Article

Subgenual Prefrontal Cortex Volumes in Major Depressive Disorder and Schizophrenia: Diagnostic Specificity and Prognostic Implications

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Objective: A variety of findings have implicated the portion of the anterior cingulate cortex ventral to the corpus callosum in the pathophysiology of familial depressive disorder. There are, as yet, few data to address the specificity of these abnormalities to depressive disorders or to characterize their stability over time.

Method: The authors studied 10 subjects who were judged to have had major depressive disorder with psychotic features, who underwent magnetic resonance imaging (MRI) protocols, and who participated in a longitudinal study of recent-onset psychosis. These were group-matched to 10 subjects with schizophrenia and to 10 well comparison subjects. Volumetric measures were made of the posterior and anterior portions of the subgenual prefrontal cortex for these 30 subjects. Followup scans done an average of 4 years after intake were available for seven subjects with major depressive disorder, nine subjects with schizophrenia, and five well comparison subjects.

Results: Volumes of the left side of the posterior subgenual prefrontal cortex differed significantly by group and were smallest for the group with psychotic major depressive disorder. Volumes of the anterior subgenual prefrontal cortex did not differ significantly by group. Patients with major depressive disorder were more likely to show increases in posterior subgenual prefrontal cortex volume on follow-up than were comparison subjects or patients with schizophrenia.

Conclusions: These findings add to the evidence that abnormalities in the subgenual region of the anterior cingulate play a role in at least some types of mood disorder.

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A convergence of findings indicates that the subgenual prefrontal cortex has particular importance among the various brain structures thought to play a role in depression. Positron emission tomography (PET) studies have demonstrated increased blood flow in this area when sadness is induced in non-ill subjects (1–3), and such changes are particularly marked in depressed patients (4). Lesions of this area block the extinction of fear conditioning in animal studies (5), and in humans the area is thought to be important in the evaluation of the consequences of social behavior (2). It may thus play a role in the heightened selfcriticism and pessimistic ruminations that characterize depressive episodes (6).

PET studies of depressed patients at rest have likewise found abnormalities in the left subgenual prefrontal cortex (6–9). Resting flow abnormalities in this area have characterized depressed patients who were recovered (10) and, in particular, those who then relapsed with tryptophan depletion (11).

Five studies have compared the volumes of the subgenual prefrontal cortex in depressed patients to those in matched comparison subjects. Three found the former to have significant volumetric deficits in the left subgenual prefrontal cortex, ranging from 19% to 48% of the values for the comparison subjects (12–14). The study that reported the largest difference between patients and comparison subjects was restricted to patients with familial pure depressive disorder (12). This diagnosis requires that one or more first-degree relatives have major depressive disorder and that none have alcoholism or antisocial personality (15).

Another of these three studies compared patients with affective disorder who had a family history of affective disorder both to those who lacked such a history and to patients with schizophrenia, and that study found that the abnormality was confined to the group with familial affective disorder (14). Bremner et al. (16) described a nonsignificant 7% reduction in subgenual prefrontal cortex volume but did not characterize the subjects by family history and did not compare left and right sides separately. Kegeles et al. (17) did confine their study group to subjects with a positive family history but found no difference in subgenual volumes on either side.

Also relevant is a volumetric study of depressed patients ages 9–17 years that measured the medial prefrontal cortex, a structure that includes the subgenual prefrontal cor-

Characteristic	Healthy Comparison Subjects (N=10)		Patients With Psychotic Major Depression (N=10)		Patients With Schizophrenia (N=10)	
	Ν		Ν		Ν	
Sex						
Male	6		6		6	
Female	4		4		4	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	22.1	6.0	21.9	4.9	22.2	4.2
Parental social class ^a	2.7	0.5	2.9	0.3	2.5	0.7
Duration of illness at baseline evaluation (years)			4.7	5.7	5.8	6.0

TABLE 1. Demographic Characteristics and Illness	s Duration of Patients Wit	h Psychotic Depression,	Patients With	Schizo-
phrenia, and Healthy Comparison Subjects				

^a According to the Hollingshead Index of Social Position.

tex (18). Subjects with familial major depressive disorder, but not those who lacked a family history of affective disorder, had volumes of the left medial prefrontal cortex that were significantly lower than those of comparison subjects.

