

# Reduced Volume of Orbitofrontal Cortex in Major Depression

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**Background:** *Functional neuroimaging studies have implicated dysfunction of orbitofrontal cortex in the symptoms of depression, and a recent postmortem study of depressed patients found reduced density of neurons and glia in this area. The purpose of this study was to measure volume of orbitofrontal cortex and other frontal cortical subregions in patients with major depression.*

**Methods:** *Magnetic resonance imaging was used to measure volume of the orbitofrontal cortex and other frontal cortical regions in patients with major depression in remission (n = 15) and comparison subjects (n = 20).*

**Results:** *Patients with depression had a statistically significant 32% smaller medial orbitofrontal (gyrus rectus) cortical volume, without smaller volumes of other frontal regions including anterior cingulate Brodmann's area 24 (subgenual gyrus), anterior cingulate Brodmann's area 32, subcallosal gyrus (Brodmann's area 25), or whole brain volume. The findings were significant after statistically controlling for brain size.*

**Conclusions:** *These findings are consistent with smaller orbitofrontal cortical volume in depression.* Biol Psychiatry 2002;51:273-279 © 2002 Society of Biological Psychiatry

**Key Words:** Frontal cortex, depression, stress, MRI

## Introduction

Major depression affects 15% of the population at some time in their lives and is associated with considerable morbidity and loss of economic productivity. Understanding the neural correlates of depression may be helpful in the development of treatments for this disorder. Neuroimaging of brain structure and function in patients with depression has developed as a promising tool for the assessment of neural correlates of depression. Studies have

used assessment of both brain structure (in earlier studies measured with computed tomography and more recently with magnetic resonance imaging [MRI]) and function (measured with positron emission tomography [PET] or single photon emission tomography [SPECT] measurement of blood flow or metabolism) in the study of patients with depression.

These studies have been most consistent in demonstrating dysfunction of the prefrontal cortex in depression (George et al 1994). Decreased blood flow and metabolism was shown in several areas of prefrontal cortex in patients with depression, including dorsolateral prefrontal cortex (Buchsbaum et al 1984; Baxter et al 1989; Hurwitz et al 1990; Martinot et al 1990; Ebert et al 1991; Austin et al 1992; Bench et al 1992; Mayberg et al 1994; Biver et al 1994; Mann et al 1996), medial prefrontal cortex/anterior cingulate (Brodmann's areas [BA] 24, 32 and 25) (Bench et al 1992; Drevets et al 1997; George et al 1997; Mayberg et al 1997), and orbitofrontal cortex (Mayberg et al 1990; Mayberg et al 1992; Ring et al 1994). We found that experimentally induced depressive relapse provoked by a tryptophan depleting drink, which lowers brain serotonin levels, was associated with decreased function in dorsolateral prefrontal and orbitofrontal cortex (Bremner et al 1997). Treatment of depression resulted in a reversal of these deficits and/or was related to baseline function in these regions (Baxter et al 1989; Martinot et al 1990; Ebert et al 1991; Wu et al 1992; Goodwin et al 1993; Ebert et al 1994; Rubin et al 1994; Scott et al 1994; Nobler et al 1994). These findings implicated dysfunction of prefrontal cortex in depression, including dorsolateral prefrontal, anterior cingulate, and orbitofrontal cortex.

Studies using structural imaging in depression have not consistently looked at frontal cortex. Early studies using computed tomography in patients with bipolar disorder found ventricular enlargement and widening of the cortical sulci (Pearlson and Veroff 1981; Kellner et al 1986; Andreasen et al 1990). Magnetic resonance imaging studies in patients with unipolar depression showed abnormalities in subcortical white matter (Krishnan et al 1992; Aylward et al 1994), and some studies (Husain et al 1991; Krishnan et al 1992), but not others (Aylward et al 1994; Bremner et al 2000), showed smaller volume of caudate. Magnetic resonance (MR) imag-

