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Predictors of treatment response to fluvoxamine in obsessive–compulsive disorder: An fMRI study

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ABSTRACT

Recent neuroimaging studies suggest that the pathophysiology of obsessive–compulsive disorder (OCD) may involve more widely distributed large-scale brain systems, including the parietal, occipital, and cerebellar areas, rather than the conventional orbitofronto-striatal model. We hypothesized that not only orbitofrontal cortex and caudate nucleus activities but also posterior brain regions might be associated with subsequent treatment response to serotonin reuptake inhibitors in OCD. The participants were 17 patients with OCD. Each patient was required to undergo fluvoxamine pharmacotherapy for 12 weeks. Before treatment, fMRI images of the subjects were obtained in the context of a symptom-provocation paradigm. The percentage changes in total Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) scores, from pre- to post-treatment, served as the index of treatment response. Statistical Parametric Mapping was used to identify brain loci where pre-treatment brain activation significantly correlated with the subsequent treatment response. Fifteen of 17 patients completed the 12-week treatment. During the symptom provocation task, patients showed brain activation in the left superior temporal gyrus (STG), left precuneus, left frontal cortices, right cerebellum, and right frontal cortices. We found that pre-treatment activation in the right cerebellum (Z-score = 5.10, $x, y, z = 22, -84, -18$) and the left STG (Z-score = 4.95, $x, y, z = -62, -22, 0$) was positively correlated with the improvement in the Y-BOCS score. Our results suggest that pre-treatment activation in the right cerebellum and in the left STG predict subsequent reduction in OCD symptom severity. There is every possibility that fMRI can be used as a tool to predict treatment response.

1. Introduction

The effectiveness of serotonin reuptake inhibitors (SRIs) in the treatment of obsessive–compulsive disorder (OCD) has been shown in placebo-controlled studies (DeVeaugh-Geiss et al., 1990; Goodman et al., 1989a; Kronig et al., 1999; Zohar and Judge, 1996), but 40–60% of patients do not have an adequate response to these drugs (Goodman et al., 1993). Previous studies have identified predictors of response to SRIs. Younger age at onset (Ackerman et al., 1994; Erzegovesi et al., 2001; Ravizza et al., 1995; Shetti et al., 2005), longer duration of illness (Shetti et al., 2005; Stein et al., 2001), higher baseline severity of OCD symptoms (Alarcon et al., 1993; Mataix-Cols et al., 1999; Shetti et al., 2005; Stein et al., 2001; Tukel et al., 2006), poor insight (Erzegovesi et al., 2001; Shetti et al., 2005), presence of hoarding obsessions and compulsions (Black et al., 1998; Mataix-Cols et al., 1999), presence of cleaning rituals (Alarcon et al., 1993; Ravizza et al., 1995; Shetti et al., 2005), and comorbid axis II disorders (Baer et al., 1992) have been identified as negative predictors in previous studies.

On the other hand, many functional neuroimaging studies of OCD found abnormalities of cerebral blood flow or glucose uptake throughout the frontal cortex and subcortical structures in patients with OCD (Baxter et al., 1987; Machlin et al., 1991; Nakao et al., 2005a; Nordahl et al., 1989; Swedo et al., 1989). Several neuroimaging studies reported activation of areas such as the orbitofrontal cortex (OFC), caudate nucleus, thalamus, and anterior cingulate cortex during provocation of obsessive–compulsive symptoms (Adler et al., 2000; Berthier et al., 1996; Nakao et al., 2005b; Rauch et al., 1994; Zohar et al., 1989). Furthermore, several functional imaging studies of OCD patients both before and after treatment using either SRIs or behavioral therapy suggested that activity in the OFC, thalamus, and caudate nucleus was decreased by success-

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ful treatment (Baxter et al., 1992; Kang et al., 2003; Nakao et al., 2005b; Nakatani et al., 2003; Saxena et al., 1999; Swedo et al., 1992). These previous findings have suggested a frontal–subcortical circuit hypothesis (Saxena et al., 1998) that explains the etiology of OCD; however, several studies have also shown abnormal activities in other brain regions (Menzies et al., 2008). Below-normal glucose metabolism in the occipital–parietal area (Nordahl et al., 1989) and above-normal glucose metabolism in the cerebellum (Swedo et al., 1989) were found in studies using [^{18}F]fluorodeoxyglucose-positron emission tomography (PET). Busatto et al. (2000) also reported higher regional cerebral blood flow in the cerebellum in patients with OCD than in healthy control subjects in a single photon emission computed tomography (SPECT) study. These researchers suggested the involvement of other areas in addition to the frontal–subcortical circuits in the pathophysiology of OCD.

