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## Effects of behavior therapy on regional cerebral blood flow in obsessive–compulsive disorder

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### Abstract

Very few functional neuroimaging studies have been performed on patients with obsessive–compulsive disorder (OCD) undergoing behavior therapy, even though it is recognized to be an effective treatment for this disorder. We measured the regional cerebral blood flow (rCBF) using the Xenon inhalation method in 31 treatment-refractory patients with OCD and the same number of age-matched normal controls. We also studied changes in rCBF in 22 OCD patients who had demonstrated a significant improvement after the behavior therapy. The OCD patients showed a significant bilateral elevation in the rCBF in the basal ganglia compared with the normal controls. After successful treatment, a significant decrease was found in the rCBF in the right head of the caudate nucleus that tended to correlate with clinical improvement.

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**Keywords:** Xenon-enhanced computed tomography; Treatment-refractory; Global Assessment of Functioning; Caudate nucleus

### 1. Introduction

Obsessive–compulsive disorder (OCD) is characterized by recurring, intrusive, distressing ideas and repetitive, ritualistic behavior. It is often chronic and may produce substantial disability. OCD has been regarded as an uncommon illness, but recent epidemiological studies show that the lifetime prevalence of OCD in the general population is approximately 2–3% (Robins et al., 1984; Kar-

no et al., 1988). Although the cause of this disorder is not yet clear, there is much evidence to support a neurological origin for OCD (Schilder, 1938; Insel, 1992; Rosenberg and Keshavan, 1998; Yaryura-Tobias et al., 2000). For example, obsessive–compulsive symptoms (OC symptoms) are often associated with several neurological diseases, such as Sydenham's chorea and Huntington's disease (Swedo et al., 1989; Cummings and Cunningham, 1992), and neuropsychological abnormalities including spatial-perceptual deficits and abnormalities in neurological soft signs (Behar et al., 1984; Head et al., 1989; Hollander et al., 1990). In addition, the beneficial effects of psychosurgical

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procedures for some patients with OCD have been demonstrated (Jenike et al., 1998).

Although OCD was previously considered to be refractory to most types of therapeutic intervention, there is now ample evidence that both pharmacological intervention, namely serotonin re-uptake inhibitors (SRIs) (Greist et al., 1995; Goodman, 1999), and specific behavior therapies that employ the principles of exposure and response prevention (E/RP), are highly effective in reducing the symptoms of OCD (Rachman et al., 1971; O'Sullivan et al., 1991).

Functional neuroimaging techniques yield images that reflect indices of brain activity, and these could provide much valuable information regarding the mediation of OC symptoms (Insel, 1992; Trivedi, 1996; Rauch and Baxter, 1998).

Investigation of the influence of effective treatments on brain function of patients with OCD seems to be useful for understanding of pathophysiology of this disorder. Benkelfat et al. (1990) with [ $^{18}\text{F}$ ]fluorodeoxyglucose (FDG) positron emission tomography (PET) re-studied eight OCD patients from their earlier cohort (Nordahl et al., 1989) after 16 weeks of clomipramine treatment. They found decreased activity in the left-caudate nucleus and in the right-orbitofrontal cortex. Swedo et al. (1992) with FDG PET studied 13 OCD patients with childhood-onset OCD before and after at least 1 year of either clomipramine or fluoxetine therapy. They found decreased activity in the orbitofrontal cortex. Perani et al. (1995) used FDG PET to study nine OCD patients before and 3 months after pharmacotherapy (various SRIs) and found decreased activity in the cingulate cortex. These previous studies suggest that the orbitofrontal cortex, the cingulate cortex and the caudate nucleus might have some relation with pathophysiology of OC symptoms. Most of these studies, however, were undertaken on patients using SRIs, and the number of studies that included behavior therapy was very limited. Only Baxter and his colleagues studied OCD patients who underwent behavior therapy. Baxter et al. (1992) used FDG PET to study nine patients with OCD before and 10 weeks after fluoxetine therapy, as well as nine different patients who underwent behavior therapy. They found that the responders

Table 1  
Demographic and clinical profiles of patients (pre-treatment)

