$^{11}$C]FLB 457 because limbic and cortical regions were suggested to be a site of antipsychotic actions (Lidow et al., 1998; Pilowsky et al., 1997). The test–retest reproducibility was good, with a mean variability of 4.5% for the thalamus, 7.7% for the frontal cortex, and 5.4% for the temporal cortex (Sudo et al., 2001). Although the regional differences of dopamine $D_2$ receptor occupancy by clozapine was reported (Pilowsky et al., 1997), there have been discussions on the methodology (Olsson and Farde, 2001) and similar occupancy values of antipsychotics were obtained in extrastriatal regions and the striatum in several studies (Nyberg et al., 1999, 2002; Takano et al., 2004; Talvik et al., 2001; Vernaleken et al., 2004; Yasuno et al., 2001). Thus, the threshold of dopamine $D_2$ receptor occupancy in the striatum was also considered to be applicable to extrastriatal regions. Third, 3 out of the 21 volunteers did not complete the 90-min PET scans, and their results were based on 60–70 min data. Nevertheless, the time to reach equilibrium was within 60 min in those regions, and a simplified reference tissue method has been reported to produce reliable BP for over 60 min (Olsson and Farde, 2001).

In summary, despite the similar registered clinical doses for sulpiride and sultopride, based on dopamine $D_2$ receptor occupancy, sultopride has ~50 times greater potency than sulpiride. As evidence for the clinical doses of conventional antipsychotics has been limited, their re-evaluation based on dopamine $D_2$ receptor occupancy is warranted for the establishment of rational antipsychotic therapy.

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## Statement of Interest

None.

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# Time course of in vivo 5-HT transporter occupancy by fluvoxamine

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## Abstract

The pharmacokinetics of drugs with specific binding sites in the brain needs to be evaluated at these sites. In this study, we measured the time course of the selective serotonin reuptake inhibitor fuvoxamine in the human brain based on serotonin transporter (5-HTT) occupancy by positron emission tomography (PET). Consecutive PET scans were performed using [$^{11}$C]DASB before and 5 hr, 26 hr and 53 hr after 50 mg of fluvoxamine administration in six healthy male volunteers (24.3 $\pm$ 4.8 y.o.). Quantification was performed using the multilinear reference tissue model 2. Mean 5-HTT occupancies were 72.9 $\pm$ 4.9% at 5 hr, 50.3 $\pm$ 11.0% at 26 hr, and 24.7 $\pm$ 15.3% at 53 hr, and plasma concentrations were 13.9 $\pm$ 5.5 ng/ml at 5 hr, 5.1 $\pm$ 3.2 ng/ml at 26 hr, and 1.5 $\pm$ 1.7 ng/ml at 53 hr. The relationship between the plasma concentration of fluvoxamine and 5-HTT occupancy at these different time points was fitted to the law of mass action.

Keywords: SSRIs, occupancy, 5-HT transporter, [$^{11}$C]DASB

## Introduction

Serotonin transporter (5-HTT) is one of the key targets for antidepressants[1]. The relationship between 5-HTT occupancy and the dose of antidepressants has recently been reported using PET with radioligands [$^{11}$C]McN(+)5652 and [$^{11}$C]DASB.[2,3] Since the pharmacokinetics of drugs with specific binding sites need to be evaluated at these sites, the time course at 5-HTT is a good surrogate index of the time course of antidepressants. However, the time course of 5-HTT occupancy by selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and citalopram in the living human brain has not yet been reported, although there was a report of a cat study.[4] In this study, we measured the time course of 5-HTT occupancy and plasma concentration of fluvoxamine in the human brain. To evaluate the reproducibility of the measurements, we also performed a test-retest study using a separate group of subjects.

## Materials and methods

### Subjects

The study was approved by the ethics and radiation safety committees of the National Institute of Radiological Sciences, Chiba, Japan. Written informed consent was obtained from each subject. Six healthy non-smoking male volunteers (24.3 $\pm$ 4.8 y.o.) were enrolled in the occupancy study. A test-retest study was performed on a

separate group of nine healthy non-smoking male subjects (23.0 ± 3.4 y.o.). None of the subjects had a history of present or past psychiatric, neurological, or somatic disorders, and none had alcohol- or drug-related problems. None had taken any kind of medication for at least one month prior to the start of the study.

**Radioligand**

Desmethyl precursor of [$^{11}$C]3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB) was kindly supplied by Alan A. Wilson (University of Toronto, Toronto, Canada)[5]. [$^{11}$C]DASB was synthesized by methylation of the corresponding desmethyl precursor with [$^{11}$C]$CH_3I$ as described previously.[5] Radiochemical purities were over 95%.

**PET studies**

In the occupancy study, PET scans were performed 4 times for each subject — before fluvoxamine administration, and 5 hr, 26 hr, and 53 hr after a single administration of 50 mg of fluvoxamine. In the test-retest study, PET scans for each subject were performed twice at an interval of 34.2 ± 51.7 (0-161) days.