Several studies of OCD patients using region of interest (ROI) methods have found that a lower pre-treatment metabolism rate within the OFC (Brody et al., 1998; Saxena et al., 1999; Swedo et al., 1992) or higher activity in the right caudate nucleus (Hendler et al., 2003; Saxena et al., 2003) was associated with better subsequent response to SRIs. On the other hand, few studies reported that posterior brain regions were associated with treatment response to SRIs. Ho Pian et al. (2005) explored possible differential effects of OCD responders and non-responders to drug treatment on the regional cerebral blood flow (rCBF) in a ^{99m}Tc-hexamethylpropyleneaminexime (HMPAO) SPECT study. They reported pretreatment cerebellar and whole brain HMPAO uptake was higher in responders to treatment with fluvoxamine compared with non-responders.

In the present study, we hypothesized that not only the OFC and caudate nucleus activities but also posterior brain regions such as the cerebellum might be associated with subsequent treatment response to selective serotonin reuptake inhibitors (SSRIs) in OCD. To validate these hypotheses, we investigated neuroimaging predictors of treatment response to fluvoxamine in functional magnetic resonance imaging (fMRI), using a whole-brain approach to the imaging analysis. fMRI provides better spatial resolution than radioimaging techniques, thereby permitting identification of smaller brain regions. In addition, fMRI can noninvasively record brain signals without the radiation exposure inherent in other scanning methods, such as PET and SPECT. To this end, fMRI might be useful for prediction of response to treatment. Moreover, we tried to discover a relationship between the region that correlates with OC symptom severity and the region associated with subsequent treatment response. To our knowledge, this is the first fMRI study to investigate treatment response prediction in OCD.

2. Materials and methods

2.1. Participants

The participants were 17 patients (seven male, ten female) with OCD who were recruited from outpatients of the Department of Neuropsychiatry of Kyushu University Hospital. They underwent fMRI scanning before treatment with fluvoxamine. The OCD and the psychosis subsections of the Structured Clinical Interview for DSM-III-R-Patient edition (SCID-P, Japanese language edition) (Spitzer et al., 1990) or DSM-IV-Patient edition (SCID-P, Japanese language edition) (First et al., 1996) were administered by a trained interviewer to confirm the inclusion criteria of OCD. An episode of comorbid major depression was also examined by the SCID-P, and subjects with current major depression were excluded. The other axis I diagnoses were assessed by screening questions of the SCID-P. Patients who displayed a comorbid axis I diagnosis, neurological disorder, head injury, serious medical condition, or history of drug/alcohol addiction were excluded. Intelligence was assessed by using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), and patients with a total IQ of less than 80 were excluded. The handedness of each patient was determined using the Edinburgh handedness inventory (Oldfield, 1971). Each patient was assessed with the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS: 0–40) (Goodman et al., 1989b,c), which measures the severity of obsessions and compulsions. Patients with a total Y-BOCS score lower than 16 were excluded. Depressive symptoms were assessed using the 17-item Hamilton Depressive Rating Scale (HDRS) (Hamilton, 1960). Patients who showed a total HDRS score higher than 18 points were excluded. In addition, the 40-item State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) was administered to measure participants' self-reported feelings of anxiety. All patients were drug-free for at least 2 weeks before the study. We checked each patient's medication record.

Seven of these participants also participated in our other randomized controlled trial (RCT) study (Nakatani et al., 2005). In the RCT study, subjects were randomly assigned to one of three treatment conditions: behavior therapy, fluvoxamine, and placebo control for 12 weeks. These seven participants were randomly assigned to treatment with fluvoxamine. There is no difference in inclusion and exclusion criteria between the RCT study and the present study.

The institutional research and ethics committee of Kyushu University approved the study (No. 138, 2001). Written informed consent for the study was obtained from each subject before the assessments began.

2.2. fMRI scanning

Before treatment, a symptom provocation task was administered during fMRI to investigate local brain changes. Each patient was scanned with a 1.5T MRI scanner (Magnetom Symphony; Siemens, Erlangen, Germany) and a standard head coil. High-resolution T1 functional images were obtained with a gradient echo-planar sequence (repetition time [TR] = 4000 ms, echo time [TE] = 50 ms, flip angle [FA] = 90°, field of view [FOV] = 230 mm, matrix = 64 × 64, slice thickness = 3 mm, gap = 1 mm, 32 axial slices). Foam padding was used to minimize the motion of the patient's head during imaging.

During scanning, patients performed a symptom provocation task (Fig. 1) using a block design paradigm in which the task trial and control trial were given by turns. Each trial comprised ten 40-s periods (total, 400 s) in which control and task conditions were alternated.

