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Single photon emission computed tomography imaging in obsessive-compulsive disorder and for stereotactic bilateral anterior cingulotomy

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Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder involving intrinsic and repetitive thoughts as well as ritualistic and irrational behavior that causes marked distress [1,2]. Kodala et al [3] have reported the lifetime and 6-month prevalence rates to be 2.9% and 1.6%, respectively. Recently, the neurobiologic basis of OCD has received much attention, with many modalities of evidence suggesting a neurologic basis for OCD. Some of the most important information has resulted from functional neuroimaging studies using functional MRI (fMRI), single photon emission tomography (SPECT), and positron emission tomography (PET) [4–10].

Neuroimaging studies provide evidence for a role in OCD of the specific frontal-subcortical brain circuit connecting the orbitofrontal cortex, the anterior cingulate gyrus, and elements of the basal ganglia and thalamus [10,11]. These defined regions in the pathogenesis of OCD were predominantly determined based on PET studies. Compared with the consistent metabolic alteration recorded on PET, the published data on blood flow studies with SPECT have been inconsistent and variable in determining cortical and subcortical structures with abnormal perfusion patterns. There may be a number of reasons for this, including inconsistency of SPECT data analysis, low spatial scanner resolution, different scanning techniques, subject variation, and intraindividual variation because of the presence or absence of OCD symptoms at the time of injection. In particular, semiquantitative measurements of the radioactivity within regions of interest (ROIs) after normalization to the cerebellar uptake are currently used as an analytic method; however, the ROI method is subjective to operator bias in that large ROIs may dilute small activation sites but small ROIs may not differentiate activation sites from noise.

Recently, voxel-based analysis using statistical parametric mapping (SPM) has become available, and in this system, an activated region is compared with a control area by statistical processes after assigning some threshold values and a probability value [12]. The resultant SPM data are more accurate than conventional semiquantitative measurements [13]. Using this sophisticated analysis method, many functional neuroimaging studies have been performed with PET; however, few SPECT data have been reported.

In this report, we evaluate the role of SPECT in OCD diagnosis by comparing the brain SPECT images of drug-free OCD patients with those of normal controls and drug-naive schizophrenia patients. We then explore the role of SPECT in surgical outcome after bilateral anterior cingulotomy

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by comparing pre- and postoperative brain SPECT imaging.

Single photon emission computed tomography for obsessive-compulsive disorder diagnosis

Seven patients with severe primary OCD (six men and one woman) were studied. The mean age (±SD) was 25.4 ± 4.7 years. All patients met the Diagnostic and Statistical Manual for Mental Disorder, 4th Edition (DSM-IV), (American Psychiatric Association, 1994) criteria for OCD as evaluated by two independent psychiatrists and a neurosurgeon who is experienced in psychosurgery. Their mean onset age of symptoms was 19.3 ± 4.7 years, and the duration of symptoms was 6.3 ± 5.5 years (range: 2–27 years). No patients had any psychotropic medications in the 4 weeks before SPECT study. The main compulsive symptoms were washing, checking, and hoarding. Exclusion criteria included histories of central neurologic disorders, tics, or substance abuse. The severity of OCD behavior was quantified by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [14], revealing an overall total score of 28.9 ± 3.23. The depression and anxiety scales were also evaluated using the Hamilton Rating Scales for Depression (HAM-D) and Anxiety (HAM-A) [15,16], revealing results of 13.6 ± 4.1 and 12.8 ± 2.6, respectively (Table 1).

The control group consisted of seven normal volunteers (four men and three women) with a mean age of 30.6 ± 6.8 years. These healthy subjects had no psychiatric or neurologic illnesses. Nine drug-naive cases of schizophrenia (three undifferentiated and six paranoid types) were also included for comparison purposes. The mean age of the schizophrenia group was 28.4 ± 8.2 years.

Single photon emission computed tomography and surgical outcome

Fifteen refractory OCD patients underwent bilateral stereotactic anterior cingulotomy using MRI guidance. Thirteen patients in this group were followed up for more than a year (mean follow-up of 22.4 months) (Table 2). Criteria for surgical candidacy included the following:

1. The patient fulfills current diagnostic criteria for OCD.
2. The duration of illness exceeds 3 years.
3. The disorder is causing substantial suffering as evidenced by ratings.
4. The disorder is causing substantial reduction in the patient's psychosocial functioning as evidenced by ratings.
5. Current and up-to-date treatment options have been tried systemically for at least 3 years without appreciable effect on the symptoms or have had to be discontinued because of intolerable side effects.
6. If a comorbid psychiatric condition is present, this disorder must also have been thoroughly addressed with appropriate trials of first-line treatments.
7. The prognosis, without neurosurgical intervention, is considered poor.
8. The patient gives informed consent.
9. The patient agrees to participate in the preoperative evaluation program and postoperative rehabilitation program.

Also excluded from consideration for surgery were patients younger than 18 years of age or older than 60 years of age, a complicating axis I diagnosis (eg, organic brain syndrome; delusional disorder; manifest abuse of alcohol, sedatives, or illicit drugs); a complicating current axis II

Table 1
Clinical findings of obsessive-compulsive disorder patients for study I

	Sex/age (years)	Onset age (years)	Symptom duration (years)	Y-BOCS	HAM-D	HAM-A	Main symptoms
Case 1	M/24	15	10	27	19	10	H, C
Case 2	M/22	20	2	28	20	15	W, C
Case 3	F/29	27	2	35	26	10	W, C
Case 4	M/29	24	5	25	18	9	W, C
Case 5	M/20	15	5	30	17	10	C, R
Case 6	M/33	16	17	27	25	14	C, R
Case 7	M/21	18	3	30	15	15	O, C

Abbreviations: M, male; F, female; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; W, washing; C, checking; O, obsession; H, hoarding; R, ordering.

Table 2
Clinical findings of obsessive-compulsive disorder patients for study II

	Sex/Age (years)	Onset age (years)	Symptom duration (years)	Y-BOCS	CGI-S	HAM-D	HAM-A	Main symptoms
Case 1	M/25	15	10	29	7	19	10	H, C
Case 2	M/34	16	17	36	7	25	13	C, W
Case 3	F/53	44	8	40	7	50	32	C, W
Case 4	M/41	36	4	34	7	47	25	C, W
Case 5	M/45	39	5	37	7	30	24	C, R
Case 6	M/26	15	10	38	7	21	8	C, W
Case 7	M/40	18	21	38	7	21	8	S, C
Case 8	F/36	20	15	39	7	41	17	C, W
Case 9	F/31	24	7	35	7	20	10	W
Case 10	M/18	14	4	28	7	13	7	C
Case 11	F/38	27	11	38	7	15	9	W
Case 12	M/48	33	15	30	6	22	20	C
Case 13	M/30	20	10	32	7	29	22	S

Abbreviations: M, male; F, female; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; CGI-S, Clinical Global Improvement of Severity Scale; W, washing; C, checking; O, obsession; H, hoarding; R, ordering; S, sin.

diagnosis from clusters A (eg, paranoid personality disorder) or B (eg, antisocial or histrionic personality disorder); and a complicating current axis III diagnosis with brain pathologic findings (eg, atrophy, tumors).