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ing studies showed smaller right hippocampal volume (Swayze et al 1992) and temporal lobe volume (Altschuler et al 1991) in bipolar patients, and alterations in hippocampal T1 relaxation time (reflective of changes in water content) (Krishnan et al 1991) with reductions in gray matter in the left temporal lobe (Sha et al 1998) in unipolar depression. Some studies (Sheline et al 1996; Bremner et al 2000) found reduction in hippocampal volume in unipolar depression, while studies in various affective disorders found larger volume of the amygdala (Bremner et al 2000; Altschuler et al 1998; Stratowski 1999; Tebartz van Elst et al 1999) (although, see Sheline et al 1998), which may explain the finding of no change in combined amygdala/hippocampal volume in unipolar depression (Axelson et al 1993). Studies in elderly patients with depression found an increase in subcortical white matter lesions on T2-weighted MR (Pantel et al 1997; Krishnan et al 1988). Most studies of prefrontal cortical structure have examined whole prefrontal cortical volume (Narayan et al 1999). Kumar et al (1997; 1998) demonstrated a reduction in whole prefrontal cortical volume in late onset depression, although other studies in late onset (Pantel et al 1997) and midlife (Bremner et al 2000) depression did not find a significant difference in whole frontal cortical volumes. One study of subregions of frontal cortex published to date found a reduction in volume of an area of the anterior cingulate (BA 24) (subgenual gyrus) (Drevets et al 1997). A review of this research suggests that additional studies are needed to look at structural changes in subregions of prefrontal cortex identified in functional imaging studies of depression.

Recent postmortem studies have been consistent with morphologic changes in the prefrontal cortex in depression. One study looked at the same frontal cortical regions (dorsolateral prefrontal cortex and medial orbitofrontal cortex [gyrus rectus]) identified in our study using functional brain imaging in depression, and found a decrease in density of neurons and glia in these areas (Rajkowska et al 1999). Other studies have found reduced density of glia (but not neurons) in anterior cingulate (BA 24) (subgenual area) (Ongur et al 1998). Until recently, there have been no neuroimaging studies to examine volume of the orbitofrontal cortex in patients with depression. Lai et al (2000) recently reported a reduction in orbitofrontal cortical volume in patients with geriatric depression. The purpose of this study was to measure volume of the orbitofrontal cortex and other prefrontal subregions in middle-aged patients with major depression and controls. We hypothesized smaller volume of the orbitofrontal cortex in midlife patients with unipolar depression.

## Methods and Materials

The study sample consisted of 15 patients with a history of depression based on the Structured Interview for DSMIV (SCID)

(Spitzer et al 1987) currently treated on an outpatient basis with antidepressant medication (paroxetine, fluoxetine, or desipramine). All subjects provided written informed consent for participation as approved by a local IRB. Patients were excluded if they had a history of meningitis, traumatic brain injury, neurologic disorder, loss of consciousness of greater than 10 min, HIV-positive status, current alcohol or substance abuse, or lifetime schizophrenia based on the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) or shrapnel or other foreign bodies which would preclude MRI scanning. In addition, patients with a history of posttraumatic stress disorder (PTSD) or current medication use other than antidepressant were excluded. Depressed patients had an average of three (4 SD, range 0–10) inpatient hospitalizations, were in remission from depression for 30 weeks (35 SD, range 6–120), and had an average of two (3 SD, range 0–10) prior episodes of depression. Comparison subjects ( $n = 20$ ) were healthy subjects selected to be similar to the patients for gender, age, years of education, and handedness. Five of 15 (33%) patients were female and 10 of 15 (66%) male; nine of 20 (45%) comparison subjects were female and 11 of 20 (55%) male. There were no differences between patients and controls in age (43 [8 SD] vs. 45 [11], years of alcohol abuse [4 (7 SD)] vs. 2 [4 SD], or years of education [14 (2 SD)] versus 15 [2 SD]). Seven percent of patients had past histories of alcohol dependence, 20% past alcohol abuse, and 13% past polysubstance abuse. Seven percent of patients had current panic disorder without agoraphobia. All subjects gave written informed consent before participation.

Magnetic resonance (MR) images were obtained and analyzed using methods previously described in detail (Bremner et al 1995; 2000). Magnetic resonance images were obtained using a protocol of 3 mm contiguous slices on a 1.5 Tesla General Electric Signa device (General Electric, Milwaukee, WI), with a spoiled GRASS (gradient recall acquisition in the steady state) sequence with TR = 25 msec, TE = 5 msec, NEX (number of excitations) = 2, matrix  $256 \times 256$ , field of view = 24 cm. Images were transferred through computer network to a Sun Sparc Workstation (Sun Microsystems, San Jose, CA), where volumetric measurements were performed using the ANALYZE program (Mayo Foundation, Rochester, MN). Volumetric assessments were made of prefrontal cortical regions outlined in Table 1. Anatomically based criteria derived from the Duvernoy (1991) Atlas were developed for subregions of frontal cortex for the purposes of this study, including orbitofrontal cortex (gyrus rectus) (Figure 1), and specific subregions of anterior cingulate (BA 24 (Figure 2), 25, and 32). The boundaries of dorsolateral prefrontal cortex are difficult to define and volumetric assessment was not included in this study of this region. The development and reliability of these MR-based measurements were previously reported in detail (Bremner et al 1998). In the current study, we performed all measures on coronal images. Anterior cingulate-BA 25 (subcallosal gyrus) was defined as the gray matter area in medial prefrontal cortex in all slices anterior to anterior commissure extending to last slice in which internal capsule is visible. Anterior cingulate-BA 24 (subgenual gyrus) is the first full gyrus visible from superior to inferior in medial prefrontal cortex measured between most anterior extension of internal capsule and most anterior extension of corpus callosum