2.2.1. Symptom provocation task

Principal manifestations related to obsessive–compulsive symptoms, such as contamination, pathological doubt, or violence, were identified for each patient. Approximately 20–30 words that evoke OC symptoms were selected through discussion with each patient. For example, the words, such as dirty toilet, feces, urine and unclean doorknob, were selected for a patient with fear of contamination. In the task condition, patients were required to generate those words one by one in their mind every 4 s, at the sound of a bell. Each patient had a rehearsal before fMRI scanning and we confirmed that these words reminded him or her of OC symptoms. Under control conditions, patients were asked to generate names of vegetables, flowers, and fruits in their mind at the same interval (Fig. 1). In both control and task conditions, patients were asked to show the subjective level of anxiety caused by each word by raising one or two fingers (one: not anxious; two: anxious).

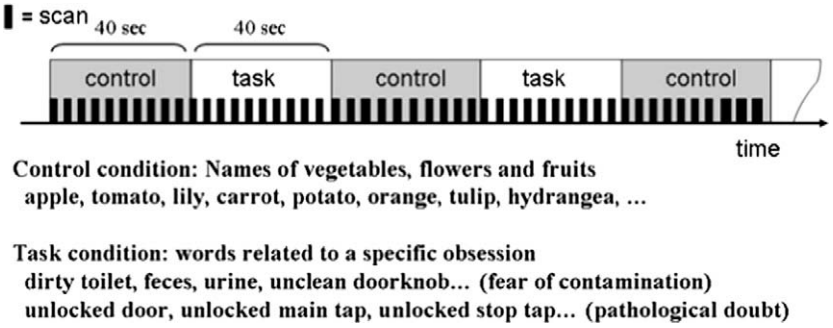

Fig. 1. Principal manifestations related to obsessive–compulsive symptoms, such as contamination, pathological doubt, or violence, were identified for each patient. Approximately 20–30 words that evoke obsessive–compulsive symptoms were selected through discussion with each patient. For example, the words, such as dirty toilet, feces, urine and unclean doorknob, were selected for a patient with fear of contamination. In the task condition, patients were required to generate those words one by one in their mind every 4 s, at the sound of a bell. Under control conditions, patients were asked to generate names of vegetables, flowers, and fruits in their mind at the same interval.

2.3. Treatment session and clinical assessment

Treatment with fluvoxamine was administered to each patient for 12 weeks. Patients started taking 25 mg/day of fluvoxamine in week 1. The dose was increased to 50 mg/day in week 2, subsequently increased every week by 50 mg/day up to a dose of 200 mg/day, and maintained at 200 mg/day for 8 weeks. Clinical symptoms were assessed using the Y-BOCS, HDRS, and STAI before and after the 12-week treatment. These scales were administered by four experienced psychiatrists who had been trained to use these measures. One assessor conducted face-to-face assessments, which were audio-taped; the recorded interviews were separately assessed by 1 of the other assessors. The inter-rater reliability was adequate to good (intraclass correlation coefficient (ICC) = 0.927).

2.4. Statistical analysis

Paired *t*-tests were performed to compare the clinical symptoms before and after treatment. The Statistical Parametric Mapping (SPM) 2 program (Wellcome Department of Cognitive Neurology, London, UK) was used for image processing and statistical analyses. To correct for motion of the subject's head, functional images from each individual were realigned to the first image in the series using 6-parameter spatial transformation. After realignment, functional images were spatially normalized with the Montreal Neurological Institute EPI template, and then convolved in space with a three-dimensional isotropic Gaussian kernel (full width at half maximum = 12 mm) for smoothing. The effect of the symptom provocation task was estimated at each and every voxel using a general linear model. Voxel values for the task versus control contrast yielded a statistical parametric map of the *t* statistic, and the values were then normalized to *Z* scores. A corresponding contrast image for each patient was also created for the group analysis.

First, group analysis was performed using a random-effects model to investigate common activation within the patients. After generating images of all subjects, we used a one-sample *t* test to compare task versus control conditions. Voxel-wise significance thresholds of $p < 0.001$ (uncorrected) were used. Only clusters with more than 10 voxels were included.

Then we examined the relationship between brain activation and OC symptom severity and the subsequent treatment response according to the Y-BOCS assessment. By using the simple regression analysis program of SPM, we examined the correlation between the contrast images and the pre-treatment total Y-BOCS scores, and the % improvements in Y-BOCS. Findings were considered significant at a voxel level of $p < 0.05$, corrected for multiple comparisons (false discovery rate (FDR)). Only clusters with more than 10 voxels were included. As to treatment response according to the Y-BOCS assessment, we performed additional analysis by the multiple regression analysis program of SPM in which the % improvements in HDRS and STAI were used as covariates. Moreover, we examined the correlation between the contrast images and % improvements in the different items derived from the Y-BOCS: 10 subscales, obsession subtotal (items 1–5) and compulsion subtotal (items 6–10).

