Reduced Dorsal and Orbital Prefrontal Gray Matter Volumes in Schizophrenia

Raquel E. Gur, MD, PhD; Patricia E. Cowell, PhD; Amanda Latshaw, BS; Bruce I. Turetsky, MD; Robert I. Grossman, MD; Steven E. Arnold, MD; Warren B. Bilker, PhD; Ruben C. Gur, PhD

Background: Converging neuroanatomic, neurophysiological, and neurobehavioral evidence implicate prefrontal subregions in schizophrenia. Neuroanatomic studies with magnetic resonance (MR) imaging enable regional volume parcellation. Inconsistent reports may relate to variable methods and small samples. We attempted to resolve volume differences within sectors of the prefrontal lobe in a large sample, relating volumes to clinical and neurocognitive features.

Methods: Magnetic resonance imaging was performed in 70 patients with schizophrenia (40 men and 30 women; 29 neuroleptic naive and 41 previously treated) and 81 healthy controls (34 men and 47 women). Gray and white matter volumes of the dorsolateral, dorsomedial, orbitolateral, and orbitomedial prefrontal cortex were quantified. Symptoms, functioning, and neurocognition were assessed concurrently.

Results: Reduced prefrontal gray matter volume was observed in patients. The reduction was evident for the dorsolateral area in men (9%) and women (11%), for the dorsomedial area only in men (9%), and for orbital regions only in women (23% and 10% for lateral and medial, respectively). The reduction of orbital volume in women was associated with poorer premorbid functioning, more severe negative symptoms, and depression. Volume of dorsal cortex was positively associated with better performance on abstraction and attention tasks across all groups.

Conclusions: Schizophrenia is associated with reduced gray matter volume in prefrontal cortex, which affects men and women in the dorsolateral sector. The effects are moderated by sex for dorsomedial and orbital regions and are related to symptom severity and cognitive function. This is not a by-product of treatment, since the differences are evident in neuroleptic-naive patients.

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The Prefrontal cortex is complex and heterogeneous, with subregions varying in cytoarchitecture and connectivity to primary, multimodal association areas and subcortical nuclei.1-4 It modulates cognition, executive functions—abstraction, attention, inhibition, planning, and working memory—motivation, and emotion.1-3 These neurobehavioral domains are aberrant in schizophrenia, leading to examination with structural5-9 and functional neuroimaging.8,12 Human in vivo and post-mortem research has converged with primate findings to elucidate intercellular processes modulating cortical circuitry.1,11-17 Magnetic resonance imaging can parcelize gray matter (GM) and white matter (WM) volumes, addressing feature variability of gyri and sulci.

Morphometric prefrontal studies in schizophrenia differed in magnetic field, scanning parameters, slice thickness and contiguity, image processing, and regions examined. Consequently, findings seem inconsistent, with some researchers noting no differences between patients and control subjects5,18,19 and others observing volume reduction in GM.6,20 WM,7 or both.21,22 Few investigations related subregional volumes to clinical or neurocognitive parameters. Higher right orbitofrontal volume was associated with positive symptom severity in 10 men,23 dorsolateral volume, with performance on abstraction, attention, and memory in 17 patients.24 Sample sizes and partial inclusion of subfrontal regions notwithstanding, these studies support the hypothesis that increased volume is associated with better performance. Sex differences were not examined, but these merit investigation, considering evidence of a more benign presentation and course and greater preponderance of affective symptoms in women.25,26 A previous report from our laboratory found no reduction in frontal lobe...
SUBJECTS AND METHODS

SUBJECTS

The sample included 70 patients with schizophrenia (40 men and 30 women) and 81 healthy controls (34 men and 47 women) from the Schizophrenia Research Center at the University of Pennsylvania School of Medicine, Philadelphia. Participants were right-handed and aged 18 through 45 years. They are a subsample, similar demographically and clinically, for whom we previously reported whole-brain data.28 The DSM-IV29 diagnosis was established using medical, neurologic, and psychiatric (Structured Clinical Interview for DSM-IV-Patient Version [SCID-P]30) evaluations performed by trained research psychiatrists.31 Patients with schizophreniform disorder at entry met criteria for schizophrenia at follow-up. The healthy controls, recruited using advertisements, underwent medical, neurologic, and psychiatric (SCID–Non-Patient Edition [SCID-NP])32 evaluations using established procedures.33 Subjects had no history of a disorder or event that might affect brain function (substance use or dependence, hypertension, cerebrovascular disease, seizure disorder, head trauma with loss of consciousness, or endocrine disorder) (Table 1). There were 29 neuroleptic-naive (16 men and 13 women) and 41 previously treated patients (24 men and 17 women). Clinical assessments, neurocognitive testing, and MR imaging were conducted within a week. After complete description of the study, written informed consent was obtained before participation.

