Orbital Frontal and Amygdala Volume Reductions in Obsessive-compulsive Disorder

Philip R. Szeszko, PhD; Delbert Robinson, MD; Jose Ma. J. Alvir, DrPH; Robert M. Bilder, PhD; Todd Lencz, PhD; Manzar Ashtari, PhD; Houwei Wu, MD; Bernhard Bogerts, MD

Background: Functional neuroimaging studies have implicated the frontal lobes and the hippocampus-amygdala complex in the pathophysiology of obsessive-compulsive disorder (OCD). These brain regions have not been well investigated in patients with OCD, however, using magnetic resonance imaging.

Methods: Volumes of the superior frontal gyrus, anterior cingulate gyrus, orbital frontal region, hippocampus, and amygdala were computed from contiguous magnetic resonance images in a sample of 26 patients with OCD and 26 healthy comparison subjects.

Results: Patients with OCD had significantly reduced bilateral orbital frontal and amygdala volumes compared with healthy comparison subjects and lacked the normal hemispheric asymmetry of the hippocampus-amygdala complex. Neither brain structure volumes nor asymmetry indices were significantly correlated with total illness duration or length of current OCD episode.

Conclusions: Findings of reduced orbital frontal and amygdala volumes in patients implicate a structural abnormality of these brain regions in the pathophysiology of OCD. Absence of the normal hemispheric asymmetry of the hippocampus-amygdala complex in patients is consistent with an anomalous neurodevelopmental process.

Arch Gen Psychiatry. 1999;56:913-919
SUBJECTS AND METHODS

SAMPLE SELECTION

This study included the same subjects as our previous MRI study of patients with OCD and healthy comparison subjects; detailed inclusion and exclusion criteria are available from that report. Criteria relevant to this study are described briefly. All patients with OCD had a DSM-III-R diagnosis of OCD by the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P), part 1, but were excluded if they met current or past (1) DSM-III-R–defined alcohol or psychoactive substance abuse or dependence; (2) dementia, delirium, schizophrenia, schizoaffective disorder, delusional disorder, brief reactive psychosis, or psychotic disorder not otherwise specified; or (3) mental retardation (based on IQ testing of patients with suspected mental retardation, clinical interview, and psychosocial history). In the first 10 comparison subjects, absence of any history of psychiatric disorders was determined by a screening questionnaire and clinical interview. Subsequent comparison subjects were assessed using a SCID-P interview. Written informed consent for the study was obtained using the guidelines of the Long Island Jewish Institutional Review Board.

MRI AND MEASUREMENT METHODS

Magnetic resonance images were acquired in the coronal plane using a 3-dimensional gradient echo FLASH (fast low-angle shots) sequence with a 30° flip angle, 40-millisecond repetition time, and 1.5-millisecond echo time on a 1.0-T whole-body superconducting imaging system (Siemens, Magnetom, Erlangen, Germany). This sequence produced 63 contiguous coronal slices (slice thickness, 3.1 mm) through the whole head in about 11 minutes, with in-plane resolution of 1.17 × 1.17 mm in a 256 × 256 matrix. All scans were reviewed by a neuroradiologist for clinical pathologic characteristics. Prior to all measurements, scans of patients with OCD and healthy comparison subjects were randomly mixed together and flipped. All measurements were thus completed by an operator (P.R.S.) unaware of group membership and hemisphere.

Measurement of mesiotemporal lobe structures was based on criteria operationalized from postmortem histologic work using a semi-automated, computerized measurement system. The anatomic regions used for measurement are illustrated elsewhere and have been used in prior MRI research. Two contiguous portions of the hippocampus-amygdala complex in each hemisphere were analyzed, which included the hippocampus and the amygdaloid complex. The hippocampus was measured from the level where the ascending fornix (ie, surrounding pulvinar) was interrupted to the slice posterior to the mamillary bodies. Measurement of the hippocampal formation included all CA segments (CA1, CA2, CA3, CA4), dentate gyrus, alveus, and the subicular region, which could not be separated in the scans. The amygdaloïd complex was measured from the slice at the level of the mammillary bodies to its anterior boundary including the uncus. Additional details regarding these delineation criteria are available on request. Intraclass correlations between 2 operators for volumes of these structures in the right and left hemispheres ranged from 0.80 to 0.97 in 10 cases.