In addition, we examined the relationship between brain activation and the subjective level of anxiety during the symptom provocation task. We compared the contrast images of anxious cases, who raised two fingers under the task condition, with non-anxious cases, who raised one finger. Findings were considered significant at a voxel level of $p < 0.05$, corrected for multiple comparisons (FDR). Only clusters with more than 10 voxels were included.

3. Results

Fifteen of 17 patients completed the 12-week treatment. Two patients dropped out as a result of clinical deterioration. One became more depressed and manifested suicidal intent. The OC symptoms of the other became worse, and the patient was unable to visit the hospital. These two dropouts were excluded from the analysis.

3.1. Demographic and clinical characteristics

The demographic characteristics of the participants are displayed in Table 1. The symptom manifestations and severity for each patient screened by Y-BOCS are shown in Table 2. Six patients had not taken any psychotropic medication before they entered this study. The remaining nine patients had been on medication. Eight of the nine had received fluvoxamine, and the medicine of one was unidentified. Six of these nine patients had stopped medication 14–28 days before entering the study, and three patients had stopped more than 29 days before.

3.2. Changes in clinical symptoms

Pre-treatment and post-treatment scores for the clinical symptoms are shown in Table 1. After 12 weeks of pharmaceutical treatment, the patients' mean (±standard deviation) Y-BOCS scores were significantly decreased, from 29.0 ± 3.2 to 21.0 ± 8.3 ($p < 0.001$). The mean percent reduction in the Y-BOCS score was 28.8 ± 24.6%. The mean scores for the HDRS ($p < 0.001$) and STAI ($p < 0.005$) scales also improved significantly (Table 1).

Table 1
Demographic characteristics and comparison of clinical symptoms before and after treatment.

	Patients with OCD (n = 15)		p-Value
	Before treatment	After treatment	
Age (years)	33.6 ± 10.0		
Sex (male/female)	7/8		
Handedness (right/left)	14/1		
Education (years)	13.9 ± 1.6		
Duration of illness (months)	123.0 ± 103.6		
Y-BOCS			
Total	29.0 ± 3.2	21.0 ± 8.3	<0.001***
Obsession (items 1–5)	14.5 ± 2.0	10.6 ± 4.5	<0.001***
Compulsion (items 6–10)	14.3 ± 1.8	10.4 ± 3.9	<0.001***
HDRS total score	5.7 ± 3.1	2.1 ± 2.1	<0.001***
GAF	44.3 ± 5.3	50.3 ± 8.1	<0.001***
STAI			
Trait anxiety	58.4 ± 9.6	50.3 ± 11.5	<0.001***
State anxiety	48.8 ± 11.5	42.6 ± 9.6	0.003**
WAIS-R estimated IQ	107.9 ± 11.3		

Data are presented as mean ± SD or n; t-test.
Y-BOCS, Yale-Brown Obsessive–Compulsive Scale; HDRS, Hamilton Depression Rating Scale; GAF, Global Assessment of Functioning; STAI, State-Trait Anxiety Inventory; WAIS-R, Wechsler Adult Intelligence Scale-revised; IQ, intelligence quotient.
** $p < 0.005$.
*** $p < 0.001$.

3.3. fMRI findings

Table 3 and Fig. 2 show pre-treatment areas of activation under the task condition during the symptom provocation task. These areas were identified by random-effects model analysis. Patients showed brain activation in the left superior temporal gyrus (STG) (BA39), left precuneus (BA7), left frontal cortices (BA10, 47), right cerebellum, and right frontal cortices (BA47).

No region showed a significant correlation between brain activation and the pre-treatment total Y-BOCS scores indicating OC severity by using simple regression analysis with SPM.

The treatment response was estimated by % improvements in Y-BOCS, and loci of significant positive correlation were found in the right cerebellum (Z-score = 5.10, $x, y, z = 22, -84, -18$) and the left STG (Z-score = 4.95, $x, y, z = -62, -22, 0$). There was no locus with a negative significant correlation. We show activation maps in Fig. 3 and correlation graphs in Fig. 4. By the additional analysis in which the % improvements in HDRS and STAI were used as covariates, brain activation in the right cerebellum (Z-score = 3.25, $x, y, z = 14, -82, -18$) and the left STG (Z-score = 4.51, $x, y, z = -58, -12, -2$) were positively correlated with % improvements in Y-BOCS.

There was no locus with a significant correlation between pre-treatment activations and % improvements in 10 subscales of Y-BOCS. In contrast, brain activation in the right cerebellum (Z-score = 4.37, $x, y, z = 26, -80, -22$) and the left STG (Z-score = 4.69, $x, y, z = -60, -16, -2$) were positively correlated with % improvements in obsession subtotal. Brain activation in the right cerebellum (Z-score = 4.63, $x, y, z = 26, -84, -20$) and the left STG (Z-score = 4.94, $x, y, z = -62, -22, 0$) were also positively correlated with % improvements in compulsion subtotal.