Sex (M/F)	16/15
Age	28.00 $\pm$ 11.20
Duration of illness (years)	9.15 $\pm$ 6.82
Y-BOCS	
Total	27.19 $\pm$ 5.34 (20–36)
Obsession	13.77 $\pm$ 2.96 (9–19)
Compulsion	13.20 $\pm$ 2.88 (9–20)
HAM-D	19.90 $\pm$ 9.16 (2–41)
GAF	36.26 $\pm$ 9.35 (20–60)

Values are given as the mean  $\pm$  S.D.

to both treatments showed a significant reduction of the glucose metabolic rate in the right caudate, whereas no significant change was found in either the non-responders or the controls. Schwartz et al. (1996) replicated these findings. They studied 18 of the previous study patients with OCD including nine subjects before and after behavioral treatment. A significant decrease in the right caudate was found in 12 responders. They suggested that the brain activity in OCD patients might show similar changes after being successfully treated with either behavior therapy or pharmacological intervention. From the results of this series of studies, they hypothesized that OC symptoms are mediated by hyperactivity in orbitofrontal–subcortical circuits, which seems to be considered the most likely explanation.

## 2. Methods

### 2.1. Subjects

Thirty-one patients from Hizen National Hospital and Kyushu University Hospital from 1995 to 1999 were selected. Twenty-eight were inpatients, and three were outpatients. The patients were diagnosed as OCD by two experienced psychiatrists based on either DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994) criteria. None of them met the criteria for any other axis I disorders, as confirmed through clinical meetings. The demographic and the clinical profiles of patients with OCD are shown in Table 1. An equal number of age-matched controls (sex, M/F; 10/21, age; mean: 29.23  $\pm$  9.82) with no psychiatric history

was selected through face-to-face interview by the first author. All subjects were right-handed and gave their informed consent to participate in this study.

## 2.2. Clinical ratings

The patients were rated with the Yale-Brown Obsessive–Compulsive Scale (YBOCS) (Goodman et al., 1989), the 24-item Hamilton Depression Scale (HAM-D) (Hamilton, 1967), and the Global Assessment of Functioning (GAF) (Endicott et al., 1976).

## 2.3. Imaging procedure

Xenon-enhanced computed tomography (Xe-CT) scans were performed for the 31 OCD patients before their behavioral treatment and the controls for comparison. For the patients, the second scans were planned after significant improvement to investigate change of brain activity after successful behavioral treatment.

Xe-CT is a method for quantitatively measuring regional cerebral blood flow (rCBF) (Obrist et al., 1975; Gur et al., 1982). In this technique, CT scans obtained during and after the inhalation of non-radioactive xenon are utilized to record the movement of lipid-soluble and radiodense gas into the brain tissues. The end-tidal xenon concentration is utilized to indirectly record the arterial concentration during the wash-in and wash-out of xenon. The xenon concentrations in the arterial blood flow are estimated by the end-tidal xenon concentrations and the hematocrit value.

All the Xe-CT examinations were performed with a CT-W400 CT scanner (Hitachi, Tokyo, Japan) combined with a Xe-inhalation system at Hizen National Hospital. The subjects were placed in a supine position with eyes closed and their heads securely fastened to minimize motion artifacts in a quiet and comfortable room. A face mask was used for Xe inhalation. After the initial non-inhaling scans were obtained, we determined the brain level where the regions of interest (ROIs) were visible, including the basal ganglia and the third ventricle. At this level, nine enhanced scans were obtained. The Xe-inhalation protocol was 3

min of inhalation of a mixture of 30% xenon in 30% oxygen and 6 min of exhalation. An AZ-7000 image processing system (Anzai, Corp., Tokyo, Japan) was used to calculate the rCBF values using the end-tidal chamber scan method. The rCBF was calculated from 12 free-hand ROIs including the bilateral frontal cortex, temporal cortex, occipital cortex, head of the caudate nucleus (Cd), basal ganglia (putamen and globus pallidus) (Bg) and thalamus. These ROIs were identified using a neuro-anatomical atlas (Kretschmann and Weinrich, 1984). We also measured the cerebral blood flow of each hemisphere. The numerical values can be directly interpreted in  $\text{ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ .

