Reduction of Orbital Frontal Cortex Volume in Geriatric Depression

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Background: Postmortem studies have documented abnormalities in the medial orbital frontal cortex in depressed patients. In this study we evaluated whether atrophy of this region can be identified in older depressed patients using magnetic resonance imaging.

Methods: Twenty elderly patients meeting DSM-IV criteria for major depression and 20 matched control subjects were studied. The orbital frontal cortex was measured in both hemispheres using magnetic resonance imaging.

Results: Depressive patients had reduced volume in the total orbital frontal cortex, right orbital frontal cortex, and left orbital frontal cortex.

Conclusions: Our finding of a reduction in orbital frontal cortex volume in both sides of the brain suggests that this region of the brain may have a critical role in the development of depression and raises questions about the etiology of the changes.

Key Words: Depression, orbital frontal cortex, neuroimaging, circuit, aging, neuropsychology

Introduction

Our group and others have described a putative neuroanatomic circuit for depression. The structures in this circuit include the amygdala, basal ganglia, and prefrontal cortex (Byrum et al 1999; Drevets 1999; Drevets et al 1999). A prior study by Coffey et al (1993) suggested that prefrontal volume is reduced in depressed patients. Drevets et al (1997) noted a reduction of regional cerebral blood flow (rCBF) and metabolism and reduction of the subgenual prefrontal cortical volume in familial forms of depression but no loss of neurons (Drevets et al 1997; Ongur et al 1998). In unmedicated subjects with primary depression Baxter et al (1989), Drevets et al (1992, 1995b), and Ebert et al (1991) have noted increased rCBF in the posterior orbital cortex. Metabolism and rCBF have also been noted to increase in these areas during experiments that induce sadness or anxiety in healthy subjects (Drevets et al 1995a). Treatment appears to reduce rCBF and metabolism in the euthymic phase relative to the depressed phase in these patients in this region (Nobler et al 1994). The relationship between depression severity and metabolic activity in this region is complex in that severity of depression appears to be inversely correlated with the blood flow and metabolism in this region (Nobler et al 1994). In more ill patients, rCBF and metabolism have been shown to be decreased rather than increased in these regions of the brain (Mayberg et al 1990).

Anatomic changes of this region have also been examined in postmortem studies of the brain. In the medial orbital prefrontal cortex and the dorsolateral prefrontal cortex a reduction in cortical thickness and smaller sizes of neuronal cell bodies were noted (Rajkowska et al 1999). The greatest reduction was noted in layer 2. Glial density was also reduced in the orbital frontal cortex (OFC; Rajkowska et al 1999). Despite these multiple imaging and postmortem studies, there is remarkably little literature available on neuroanatomic changes in vivo in this part of the prefrontal cortex.

In this study we evaluated the medial prefrontal cortex in patients with depression from our clinical research center and compared it with a group of control subjects. We hypothesized that, compared with age-matched elderly control subjects, older depressive patients would have smaller volumes of the OFC.

Methods and Materials

Subjects

All subjects were participants in the National Institute of Mental Health (NIMH) Mental Health Clinical Research Center (MHCRC) for the Study of Depression in Later Life, located at Duke University. The MHCRC operates in a naturalistic treatment milieu and screens for both incident and prevalent cases. Inpatients and outpatients of the Duke University Psychiatric Service presenting with clinically significant depressive symp-
toms or a previous diagnosis of mood disorder were screened with the Center for Epidemiologic Studies Depression Scale (Radloff 1977). All enrolled subjects were 60 years or older. Exclusion criteria included 1) another major psychiatric illness, such as bipolar disorder, schizophrenia, and schizoaffective disorder; 2) active alcohol or drug dependence; 3) primary neurologic illness, such as dementia, stroke, Parkinson’s disease, seizure disorder, and multiple sclerosis; 4) medications or medical illness that may affect cognitive function; 5) physical disability that precludes cognitive testing; and 6) metal in the body that precludes magnetic resonance imaging (MRI). Patients were excluded if they had dementia or suspected dementia at baseline. Study geriatric psychiatrists clinically examined all subjects, performed a standardized neurologic examination, reviewed medical records, and conferred with referring physicians for all patients. Although most MHCRC subjects have baseline Mini Mental State Examination (MMSE; Folstein et al 1975) scores above 25, some severely depressed patients have scores below 25. The MHCRC protocol is to observe such patients through an acute (8 week) phase of treatment to determine if cognition improves. Subjects whose MMSE scores remain below 25 are not observed longitudinally in the MHCRC. Thus, in the clinical judgment of study geriatric psychiatrists, dementia is effectively excluded at or close to baseline in all elderly depressed MHCRC subjects.

DSM-IV diagnoses were assigned to all subjects by a consensus diagnostic conference that included a board-certified or board-eligible psychiatrist, using procedures conforming to the Longitudinal, Expert, and Available Data standard (Spitzer 1983) and informed by screening data, the Duke Depression Evaluation Schedule (DDES), and the clinical data listed above (George et al 1989). All patients met DSM-IV criteria for major depression.