The mean age of the patients (nine men and four women) was 35.8 ± 9.9 years. The average symptom onset age was 24.7 ± 10.2 years, and symptom duration was 10.5 ± 5.3 years. No patients had taken any psychotropic medications in the 4 weeks before SPECT study (before and after surgery).

Surgical procedure

Patients were placed under local anesthesia, and bilateral burr holes were made in front of the coronal suture 20 mm laterally from the midline. Stereotactic localization of the targets was achieved using the MRI-compatible Leksell stereotactic frame (Elekta Instruments, Atlanta, GA) on a General Electric Signa 1.5-T unit (Milwaukee, WI). A 1.8-mm electrode with a 10-mm bare tip (Radionics, Burlington, MA) was inserted into the target to create radiofrequency thermocoagulation lesions at 85°C for 90 seconds using a lesion generator (RFG-3C; Radionics). Four lesions along two tracks were created on either side of the anterior cingulate gyrus. The first lesion was made 15 mm posterior to the frontal horn of the lateral vehicle, 2 mm above the roof of the ventricle, and 7 mm lateral to the midline. The electrode was then withdrawn 8 mm to produce the second lesion. The third lesion was made 22 mm posterior to the frontal horn of the lateral ventricle, 2 mm above the roof of the ventricle, and 7 mm lateral to the midline. The electrode was then withdrawn 8 mm to produce the fourth lesion. The result was an elliptocylindrically shaped lesion approximately 18 mm high, 13 mm in anteroposterior (AP) dimension, and 6 mm in lateral dimension (Figs. 1 and 2). Fig. 1 demonstrates the diffuse perilesional edema along the radiofrequency lesions immediately after cingulotomy. This edema resolved gradually, however. Fig. 2 demonstrates the resolved perilesional edema along the radiofrequency lesions 3 months after cingulotomy. Lesions were confined to the anterior cingulate gyrus.

Imaging procedures

The SPECT procedure was performed for patients and controls after an intravenous injection of 740 MBq of Tc 99m ethyl cysteinate (ECD). Brain images were obtained using a brain-dedicated annular crystal gamma camera (RASPECT; Digital Scintigraphic Incorporation, (Waltham, MA) equipped with low-energy, high-resolution, parallel-hole collimators. The SPECT study was acquired in a 128 × 128 matrix with 3° of angular increment for 20 minutes. Transaxial images were obtained by the filtered-back projection method using a Butterworth filter (cutoff frequency of 1.1 cycle per centimeter, order no. 10). Attenuation correction was performed by Chang's method, and coronal and sagittal images were calculated.

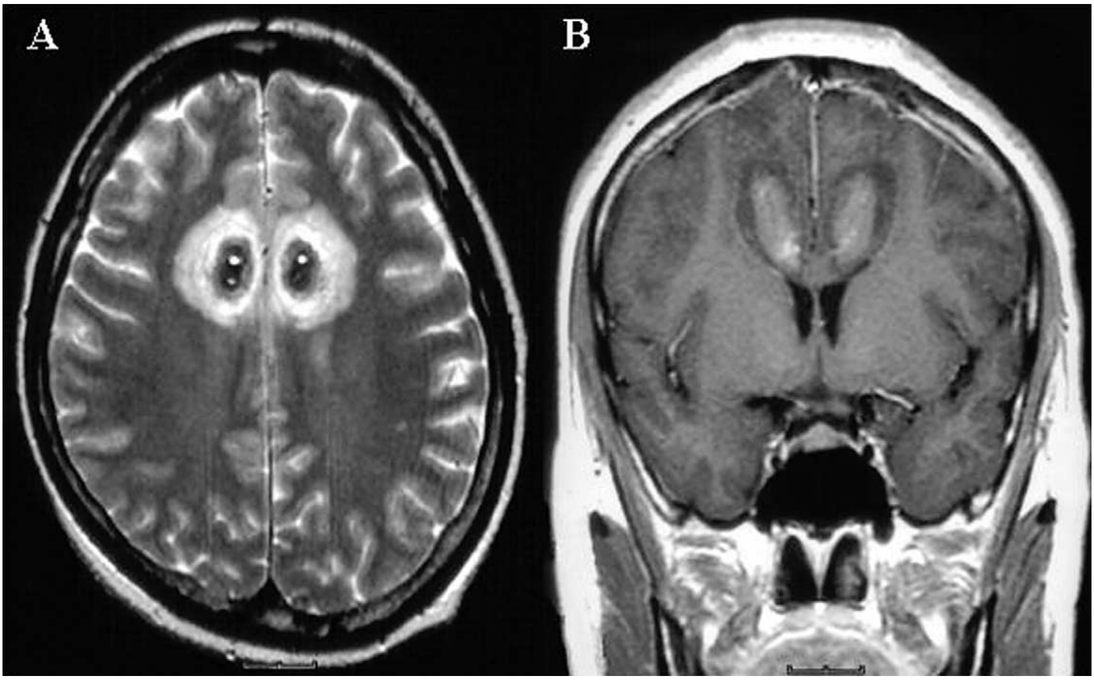

Fig. 1. T2-weighted MRI 3 days after cingulotomy demonstrated the diffuse perilesional edema along the radiofrequency lesions. (A) The axial image. (B) The coronal image.