## 2.4. Treatment

At the time of the first scan study, 21 of the 31 patients had received pharmacological treatment (clomipramine; the only licensed SRI in Japan at that time) (mean dose  $132.4 \pm 57.6 \text{ mg/day}$ ) without any appreciable response, and they were suffering from severe OC symptoms. Therefore, additional behavior therapy was considered indicated for them. The behavior therapy was performed by psychiatrists and consisted of the following elements: (1) behavioral psycho-education for motivating patients by using our original treatment manual; (2) behavioral analysis of OC symptoms; (3) therapist-attended E/RP; (4) self-managed E/RP; (5) relapse prevention; and (6) clinical staff meetings throughout the treatment period. All patients were treated with the program until they received adequate daily function. Time for discharge from the program was determined for each patient at the clinical staff meeting, and then the second scan was performed.

## 2.5. Statistical analysis

A comparison between the OCD patients and normal controls was performed by unpaired *t*-tests. Paired *t*-tests were used to compare the rCBF data and clinical ratings both before and after treatment. Correlations between the clinical ratings and the rCBF data were examined by Pearson production-moment coefficients of correlation.

Table 2  
rCBF of each ROI/hem in patients (pre-treatment) and normal controls

ROI	Patients ( $n=31$ )	Controls ( $n=31$ )
	Mean $\pm$ S.D.	Mean $\pm$ S.D.
Rt Frontal cortex	1.25 $\pm$ 0.42	1.25 $\pm$ 0.17
Lt Frontal cortex	1.26 $\pm$ 0.45	1.20 $\pm$ 0.22
Rt Temporal cortex	1.28 $\pm$ 0.29	1.33 $\pm$ 0.17
Lt Temporal cortex	1.25 $\pm$ 0.20	1.17 $\pm$ 0.19
Rt Occipital cortex	1.07 $\pm$ 0.35	1.16 $\pm$ 0.36
Lt Occipital cortex	1.00 $\pm$ 0.25	1.07 $\pm$ 0.29
Rt Head of caudate nucleus	1.23 $\pm$ 0.27	1.15 $\pm$ 0.27
Lt Head of caudate nucleus	1.28 $\pm$ 0.29	1.25 $\pm$ 0.34
Rt Basal ganglia	1.18 $\pm$ 0.28	0.91 $\pm$ 0.31***
Lt Basal ganglia	1.25 $\pm$ 0.26	1.03 $\pm$ 0.28**
Rt Thalamus	1.46 $\pm$ 0.26	1.47 $\pm$ 0.37
Lt Thalamus	1.44 $\pm$ 0.22	1.51 $\pm$ 0.36

\*\*  $P < 0.005$ .

\*\*\*  $P < 0.001$ .

### 3. Results

#### 3.1. Pre-treatment OCD vs. normal controls

Because 21 patients were taking clomipramine at the time of scanning, we examined the effects of clomipramine on the rCBF. We compared the absolute rCBF of both ROIs and each hemisphere between the clomipramine-free patients (CMI-free patients) and the patients taking clomipramine (CMI patients). The CMI patients' absolute hemisphere (hem) rCBF was significantly ( $P < 0.05$ ) higher than that of the CMI-free patients bilaterally. In the head of the caudate nucleus, the basal ganglia and the thalamus, the CMI-patients' absolute rCBF was higher than that of CMI-free patients bilaterally as well. After comparing the absolute rCBF of each ROI divided by the ipsilateral hemisphere (ROI/hem) between the CMI-free patients and the CMI patients, no significant difference was found. To rule out any influence of clomipramine on the rCBF, we used ROI/hem for comparison purposes. Table 2 presents the rCBF of each ROI/hem in the 31 patients with OCD compared to the same number of age-matched normal controls. We found a significant increase in the right Bg/hem ( $P < 0.0007$ ) and in the left Bg/hem ( $P < 0.002$ ).

As for the relationship between brain activity and clinical ratings, we found a significant nega-

tive correlation between the GAF score and the right Cd/hem ( $r = -0.470$ ,  $P < 0.007$ ) and a significant positive correlation between the total YBOCS score and the left thalamus/hem ( $r = 0.436$ ,  $P < 0.013$ ).