ASSESSMENT

Clinical

Symptoms and functioning were assessed by reliable (intraclass correlation coefficient >0.83) investigators.31 Ratings included the Scale for the Assessment of Negative Symptoms (SANS34), Scale for the Assessment of Positive Symptoms (SAPs35), and the Hamilton Depression Scale (HAM),36 obtained for correlations between mood and orbital prefrontal volume. Functional assessment included the Premorbid Adjustment scale (PAS)37 and Quality of Life Scale (QLS).38 The sample was mildly to moderately impaired (Table 2).

MR IMAGING MEASUREMENTS

Image Acquisition

Magnetic resonance imaging scans were acquired on a 1.5-T scanner (Signa; General Electric Co, Milwaukee, Wis) with a spoiled gradient-recalled pulse sequence using the following parameters: flip angle of 35°, repetition time of 35 milliseconds, echo time of 6 milliseconds, field of view of 24 cm, 1 repetition, 1-mm slice thickness, and no interslice gaps. Transaxial images were in planes parallel to the orbitomeatal line, with resolution of 0.9375 × 0.9375 mm. Images were resliced along the anterior-to-posterior commissural (AC-PC) axis to standardize for head tilt. The axial MR image is rotated according to the AC-PC axis in the transaxial plane, the eyeballs in the coronal plane, and midline in the sagittal plane. Sagittal images are rotated so that the AC-PC axes are oriented to straight horizontal positions. No parenchymal lesions or skull abnormalities were evident neuroradiologically.

Prefrontal Subregions

Subdivisions were derived with neuroradiological and neuroanatomic input, using topographical triangulation and tissue segmentation techniques to maximize the precision and reliability of region delineation. Prefrontal cortex was divided into dorsolateral, dorsomedial, and lateral and medial orbital sectors. Regions were drawn on the sagittal series with 3-dimensional visualization tools (Figure 1).

RESULTS

The MANCOVA showed an effect of diagnosis (F16,130 = 2.09 [P = .005]), indicating that patients had overall smaller prefrontal volumes (Table 3). The main effect for sex was not significant, indicating that after correction for cranial volume, men and women do not differ in prefrontal cortex volume. A within-group main effect was obtained for compartment (F1,145 = 33.55 [P < .001]), GM having higher volume than WM in these regions. A dorsal vs orbital by compartment interaction (F1,145 = 29.74 [P < .001]) indicated that this difference was more pronounced for orbital than for dorsal regions. A compartment by diagnosis interaction (F1,145 = 18.36 [P < .001]) reflected that the reduced prefrontal parenchymal volume in patients was spe-
The prefrontal region for each hemisphere extends from midline to the lateral cortical perimeters. The dorsal and orbital regions are separated by a line drawn at the level of the AC. This dividing landmark is used throughout the mediolateral extent of the frontal lobe. The inferior genu of the corpus callosum at midline marks the posterior border of the dorsal prefrontal region. The posterior border of the orbitomedial region is a line drawn from coordinates determined by the anterior tip of the corpus callosum and the inferior cortical border at the first appearance of caudate. Laterally, the posterior border of this region is a line drawn from the head of the caudate. The posterior border of the orbitolateral region is marked by the caudate and the insula. For dorsal and orbital regions, an axial view of the gray-white segmented image is used to determine the border between the medial and lateral regions; they are divided by the medial-most aspect of cortical GM, which runs along the transverse orbital sulcus at the slice superior to the last view of the medial orbital sulcus.