Statistical parametric mapping

Analysis of data was performed on a SUN UltraSpare 10 workstation (Sun Microsystems, Silicon Valley, CA) using automatic image registration (AIR) [17] and SPM (SPM96; Institute of Neurology, University College of London, London, UK) software [18]. After attenuation and scatter correction, the reconstructed SPECT data were reformatted into Analyze (Mayo Foundation, Baltimore, MD) header format consisting of 4096 bytes of header, 1.67 mm of *x* and *y* pixel size, 3.34 mm of slice thickness, and 2 bytes of signed integer of pixel values. The SPECT images of the

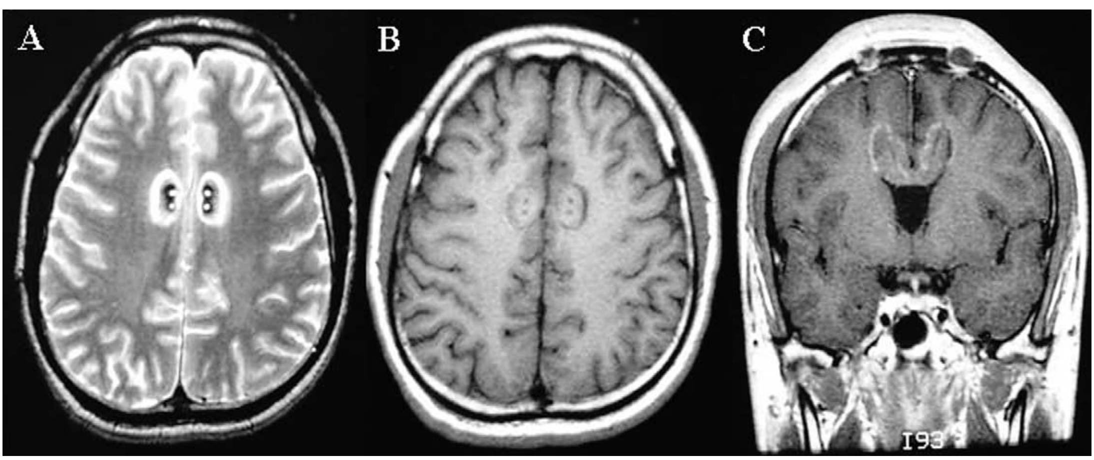

Fig. 2. T1- and T2-weighted MRI 3 months after cingulotomy demonstrated the resolved perilesional edema along the radiofrequency lesions. Lesions were confined in the anterior cingulate gyrus. (A) T2-weighted axial image. (B) T1-weighted axial image. (C) The coronal image.

normal and patient groups were separately coregistered to remove variations resulting from differences in the size and shape of individual brains. The parameters for co-registration were: intra-modality, 5000 pixel value for thresholds to be used for organ of interest in both the standard and the reslice images, linear algorithm, 12 affine parameter model for controlling the number of degrees of freedom used in registration, and trilinear interpolation. The data were then normalized to a PET template (MNI template; Montreal Neurological Institute, Montreal, Quebec, Canada) [2,18,19] and smoothed with 8-mm Full Width Half Maximum (FWHM) before SPM statistical analysis. The statistical analysis was performed to compare the mean SPECT images of the OCD group with those of the schizophrenia and normal control groups and the postoperative images with preoperative images in the surgical group. The resulting *t* statistic, SPM{t}, was transformed to SPM{Z} with a threshold of 3.09 or 1.64. The statistical results were displayed by rendering on the reference three-dimensional MRI images with a probability value of 0.001 or 0.05 and a corrected extent threshold probability value of 0.05 for SPM{Z}. Individual OCD images were also compared with the normal group by shifting the SPM parameters to a probability value of 0.005 and a Z value of 2.58. For graphic presentation of the results, sections were displayed as transverse, sagittal, and coronal slices with hot color maps.

Clinical assessment and follow-up

Clinical findings, complications, and patient progress were prospectively recorded. All patients were evaluated at or as near to 6-month intervals as possible after surgery in our hospital. Evaluation by the neurocognitive battery and by postoperative SPECT was performed between 6 and 12 months after surgery. All patients were followed up with a personal interview conducted by the psychiatrists. The severity of OCD behaviors was quantified by the Y-BOCS [14]. The surgical outcome was also assessed/evaluated by the results of Clinical Global Improvement Scale (CGI) as well as the HAM-D and the HAM-A tests [15,16,20]. Statistical analyses were conducted to examine the effects of cingulotomy. The differences in these scales between the preoperative state and postoperative state (6 months, 12 months) were assessed using a Wilcoxon signed rank test. A probability of less than 0.01 was considered significant.

Neuropsychologic evaluation

Patients were evaluated using a battery of neurocognitive/neuropsychologic evaluation methods designed to measure the functional domains of language, visual integration, learning and memory, executive control, attention, motor control, and general intellectual function. The neurocognitive battery of tests to assess each domain consisted of the following standardized tests with well-established reliability and validity: intellectual functioning by the Korean Wechsler Adult Intelligence Scale (K-WAIS); verbal memory, including immediate and delayed memory, by Hopkins Verbal Learning Test (HVLT); visuospatial construction and memory, including immediate and delayed memory, by the Rey-Osterrieth Complex Figure Test (RCFT); attention and executive functions by the Wisconsin Card Sorting Test (WCST) and Stroop test; and verbal fluency by Controlled Oral Word Association Test (COWA).

In addition to this battery of standard neurocognitive tests, we evaluated all patients on postoperative day 14 with the Korean version of the Short Blessed Test (SBT-K) [21], which was adapted from a six-item Orientation-Memory-Concentration Test [22]. The optimal cutoff point to differentiate patients with dementia from control subjects was 10/11 on the SBT-K.

Results of single photon emission computed tomography for obsessive-compulsive disorder diagnosis

The mean image of the OCD group at a threshold probability value of 0.001, with a Z value of 3.09 and a corrected extent threshold probability value of 0.05, showed increased perfusion within the anterior cingulate gyrus, the left basal ganglia, and the front lobe (Fig. 3). Hyperperfusion within the orbitofrontal cortex or the caudate nucleus was not evident; however, diffusely decreased perfusion within the bilateral cerebral and cerebellar cortices, including the inferior frontal gyrus, was seen in the OCD group (Fig. 4). When individual SPECT images of the OCD patients were compared with the mean images of the normal control group, increased perfusion was seen within the anterior cingulate gyrus in five patients and the frontal lobe in two. Increased perfusion within the basal ganglia, the thalamus, and the orbitofrontal cortex was seen in only one patient (Fig. 5).