The purpose of the MHCRC and its procedures were explained to each patient, and those who provided written informed consent were enrolled. At baseline, all enrolled subjects underwent an MRI scan of the brain, using standardized procedures. A trained interviewer administered the DDES to each subject. The DDES, a composite diagnostic interview instrument, includes sections of the NIMH Diagnostic Interview Schedule (Robins et al 1981) assessing depression, enriched with items assessing sleep problems and the clinical features of melancholia and psychosis, dysthymia, mania, and alcohol abuse or dependence (Krishnan et al 1997). The DDES also includes the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979), the MMSE (Folstein et al 1975), the Global Assessment Scale (Endicott et al 1976), items assessing self-reported physical health, four subscales of the Duke Social Support Index (George et al 1989; Landerman et al 1989), and a scale assessing frequency and severity of stressful life events during the year preceding the interview (Landerman et al 1989).

Control subjects were recruited from the Aging Center Subject Registry at Duke University, which includes a listing of over 1900 community-dwelling elders in the Durham/Chapel Hill and Raleigh areas who have expressed a willingness to participate in Duke Aging Center research. Registry subjects may be selected by race, gender, age, and socioeconomic strata. Eligible control subjects had a nonfocal neurologic examination, no self-report of neurologic or depressive illness, no evidence of a depression diagnosis based on the Diagnostic Interview Schedule portion of the DDES, and no other Axis I psychiatric disorders.

Subjects of this study were from the MHCRC, 20 cases and 20 control subjects matched on age at enrollment (within 5 years). The aims of this study were to compare the difference in volumes of the OFC between the depressed patients and healthy control subjects and to investigate the relationship of the volume of OFC and age of onset, MADRS, and MMSE.

Magnetic Resonance Imaging

MRI Acquisition. All subjects were screened for the presence of cardiac pacemakers, neurostimulators, metallic implants, metal in the orbit, aneurysm clips, or any other condition where MRI is contraindicated. Subjects were imaged with a 1.5-T whole-body MRI system (Signa, GE Medical Systems, Milwaukee) using the standard head (volumetric) radio frequency coil. Padding was used to immobilize the head without causing discomfort. The scanner alignment light was used to adjust the head tilt and rotation so that the axial plane lights passed across the canthomeatal line and the sagittal lights were aligned with the center of the nose. Reference standards consisting of water with added contrast agent to obtain T2 values of approximately 80 msec and 120 msec were included within the field of view on the left and right sides of the head. A rapid sagittal localizer scan was acquired to confirm the alignment.

High-Resolution Imaging for Volume Measurements. A dual-echo fast spin echo acquisition was obtained in the axial plane for morphometry. The pulse sequence parameters were repetition time = 4000 msec, echo times = 30 and 135 msec, 32-kHz imaging bandwidth, and echo train length = 16, with a 256 × 256 matrix, 3-mm section thickness, and one excitation per phase-encoding increment, 20-cm field of view. Saturation of spins outside the imaging volume (standard gap 15 mm) was employed to minimize artifacts due to flowing blood and cerebrospinal fluid. The images were acquired in two separate acquisitions with a 3-mm gap between sections for each acquisition. The second acquisition was offset by 3 mm from the first so that the resulting data set consisted of contiguous sections.

MR Image Processing

The MR images were transferred to the Neuropsychiatric Imaging Research Laboratory (NIRL), located at Duke University Medical Center, for processing on SUN (Sun Microsystems, Palo Alto, CA) workstations. Dual-echo images, consisting of proton density– and T2-weighted images, were used for all processing. Volume measurements were made using a NIRL-modified version of MRX Software, which was created by GE Corporate Research and Development (Schenectady, NY) and originally modified by Brigham and Women’s Hospital (Boston) for image segmentation.

MRX Procedures (for Whole Brain, Cerebral Hemispheres, and Orbitofrontal Gyri). Our basic segmentation protocol is a modified version of that developed by
Kikinis et al (1992) and has been described previously (Byrum et al 1996). Once the brain was segmented into tissue types and the nonbrain tissue stripped away through a masking procedure, specific regions of interest were assessed using tracing and connectivity functions. The cerebral hemispheres and orbitofrontal gyri (OFG) were traced and a mask was created that could be applied to the segmented brain.

**DEFINITION OF THE OFG.** The following borders were used for the OFG tissue (see Figure 1):

- **Inferior border.** Began with first appearance of frontal lobe tissue as one moves superiorly from the base of the brain on consecutive axial slices. At the most inferior level, there is no connection between OFG and the rest of the brain, and all of the OFG tissue is included.

- **Lateral and posterior borders.** As one moves superiorly, the limen insula (temporal stem) appears connecting OFG and temporal lobes. The posterior boundary of OFG was determined by the anterior appearance of the circular insular sulcus. If the cistern at the medial frontotemporal notch was 20 or more pixels across, then lines were drawn from the circular insular sulcus to the lateral end of the cistern on each hemisphere. If the cistern was less than 20 pixels across, then a line was drawn joining the circular insular sulci of each hemisphere. The entire lateral extent of the frontal lobe was included until the superior border was reached.