The dorsal prefrontal region includes the frontal pole and frontomarginal, superior frontal, and anterior sections of the middle and inferior gyri; portions of the anterior cingulate may also be included at midline. The lateral portion of the dorsal region includes the lateral aspects of the Brodmann areas 8, 9, 45, 46, and dorsolateral aspects of area 10. The medial portion of this region corresponds to the medial aspects of areas 8 and 9, dorsal portions of areas 32 and 24, and dorsomedial aspects of area 10. The orbital prefrontal region includes the rectal, medial orbital, and suborbital gyri; the ventral portion of the mesial superior gyrus; and the anterior, posterior, and lateral orbital gyri. The lateral portion of the orbitomedial region includes area 47, lateral portions of area 11, and inferolateral portions of area 10. The medial portion of the orbitomedial region corresponds to areas 12, 23, medial 11, inferomedial 10, and ventral 32 and 24.

Reliability

Two raters (P.E.C. and A.L.) independently parcellated 10 randomly selected cases (5 controls and 5 patients). The unbiased intraclass correlations for the 4 sectors in each hemisphere for GM and WM ranged from 0.88 to 0.98.

Image Processing

Brain volume was extracted by semiautomatically stripping scalp, skull, and meninges using optimal thresholding and morphologic operations previously detailed. The stripped parenchyma was segmented into GM and WM using adaptive Bayesian algorithms.

DATA ANALYSIS

Brain volumes in milliliters were dependent measures in multivariate analyses of covariance (MANCOVA), with diagnosis and sex as grouping factors and region (dorsal vs orbital × lateral vs medial) by hemisphere by compartment (GM and WM) as repeated-measures (within-group) factors. Because patients were about 2 years older, and because age affects brain volume, age was a covariate. Analysis was also performed comparing patients experiencing a first episode with patients treated previously and comparing deficit with nondeficit subtypes. Cranial volume calculated from T2-weighted images and total brain GM volume were also covaried in separate analyses because of sex and diagnosis effects, without altering the findings.

To associate volumes with neurocognition, we correlated GM in subregions with performance on the 6 domains. Two domains, Abstraction-Flexibility and Attention, are hypothesized to relate to prefrontal functioning. This was tested with a Pearson correlation coefficient with a level set at .05. Correlations with the other 4 domains were exploratory, and the P value was Bonferroni-corrected, so that a P value of .01 (.05/4) was considered significant at P = .05. The link between volumes and clinical variables was examined by correlating GM with symptom severity (SANS, SAPS, and HAM) where we had no directional expectations, premorbid function (PAS average) and quality of life (QLS) where higher volumes are expected to correlate with more favorable ratings. Here P values were Bonferroni-corrected using the 5 measures in the denominator so that a P value of .01 was considered significant at P = .05. All P values were 2-tailed.

cific to GM. A dorsal vs orbital by compartment by diagnosis interaction (F1,145 = 7.66 [P = .007]) indicated a disproportionate reduction in patients for the dorsal GM compartment. There were several significant interactions involving diagnosis and sex (Figure 2): for diagnosis by sex (F16,130 = 2.68 [P < .001]), women with schizophrenia showed greater overall reduction than men relative to their healthy counterparts; lateral vs medial by diagnosis by sex (F1,145 = 7.22 [P = .006]), indicated that this sex difference was more pronounced in lateral than in medial prefrontal regions; and dorsal vs orbital by compartment by diagnosis by sex (F1,145 = 4.60 [P = .03]) indicated that for GM, women with schizophrenia showed reduction in dorsal and orbital cortex, whereas men showed reduced volume only in dorsal prefrontal cortex.

Several significant interactions involved hemisphere, indicating the following lateralized effects: hemisphere by diagnosis (F1,145 = 4.40 [P = .04]), hemisphere by diagnosis by sex (F1,145 = 6.59 [P = .01]), dorsal vs orbital by hemisphere by diagnosis by sex (F1,145 = 6.11 [P = .02]), and lateral vs medial by compartment by hemisphere by sex (F1,145 = 5.39 [P = .02]). Follow-up univariate contrasts traced the source of these interactions to the dorsolateral GM, where for women with schizophrenia the reduction was lateralized to the right. Although for healthy people and men with schizophrenia the dorsolateral region is relatively larger on the right, in women with schizophrenia it is symmetrical. No other effects were significant. Analyses within patient groups by neuroleptic status (naive vs previously treated) and by the deficit-nondeficit classification showed no significant effects or interactions.