During the symptom provocation task in fMRI, four of 15 patients reported anxiety, as indicated by raising their fingers, under the task condition. Comparison of the contrast images of these four anxious patients with those of the 11 non-anxious patients revealed that the anxious patients did not show any greater or smaller activation than the non-anxious patients during the symptom provocation task.

Table 3
Activated regions during symptom provocation task before treatment.

Region	BA	x	y	z	Z-score
L Superior temporal gyrus	39	−50	−58	22	3.60
L Parietal lobe; Precuneus	7	−6	−76	56	3.57
L Inferior frontal gyrus	47	−58	24	−4	3.53
L Inferior frontal gyrus	10	−46	48	0	3.47
R Cerebellum		28	−80	−44	3.42
R Inferior frontal gyrus	47	38	26	−12	3.33

Random-effects model, $p < 0.001$, uncorrected.
These brain regions were estimated using the standard Talairach space. BA, Brodmann's area; R, right; L, left.

4. Discussion

During the symptom provocation task, patients showed brain activation in the left STG, left precuneus, left frontal cortex, right cerebellum, and right frontal cortex by group analysis, suggesting that it might be appropriate to investigate the correlation between brain activations during this task and the clinical variables of OCD,

Table 2
Manifestation of symptoms and their severity for each subject.

Patient no.	Gender	Age (years)	Y-BOCS score		Symptom manifestation		Reduction of Y-BOCS after treatment (%)
			Before	After	Obsession[a]	Compulsion[b]	
1	F	30	25	14	6	2, 5	44.0
2	M	25	25	2	2, 7	2, 7	92.0
3	M	37	34	33	2, 3, 5	1, 3	2.9
4	F	39	32	25	2	1	21.9
5	F	40	33	22	2	1	33.3
6	F	35	29	25	1	2	13.8
7	F	31	28	23	1, 2	1, 2	17.9
8	M	23	32	30	2	1	6.3
9	F	51	28	15	2	1	46.4
10	M	56	29	22	1	2	24.1
11	M	32	29	11	1, 4	2, 6	62.1
12	F	34	27	24	1, 4	2, 3, 4	11.1
13	M	23	27	17	1, 2, 6	1, 3, 5	37.0
14	F	21	33	32	2, 4	1, 6	3.0
15	M	27	24	20	1, 2, 6, 7, 8	1, 2, 7	16.7

Y-BOCS, Yale-Brown Obsessive–Compulsive Scale; F, female; M, male.
[a] Obsession: 1 = aggression; 2 = contamination; 3 = sexual; 4 = hoarding; 5 = religious; 6 = symmetry; 7 = miscellaneous; 8 = somatic.
[b] Compulsion: 1 = cleaning; 2 = checking; 3 = repeating; 4 = counting; 5 = ordering; 6 = hoarding; 7 = miscellaneous.

including the subsequent treatment response and baseline severity. We hypothesized that activities of not only the OFC and caudate nucleus but also posterior brain regions such as the cerebellum might be associated with subsequent treatment

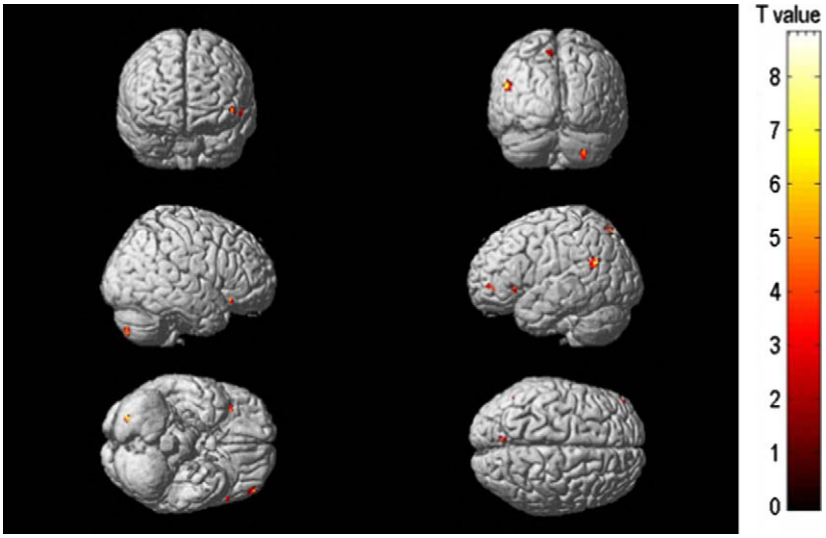

Fig. 2. Patients showed brain activation in the left superior temporal gyrus (BA39), left precuneus (BA7), left frontal cortices (BA10, 47), right cerebellum, and right frontal cortices (BA47) during the symptom provocation task. These areas were identified with random-effects model analysis. Findings were considered significant at a voxel level of $p < 0.001$, uncorrected (see Table 3).