Two reports have provided evidence that the structural abnormality of the subgenual prefrontal cortex is stable over time. In one of these studies (13), patients with firstonset depression had the same degree of volumetric reduction as did patients who had had recurrent episodes. Another (12) found no change when patients were rescanned after a 3-month interval, regardless of whether their symptoms had resolved.

The analysis described in this article drew from an existing pool of subjects who underwent baseline magnetic resonance imaging (MRI) scans, thorough diagnostic assessments, and a prospective follow-up. Its purposes were to further test the diagnostic specificity of deficits in the volume of the left subgenual prefrontal cortex to major depression and to determine whether that specificity is stable over a follow-up of years rather than months.

The group with major depressive disorder was confined to individuals with mood-congruent or mood-incongruent psychotic features rather than to those with a positive family history of depression. Earlier studies have shown that many patients in episodes of familial pure depression have evidence of hypothalamic-pituitary-adrenal (HPA) axis hyperactivity as manifested in abnormal results on the dexamethasone suppression test (19–21). High proportions of patients with psychotic depression likewise show evidence of HPA axis hyperactivity (22). Because abnormalities in the subgenual prefrontal cortex are likely to affect hypothalamic functioning, we predicted that the volumetric deficits described in familial depressive disorder should manifest as well among depressed patients who have psychotic features.

Method

Subjects

All the subjects described were enrolled in the Iowa Longitudinal Study of the Outcome of Early Psychosis (23) at the University of Iowa Mental Health Clinical Research Center (24). The database included 10 patients who, after the completion of baseline assessments, were judged to have major depressive disorder with psychotic features and who underwent MRI protocols using a 1.5-T scanner. Participation in the longitudinal study required that the subjects had been first hospitalized no more than 5 years prior to intake and that they were no older than 35 years. The 10 subjects were group-matched by age, sex, handedness, and parental socioeconomic status to 10 subjects with DSM-III-R schizo-phrenia and to 10 healthy comparison subjects (Table 1).

Diagnostic Assessment

Raters trained to a requisite level of reliability used the Comprehensive Assessment of Symptoms and History (25) to interview participants. Item ratings integrated the subjects' responses with information from informants and from medical records. Senior medical staff considered this information in consensus diagnostic meetings held shortly after admission and again at discharge. Final diagnostic determinations thus reflected repeated assessments during the course of the index hospitalization.

Image Processing

MR data were processed on Silicon Graphics workstations (Silicon Graphics, Mountain View, Calif.) by using locally developed software, BRAINS2 (26). The T₁-weighted images were spatially normalized and resampled to 1.0-mm³ voxels so that the anteriorposterior axis of the brain was realigned parallel to the anterior commissure-posterior commissure line and the interhemispheric fissure aligned on the other two axes. The T2- and proton-densityweighted images were aligned to the spatially normalized T₁weighted image. The data sets were then segmented by using the multispectral data and a discriminant analysis method based on automated training class selection (27). Tissue-classified images were processed by using the BRAINSURF program (28), which generates a visual map and quantitative measures of brain surface anatomy. The segmented image was used to extract a trianglebased polygonal model of an iso-surface by using a threshold of 130. This represented pure gray matter and corresponded to the parametric center of the cortex. The triangulated surface was used as the basis for our calculations of cortical area (in square millimeters), depth (in millimeters, representing an average value for the entire region of interest), and volume (in cubic centimeters) (29).

Definition of Regions of Interest

We adopted the guidelines for topographic segmentation developed in the Iowa Image Processing Laboratory (29) by using an approach that took advantage of simultaneous visualization in three planes to better reflect interindividual variation. This work yielded guidelines for 41 subregions of the cerebral cortex, one of which was designated the subcallosal area.