Within the limited age range, several regions correlated with age. For healthy men, age was associated with...
decreased volume in dorsolateral \( r = -0.49 \) \( P = .003 \) and in dorsomedial \( r = -0.46 \) \( P = .006 \) cortex. In healthy women, the dorsomedial and orbitomedial volumes correlated with age \( r = -0.29 \) \( P = .046 \) and \( r = -0.30 \) \( P = .04 \), respectively. For patients, dorsomedial volume correlated with age for men \( r = -0.38 \) \( P = .02 \) and for women \( r = -0.36 \) \( P = .047 \). This supported covarying age in the correlational analyses, which did not affect significance of reported correlations.

**CORRELATION OF MR IMAGING WITH ASSESSMENT MEASURES**

**Clinical**

Since the differences between patients and controls were in GM, only GM volumes were correlated with clinical measures, reducing the number of statistical tests. Correlations were computed separately for men and women with schizophrenia because of the interactions of neuroanatomic measures with sex. In men, volume did not correlate with any clinical measure. In women, lower volume in the lateral and medial orbital cortex was associated with more severe negative symptoms (SANS) \( r = -0.44 \) \( P = .03 \) and \( r = -0.37 \) \( P = .05 \), respectively and with poorer premorbid adjustment \( r = -0.50 \) \( P = .02 \) and \( r = -0.58 \) \( P = .006 \), respectively. Lower orbitomedial volume was associated with more depressed mood (HAM) \( r = -0.40 \) \( P = .045 \). There were no correlations for men or women between volumes and duration of illness.

**Neurocognitive**

The correlations for healthy men were significant between dorsolateral volume and Abstraction \( r = 0.51 \) \( P = .01 \) and between dorsolateral and dorsomedial volumes and Attention \( r = 0.34 \) \( P = .05 \) and \( r = 0.39 \) \( P = .03 \), respectively. For healthy women, larger volumes of dorsolateral and dorsomedial regions were associated with better Abstraction \( r = 0.44 \) \( P = .002 \) and \( r = 0.40 \) \( P = .02 \), respectively. Exploratory analysis of other neurocognitive domains showed that larger volumes of lateral and medial orbital cortex was associated with better Spatial memory \( r = 0.46 \) \( P = .004 \) and \( r = 0.40 \) \( P = .02 \), respectively, and lateral orbital volume with better Spatial ability \( r = 0.38 \) \( P = .04 \). The correlations between volume and performance were attenuated in men with schizophrenia, and only that between dorsomedial volume and Attention reached significance \( r = 0.33 \) \( P = .05 \). In women with schizophrenia, higher dorsolateral volume was associated with better Attention \( r = 0.40 \) \( P = .04 \). Higher volume of orbitomedial region was associated with better Verbal memory \( r = 0.49 \) \( P = .04 \).

**COMMENT**

High-resolution MR imaging with reliable procedures for examination of prefrontal sectors found that patients with schizophrenia have volume reduction specific to GM, which is more marked in dorsal than in orbital cortex. Reduced prefrontal GM is evident in first-episode neuroleptic-naive patients, confirming observations that neuroanatomic abnormalities manifest at clinical presentation.\textsuperscript{28, 47-49} Our results differ from studies reporting no prefrontal reduction,\textsuperscript{49} reduced WM overall and GM in the inferior region,\textsuperscript{22} and increased right, relative to left, orbital volume in men.\textsuperscript{23} It is difficult to interpret these discrepancies, since the studies vary in the number and demarcation of subregions, imaging parameters, and sample sizes. Differences could be missed in smaller samples using thicker slices. Our volume estimates are comparable with studies for regions that overlap.

The prefrontal cortex contains sectors with distinct anatomic and functional connections.\textsuperscript{1, 14} Postmortem studies report cellular differences between patients with schizophrenia and comparison subjects, including increased neuronal density and decreased cortical thickness, suggesting reduced intraneuronal...
neuropil. This is consistent with MR spectroscopy documenting dorsolateral aberrations of neuronal integrity measures. Our results further demonstrate that prefrontal volume reduction is limited to GM and exceeds the global reduction, as indicated by the covariance analyses that partial out cranial and global GM volumes.

We documented sex differences in the effects of schizophrenia on regional anatomy of prefrontal cortex, which were not hitherto examined with sufficient power. Women with schizophrenia had similar reduction (11%) to men (9%) for dorsolateral prefrontal cortex, supporting the hypothesis that this region is dysfunctional in schizophrenia. However, in women this reduction was lateralized to the right hemisphere. Women also showed smaller reduction (5%) than men (9.0%) for dorsomedial cortex.