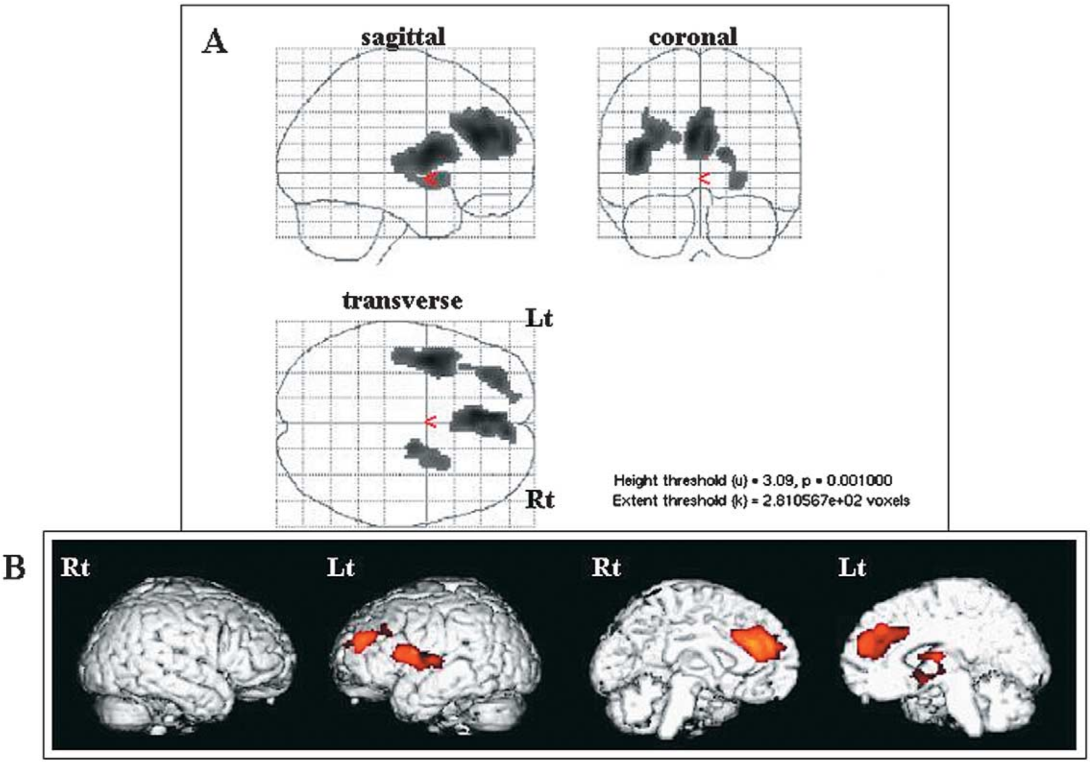

Fig. 3. Group comparison of obsessive-compulsive disorder (OCD) patients with healthy control subjects at the threshold of $P < 0.001$. (A) Statistical parametric mapping (SPM) results showing areas of hyperperfusion in OCD patients. (B) SPM results rendered on the reference three-dimensional MRI revealed significantly increased perfusion of the anterior cingulate cortex on the reference three-dimensional MRI.

When the SPM parameters were shifted to the threshold probability value of 0.005, with a Z value of 2.58 and a corrected extent threshold probability value of 0.05, hyperperfusion was seen within the anterior cingulate gyrus in all patients, within the thalamus in five, within the basal ganglia in four, within the caudate nucleus in three, and within the orbitofrontal cortex in three (Table 3).

The OCD group showed increased perfusion within the anterior cingulate gyrus, the bilateral frontal, and the temporo-occipital areas compared with the schizophrenia group (Fig. 6).

Outcome of anterior bilateral cingulotomy

All patients demonstrated improvement in their Y-BOCS score after cingulotomy (Table 4). The mean Y-BOCS score was 34.9 ± 4.0 before surgery, whereas those at 6 and 12 months after cingulotomy were reduced significantly to 24.3 ± 7.4 and 21.5 ± 6.6, respectively ($P < 0.01$). The mean CGI-Severity score was also reduced significantly from 6.9 before surgery to 4.8 and 4.2 at 6 and 12 months, respectively ($P < 0.01$). The mean CGI score at 12 months was 2.1. All OCD symptoms seemed to respond to surgery, except hoarding behavior.

Most patients experienced an immediate reduction in depression and anxiety after cingulotomy. The mean HAM-D score was also reduced significantly from 27.5 ± 11.8 before surgery to 16.2 ± 10.6 and 10.0 ± 6.0 at 6 and 12 months after cingulotomy, respectively ($P < 0.01$). Also reduced significantly was the mean HAM-A score from 16.1 ± 7.8 before surgery to 9.2 ± 7.1 and 6.3 ± 5.4 at 6 and 12 months after cingulotomy, respectively ($P < 0.01$). The mean postoperative SBT-K score was 6.9 ± 2.1. All patients scored below the optimal cutoff point for differentiation of dementia (10/11) on the SBT-K.

The patients tolerated the procedure well, and none experienced serious permanent complications related to the procedure. Three patients