FIGURE 1. Three-Dimensional Surface Showing the Medial Wall of the Left Cerebral Hemisphere



The subcallosal area overlaps with Brodmann's area 25 and differs from the subgenual prefrontal cortex described by Drevets et al. (12). While both structures lie beneath the genual area of the corpus callosum, the area described by Drevets et al. is the more anterior portion and the subcallosal area is directly posterior. For simplicity, the following will refer to the subcallosal area as the posterior subgenual prefrontal cortex. The anterior subgenual prefrontal cortex, the subgenual prefrontal cortex described by Drevets et al., begins at the coronal plane defined by the rostral extreme of the genu of the corpus. From this plane, proceeding caudally, the anterior subgenual prefrontal cortex is traced on each consecutive coronal slice with the corpus callosum as the superior boundary and the cingulate sulcus as the inferior boundary. The posterior boundary of the anterior subgenual prefrontal cortex is a coronal plane defined as the last slice before the internal capsule is first visualized. This plane then is also the anterior boundary of the posterior subgenual prefrontal cortex. The posterior subgenual prefrontal cortex was traced in each consecutive coronal slice with the inferior border of the corpus callosum as the superior boundary and the medial border of the straight gyrus (gyrus rectus) as the inferior boundary. The posterior subgenual prefrontal cortex extends caudally to the natural limit of the gyrus (Figure 1).

We predicted that subjects with psychotic major depression would have lower mean volumes of both the anterior and posterior subgenual prefrontal cortex than would either the normal comparison subjects or the subjects with schizophrenia. A finding of smaller anterior volumes would replicate earlier results (12–14). We anticipated similar, if not greater, volumetric differences for the posterior subgenual prefrontal cortex because of its extensive overlap with Brodmann's area 25 and because of evidence that this area has the heaviest projections to the medial hypothalamus (30–32).

Reliability

The interrater reliability for the anterior subgenual prefrontal cortex was performed on a set of 10 brains separate from the data set. The intraclass R coefficient for this region was R=0.96 for the

left side and R=0.91 for the right side. The posterior subgenual prefrontal cortex region was developed locally. Thus, this region was available on a set of 10 "gold standard" brains to determine interrater reliability. The intraclass R coefficient for the right side was R=0.92 and for the left side was R=0.92.

For the current analysis one of the authors (W.C.) reviewed all follow-up assessments for the 10 patients initially thought to have major depressive disorder with psychotic features and for the matching patients with schizophrenia. This review showed all of the subjects to be diagnostically stable on follow-up with the exception of two of the depressed subjects, who developed manic episodes following their index hospitalizations and thus proved to have bipolar type I affective disorder.

Follow-Up

Follow-up assessments took place at 6-month intervals and were conducted with the Psychosocial Status You Currently Have on Follow-Up (PSYCH-UP), an instrument adapted from the Longitudinal Interval Follow-Up Evaluation (33). As with the baseline assessments, the follow-up ratings integrated information from the direct interview of the subject with that from medical records and from informants when this was available. The PSYCH-UP uses the scores on the Global Assessment Scale (GAS) (34) as an index of overall severity of illness. Scores were calculated as the worst level that the subject maintained for at least 1 week in each of the previous 6 months. These six GAS scores were then summed and averaged for each follow-up GAS score.

To quantify changes over time in gray matter amounts, we determined the absolute difference between the baseline MRI measure and the last available MRI measure. A change was assigned a positive or negative value if the measure had increased or decreased, respectively.

