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

Current hypotheses regarding the pathophysiology of obsessive-compulsive disorder (OCD) have emphasized abnormalities in cortical-striatal-thalamic-cortical circuits, and within these circuits the frontal lobes have been regarded as an important area for investigation. In particular, orbital frontal and anterior cingulate regions have been hypothesized to play an important role in producing the symptoms associated with the disorder. Neuropsychological studies have supported the hypothesis of abnormal orbital frontal functioning in OCD. The strongest evidence for dysfunction of these brain regions, however, comes from functional imaging studies, which have identified hypermetabolism during base-line conditions and symptom provocation as well as reduced metabolic activity with treatment. In contrast to orbital frontal and anterior cingulate regions, the evidence for abnormalities in other parts of the frontal lobes has been much less compelling, although some functional imaging studies have also implicated dysfunction of lateral (including superior, middle, and/or inferior) frontal gyri.

Abnormalities in the mesiotemporal lobe may also be important in understanding the repetitive thoughts and behaviors associated with OCD. Amygdalocentric models of OCD are particularly relevant given the amygdala’s involvement in the emotional appraisal of external stimuli and the acquisition and consolidation of conditioned fear and anxiety responses. Moreover, medications that are efficacious in the treatment of OCD (eg, serotonergic reuptake inhibitors) and in alleviating the concomitant anxiety associated with the disorder (eg, benzodiazepines) have been shown in animal studies to exert their effects on receptors in various amygdaloid nuclei. Consistent with these notions are the results from several functional imaging studies that have implicated amygdala pathology in OCD.

Abnormalities in other parts of the mesiotemporal lobe, such as the hippocampus, have also been implicated in the pathophysiology of OCD. Moreover, the cybernetic models proposed by Gray and Pitman both posit that the hippocampus plays important, albeit different roles, in compulsive behavior.
SUBJECTS AND METHODS

SAMPLE SELECTION

This study included the same subjects as our previous MRI study of patients with OCD and healthy comparison subjects in different parts of the frontal lobes and in mesiotemporal-limbic structures of patients with OCD, these regions have not been well investigated using magnetic resonance imaging (MRI). Several MRI studies reported no significant differences between patients with OCD and healthy comparison subjects in either frontal or mesiotemporal lobe brain structure volumes. In contrast, one study identified increased anterior cingulate gyrus volume in neuroleptic-naive pediatric patients with OCD compared with healthy control subjects.

Given the importance of frontal lobe and mesiotemporal-limbic regions to pathophysiologic hypotheses of OCD, we investigated whether patients with OCD had volumetric abnormalities of these brain structures using MRI scans obtained from our previous study. In that study, we found that patients with OCD had reduced volume of the caudate nucleus compared with healthy subjects. The methods for measuring the frontal lobe subregions were developed recently in our laboratory and were therefore unavailable at the time of our original study. We also examined the relationship between frontal and mesiotemporal-limbic structure volumes and measures of illness duration.

Desired evidence for functional abnormalities in different parts of the frontal lobes in mesiotemporal-limbic structures of patients with OCD, the hippocampus was measured from the level where the ascending fornix (i.e., surrounding pulvinar) was interrupted to the slice posterior to the mammillary 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.

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 Depression Rating Scale score was 22.4 ± 6.9 (range, 8-37).
Depression Rating Scale 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-model analyses revealed significant main effects of group for orbital frontal (F{sub}1,47 = 5.64, P = .02) and amygdala (F{sub}1,47 = 6.60, 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 (F{sub}1,47 = 4.18, P = .06) such that patients with OCD had significantly reduced right amygdala volume compared with healthy comparison subjects (mean volume = 1321 cm{sup 3}) and healthy comparison subjects (mean volume = 1324 cm{sup 3}). 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, but 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 to investigate the potential effects of these variables on significant findings. Mean values are given with SDs.
with OCD had significantly less asymmetry in amygdala ($F_{1,40} = 10.11, P = .003$) and hippocampus ($F_{1,40} = 5.38, P = .02$) 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 ($F_{1,22} = 6.91, P = .02$).

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-
tural 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.39 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 our study, however, is that Grachev et al.39 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.40 reported no group differences in amygdala volume using the same OCD and healthy comparison groups as the study by Grachev et al.39 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 Sanides56 may provide a useful framework in which to interpret the findings of reduced orbital frontal and amygdala volumes. According to Sanides,56 6-layered isocortex in the frontal lobes develops from 2 primordial moieties: hippocampal (“archicortical”) and olfactory (“paleocortical”). The archicortical trend includes the hippocampal formation, cingulate gyrus, and dorsal prefrontal cortices, whereas in the paleocortical trend cortical development is hypothesized to originate in the olfactory cortex and has higher phases of development in peri-insular, temporal polar (ie, amygdala), and ventral neocortices (ie, orbital frontal cortex). Results of Sanides’ early studies have since been supported by modern cytoarchitectonic data, including anatomical studies of both long- and short-range connectivity patterns, and by patterns of laminar organization.57,58 Thus, the amygdala and orbital frontal cortical regions can be considered part of a trend in brain development deriving from an olfactory (ie, paleocortical) moiety.57,58,59 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,9,14,21 this finding was consistent with previous MRI investigations in adults with OCD, which have also yielded negative findings.39,60 One possible explanation for our negative finding could be related to the lack of sensitivity of our MRI measure for detecting subtle neuronal loss or other abnormalities specifically in 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.60

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 gestation61,62 and both hormonal and genetic influences probably contribute to this effect.63,64

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>Table 2. Mean Asymmetry Indices*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
</tr>
<tr>
<td>Anterior cingulate gyrus</td>
</tr>
<tr>
<td>Orbital frontal region†</td>
</tr>
<tr>
<td>Hippocampus</td>
</tr>
<tr>
<td>Amygdala</td>
</tr>
</tbody>
</table>
| *Asymmetry index, given as mean (SD), was computed using the formula: 

\[
\frac{(right − left)/(right + left)}{2} \times 100. \text{ OCD indicates obsessive-compulsive disorder; CI, confidence interval.}
\]

†Adjusted for age.

‡Sample sizes (n) were 24 and 22, respectively.

§P<.01.

©1999 American Medical Association. All rights reserved.
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.

In summary, these results complement our previous MRI investigation 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 11040 (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 discrimi- nation. Psychopharmacology. 1987;92:491-504.

©1999 American Medical Association. All rights reserved.