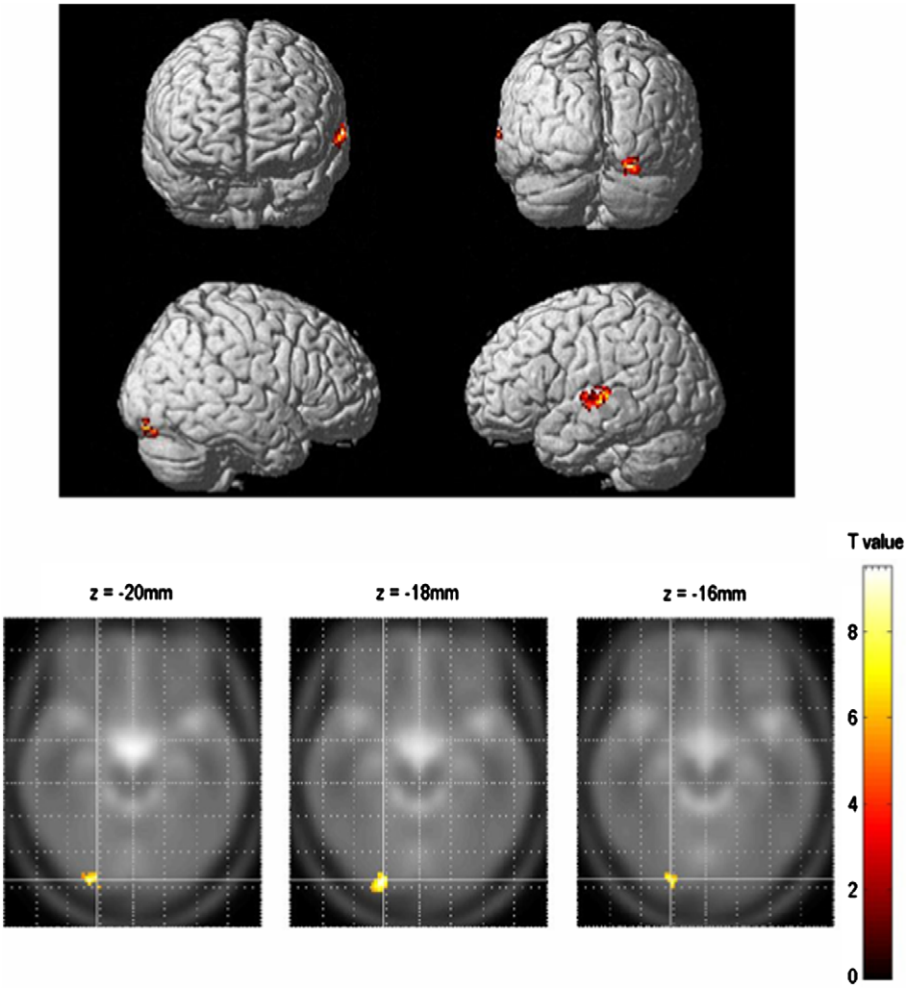

Fig. 3. SPM2 illustrates the right cerebellum (Z-score = 5.10, $x, y, z = 22, -84, -18$) and the left superior temporal gyrus (Z-score = 4.95, $x, y, z = -62, -22, 0$) with significant positive correlations between activation during symptom provocation task and subsequent response to fluvoxamine. There was no such region with negative significant correlation. Findings were considered significant at a voxel-level of $p < 0.05$, corrected for multiple comparisons.