Data Analysis

Group comparisons for the baseline and follow-up volume measures used analyses of covariance (ANCOVAs) with diagnostic group (comparison versus depression versus schizophrenia) as the between-subjects factor and covaried for age and total frontal

TABLE 2. Measures of the Posterior and	Anterior Subgenual Prefr	ontal Cortex in Patients V	Vith Psychotic Depression,
Patients With Schizophrenia, and Health	y Comparison Subjects		

	Hea Comparisc (N=	Healthy Comparison Subjects (N=10)		Patients With Psychotic Major Depression (N=10)		Patients With Schizophrenia (N=10)	
Brain Region and Measure	Mean	SD	Mean	SD	Mean	SD	
Anterior subgenual prefrontal cortex							
Adjusted volume ^a of right side (mm ³)	321	87	301	158	288	53	
Adjusted volume ^a of left side (mm ³)	333	134	315	117	268	79	
Posterior subgenual prefrontal cortex							
Adjusted volume ^a of right side (mm ³)	487	181	366	151	440	175	
Left side							
Adjusted volume ^a (mm ³) ^b	509	251	424	189	621	229	
Area (mm ²)	110	65	94	36	134	48	
Depth (mm) ^c	4.9	0.6	3.7	0.4	4.0	0.7	

^a Adjusted for age and total frontal lobe volume.

^b Significant difference among groups (F=3.8, df=2, 25, p=0.04). Post hoc tests showed a significant difference between the patients with major depression and those with schizophrenia (t=2.6, df=25, p=0.02).

^c Significant difference among groups (F=8.9, df=2, 25, p=0.002). Post hoc tests showed significant differences between the patients with major depression and the comparison subjects (t=4.2, df=25, p=0.0003) and between the patients with schizophrenia and the comparison subjects (t=3.1, df=25, p=0.005).

lobe volume. Significant group differences in the main ANCOVA were followed by pairwise comparisons using post hoc t tests. Structure and function relationships were explored by using Spearman partial correlations (correcting for age) between the structural measures and the follow-up GAS score. In order to minimize type I error, the correlational analyses were limited to those regions of interest that differed significantly from those of the comparison group.

Results

Baseline Volumetric Measures

The volumes of the anterior subgenual prefrontal cortex were not significantly different across the groups. The volumes of the left-sided posterior subgenual prefrontal cortex confirmed our predictions that the diagnostic groups would differ and that the patients with psychotic major depression would have the smallest volumes (Table 2). Post hoc pairwise tests were significant only for the comparison between major depressive disorder and schizophrenia, however. The difference in left-sided posterior subgenual prefrontal cortex volumes was explored further by comparing other measures of structure in this region surface area and cortical depth. Although surface area did not differ significantly among the three groups, the depth was substantially less in the major depression group than in the comparison group.

Follow-Up Measures

Follow-up MRI scans were available for five of the comparison subjects, seven of the subjects with major depressive disorder, and nine of the subjects with schizophrenia. Because follow-up intervals differed significantly by diagnosis (Table 3), group comparisons controlled for followup interval as well as for sex and age. According to pairedcomparison t tests, none of the three groups showed a significant change from baseline to follow-up in the volume of the left-sided posterior subgenual prefrontal cortex, and the group ranking by volume on follow-up resembled that at the baseline scan (Figure 2). Moreover, the degree to which the volume increased in the depressed group was unaffected by removal of the two subjects who manifested bipolarity during follow-up. The unadjusted mean increases in volume were 77.4 mm³ (SD=53.1) with these two individuals and 80.1 mm³ (SD=64.7) without them.

The patients with major depressive disorder and those with schizophrenia had mean GAS scores on follow-up of 53.9 (SD=13.6) and 40.4 (SD=3.9), respectively (t=3.0, df= 10.6, p=0.02). The baseline volume of the left-sided posterior subgenual prefrontal cortex did not correlate with the follow-up GAS score for either illness, but for the depressed group the baseline depth of the posterior subgenual prefrontal cortex predicted outcome, such that those with the more abnormal baseline measures had poorer outcomes ($r_s=0.92$, N=7, p=0.01).