Table 1. Volume of Prefrontal Cortical Regions in Major Depression and Controls

	Major depression ( <i>n</i> = 15)	SD	Comparison subjects ( <i>n</i> = 20)	SD	Percent difference	<i>F</i> Value <sup>a</sup>	<i>p</i> Value
Orbitofrontal cortex (gyrus rectus)	338	125	495	230	-32	5.65	.02
Subcallosal gyrus (BA 25)	464	294	395	147	17	1.34	.25
Anterior cingulate (BA 24)	588	296	634	262	-7	.23	.63
Anterior cingulate (BA 32)	6317	1114	6837	2118	-8	.74	.39
Whole brain	1266035	144942	1233333	152098	3	.41	.52

BA, Brodmann's area.

Volumes expressed in cubic mm.

<sup>a</sup> *df* = 1,33

visualized in the coronal plane. Anterior cingulate-BA 32 is the second full gyrus visible from inferior to superior in medial prefrontal cortex measured in the first three slices anterior to the most anterior extension of corpus callosum visualized in the coronal plane. Gyrus rectus is all gray matter in medial prefrontal cortex inferior to a line drawn connecting the most superior extension of the left and right medial orbital sulci measured between the most anterior extension of the internal capsule and the most anterior extension of corpus callosum visualized in coronal plane. Results for prefrontal regions on interrater reliability as measured with the intra-class coefficient (ICC) where 0 represented no agreement and 1 represents perfect agreement between two raters were as follows: gyrus rectus (ICC = .86;  $p < .05$ ); anterior cingulate-BA 25 (subcallosal gyrus) (ICC = .67;  $p < .05$ ); anterior cingulate-BA 24 (subgenual gyrus) (ICC = .68;  $p < .05$ ). These data showed good agreement between raters for these subregions of prefrontal cortex. Interrater reliability for anterior cingulate-BA 32 was not assessed, but this area was found to be more unreliable because of the heterogeneity between subjects in the number of gyri separating superior frontal gyrus from anterior cingulate, therefore results from this area should be interpreted with caution.

Analysis of variance (ANOVA) was used to compare prefrontal cortical volumes between patients and controls. Multiple linear regression was used to examine the relationship between prefrontal cortical volume and diagnosis while controlling for whole brain volume.

## Results

Patients with major depression had 32% smaller volume of the medial orbitofrontal cortex (gyrus rectus) compared with controls which was statistically significant based on analysis of variance (ANOVA) (Table 1; Figure 1; Figure 2). This difference was also seen after controlling for differences in whole brain size using ANOVA with whole brain volume added as a factor in the analysis ( $F = 6.77$ ;  $df = 2,32$ ;  $p < .05$ ). There were no differences in size of other prefrontal cortical regions measured in this study, including subcallosal gyrus (BA 25), anterior cingulate BA 24 (subgenual gyrus) (Figure 3), or anterior cingulate BA 32 (Table 1). There were no differences between patients and controls in whole brain volume.

There was no correlation between orbitofrontal cortical

volume and clinical variables, including number of weeks in remission, number of prior episodes of depression, or number of hospitalizations for depression. When potentially confounding factors including age, years of education, and years of alcohol abuse were entered into the model, there continued to be a difference in orbitofrontal cortical volume between patients and control subjects.

## Discussion

Patients with remitted major depression in this study showed a 32% smaller volume of the orbitofrontal cortex (gyrus rectus) in comparison with control subjects. There were no differences in volumes of other subregions of prefrontal cortex, including subcallosal gyrus (BA 25), anterior cingulate-BA 24 (subgenual gyrus) or BA 32, or in whole brain volume. We have previously reported no difference in volume of the entire prefrontal cortex in patients with major depression relative to controls (Bremner et al 2000).