- **Superior border.** To determine the superiormost slice to include in OFG, each hemisphere was assessed separately. If the cerebrospinal fluid of the olfactory sulcus plus the gray matter extending posteriorly from the sulcus was at least three fourths of the OFG length (anterior to posterior), OFG were included on that hemisphere.

**CALCULATION OF VOLUMES.** The final step was to run a summarizing program that calculated the volumes of each tissue type within each region. Volumes were determined for the whole brain, cerebral hemispheres, and OFG. Only OFG gray matter was included in the OFC volumes presented here.

**TRAINING AND RELIABILITY.** All technicians received extensive training by experienced volumetric analysts. Reliability was established by repeat measurements on multiple MR scans before raters were approved to process study data. Intraclass correlation coefficients were left cerebral hemisphere = .99, right cerebral hemisphere = .99, left OFC = .96, right OFC = .90, and total OFC = .94.

**Statistical Analyses**

Two separate statistical analyses were conducted:

1. The mean total volume of the OFC, mean right volume of the OFC, mean left volume of the OFC, standardized total OFC (total OFC/total cerebral hemispheres), standardized right OFC (right OFC/total cerebral hemispheres), and standardized left OFC (left OFC/total cerebral hemispheres) between the depressed and control groups using the general linear models (GLM) procedure of SAS Software (Cary, NC). Linear regression was used with GLM. Data are described as means ± SDs.

2. In the patient group, Pearson correlation matrices were used to evaluate the relationship between the OFC and age of depression onset, MADRS score, and MMSE score.

**Results**

As shown in Table 1, the gender and race of the depressive patients and healthy control subjects were not statistically significantly different, except healthy control subjects were, on average, about 5 years older at time of MRI. Many depressive patients had long histories of depression, with mean age of onset of depression about 45 years. Depressed patients were, on average, moderately depressed at baseline, as indicated by a mean MADRS score of 23. The mean number of previous hospitalizations of the depressive patients was 2.75, ranging from 0 to 6 times. Half of the patients had been thinking about suicide. Four patients had history of psychotic depression. Fifteen patients were taking antidepressants at time of enrollment.
One patient had depression for 1 month and 19 patients had depression for between 6 and 12 months at enrollment. Nine patients had onset of depression after the age of 50. The range of previous depressive episodes was 0 to “20 or more,” the latter reported in two cases.

Past history of alcohol or substance abuse or dependence was ruled out in control subjects during enrollment. One patient had past alcohol abuse, and one patient had past alcohol dependence.

The mean score of MMSE in patients was 28.35 ± 6.44. The ranges of MMSE were from 20 to 30 at baseline.

Table 2 shows that depressive patients demonstrated reduced volume compared with control subjects in total OFC, right OFC, and left OFC. After adjustment to percentage of total cerebral hemispheres (total OFC/total cerebral hemispheres, right OFC/total cerebral hemispheres, left OFC/total cerebral hemispheres), depressive patients had significantly reduced volume in total OFC, right OFC and left OFC, relative to control subjects. We used linear regression to covary for age and gender. The differences in total OFG, right OGF, left OGF, corrected total OGF, corrected right OGF, and corrected left OGF between cases and control subjects were still statistically significant. No significant correlations were observed between MADRS scores, MMSE scores, or age of onset, and these volumes.

Discussion

Our main finding of a significant reduction in the OFC brain volumes of patients as compared with control subjects is consistent with the hypothesis that this region of the brain is involved in depression. It is also quite consistent with postmortem studies that demonstrate a reduction in thickness and reduction in size of neurons, neuronal cell bodies, and glial density in this region of the brain (Rajkowska et al 1999).

The findings contribute to the growing evidence that the orbital cortex is critically involved in affective disorders. Previous rCBF and metabolic studies demonstrated increased metabolism in milder patients and decreased metabolism in more ill patients. Serotonin depletion produces rCBF changes and metabolic changes in these same regions of the brain (Bremner et al 1997). It is also consistent with Mayberg’s study reporting reductions in orbital cortex metabolism in Parkinson’s patients with depression relative to nondepressed Parkinson’s patients (Mayberg et al 1990). Numerous studies have suggested that the pyramidal cells of the orbital cortex play a role in extinguishing unreinforced responses to appetitive stimuli (Rolls 1995). This probably involves an interaction with the amygdala and other limbic structures. Neuropsychologic analysis of humans with orbital cortex lesions has demonstrated impaired performance on tasks evaluating emotional performance (Angrilli et al 1999). Subjects also exhibited difficulty shifting intellectual strategies in response to changing demands and perseveration. These studies are concomitant and consistent with findings in animal studies (Rolls et al 1994). Our study may be limited by small sample size, although our significant finding is noteworthy for such a relatively small sample. The mismatch on age, though slight, was significant; however, the fact that control subjects were older would likely bias against our finding a significant difference, making our results even more
striking. This adds to the growing evidence that the neuroanatomic circuit involved in depression involves the medial OFC besides the other structures implicated in the circuit—namely, the amygdala, basal ganglia, and the thalamus. Further research is needed to determine the relationship between these changes and the pathogenesis of depression as well as the mechanisms by which these changes could predispose to depression.

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References