For measurement of the frontal lobe subregions, a modified version of Analysis of Functional NeuroImages was used to resample images in the 3 orthogonal planes using 1.5-mm isotropic voxels, align all cases along the anterior and posterior commissures space, and to manually delineate the subregions on a slice-by-slice, voxel-by-voxel basis. In-house programming modifications to Analysis

RESULTS

SUBJECTS

The demographic characteristics for the 26 patients and 26 healthy comparison subjects were described previously and information relevant to this study is summarized. Patients with OCD (14 men, 12 women) had a mean age of 32.2 ± 8.0 years (range, 19−44 years). Healthy comparison subjects (16 men, 10 women) had a mean age of 29.8 ± 6.3 years (age range, 20−45 years). Twenty-two patients with OCD and 22 of the healthy comparison subjects were right-handed as assessed by a modified 20-item Edinburgh Inventory. Handedness was not determined for 1 healthy comparison subject. Patients with OCD had been ill an extended time (mean onset of illness prior to the scans was 13.8 ± 6.2 years; range, 3−28 years) and their symptoms were of moderate severity (mean total of the 10 items for obsessions and compulsions on the Yale-Brown Obsessive Compulsive Scale was 22.4 ± 6.9; range, 8−37). Most patients (n = 20) had received prior treatment for their disorder, including selective serotonin reuptake inhibitors or clomipramine hydrochloride, for 4 or more weeks. The mean Hamilton

©1999 American Medical Association. All rights reserved.
of Functional NeuroImages allowed operators to “paint” a sulcus in the plane where it was optimally visible and have it appear simultaneously in the other 2 planes, thereby facilitating identification of sulci for measurement of frontal lobe subregions.

Methods for measuring the frontal lobe subregions were adapted from Rademacher et al63 with several modifications for use in our magnetic resonance images.64 An illustration of the frontal lobe subregions with their corresponding boundaries is provided elsewhere.65 The boundaries of the superior frontal gyri were (anterior, posterior, lateral, medial) tip of the cingulate sulcus, connection of the superior and precentral sulci, superior frontal sulcus, and cingulate sulcus. The boundaries of the anterior cingulate gyri were (anterior, posterior, ventral, dorsal) tip of the cingulate sulcus, connection of the superior and precentral sulci, callosal sulcus, and cingulate sulcus. The boundaries of the orbital frontal region were (anterior, posterior, lateral, and medial) last appearance of the anterior horizontal ramus, last appearance of the olfactory sulcus, anterior horizontal ramus or circular sulcus of insula, and the olfactory sulcus. All frontal lobe subregions included gray and white matter. Intraclass correlations between 2 operators for volumes of the frontal lobe subregions ranged from 0.84 to 0.98 in 12 cases. Because one of the limiting sulci required for measurement of the orbital frontal region (ie, the anterior horizontal ramus) was not present in every hemisphere, total orbital frontal volumes were not computed for 2 patients with OCD and 4 healthy comparison subjects.

STATISTICAL PROCEDURES

Mixed-models analyses from SAS-PC (version 6.12; SAS Institute, Cary, NC) were used to compare the brain structure volumes between the OCD and healthy comparison groups. Brain structures were examined separately because of their functional and neuroanatomical heterogeneity and the possibility that OCD may involve structural pathology in a single frontal or mesiotemporal lobe brain region. Group (OCD patients vs healthy comparison subjects) and sex were between-subjects factors and hemisphere (right vs left) was a within-subjects factor. To examine possible group differences in brain asymmetry, we computed asymmetry indices according to the following formula: [(right − left)/(right + left)] × 100.62 Thus, when the right hemisphere volume is larger than the left, the asymmetry index is positive, and when the left is larger than the right, the asymmetry index is negative. Group and sex served as between-subjects factors for analyses investigating asymmetry. Asymmetry indices were examined for the entire sample and then subsequently for right-handed individuals only because asymmetry may be influenced by handedness.62 Pearson product moment correlations were used to investigate brain structure volumes and asymmetry indices in relationship to measures of illness duration.

All analyses were 2 tailed and α was set at .05. Although whole brain volume was comparable between patients with OCD (mean volume = 1321 cm³) and healthy comparison subjects (mean volume = 1324 cm³), we included it as a covariate in analyses investigating brain structure volumes because it explained part of the variance in these volumes. Because of the age differences between groups and the finding that age explained some variance in brain structure volumes, it also was included as a covariate. We considered the possibility that educational level might also be a suitable covariate; however, because it did not correlate with any brain structure volume in either the patient or comparison group, it was not included as a covariate. Additional analyses subdivided the OCD patient group by history of depression and prior psychotropic medication use to investigate the potential effects of these variables on significant findings. Mean values are given with SDs.

Depression Rating Scale55 score (17 items minus the obsessive-compulsive item) for patients was 7.3 ± 4.9, indicating that they were not depressed, although 8 patients did have a history of major depression.

BRAIN MEASURES

Unadjusted frontal lobe and hippocampus-amygdala volumes are presented in Table 1 along with the 95% confidence intervals for the difference between group means after adjustment for age and total brain volume (healthy comparison group – OCD patient group).

