



Changes after behavior therapy among responsive and nonresponsive patients with obsessive-compulsive disorder

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ABSTRACT

Neuroimaging studies have suggested that behavior therapy (BT) might change abnormal activity in the frontal-subcortical circuits of the brain in patients with obsessive-compulsive disorder (OCD). However, the results of these studies have been rather inconsistent. The aim of the present study was to use statistical parametric mapping (SPM) analysis to explore the effects of successful BT on regional cerebral blood flow (rCBF) in patients with OCD. Forty-five OCD patients who were treatment-resistant to a single serotonin reuptake inhibitor (SRI) trial were examined. Single photon emission computed tomography (SPECT) using 99mTc-ECD was performed before and after the completion of 12 weeks of BT. Although no significant differences in pre-treatment rCBF were observed between responders and nonresponders to BT, the post-treatment rCBF values in the left medial prefrontal cortex (Brodmann area 10) and bilateral middle frontal gyri (Brodmann area 10) were significantly lower in the responders than in the nonresponders. Furthermore, the baseline rCBF in the bilateral orbitofrontal cortex (OFC) was significantly correlated with the change in the Y-BOCS score among the responders. Our results support the hypothesis that while the OFC may be associated with the BT response, BT may result in changes in rCBF in the medial and middle frontal cortex.

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1. Introduction

The orbitofrontal cortex (OFC)-striatal circuit plays an important role in the pathogenesis of obsessive-compulsive disorder (OCD). Both the administration of serotonin reuptake inhibitors (SRIs) and behavior therapy (BT), composed of exposure and response prevention (ERP), have been found to be effective for the treatment of OCD (Jenike, 1998). The effects of SRI therapy are thought to be associated with changes in neural activity in either the OFC or the caudate nucleus (Brody et al., 1998; Saxena et al., 1999, 2002, 2003).

In contrast, only six studies have investigated the neural effect of BT in patients with OCD. The first neuroimaging study on patients with OCD was reported by Baxter et al. (1992), who used positron emission tomography (PET) to examine the effects of BT ($n=9$) versus fluoxetine treatment ($n=9$) in OCD patients. Decreased right caudate

metabolic rates were found in both groups. In a follow-up study, Schwartz et al. (1996) added nine OCD patients to the previous study group (Baxter et al., 1992) and replicated their previous findings ($n=18$). Brody et al. (1998) analyzed the pre-treatment metabolism of patients who responded to either BT ($n=18$) or fluoxetine treatment ($n=9$); the patients in Brody's study had been previously described in two other studies (Baxter et al., 1992; Schwarz et al., 1996). They found that a higher pretreatment metabolic activity in the left OFC was associated with a better response to BT. In contrast, a lower left OFC pretreatment level of metabolic activity was associated with a better response to fluoxetine. This study suggested that the pre-treatment metabolic activity in the OFC was correlated differently with BT and fluoxetine. Recently, Saxena et al. (2009) reported that the rapid response of OCD patients to intensive cognitive-behavior therapy (CBT) might be mediated by a distinct pattern of changes in regional brain function (decrease in bilateral thalamic activity vs. increase in anterior cingulate cortex [ACC]).

Several neuroimaging studies of psychotherapy in Japanese patients with OCD have recently been conducted. One study (Nakatani et al., 2003) used xenon-enhanced computed tomography (Xe-CT)

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and reported a significant reduction in the regional cerebral blood flow (rCBF) in the right caudate nucleus following BT in patients with OCD ($n = 22$). Another group (Nakao et al., 2005a,b) used functional magnetic resonance imaging (fMRI) to conduct a provocation study of the BT effect in patients with OCD. After combining the data from both BT ($n = 4$) and SRI therapy ($n = 6$) groups, they observed changes in broadly activated areas associated with prefrontal-subcortical-cerebellar connections.

However, all previous studies on the neural effects of BT in patients with OCD have several limitations. Firstly, the sample sizes were relatively small: the largest sample number was only 22 patients. Secondly, all previous studies except one (Nakao et al., 2005b) investigated the effect of BT using a region-of-interest (ROI) approach. An ROI approach may increase the effects of statistical artifacts, such as type I errors, if either a large area or only one region is inappropriately chosen (Bonne et al., 2003). In contrast, a voxel-based analysis using statistical parametric mapping (SPM) has the advantage of a greater statistical power to identify relative changes in significant patterns of rCBF. However, the disadvantage of this technique lies in the possibility of producing type II errors. Another disadvantage lies in the process of spatial normalization, in which each voxel in all the subjects is transformed in the same stereotactic space. A recent study by Saxena et al. (2009) suggested that a magnetic resonance imaging (MRI)-based ROI analysis in each subject may be preferable to an SPM analysis because the normalization process used during SPM analysis can produce errors as a result of anatomic variability among OCD patients. Therefore, the results of both methods (SPM and MRI-based ROI analysis) should be compared in a single study. Thirdly, the neural mechanisms between responders to BT and nonresponders to BT remain unclear.