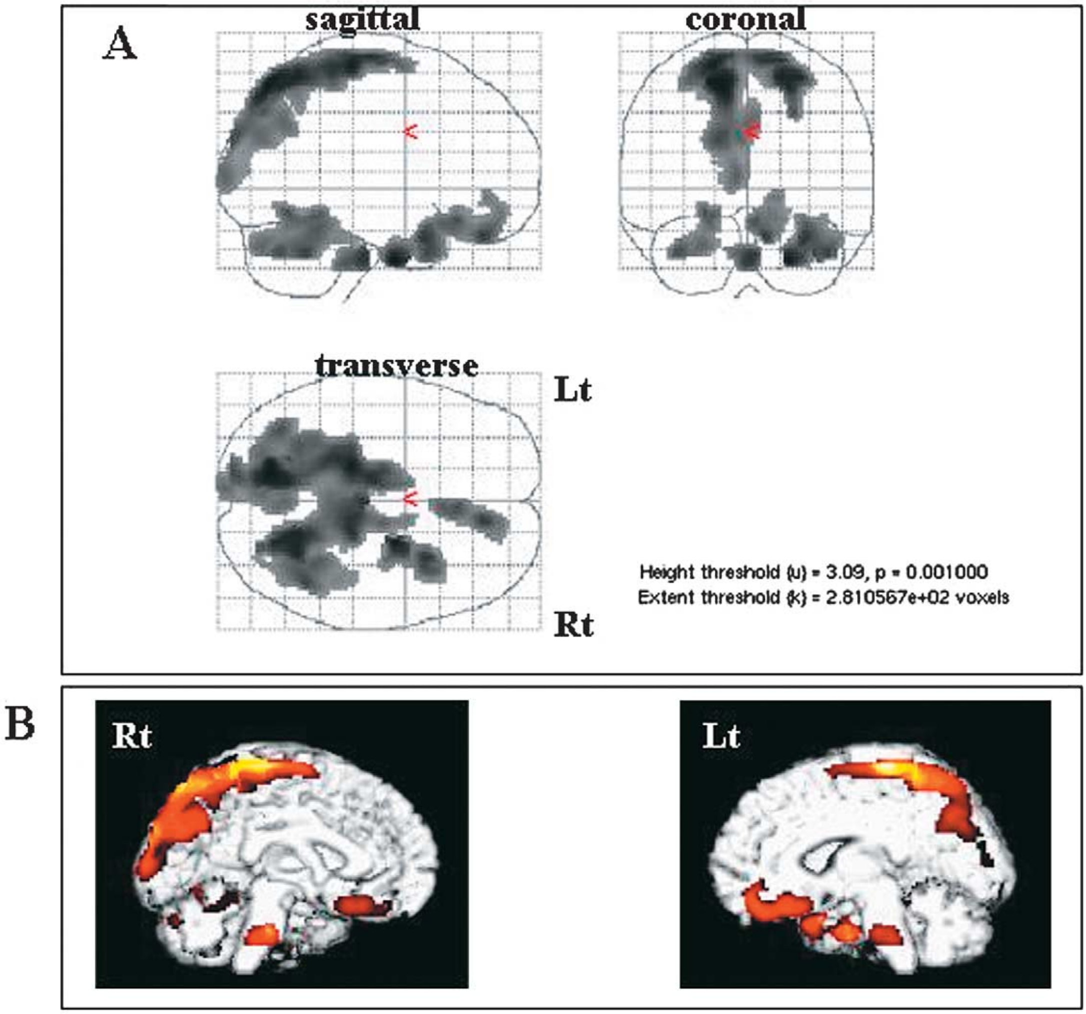

Fig. 4. Group comparison of healthy control subjects with obsessive-compulsive disorder (OCD) patients at the threshold of $P<0.001$. (A) Statistical parametric mapping (SPM) results showing areas of decreased perfusion in OCD patients (increased perfusion in healthy control subjects). (B) SPM results rendered on the reference three-dimensional MRI showing decreased perfusion within bilateral parieto-occipital, inferior frontal, and cerebellar areas.

showed transient disorientation during the postoperative period. One case of wound dehiscence occurred from scratching of the wound as a result of compulsive behavior; however, the wound healed well after reclosure. Several patients experienced minor interference with verbal fluency and minor personality changes; however, these patients recovered from their minor problems within the first operative month.

The neuropsychologic testing demonstrated that cingulotomy did not cause any significant cognitive problems in areas like intelligence, language, visuospatial skills, and frontal executive function. On the contrary, we observed an improvement of intellectual function after cingulotomy in several patients, although it was not statistically significant (mean preoperative IQ = 99, postoperative [Ed-corrected] IQ = 105).

Single photon emission computed tomography and anterior bilateral cingulotomy

We performed postoperative SPECT in eight patients after cingulotomy; the other five patients refused for various reasons. After surgery, the OCD patients demonstrated reduced perfusion

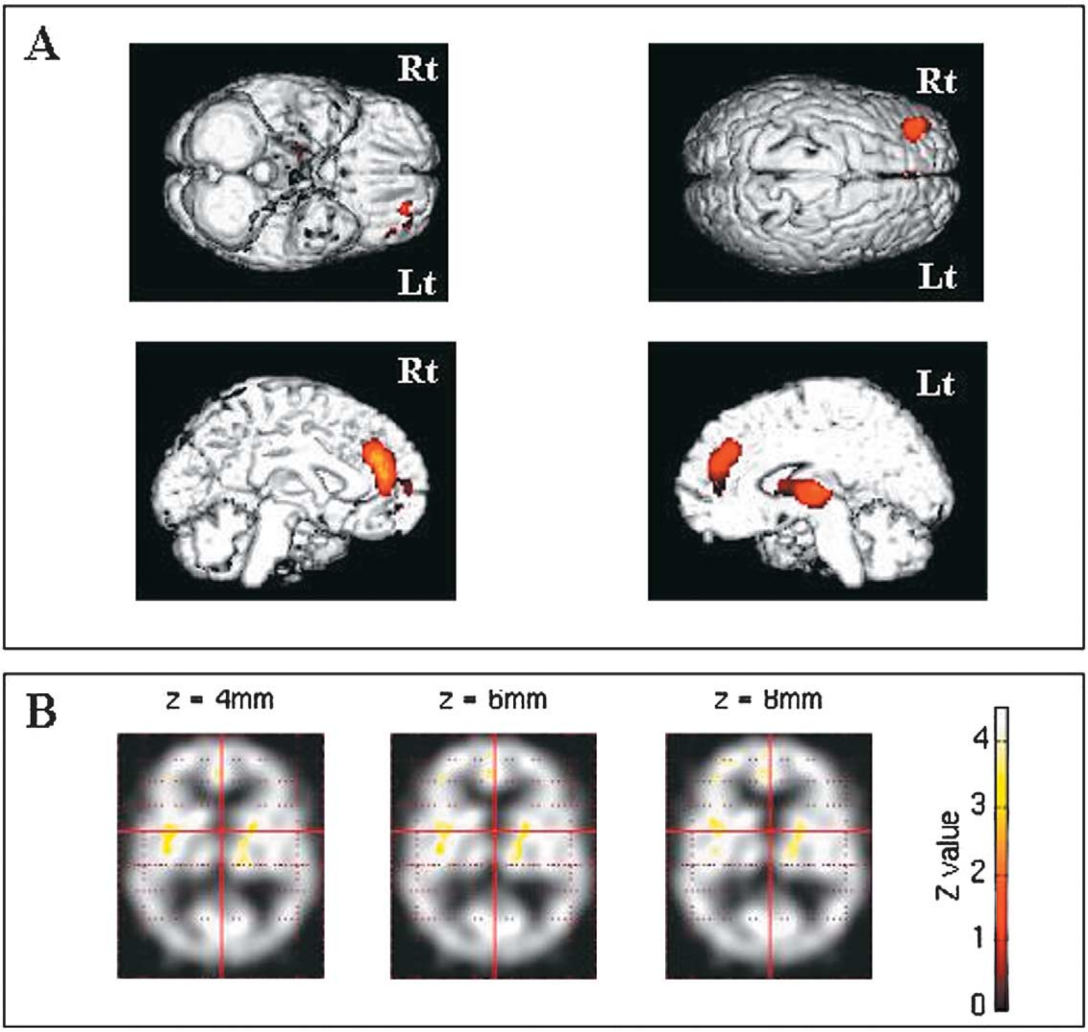

Fig. 5. A single case analysis of an obsessive-compulsive disorder patient (case 6) at the threshold of $P < 0.005$ revealed hyperperfusion within the anterior cingulate cortex, a bilateral lentiform nucleus, the left head of the caudate nucleus, and the thalamus. (A) Statistical parametric mapping (SPM) results rendered on the reference three-dimensional MRI. (B) SPM results rendered on the sagittal single photon emission computed tomography image.

within the anterior cingulate gyrus and the right orbitofrontal cortex in the summated and subtracted postoperative SPECT images compared with the preoperative SPECT images ($P < 0.01$) (Fig. 7).