Mixed-models analyses revealed significant main effects of group for orbital frontal (F1,47 = 5.64, P = .002) and amygdala (F1,47 = 6.00, P = .01) volumes, such that patients with OCD had reduced overall volumes of these structures. The interaction of group and hemisphere was statistically significant for amygdala volume (F1,50 = 4.18, P = .046) such that patients with OCD had significantly reduced right amygdala volume compared with healthy comparison subjects (t1,50 = 3.27, P = .002; Table 1). Other results included a significant main effect of hemisphere for anterior cingulate (F1,50 = 12.43, P < .001), amygdala (F1,50 = 12.39, P < .001), and orbital frontal (F1,44 = 7.94, P = .007) volumes, with larger anterior cingulate and amygdala volumes in the right hemisphere and larger orbital frontal volume in the left hemisphere in patients with OCD and healthy comparison subjects. There was also a significant main effect of sex for superior frontal gyrus (F1,47 = 10.0, P = .003) and amygdala (F1,47 = 8.92, P = .005) volumes, with larger anterior cingulate and amygdala volumes in the right hemisphere and men had larger amygdala volume. None of the group × sex interactions was statistically significant for any of the brain structure volumes. The distributions of the unadjusted total orbital frontal and amygdala volumes are presented in Figure 1 and Figure 2, respectively.

Unadjusted asymmetry indices for the frontal and mesiotemporal lobe structures are presented in Table 2 along with the 95% confidence intervals for the difference between group means after adjustment for age (healthy comparison group – OCD patient group). These analyses revealed that compared with healthy comparison subjects, patients with OCD had significantly less asymmetry in amygdala volume (F1,48 = 7.61, P = .008) with a trend for less asymmetry in hippocampus volume (F1,48 = 3.25, P = .08). When analyses were restricted to right-handed individuals, results indicated that patients...
with OCD had significantly less asymmetry in amygdala (F1,40 = 10.11, P = .003) and hippocampus (F1,40 = 5.38, P = .02) volume compared with healthy comparison subjects.

We investigated the effects of having a history of major depression and prior exposure to psychotropic medications on (1) orbital frontal and amygdala volumes and (2) hippocampus and amygdala asymmetry indices (for the total sample and for right-handed subjects only). Although we found no evidence for an effect of these variables on orbital frontal and amygdala volumes, patients with OCD (including the left-handed individuals) without a history of major depression had significantly less asymmetry of the amygdala compared with OCD patients with a history of major depression (F1,22 = 6.91, P = .02).

We also investigated total orbital frontal and total amygdala volumes and hippocampus and amygdala asymmetry indices (again for the total sample and then restricted to right-handed individuals) in relation to duration of current OCD episode and total illness duration, but none of these correlations was statistically significant.

**COMMENT**

Using parcellation methods based on sulcal anatomy, these findings provide the first MRI evidence to our knowledge of reduced orbital frontal volume in patients with OCD compared with healthy comparison subjects. It is noteworthy that reduced orbital frontal volume was identified in this sample of patients without associated struc-
ultural compromise of other frontal lobe subregions including the anterior cingulate and superior frontal gyri. Investigation of mesiotemporal-limbic structures revealed that patients with OCD had reduced amygdala volume as well as an absence in the normal hemispheric asymmetry of the hippocampus-amygdala complex. Although these findings were unrelated to prior medication treatment, less asymmetry of the amygdala was more characteristic of OCD patients without a history of major depression.

There have been relatively few MRI investigations in OCD; thus, it is difficult to compare our results with prior studies. Grachev et al reported no volume differences in the orbital frontal region between 10 female patients with OCD and 10 healthy female comparison subjects. An important difference between their study and ours, however, is that Grachev et al used methods for neocortical parcellation and thus their measure included cortical gray matter alone whereas our measure included both gray and white matter. In another MRI study, Jenike et al reported no group differences in amygdala volume using the same OCD and healthy comparison groups as the study by Grachev et al. As noted by these authors, however, the small sample size may have limited statistical power. There is also the possibility, however, that OCD may be a heterogeneous disorder and that our study and their studies used different subgroups of patients. It is unlikely that different findings between the studies were due to the inclusion of male patients with OCD in our sample because there was no significant interaction of group and sex for any of the brain structure volumes.

The evolutionary cytoarchitectonic theory of cerebral cortex development proposed by Sanides may provide a useful framework in which to interpret the findings of reduced orbital frontal and amygdala volumes. According to Sanides, 6-layered isocortex in the frontal lobes develops from 2 primordial moieties: hippocampal (“archicortical”) and olfactory (“paleocortical”). The archicortical trend includes the hippocampal (“archicortical”) and olfactory (“paleocortical”) moiety. The findings from this study would therefore be consistent with a pathophysiologic process involving paleocortical, but not archicortical brain regions in OCD.