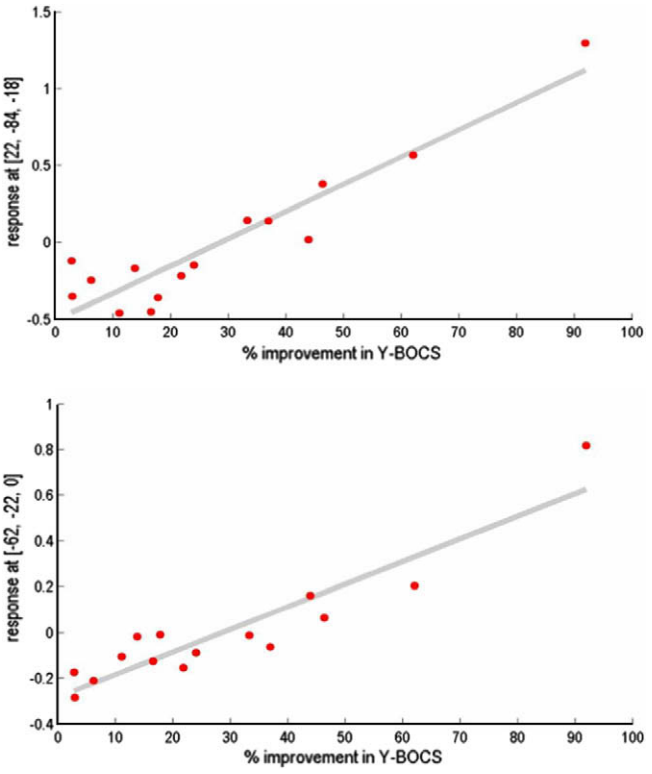

Fig. 4. Correlation between pre-treatment activation in the right cerebellum $(x, y, z = 22, -84, -18)$, the left superior temporal gyrus $(x, y, z = -62, -22, 0)$, and change in Y-BOCS score of 15 fluvoxamine-treated patients with OCD.

response to SSRIs in OCD. In the present study, we found that pre-treatment activation in the right cerebellum and in the left STG during the fMRI trial using the symptom provocation task predicted the subsequent reduction in OCD symptom severity associated with fluvoxamine treatment. These results verified our hypothesis.

Several studies that implicated cerebellar involvement in the pathophysiology of OCD reported cerebellar hyperactivity in patients with OCD (Busatto et al., 2000; Swedo et al., 1989). Kang et al. (2003) investigated brain glucose metabolic changes after 4 months of pharmacotherapy with SSRI in OCD patients, and reported significant metabolic decreases in the OFC, right hippocampus, cerebellum, and right putamen, and that the metabolic changes of the putamen, cerebellum, and hippocampus were significantly correlated with improvement of the immediate- and delayed-recall scores of the Rey-Osterrich Complex Figure Test. Furthermore, recent anatomical and functional studies have indicated that the cerebellum is involved with a variety of cognitive functions, such as attention (Allen et al., 1997; Courchesne et al., 1994), verbal learning and memory (Andreasen et al., 1996), and cognitive planning (Kim et al., 1994), as well as coordination of movement and motor learning. Gorlyn et al. (2008) suggested poor global cognitive functioning was predictive of SSRI treatment non-response in depressed subjects. In our previous fMRI study using the Stroop task, we found less activation in the right cerebellum in the patients than in normal controls, and after 12 weeks of successful behavior therapy, the cerebellum showed increased activation (Nabeyama et al., 2008). We suggested that because of abnormally high activity of the cerebellum in pre-treatment patients during the control condition, there were not so much more activations in this area during the task condition than the control condition. In the present study, our results might mean that lower activity of the cerebellum during the control condition rather than higher activity during the task condition was associated with subsequent better response to fluvoxamine treatment. Moreover, low cerebellum activity of during the control condition might indicate maintenance of the cerebellar functions.

Some researchers, on the other hand, have suggested the STG may be involved in the pathophysiology of OCD. Cottraux et al. (1996) reported that OCD patients with checking rituals have higher rCBF in the STG in the resting state, and that processing of both obsessive and neutral auditory stimulation increases rCBF in the STG. Adler et al. (2000) examined the effects of symptom induction on fMRI neural activation in patients with OCD. They found significant activation in the frontal and temporal cortices and right anterior cingulate. Maihofner et al. (2007) observed increased fast magnetoencephalographic (MEG) activity in the left STG in OCD patients. Choi et al. (2006) reported that gray matter volumes of the STG were significantly reduced in OCD patients compared to controls. Our results also showed the STG might be involved in the pathophysiology of OCD.

Rotge et al. (2008) conducted a voxel-based meta-analysis to provide a quantitative estimation of cerebral activation patterns related to the performance of a symptom provocation task by OCD patients. They found that the left STG demonstrated significant likelihoods of activation during the symptom provocation task, and suggested that the left STG was involved in the mediation of anxiety manifestations commonly experienced by patients with OCD rather than in the genesis of obsessive–compulsive symptoms. SSRIs might partially augment this mediation of anxiety manifestations, so that the pre-treatment activation of the left STG is predictive of good response to fluvoxamine.

In the present study, not only Y-BOCS score but also HDRS and STAI score were significantly decreased after fluvoxamine treatment. It may be hypothesized that pre-treatment cerebellar and STG activations could be associated with an improvement of depressive or anxiety symptoms. However, the activations in these areas might be directly associated with the improvement of OC symptoms because we found the similar brain activation in the right cerebellum and the left STG by the additional analysis in which HDRS and STAI score were controlled.