The groups differed significantly by the amounts of change in area and depth (Table 3), and only the volume of the subjects with major depressive disorder registered a tendency to increase (Figure 2). Six of the seven patients in the depressed group had volumes that had increased at least somewhat on follow-up, while this was true of only three of the nine subjects with schizophrenia (p=0.051, Fisher's exact test). Increase in volume was significantly correlated with follow-up GAS score for those with major depressive disorder (r_s =0.88, N=7, p=0.02), but there was no relationship between volume change and final GAS score for the schizophrenia group (r_s =0.37).

Discussion

The results did not confirm the predictions regarding the anterior subgenual prefrontal cortex. The group differences did not reach significance, and although the depression group had somewhat smaller volumes than the healthy comparison subjects, the differences were not greater on the left and the schizophrenia group had the smallest volumes bilaterally.

TABLE 3. Change on Follow-Up in Measures of the Left-Sided Posterior Subgenual Prefrontal Cortex in Patien	ts With
Psychotic Depression, Patients With Schizophrenia, and Healthy Comparison Subjects	

Characteristic	Healthy Comparison Subjects (N=5)		Patients With Psychotic Major Depression (N=7)		Patients With Schizophrenia (N=9)	
	N		Ν		Ν	
Sex						
Male	4		3		5	
Female	1		4		4	
	Mean	SD	Mean	SD	Mean	SD
	22.0	6.0	22.2	5.2	22.7	4.2
Age (years)	22.6	6.8	23.3	5.2	22.7	4.2
Follow-up interval (months) ^a	41.6	16.6	66.4	22.6	40.4	13.3
Measures of left-sided posterior subgenual prefrontal cortex						
Change in volume (mm ³)	-41.6	137.6	59.9	76.2	-25.0	98.7
Change in area (mm ²) ^b	-15.5	9.7	13.6	9.6	-11.7	18.7
Change in depth (mm) ^c	-0.409	0.251	0.322	0.421	-0.032	0.201

^a Significant difference among groups (F=4.9, df=2, 18, p=0.02). Post hoc tests showed a significant difference between the healthy comparison subjects and the patients with major depression (t=2.4, df=18, p=0.02) and between the patients with major depression and those with schizophrenia (t=2.9, df=18, p=0.009).

^b ANCOVA controlling for age, sex, and follow-up interval showed a significant difference among groups (R²=0.77; F=7.9, df=2, 13, p=0.006). Post hoc tests showed significant differences between the patients with major depression and the comparison subjects (t=-3.6, df=13, p=0.004) and between the patients with major depression and those with schizophrenia (t=-3.4, df=13, p=0.005).

^c ANCOVA controlling for age, sex, and follow-up interval showed a significant difference among groups (R^2 =0.77; F=20.3, df=2, 13, p=0.0001). Post hoc tests showed that the patients with major depression differed significantly from both the comparison subjects (t=6.4, df=13, p<0.0001) and the patients with schizophrenia (t=3.7, df=13, p=0.003).

FIGURE 2. Volume of the Left Posterior Subgenual Prefrontal Cortex at Baseline and Follow-Up for Patients With Psychotic Depression, Patients With Schizophrenia, and Healthy Comparison Subjects



These analyses did show the predicted relationships between diagnosis and volume of the left-sided posterior subgenual prefrontal cortex. The group with psychotic major depression had the smallest volumes bilaterally, and the group difference was significant for the left side. The post hoc, pairwise analysis revealed a significant difference between the depression group and the schizophrenia group but not between the depression group and the healthy comparison subjects. However, the ratio of the volumes of the depressed and comparison groups, 0.83, was close to the 0.80 reported by Hirayasu et al. (14) and the 0.78 found by Botteron et al. (13) in their comparisons of anterior subgenual prefrontal cortex volumes.