These findings are congruent with our prior functional imaging studies of depression and postmortem studies of

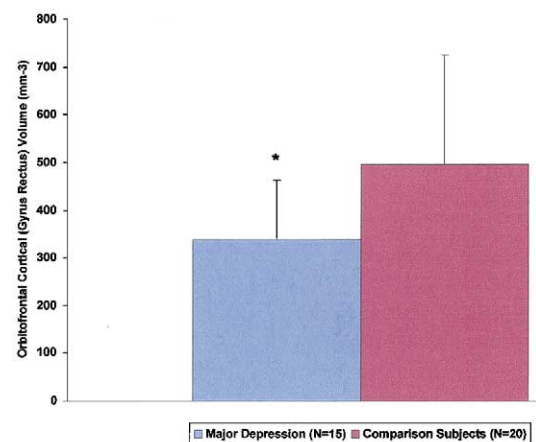


Figure 1. Orbitofrontal cortex (gyrus rectus) volume in patients with major depression ( $n = 15$ ) and controls ( $n = 20$ ). There was a statistically significant 32% reduction in orbitofrontal cortical volume in the patients with depression relative to the controls.

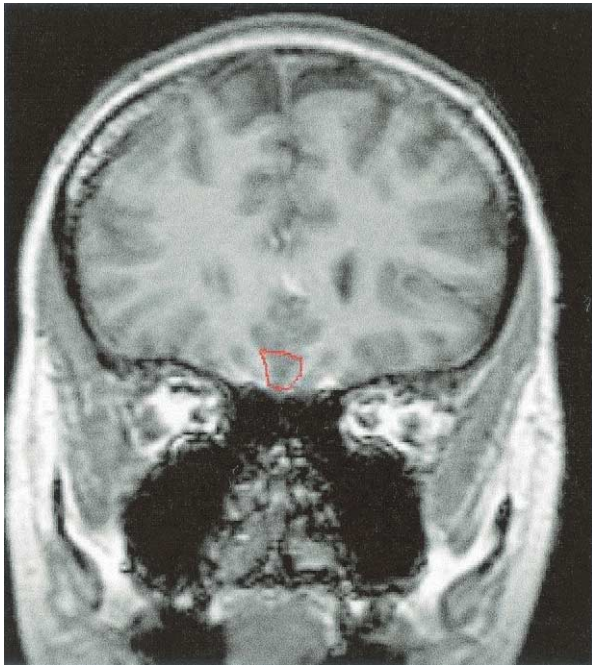


Figure 2. Coronal MRI showing the outline of the gyrus rectus. The gyrus rectus is outlined in red in this single coronal MR image. In the current study, gyrus rectus was defined as all gray matter in medial prefrontal cortex inferior to a line drawn connecting the most superior extension of the left and right medial orbital sulci measured between the most anterior extension of the internal capsule and the most anterior extension of corpus callosum visualized in the coronal plane. MRI, magnetic resonance imaging.

brain morphology. In our prior PET study, we found a decrease in orbitofrontal cortical metabolism with depressive relapse in the same area implicated in the current study of morphology (Bremner et al 1997). Since that prior study used a within-subjects design, the findings suggest that alterations in orbitofrontal metabolism are not related to a partial volume effect secondary to volume loss. Subsequent postmortem studies in patients with depression found a decreased density of neurons and glia in orbitofrontal cortical areas adjacent to those implicated in our prior PET study and the current MR study (Rajkowska et al 1999). In the current study, we measured volume of the gyrus rectus, while our PET findings of reduced orbitofrontal cortical metabolism with tryptophan depletion-induced depressive relapse (Bremner et al 1997) included gyrus rectus and adjacent medial orbital gyrus. Rajkowska et al (1999) examined more posterior (rostral) portions of orbitofrontal cortex and the lateral and middle orbital gyri. Nevertheless, all of these studies involved assessments of orbitofrontal cortex and there is no evidence to support the idea that different regions of orbitofrontal cortex serve different functions. The findings of the current study of reduced orbitofrontal cortical volume are

also congruent with a recent report by Lai et al (2000) of reduced orbitofrontal volume in geriatric depression (the current study assessed midlife depression). In summary, the findings are consistent with alterations in orbitofrontal cortical structure and function in patients with depression, and suggest that these deficits underlie at least in part symptoms of depression.

There are several regions of frontal cortex that are of interest in the pathophysiology of depression. Vogt et al (1992) have differentiated the anterior cingulate portion of frontal cortex from other areas of prefrontal cortex including orbitofrontal cortex. Anterior cingulate (moving from superior to inferior) includes BA 32 (which commonly activates with the Stroop task), area 24 (described as subgenual area, due to its location below the genu, or "knee," of the corpus callosum), and area 25 (also known as subcallosal gyrus, due to its location below the corpus callosum). Inferior to the anterior cingulate and immediately above the eyes (hence its nomenclature) is the orbitofrontal cortex. Gyrus rectus and medial orbital gyrus are two gyri that lie adjacent to each other and are the most medial structures of this area; lateral orbital gyrus is lateral to these structures. In the PET study and anatomical study described above, this medial portion of orbitofrontal cortex was implicated in depression. In the current study, gyrus rectus was measured as it is easily and reliably identified and measured.