Several previous neuroimaging studies of OCD patients using ROI methods found that activity of the OFC or caudate nucleus was associated with treatment response to SRIs (Brody et al., 1998; Hendler et al., 2003; Saxena et al., 1999, 2003; Swedo et al., 1992). Rauch et al. (2002) used SPM methods to investigate predictors of fluvoxamine treatment response with contamination-related OCD patients in a PET study in the context of a symptom-provocation paradigm, and reported that lower rCBF values in the OFC and higher rCBF values in the posterior cingulate cortex predicted better treatment response. However, we were not able to identify activation in the OFC and caudate nucleus during the symptom provocation task and did not find that activation of these regions predicted subsequent treatment response. These results might be related to insufficient symptom provocation activation during the task condition, judging from the fact that only a few patients reported anxiety by raising their fingers. We did not find a relationship between brain activation and the subjective level of anxiety during the symptom provocation task. Our negative findings in the OFC and caudate nucleus, however, might be due to the small sample size. In addition, the discrepancy in results between the present study and prior studies might be related to methodological differences and phenotypic variations in the subjects because, in most previous studies, the results were found by using ROI methods and the subjects of the other study using SPM methods were contamination-related OCD patients.

No region showed a significant correlation between brain activation and the pre-treatment total Y-BOCS scores indicating OC severity. Higher baseline severity of OCD symptoms has been

identified as a negative predictor of response to SRIs in previous studies (Alarcon et al., 1993; Mataix-Cols et al., 1999; Shetti et al., 2005; Stein et al., 2001; Tukel et al., 2006), but the regions associated with subsequent treatment response were irrelevant to the baseline severity of OCD symptoms.

Goodman et al. (1989a) reported that fluvoxamine pharmacotherapy improved obsessional symptoms earlier than compulsive symptoms. We examined the correlation between pre-treatment activations and % improvements in the different items derived from the Y-BOCS, such as 10 subscales, obsession and compulsion subtotal. However, we did not find a specific item that was associated with the regions related to treatment response to fluvoxamine.

The present study has several limitations. First, the sample size was small. We need a larger number of subjects to analyze the results with reference to the heterogeneity of OCD and to investigate the relationship between brain activation and the subjective level of anxiety during the symptom provocation task.

Second, inter-individual variations in neuroanatomy affected our results. In contrast to ROI approaches, SPM-based approaches have the advantage of being data driven and facilitate the ability to search salient sub-territories for relevant treatment responses. However, SPM-based approaches are subject to errors related to imprecision in procedure whereby the brain data from various subjects are transformed into a common space (Evans et al., 2006). In our study, Japanese brains were transformed into the standard brain based on Caucasians for statistical analysis. Zilles et al. (2001) reported that Japanese hemispheres are relatively shorter, but wider than European hemispheres. In the standardization procedure, more errors might have occurred in our study of Japanese subjects than in previous studies of Caucasians. These errors might also contribute to the differences in findings from previous studies.

Third, the maximal dosage of fluvoxamine was low because it has been licensed in Japan for use at less than 150 mg/day. In general, dosages higher than those used for depression are necessary to obtain an optimal anti-OCD effect, and the maximal recommended dosage of fluvoxamine for treatment of OCD is 300 mg/day (Blier et al., 2006). If the maximal dosage had been higher, more patients may have responded to fluvoxamine.

In addition, a 2-week wash out is a relatively short, though all patients were drug-free for at least 2 weeks before entering the study. We cannot be denied carry-over effect related to previous treatment with SRI. Moreover, raters were not blind to response status of patients previously responsive to fluvoxamine. It might cause rater bias.

Another limitation is the fMRI task design. Our symptom provocation task did not sufficiently induce subjective anxiety related to OC symptoms. It might be associated with negative finding in the OFC and caudate nucleus. Additionally, we had only task and control trials of the symptom provocation task without a neutral trial as a baseline resting condition. As a result, we were unable to evaluate the Blood Oxygenation Level Dependent activation at rest.

In spite of these limitations, to our knowledge, this is the first fMRI study to investigate treatment response prediction in patients with OCD. There is every possibility that fMRI is a useful tool to predict treatment response because it has no inherent risk of radiation and is an easier method to perform than PET and SPECT. Our results suggest that treatment efficacy may be predicted by patterns of pre-treatment brain activity. In addition, recent studies suggest that more widely distributed large-scale brain systems including the parietal, occipital and cerebellar areas rather than orbitofronto-striatal regions may be involved in OCD (Kang et al., 2003; Menzies et al., 2008; Nabeyama et al., 2008). The present results might partially support this conclusion.

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Contributors

The authors of this paper are the contributors of this study.

Conflict of interest statement

The authors do not have any conflict of interests.

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