Discussion

Outcome of bilateral anterior cingulotomy for obsessive-compulsive disorder

There was an overall significant improvement in the Y-BOCS and HAM-D scores, with no significant change in neuropsychologic testing after stereotactic bilateral anterior cingulotomy.

In general, bilateral anterior cingulotomy is regarded as an important therapeutic option for intractable OCD [23,24]. Studies on the effects of cingulotomy for OCD during the last decade have demonstrated that about one third of patients were improved after cingulotomy [25]. As reported previously [23,24], there was a general delay in the onset of improvements of symptoms. In our series, all patients showed gradual improvement after surgery, and this delayed process may suggest that effects are related not only to

Table 3
Statistical parametric mapping data of obsessive-compulsive disorder versus healthy control group

	Anterior cingulate		Caudate		Basal ganglia		OFC		Thalamus		Other areas	
	$P < 0.001$	$P < 0.005$	$P < 0.001$	$P < 0.005$	$P < 0.001$	$P < 0.005$	$P < 0.001$	$P < 0.005$	$P < 0.001$	$P < 0.005$	$P < 0.001$	$P < 0.005$
Case 1	+	+	–	–	–	–	–	Lt	–	Lt	–	Frontal Occipital Temporal
Case 2	+	+	–	Bilat	Bilat	Bilat	Lt	Lt	Lt	Lt	Frontal (Rt)	Frontal Temporal
Case 3	+	+	–	Lt	–	–	–	Bilat	–	–	–	Temporal Occipital
Case 4	+	+	–	–	–	Rt	–	–	–	Rt	Frontal (Bilat)	Temporal
Case 5	+	+	–	Lt	–	–	–	–	–	Lt	–	Temporal
Case 6	–	+	–	–	–	Bilat	–	–	–	Lt	–	–
Case 7	–	+	–	–	–	–	–	–	–	–	–	Occipital

Abbreviations: OFC, orbitofrontal cortex; Bilat, bilateral; Lt, left; Rt, right.

interruption but to reorganization of neural pathways after surgery. Prior reports have claimed that only 39% of patients were considered responders or possible responders on the basis of demonstrating an improvement on the Y-BOCS of more than 35% or a CGI score of 1 or 2 [24].

Our entire group improved significantly in terms of functional status ($P < 0.01$), and no significant adverse effects were encountered after cingulotomy. The responder and possible responder ratios were 30.8% and 30.7%, respectively, on the basis of an improvement on the Y-BOCS of more than 35% or a CGI score of 1 or 2. Our study featured more possible responders than those of previous reports [20,24]. One possible explanation for this is that our lesion is larger than those used in other studies. We did experience minor and transient mental deterioration (subsided within 1 week), described as a nonresponsive/flat affect, minor interference with verbal fluency, lack of spontaneity, and minor personality changes. This transient postoperative complication seemed to occur as a result of temporary perilesional brain edema around the lesions, as evident in Fig. 1. Our neurocognitive/neuropsychologic battery of tests in these patients demonstrated that cingulotomy did not cause any significant cognitive problems in areas like intelligence, language, visuospatial skills, and frontal executive function.

For patients undergoing stereotactic bilateral anterior cingulotomies, it becomes important to have the proper target location and the optimal lesion volume in the anterior cingulate gyrus. We are not recommending that our positive results justify general adoption of the procedure as a routine treatment for OCD, however. As Cohen et al [26] reported, subtle personality and functional changes could remain. We believe that these minor neurobehavioral sequelae do not hinder the performance of cingulotomy as a treatment method for a certain portion of intractable OCD patients so as to improve their quality of life.

Single photon emission computed tomography and obsessive-compulsive disorder

A number of neuroimaging studies using PET have determined abnormal activity in the orbitofrontal cortex, the anterior cingulate gyrus, and the head of the caudate nucleus. These areas are interconnected anatomically and are among the regions implicated in the pathophysiology of OCD.

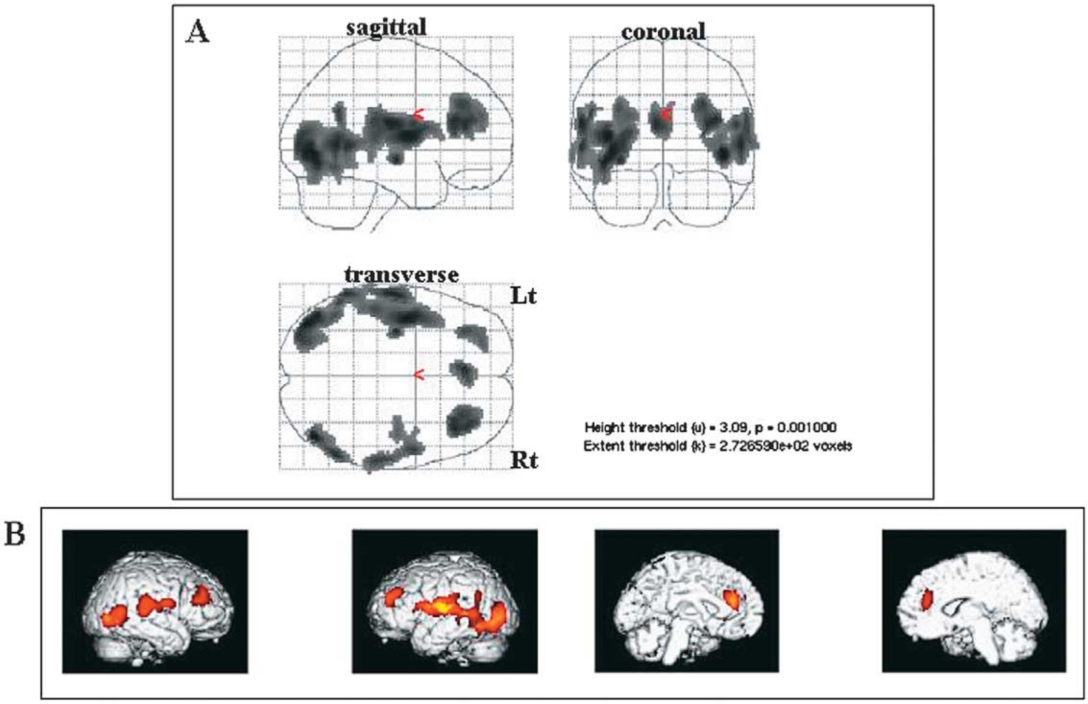

Fig. 6. Group comparison of obsessive-compulsive disorder (OCD) patients with drug-naive schizophrenia at the threshold of $P < 0.001$. (A) Statistical parametric mapping (SPM) results showing areas of hyperperfusion in OCD patients. (B) SPM results rendered on the reference three-dimensional MRI showing hyperperfusion within a bilateral anterior cingulate cortex and the frontal and parieto-occipital areas.