There are several possible explanations for our findings

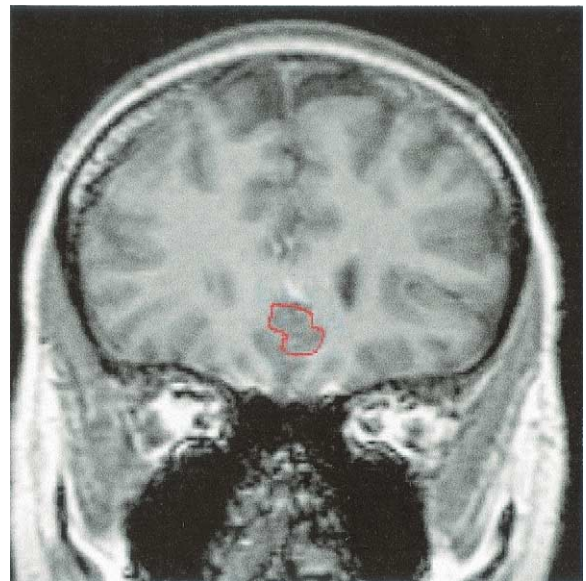


Figure 3. Coronal MRI showing the outline of BA 24 (subgenual gyrus) (outlined in red) as defined in this study. Anterior cingulate-BA 24 (subgenual gyrus) is the first full gyrus visible from superior to inferior in medial prefrontal cortex measured between most anterior extension of internal capsule and most anterior extension of corpus callosum visualized in the coronal plane. BA, Brodmann's area; MRI, magnetic resonance imaging.

of orbitofrontal cortical volume reduction in depression. The study of Rajkowska et al (1999) mentioned above suggests that reduced density of neurons and glia in patients with depression contributes to smaller volume of orbitofrontal cortex. Rajkowska (2000) has hypothesized that atrophy of neurons in this region may contribute to volumetric reductions in patients with depression. The exact mechanism of this volume loss is unclear; however, the capacity for neurogenesis was recently demonstrated in the prefrontal cortex (Gould et al 1999), and in other brain areas (hippocampus), stress and elevations in glucocorticoids were associated with both neuronal atrophy and inhibition of neurogenesis (McEwen et al 1992; Sapolsky 1996; Gould et al 1998; Bremner 1999). Patients with depression have elevations in glucocorticoids during depressive episodes; therefore these studies suggest a model for how depression could lead to neuronal loss in orbitofrontal cortex, although this has not been investigated for orbitofrontal cortex. It is also possible that individuals born with smaller volume of the orbitofrontal cortex, or who have damage related to, for example, perinatal injury, may be at increased risk for depression, possibly through a causal effect of smaller structural changes in orbitofrontal cortex mediating symptoms of depression.

The orbitofrontal cortex belongs to the medial and anterior portions of prefrontal cortex, felt to play a role in emotional and visceral regulation. Damage to the prefrontal cortex, specifically medial prefrontal cortex including the anterior cingulate, anteromedial prefrontal cortex, and orbitofrontal cortex, results in deficits in emotion, mood, and social regulation, while cognition remains intact (Damasio et al 1994). In addition, the well-known blunting of affect following frontal lobotomy, which involves lesions primarily of orbitofrontal cortex, suggests a role for this area in the regulation of emotion and mood. Lesion studies in animals show that the medial prefrontal cortex (including orbitofrontal cortex) plays an important role in regulation of emotional responses through inhibitory inputs to the amygdala (Morgan et al 1993). In addition, through connections with other brain regions such as thalamus, caudate, and hippocampus, orbitofrontal cortex may mediate symptoms of depression, including blunting of emotional affect and impaired social functioning. We previously reported a correlation between magnitude of increase in depressive symptoms with tryptophan depletion and decreased orbitofrontal cortical metabolism, which indicates that orbitofrontal cortical dysfunction may play a causal role in the development of depressed mood. Alternatively, smaller orbitofrontal cortical volume present at birth could confer an increased vulnerability or risk for the development of depression.

Unlike prior reports, we did not find a smaller volume

of the anterior cingulate BA 24 (subgenual gyrus) in depression (Drevets et al 1997). This may be related to differences in patient populations or other factors. The current study had a small sample size. The findings of the current study should be replicated in future samples with larger numbers of subjects, including patients without treated depression.

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