#### 3.2. Pre- vs. post-treatment

Eight of our patients with OCD were not re-scanned because their treatment had not been completed. One patient whose second scan demonstrated excessive movement artifacts was eliminated from the study. As a result, 22 patients (19 inpatients/3 outpatients) underwent behavior therapy and had their second Xe-CT scan 7.55  $\pm$  4.68 months after the first one. During this period, 13 of the 22 patients maintained the dosage of CMI, five decreased dosage, and only four patients had a meaningful increase of CMI dosage. We checked that the behavior therapy mainly influenced the improvement of OC symptoms through face-to-face interview with the therapists. The demographic and clinical profiles of the 22 OCD patients before and after the treatment are presented in Table 3. There was a highly significant change in the scores on the total Y-BOCS (26.77  $\rightarrow$  12.09,  $P < 0.0001$ ), HAM-D (14.14  $\rightarrow$  7.18,  $P < 0.0008$ ) and GAF (34.23  $\rightarrow$  63.73,  $P < 0.0001$ ).

Table 4 shows the rCBF of each ROI/hem in the 22 patients with OCD before and after treat-

ment. As shown in Table 4, a significant reduction occurred only in the right Cd/hem after behavior therapy ( $P < 0.013$ ).

Because of this finding, we further investigated the relationship between the percentage change in the clinical ratings before and after treatment, and the percentage change of the right Cd/hem. We found a significant negative correlation between the change of the GAF score and the change of the right Cd/hem before and after treatment ( $r = -0.459$ ,  $P < 0.045$ ), although no significant correlation between the change of the total YBOCS score and the change of the right Cd/hem before and after treatment was seen.

#### 4. Discussion

Many functional neuroimaging studies have been undertaken to assess the differences of brain activity between patients with OCD and controls. While these studies vary in the number of subjects, neuroimaging methodology and the existence of comorbidity, the most consistent findings are brain dysfunction in the orbitofrontal cortex, anterior cingulate cortex and the caudate nucleus in OCD patients (Baxter et al., 1987, 1988; Nordahl et al., 1989; Rubin et al., 1992; Swedo et al., 1992; Adams et al., 1993; Perani et al., 1995; Lucey et al., 1997; Alptekin et al., 2001). Our results are partially consistent with these recent findings in terms of the brain dysfunction in the Bg/hem among OCD patients compared with normal con-

Table 4

rCBF of each ROI/hem in patients ( $n = 22$ ) before and after behavior therapy

ROI	Pre-treatment	Post-treatment
	Mean $\pm$ S.D.	Mean $\pm$ S.D.
Rt Frontal cortex	1.25 $\pm$ 0.48	1.20 $\pm$ 0.22
Lt Frontal cortex	1.29 $\pm$ 0.52	1.18 $\pm$ 0.20
Rt Temporal cortex	1.23 $\pm$ 0.30	1.21 $\pm$ 0.24
Lt Temporal cortex	1.20 $\pm$ 0.17	1.12 $\pm$ 0.20
Rt Occipital cortex	1.03 $\pm$ 0.33	1.10 $\pm$ 0.41
Lt Occipital cortex	0.98 $\pm$ 0.23	1.07 $\pm$ 0.35
Rt Head of caudate nucleus	1.29 $\pm$ 0.20	1.08 $\pm$ 0.28*
Lt Head of caudate nucleus	1.30 $\pm$ 0.28	1.28 $\pm$ 0.24
Rt Basal ganglia	1.22 $\pm$ 0.28	1.16 $\pm$ 0.23
Lt Basal ganglia	1.31 $\pm$ 0.24	1.23 $\pm$ 0.21
Rt Thalamus	1.45 $\pm$ 0.26	1.45 $\pm$ 0.29
Lt Thalamus	1.47 $\pm$ 0.18	1.38 $\pm$ 0.23

\*  $P < 0.05$ .

trols, though no significant difference was found in the frontal region. Our findings seem to be reliable because some significant correlations were found between the clinical rating scores of our patients and the brain activity in regions where the previous studies indicated abnormality.