Although the nonsignificant group differences in anterior cingulate gyrus volume may be difficult to reconcile with functional imaging studies that have implicated abnormalities of this region in OCD, this finding was consistent with previous MRI investigations in adults with OCD, which have also yielded negative findings. One possible explanation for our negative findings could be related to the lack of sensitivity of our MRI measure for detecting subtle neuronal loss or other abnormalities specific to the anterior cingulate as compared with other measures such as H-magnetic resonance spectroscopy of N-acetylaspartate, which have identified abnormalities of this region in patients with OCD.

Because most patients with OCD in this study had a long duration of symptoms prior to seeking treatment, the possibility of reduced brain volumes or abnormal asymmetry reflecting a neurodegenerative process occurring sometime during the first few years of symptoms cannot be entirely ruled out. There are, however, several reasons to argue against a neurodegenerative process. In this study we found no significant association of either brain structure volumes or asymmetry indices with duration of current OCD episode or total illness duration. Moreover, because we are unaware of any evidence that brain asymmetry can be diminished by a neurodegenerative process (at least among healthy individuals), the finding of anomalous hippocampus-amygdala asymmetry is probably more consistent with an aberrant neurodevelopmental process. Although the neurodevelopmental mechanisms underlying establishment of normal brain asymmetry are not fully understood, gross asymmetries are apparent as early as week 16 of gestation and both hormonal and genetic influences probably contribute to this effect.

There were several limitations of the morphometric delineation criteria that preclude firm conclusions. One limitation of the hippocampus-amygdala delineation methods was that precise separation of the hippocampus from the amygdala was not possible in these FLASH images. Thus, the amygdala volume included the most rostral part of the hippocampal formation, while the hippocampal volume included the most caudal part of the amygdala. In addition, because of methodological limitations, we did not use methods for gray and white matter segmentation and thus could not determine whether reduced orbital frontal volume was specific to the gray or white matter. An assumption in measuring the frontal lobe subregions based on sulcal anatomy is that these sulci provide accurate and meaningful bound-

<table>
<thead>
<tr>
<th>Region</th>
<th>Patients With OCD (n = 26)</th>
<th>Healthy Comparison Subjects (n = 26)</th>
<th>Adjusted Difference</th>
<th>95% CI of Difference Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior frontal gyrus</td>
<td>-0.2 (6.6)</td>
<td>-0.8 (4.9)</td>
<td>-3.1 to 3.2</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate gyrus</td>
<td>11.6 (15.6)</td>
<td>8.4 (20.0)</td>
<td>-13.9 to 6.7</td>
<td></td>
</tr>
<tr>
<td>Orbital frontal region</td>
<td>-5.8 (15.3)</td>
<td>-7.2 (14.5)</td>
<td>-11.0 to 7.5</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-0.4 (9.0)</td>
<td>-4.9 (8.3)</td>
<td>-9.4 to 0.5</td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>2.3 (8.2)</td>
<td>8.7 (8.3)</td>
<td>1.8 to 11.3§</td>
<td></td>
</tr>
</tbody>
</table>

*Asymmetry index, given as mean (SD), was computed using the formula: [(right − left)/(right + left)] × 100. OCD indicates obsessive-compulsive disorder; CI, confidence interval.
†Adjusted for age.
‡Sample sizes (n) were 24 and 22, respectively.
§P < .01.
aries between adjacent cytoarchitectonic areas. Although this study attempted to use theoretically meaningful sulcal boundaries, it is important to acknowledge that the size of architectonic fields can vary considerably among individuals and even among hemispheres of the same individual, and that these variations may not always map neatly onto the sulcal anatomy of the cortex.65-67

In summary, these results complement our previous MRI investigation68 by identifying pathological involvement of additional brain regions in OCD. Future morphometric studies in OCD should focus on the thalamus, which could not be measured in the present study because of technical limitations of the imaging protocol, and use methods for gray and white matter segmentation of pathophysiologically relevant cortical subregions. An additional goal should be to address the relationship between abnormal structure and function in the same patients.

Accepted for publication June 16, 1999.

This work was supported by a grant from the Obsessive-Compulsive Foundation, Milford, Conn (Dr Szeszko), and grant MH46663-01A2 from the National Institute of Mental Health, Rockville, Md (Dr Robinson). This study was performed in association with The Brain Morphometry and Image Analysis Center of the North-Shore Long Island Jewish Health System, Glen Oaks, NY, supported by a grant from the Helen and Irving Schneider Family.

This study was presented in part at the Meeting of the Society for Biological Psychiatry, Toronto, Ontario, May 28, 1998.

Reprints: Philip R. Szeszko, PhD, Hillside Hospital, Department of Psychiatry Research, 75-59 263rd St, Glen Oaks, NY 11004 (e-mail: szeszko@lij.edu).

REFERENCES

31. Hodges H, Green S, Glenn B. Evidence that the amygdala is involved in benzodiazepine and serotonergic effects on punished responding but not on discrimination, learning, and memory. Psychopharmacology. 1987;92:491-504.