Our brain perfusion study of OCD patients using high-resolution SPECT showed consistently increased perfusion within the anterior cingulate gyrus compared with that of normal controls and other psychiatric patients (drug-naive schizophrenia). Hyperperfusion within the caudate nucleus or the orbitofrontal cortex was less frequently observed. Our results have shown outcomes using SPECT for the first time and have correlated it to clinical improvements as determined by standardized tests. SPECT results demonstrated reduced perfusion within the anterior cingulate gyrus and the right orbitofrontal cortex after surgery.

Functional imaging of OCD with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET at resting state demonstrated the hyperactivity of various anatomic structures, such as the basal ganglia, the thalamus, and, in particular, the orbitofrontal cortex. In addition to resting PET, comparative studies of the OCD patients before and after

Table 4
Surgical outcome after cingulotomy for study II

Evaluation method	Preoperative	Postoperative 6-month	Postoperative 12-month
Y-BOCS (mean ± SD)	34.9 ± 4.01	24.3 ± 7.431*	21.5 ± 6.612*
CGI-S (mean)	6.9	4.83*	4.24*
CGI		2.4	2.1
HAM-D (mean ± SD)	27.5 ± 11.75	16.2 ± 10.621*	10.0 ± 5.982*
HAM-A (mean ± SD)	16.1 ± 7.88	9.2 ± 7.123*	6.3 ± 5.414*

Abbreviations: Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; CGI-S, Clinical Global Improvement of Severity Scale; CGI, Clinical Global Improvement.

* $P < 0.01$ (Wilcoxon signed rank test).

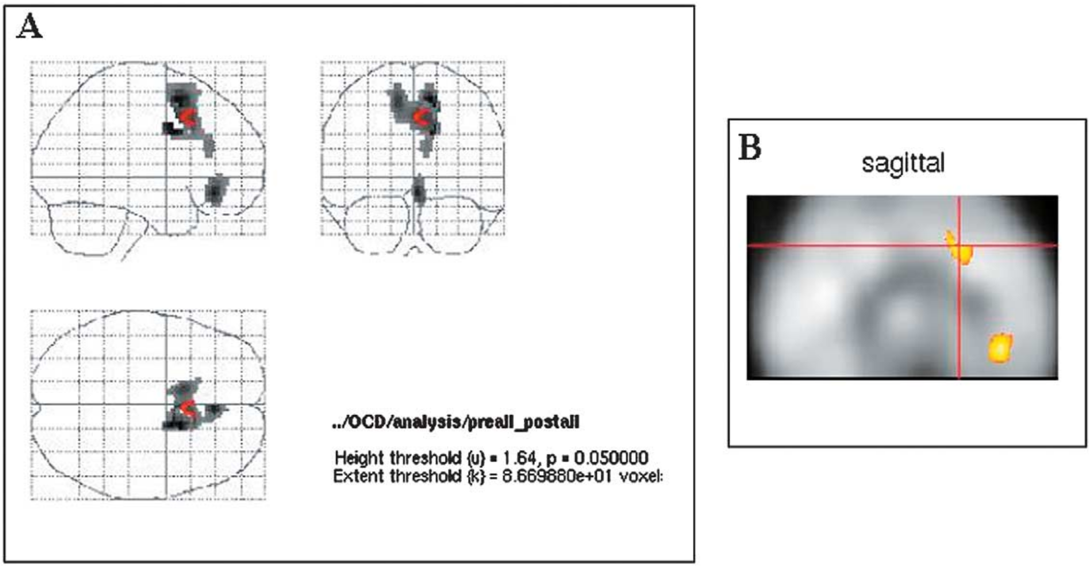

Fig. 7. Group comparison of preoperative images with postoperative images at the threshold of $P < 0.05$. (A) Statistical parametric mapping (SPM) results showing decreased perfusion at the anterior cingulate gyrus and the right orbitofrontal cortex. (B) SPM results rendered on the sagittal single photon emission computed tomography image.

treatment have shown a decrease in cerebral glucose metabolism within the caudate nucleus, the orbitofrontal cortex [4,5,10,11], and the anterior cingulate gyrus [27]. This decrease in metabolism was correlated with a significant improvement in OCD symptoms. Despite these findings, however, there are several inconsistencies in the published data. For example, Swedo et al [28,29] showed increased metabolic rates within the orbitofrontal cortex and the anterior cingulate gyrus, whereas Baxter et al [4,5] found increased metabolism in the whole brain, especially in the orbitofrontal cortex and the caudate nucleus but not in the anterior cingulate gyrus. Perani et al [27] described hypermetabolism within the anterior cingulate gyrus, thalamus, and basal ganglia but not in the orbitofrontal cortex. Nordahl et al [30] found no difference in activity within the caudate nucleus. Mindus and Jenike [31] found that orbital and caudate glucose metabolic rates decreased significantly 1 year after bilateral anterior capsulotomy compared with those before surgery.

Regardless of the specific treatment or type of imaging modality used, it is apparent that studies of pretreatment and posttreatment OCD have most consistently shown findings of decreased orbitofrontal cortex and caudate activity after treatment.

The difference between PET and SPECT may stem from several factors. First, the PET studies were conducted using ^{18}F-FDG, which requires 40 to 60 minutes between injection and imaging. ^{99m}Tc EDC for brain SPECT, however, is rapidly taken up by the neurons in the brain within a few minutes, proportional to the cerebral blood flow [32]. Therefore, the emotional state and presenting symptoms at the time of injection are important determinants in brain perfusion SPECT but are less critical in PET. In fact, regional cerebral blood flow measured during symptom provocation using oxygen-15–labeled carbon dioxide PET showed increased blood flow within the caudate nucleus, the anterior cingulate gyrus, and the orbitofrontal cortex [33], although resting brain SPECT has demonstrated contradictory findings, such as decreased perfusion in the orbitofrontal cortex [34] and the caudate nucleus [8,35]. Therefore, a SPECT study performed during symptom provocation would be better than resting SPECT to evaluate the pathophysiologic mechanism of OCD.