Because OCD vs. normal control studies are merely intended to determine whether specific regions exhibit any abnormal activity in patients with OCD, these studies do not allow us to distinguish between the state and trait characteristics of such abnormalities. Pre- vs. post-treatment

Table 3

Demographic and clinical profiles of patients, before and after behavior therapy

	Pre-treatment	Post-treatment	% Change (pre-post)/pre
Sex (M/F)	8/14		
Age	29.68 $\pm$ 12.01		
Duration of illness (yrs)	9.59 $\pm$ 7.10		
Y-BOCS			
Total	26.77 $\pm$ 5.30 (20–36)	12.09 $\pm$ 4.68 (1–19)****	52.9
Obsession	13.82 $\pm$ 3.13 (9–19)	6.68 $\pm$ 2.72 (1–11)****	49.4
Compulsion	12.96 $\pm$ 2.68 (9–18)	5.41 $\pm$ 2.46 (0–9)****	56.4
HAM-D	14.14 $\pm$ 9.74 (2–41)	7.18 $\pm$ 4.17 (0–14)***	26.0
GAF	34.23 $\pm$ 5.86 (20–43)	63.73 $\pm$ 9.72 (45–85)****	–90.7

Values are given as mean  $\pm$  S.D.

\*\*\*  $P < 0.001$ .

\*\*\*\*  $P < 0.0001$ .

studies by functional neuroimaging might, therefore, help us to address this problem.

Since behavior therapy and SRIs are recognized as effective treatments for OCD, it is essential to investigate whether the same results earlier reported for pharmacotherapy are found among patients who are successfully treated by behavior therapy (Kobak et al., 1998). There have been, however, very few functional neuroimaging studies after behavior therapy. As far as we know, only Baxter et al. (1992) did a pre-post treatment study using both SRIs and behavior therapy. As well as a significant reduction of the glucose metabolic rate in the right Cd/hem in treatment responders, they found that the percentage change in the total YBOCS score before and after treatment and the percentage change in the right Cd/hem were significantly correlated for patients receiving drug therapy, and there was a trend for the correlation in those who underwent behavior therapy. Our findings are mostly consistent with their results, including the correlation between the clinical improvement and the change of brain activity in the right Cd/hem among the treatment responders.

Our study, however, has two main limitations. Firstly, the design of our study was not controlled, which was caused by ethical concerns. We were not able to use waiting list controls. We should have done the second scan after a fixed time interval to determine the relationship between the severity of OC symptoms and the change of brain activity more accurately. Besides, we did not have a controlled medication program and we, therefore, could not clarify the relationship between the effect of behavior therapy and the change of brain activity. Secondly, our study was done by Xe-enhanced computed tomography. This technique is considered less optimal than other methods for looking at subcortical structures. The data from subcortical regions, therefore, must be treated with caution (Rauch and Baxter, 1998; Saxena et al., 1998). Furthermore, as we did not have any sophisticated software to determine brain regions exactly, we could not identify brain regions precisely.

Despite these limitations, the advantage of our study is that we managed to investigate the change of brain activity in as many as 22 treatment

responders. To our knowledge, this number is the largest among the previous studies of this kind. The lack of significant correlation between the rate of YBOCS score reduction and the percentage reduction of brain activity among the treatment responders might be due to the characteristics of our patients. The YBOCS score tends not to reflect the severity of OCD when patients do not attempt activity, to avoid being annoyed by their symptoms. As two of the very few institutions for treatment-refractory OCD patients in Japan, we see patients whose daily lives are extremely disturbed by their severe symptoms and/or avoidance, which is easily judged by the quite low GAF scores and high HDRS scores of our patients. Because of this clinical requirement, our study was not able to use a fixed treatment design, and we had to extend the duration of treatment until each patient reached sufficient improvement. However, we consequently could answer the following question. If non-responders to the previous studies had received treatment until they reached the point of maximum effectiveness without any limitations in the treatment duration, would the non-responders then have also revealed similar changes in brain activity as the responders? Namely, adequately tailored and successful treatment, so far, seems to bring a similar change in brain activity, no matter how severely patient's daily lives are disturbed.

In conclusion, when the results of the comparison with the normal controls are taken together, the head of the caudate nucleus, basal ganglia and thalamus might mediate OC symptoms. More sophisticated functional neuroimaging techniques are likely to lead to a more detailed understanding of the relationship between subcortical dysfunction and OC symptoms.

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