The follow-up group comparisons by volume area and depth were exploratory, in that we had no predictions that one rather than the other would show significant differences. We can consider the three three-way group comparisons of changes in posterior subgenual prefrontal cortex volume, area, and depth to be exploratory, and the p values for changes in area and depth were both smaller than the corrected alpha level of 0.017. We explored relationships between baseline volumetric measures and outcome with the intuitive expectation that greater baseline abnormality in the group with major depressive disorder would be associated with more morbidity on follow-up. We had no predictions for which of the three baseline measures would best show this association, however. Nevertheless, the correlation between baseline depth and later GAS score was in the expected direction and generated a p value less than the alpha of 0.017 adjusted for three exploratory tests. We also expected that the changes in volumetric measures toward the values for the healthy comparison group would be associated with better outcomes. The correlation between volume change and final GAS score was in the expected direction, but the p value was greater than the corrected alpha value.

That the group with psychotic major depression was the only one that showed increases in gray matter area and depth is nevertheless remarkable given the repeatedly described loss of gray matter across the age span among normal individuals. Some studies that have focused on age effects in normal individuals have found linear relationships between age and decreases in gray matter (35, 36), while others have found a curvilinear relationship (37). All described gray matter loss in the prefrontal region for individuals in the age range that characterizes the study group described here. Thus, the healthy comparison group showed qualitatively normal changes in gray matter measures over time. In contrast, the depressed group began the observation period with gray matter depth measures significantly lower than those of the well comparison subjects and then showed an increase in depth over time. Gray matter depth in this area may therefore reflect the ongoing severity of the pathological mechanisms underlying depressive disorder. Gray matter amounts may be smallest when the illness is most active and may then change toward volume restoration to the extent that the underlying illness remits.

The literature is complicated by variance in the use of the term "subgenual" as it applies to the anterior cingulate gyrus. The Drevets group (6), for example, described a portion of Brodmann's area 24, Mayberg et al. (1, 38) consistently referred to Brodmann's area 25 as the subgenual area, and Kegeles et al. (17) included sections of Brodmann's areas 32 and 33 together with Brodmann's area 24. Although the area described by Drevets et al. (6) does not overlap with the area described here, both lie beneath the genu of the corpus callosum and can thus be properly called subgenual. The two areas may play somewhat different roles in affective disorder, however. The posterior subgenual prefrontal cortex overlaps substantially with Brodmann's area 25, the portion of the anterior cingulate with the heaviest projections to and from the medial hypothalamus (30-32). There is now considerable evidence that abnormalities in the medial prefrontal cortex disinhibit the HPA axis (39-41) and that high concentrations of glucocorticoids limit the proliferation of glia in the medial prefrontal cortex. The possibility that this reciprocal relationship may be particularly strong in the posterior subgenual prefrontal cortex is relevant to our findings. Hyperactivity of the HPA axis is more likely in major depressive disorder with psychotic features than in any other subtype of major depressive disorder (22). While familial pure depressive disorder has also been associated with HPA axis hyperactivity (19), a number of studies have failed to confirm this (42–44). The pathophysiology that underlies the volumetric abnormalities in the anterior subgenual prefrontal cortex of patients with familial pure depressive disorder may therefore differ from the process that leads to the lower volumes in the posterior subgenual prefrontal cortex described in the current, psychotic subjects.

Depth was the only baseline measure that significantly distinguished the subjects with psychotic depression from the comparison subjects. The observation that the patients with major depression who differed the most from the well comparison subjects in baseline depth of the pos-

terior subgenual prefrontal cortex were also the ones with the poorest outcome a mean of 5.5 years later raises several possibilities. This measure may reflect a congenital abnormality in the posterior subgenual prefrontal cortex that leaves the HPA axis particularly prone to disinhibition. This propensity to disinhibition would then tend to prolong depressive episodes and shorten symptom-free periods. Cortical depth in this area may, on the other hand, reflect the intensity and persistence of HPA axis inhibition that predated baseline assessment. These are not mutually exclusive possibilities, and both may be operative to differing degrees. The finding that the posterior subgenual prefrontal cortex structural abnormality lessens over time and that volumetric increase correlates with outcome suggests that the anatomical deficits, at least in part, are reversible results of a disease process and are thus dynamic rather than static.

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