The spatial resolution of current cameras used may be another important factor, because the orbitofrontal cortex and caudate nucleus are relatively smaller and thinner than the anterior cingulate gyrus, especially on transaxial images. Therefore, small activation sites within these small areas might be obscured and diluted by the surrounding normal cells or background activity as a result of the poor spatial resolution of SPECT cameras.

The analytic method of measuring radioactivity in terms of ROI or calculation of hemispheric ratio may contribute to false-negative results as well as false-positive results as previously described. In this study, data were analyzed using an SPM method in which relative activity distribution between the subject and control groups was compared and transformed to the unit of normal distribution in terms of z values and then displayed in coronal, axial, and sagittal views showing only those voxels that reach a statistical significance of $P < 0.001$ or $P < 0.005$. The SPM analysis is known to be more accurate and reliable than semiquantitative measurement [13]. In this study, although five of the seven patients showed hyperperfusion within the anterior cingulate cortex on higher z and probability values (3.09 and 0.001, respectively), all patients showed anterior cingulate hyperperfusion on lower thresholds (z value of 2.58 and $P < 0.005$). In addition, hyperperfusion within the caudate nucleus ($n = 3$), the orbitofrontal cortex ($n = 3$), and the thalamus ($n = 5$) was frequently observed. Therefore, in SPECT or even PET studies without SPM, analysis may be inconsistent and conflicting in cases with slightly increased radioactivity within an activation site.

Although not all studies agree, a review of the OCD functional brain imaging literature reveals a remarkable amount of data suggesting the presence of abnormalities in the orbitofrontal cortex, the anterior cingulate gyrus, the caudate, and the thalamus, all of which are structures linked by well-described neuroanatomic circuits [10].

In our study, the OCD patients exhibited increased perfusion in the anterior cingulate gyrus compared with both the healthy controls and the schizophrenic patients (see Figs. 2 and 3). A more interesting finding was the observation of postoperative hypoperfusion in the anterior cingulate gyrus and the right orbitofrontal cortex in the OCD patients. We assumed that the perfusion in the anterior cingulate gyrus was caused by the cingulotomy itself; however, the reduction of perfusion in the right orbitofrontal cortex was an interesting result. In the literature, there are many reports concerning the role of the orbitofrontal cortex in the genesis of OCD and many PET studies demonstrating a decrease in cerebral glucose metabolism in the orbitofrontal cortex after OCD treatment [4,11,36]. Those reports also showed an increased glucose metabolism in the caudate nucleus and the orbitofrontal cortex before the treatment. In our study, however, there was no observation of any hyperperfusion in the orbitofrontal cortex before the treatment. The only equivalent observation was in the anterior cingulate gyrus.

We suggest two potential explanations for this divergence of results. First, as previously discussed, SPECT has many weaknesses, including poor spatial resolution. The caudate nucleus and the orbitofrontal cortex are relatively smaller and thinner than the anterior cingulate gyrus, especially on transaxial images, allowing the possibility for small activation sites within these small areas to be obscured and diluted by the surrounding normal cells or background activity as a result of poor spatial resolution. Second, the disparity between various studies, including PET and SPECT images, in terms of secondary change of perfusion according to cingulotomy has not been fully elucidated. The SPECT data may correctly demonstrate the major changes of perfusion after cingulotomy. Thus, the anterior cingulate gyrus may be the key center for the genesis of OCD, and the improvement of OCD symptoms may be related to change of the orbitofrontal cortex.

Of special note was the observed decrease of perfusion in the right side of the orbitofrontal cortex. Several studies comparing therapy-related regional cerebral metabolic effects in patients with OCD have demonstrated orbitofrontal hypermetabolism on the right side before treatment [28,29,37]. Right-sided orbitofrontal metabolic reduction was noted in the same reports. Lippitz et al [38] also suggested the crucial role of the right hemisphere in OCD.

The observation that obsessive-compulsive behaviors can be controlled by lesioning at several targets, including the orbitofrontal cortex, internal capsule, and anterior cingulate gyrus, supports the hypothesis that these structures are closely related and involved with the neuronal circuitry of OCD.

Neuroanatomic studies have also shown that the striatum contains a complex system—neurochemically specialized zones called striosomes dispersed within a larger compartment called the matrix [7,39]. The striosomes of the caudate nucleus receive inputs from the orbitofrontal cortex and the anterior cingulate gyrus, and the caudate processes the cortical information in preparation for an initiation of behavioral responses [10,11]. The imbalance of this neuronal circuit is important for the generation of OCD symptoms. Our findings of reduced perfusion in the right orbitofrontal cortex after cingulotomy may offer an explanation for the improvement of OCD symptoms being related not only to the anterior cingulate gyrus but to the orbitofrontal cortex.

Over the last several decades, many attempts have been made to investigate the outcome of surgery prospectively. Although it is difficult to compare the results because of lack of control groups, the OCD perfusion patterns were distinguished from those of schizophrenia in this study. Because a certain population (reported to be 26% in Porto's analysis of schizophrenia) has comorbid OCD, and given that schizophrenia also involves the frontostriatal-thalamic circuit [3], we performed a group comparison of SPECT images between OCD and drug-naive cases of schizophrenia using SPM. The results demonstrated that the OCD patient group had a significant increase of blood flow in the anterior cingulate gyrus as well as in the temporo-occipital area. This finding is consistent with the neuropathologic analysis of schizophrenia, which demonstrated cytoarchitectural alteration of the anterior cingulate gyrus and the superior temporal gyrus as well as decreased volume and cell number of the mediodorsal thalamic nucleus [40].

Summary

In conclusion, the present study suggests that SPECT, using a sophisticated SPM analysis method, may be useful as a potential diagnostic tool for OCD and a possible predictor of treatment outcome for OCD patients undergoing bilateral anterior cingulotomy. The anterior cingulate gyrus seems to be an important structure in the pathogenesis of OCD symptoms. Furthermore, our operative technique of anterior cingulotomy, featuring a larger lesion, seems to be effective in ameliorating the symptoms of OCD without causing any serious complications.

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