**PET procedures**

PET scans were carried out with an ECAT 47 (CTI-Siemens, Knoxville, TN, USA) scanner that provides 47 slices with 3.375 mm (center-to-center) thickness. A head

fixation device was used during the scans (Fixter Instruments, Stockholm, Sweden). A 10 min transmission scan was done to correct for attenuation. In the occupancy study, dynamic PET scans were carried out for 90 min in 2D mode immediately after a bolus injection of [$^{11}$C]DASB. Subjects in the occupancy study received a dose of 481.7 – 755.9 (mean ± SD, 613.1 ± 71.0) MBq of [$^{11}$C]DASB with specific radioactivity of 66.1 – 414.2 (mean ± SD, 240.0 ± 78.2) GBq/ $\mu$ mol at the time of injection. Subjects in the test-retest study received a dose of 410.0 – 755.9 (mean ± SD, 620.4 ± 74.9) MBq of [$^{11}$C]DASB with specific radioactivities of 108.7 – 318.0 (mean ± SD, 238.5 ± 66.7) GBq/ $\mu$ mol at the time of injection.

**MRI procedures**

MRIs were acquired on Gyroscan NT (Phillips Medical Systems, Best, The Netherlands) (1.5T) to obtain T1-weighted images of the brain.

**Plasma concentration of fluvoxamine**

Blood samples were taken to measure the concentrations of fluvoxamine at certain intervals (5, 26, and 53 hr) after fluvoxamine administration. Measurement of the plasma concentrations of fluvoxamine was conducted by Meiji Seika Kaisha, LTD. (Tokyo, Japan). Plasma (0.5 ml) was added to the internal standard solution (clovoxamine fumarate) and extracted with 4 ml of a mixture of organic solution. The

organic phase was evaporated to dryness under a stream of $N_2$. The residue was dissolved in 200 ml of 0.1 vol% acetic acid / methanol solution. 20 μl of the solution was injected to LC-MS/MS to measure the plasma concentration of fluvoxamine.

**Data analysis**

All emission scans were reconstructed with a Ramp filter cut-off frequency of 0.5 (full-width half-maximum [FWHM], 6.3mm). Regions of interest (ROIs) for prefrontal cortex, thalamus, striatum, amygdala, hippocampus and cerebellum were drawn on the co-registered PET/MRI images using a template-based method.[6] Quantification of [$^{11}$C]DASB binding was performed using multilinear reference tissue model 2 (MRTM2) to estimate the binding potential (BP).[7] The cerebellum was used as the reference tissue because of its negligible density of 5-HTT. The 5-HTT occupancy by fluvoxamine was calculated using the following equation: $Occu = (BP_{baseline} - BP_{drug}) \times 100/BP_{baseline}$, where Occu is the 5-HTT occupancy, $BP_{baseline}$ is BP in the drug-free state, and $BP_{drug}$ is BP of the subjects on the drug. The plasma concentration of fluvoxamine was plotted against 5-HTT occupancy. The relationship between them was modeled by the equation $Occu = 100 \times C/(C+ED_{50})$, where Occu is the 5-HTT occupancy, C is the plasma concentration of fluvoxamine, and $ED_{50}$, a constant, is the plasma concentration to induce 50% of 5-HTT occupancy.

For test-retest reproducibility, the within-subject variability was defined as the absolute value of the difference between the test and retest measurements expressed as the percentage of the mean value of the two measurements as follows: variability (%) = 100 x (test - retest)/(test + retest) / 2. Measure of the reliability was assessed by the intraclass correlation coefficient (ICC) according to the following equation: ICC = (MSBS-MSWS)/(MSBS + MSWS), where MSBS is the mean sum of squares between subjects, and MSWS is the mean sum of squares within subjects. This coefficient is an estimate of the reliability of the two sets of measurement and varies from –1 (no reliability) to +1 (perfect reliability, i.e. identical test and retest measurements).

**Results**

Test-retest reproducibility calculated by MRTM2 is summarized in Table 1. All BP measurements in the 5 regions showed good reproducibility with high ICCs (0.87-0.96). The mean 5-HTT occupancies of the 5 regions of 6 subjects were 72.9 ± 4.9% at 5 hr, 50.3 ± 11.0% at 26 hr, and 24.7 ± 15.3% at 53 hr after a single oral dose of 50 mg of fluvoxamine (Table 2). The mean plasma concentrations of fluvoxamine were 13.9 ± 5.5 ng/ml at 5 hr, 5.1 ± 3.2 ng/ml at 26 hr, and 1.5 ± 1.7 ng/ml at 53 hr (Table 2). There were no significant regional differences in 5-HTT occupancy among the 5 regions. The mean 5-HTT occupancies were plotted against plasma concentration of fluvoxamine