In the present study, we examined rCBF changes after successful BT treatment in a relatively large number of patients ($n = 45$) with OCD using an SPM analysis of 99mTc-ECD single photon emission computed tomography (SPECT) images. The aims of the study were: 1) to compare rCBF between responders versus nonresponders both before and after treatment; 2) determine in which areas baseline rCBF values changed significantly after the completion of BT in responders and nonresponders; and 3) to determine whether pre-treatment rCBF can predict a response to BT in patients with OCD. In addition, we performed an MRI-based ROI approach to confirm the results of the SPM analysis. We hypothesized that changes would occur in the OFC-striatal circuits of patients with OCD who responded to BT.

2. Methods

2.1. Subjects

Japanese patients with OCD were recruited at Nagoya City University Hospital. Diagnoses were made on the basis of structured interviews conducted by trained psychiatrists using the Structured Clinical Interview for DSM-IV Patient Version (SCID-P). Before their enrollment in this study, all the OCD patients had been taking SRIs for at least 3 months. During the 3 months, these OCD patients did not respond to at least one course of full-dose SRI therapy at our hospital (minimum doses: clomipramine, 150 mg/day; fluvoxamine, 200 mg/day; paroxetine, 40 mg/day) (Tolin et al., 2004). Therefore, these OCD patients were regarded as treatment-resistant to SRIs because they had failed one adequate trial of an SRI (Pallanti et al., 2004). In accordance with the criteria used by many pharmacological trials (Kampman et al., 2002; Tolin et al., 2005; Ninan et al., 2006), the treatment was classified as unsuccessful when a decrease of less than 25% in the global Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score was observed.

The SRI dose administered to each patient was not altered during the entire course of BT. The OCD patients were not permitted to use any psychotropic medication other than SRIs during the study. The

equivalence of each drug was calculated according to a previously described method (Bollini et al., 1999), in which the recommended therapeutic dose was standardized with respect to the recommended dose of clomipramine (150 mg/day).

The exclusion criteria were presence of a current or past neurological or other significant medical illness, substance dependence, mental retardation, or pregnancy. Patients with other axis I disorders were excluded. Although we did not utilize the SCID-P criteria to exclude patients, trained psychiatrists confirmed these criteria based on a clinical diagnostic interview and the DSM-IV. Patients with other axis I disorders were excluded. Patients with either a current major depressive disorder or a lifetime history of bipolar disorder were also excluded.

The study's protocol was approved by the Ethics Committee of Nagoya City University Graduate School of Medical Sciences, and all the subjects provided their written informed consent.

2.2. Clinical assessments

OCD severity was assessed using the clinician-rated 10-item Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989a, b). An improvement in the global Y-BOCS score of 40% or greater was considered to represent a clinical response because a recent study suggested that patients whose Y-BOCS scores decreased by 39% or less were still rated as moderately ill at post-treatment (Tolin et al., 2005). Furthermore, Tolin et al. (2005) suggested that treatment responders, as defined by a Y-BOCS reduction cutoff of 40% to 50%, were in remission. Therefore, we adopted a more stringent criterion for the clinical outcome of BT than for SRI therapy. Two trained clinical psychiatrists assessed the Y-BOCS independently. The intraclass correlation was 0.87 (95% IC: 0.75 to 0.93) for the pretreatment Y-BOCS scores and 0.85 (95% IC: 0.70 to 0.92) for the post-treatment Y-BOCS scores, suggesting an excellent inter-rater reliability. The clinical subtypes of OCD were identified using the Y-BOCS symptom checklist. In addition, the severity of depression was assessed using the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996), while the severity of anxiety was assessed using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970). These clinical ratings were assessed at baseline and at the completion of BT. However, both the pre-Y-BOCS and the post-Y-BOCS were assessed on the days of the pre- and post-treatment SPECT examinations, respectively.

Two-tailed *t*-tests were used to compare demographic data between the groups (responders vs. nonresponders). The male/female ratio was compared using the Fisher exact test. In addition, we compared the changes in the clinical treatment effects before and after BT among both the responders and the nonresponders using paired *t*-tests.

2.3. Procedure

2.3.1. Treatment

Individual BT led by experienced psychiatrists was performed using a detailed treatment manual (Iikura, 1999). This treatment manual has been used successfully in previous outcome trials (Nakatani et al., 2005). The treatments consisted of 45-min sessions one to five times a week for approximately 12 consecutive weeks. The mean time from the first session to the completion of BT was 90.7 ± 5.2 days. All the patients who participated in this study were treated by at least two psychiatrists under the supervision of an ERP expert to monitor the quality of therapy. BT consisted of the following sessions: The first session included psycho-education about the nature of OCD and the BT model for the treatment of OCD. The second session began with treatment-planning based on both the behavior analysis and an exposure hierarchy of anxiety-evoking situations. Following the planning sessions, the ERP sessions began. Exposure exercises were arranged hierarchically, beginning with mild or moderately distressing ones. Patients were encouraged to persist with each exposure until their distress decreased noticeably. All patients received therapist-guided

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