In contrast to equal or lesser aberrations in women compared with men with schizophrenia for dorsal cortex, only women showed lower volume in orbitofrontal cortex exceeding the 6% whole-brain reduction (23% and 10% for orbitolateral and orbitomedial, respectively, compared with 0% and 5%, respectively, in men). The impact of lesions in orbital regions on emotional and social behavior has been noted in neurodegenerative disorders and more focal insults. Thus, reduced orbital cortex may relate to the greater preponderance of affective symptoms in women with schizophrenia. This link is supported by the association between lower orbitofrontal volumes and higher depression ratings. Caudal and rostral regions of the orbitofrontal cortex have extensive connections to limbic cortices and the amygdala. Orbifrontal cortex plays a role in emotion and olfactory...
Table 3. Prefrontal Volumes for Patients With Schizophrenia and Healthy Controls*

<table>
<thead>
<tr>
<th>Subregion</th>
<th>Volume, Mean (SD), mL</th>
<th>Controls</th>
<th>Effect Size, Men/Women</th>
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<tr>
<td></td>
<td>Patients</td>
<td>Men (n = 40)</td>
<td>Women (n = 30)</td>
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<tr>
<td>Dorsolateral</td>
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<td>Left</td>
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<tr>
<td>GM</td>
<td>14.1 (2.1)</td>
<td>12.6 (2.0)</td>
<td>15.4 (3.1)</td>
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<td>WM</td>
<td>11.5 (2.6)</td>
<td>9.1 (2.0)</td>
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<td>Right</td>
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<tr>
<td>GM</td>
<td>15.1 (2.3)</td>
<td>12.6 (1.9)</td>
<td>16.4 (3.1)</td>
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<tr>
<td>WM</td>
<td>13.7 (3.3)</td>
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<td>Dorsomedial</td>
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<td>GM</td>
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<td>WM</td>
<td>10.2 (2.5)</td>
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<td>WM</td>
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<td>WM</td>
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</table>

*GM indicates gray matter; WM, white matter.

Figure 2. Mean (± SEM) for gray matter volume of healthy men and women and patients with schizophrenia for lateral and medial aspects of dorsal and orbital prefrontal cortex. HC indicates healthy controls (37 men and 44 women); SCH, patients with schizophrenia (40 men and 30 women).
processes, both showing normal sex differences and impairment in schizophrenia.\textsuperscript{53-56}

Exploratory analyses of correlations between volumes and clinical measures showed associations only in women and only for the orbital regions. This suggests that although dorsal prefrontal reduction occurs in both sexes with schizophrenia, its magnitude is unrelated to clinical severity within the present range of mild to moderate symptoms. However, in women with lateral and medial orbital volume reduction, depressive as well as negative symptoms are relatively more prominent although, as a group, they tend to have less severe negative symptoms.\textsuperscript{25,57} Although these results are tentative and should be interpreted with caution, our study provides a step toward elucidating neural underpinnings of sex differences and encourages further investigation.

Consistent with reports on whole brain measures,\textsuperscript{42,58-62} higher volume of dorsal and orbital cortex were associated with better neurocognitive performance in healthy people and in patients. Similar to the clinical measures, the correlations were stronger for women than for men with schizophrenia. These correlations sustained correction for age and cranial and whole brain volumes. The general similarity of volume and performance correlations for patients and controls indicates that although schizophrenia is associated with reduced volume and performance, it does not alter the fundamental coupling between anatomy and behavior. The results underscore the need to examine the extent to which tissue integrity is necessary for adequate performance. Measures obtained with functional imaging could be limited in accounting for the cognitive deficits unless anatomy is also considered. Nonetheless, our results support neuroimaging, postmortem, and nonhuman primate studies that implicate prefrontal regions in schizophrenia.

We limited the parcellation to major sectors of prefrontal cortex where high reliability can be achieved. The results encourage further evaluation of smaller components. Such studies in large samples will be feasible with more automated procedures using warping algorithms to accommodate variability in the complex sulcal and gyral patterns of cortical regions. Another shortcoming of our study is the limited age range of participants, which does not provide a life-span perspective necessary for accurate evaluation of age effects as they interact with sex. Finally, the cross-sectional design precludes evaluation of change.

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Reprints: Raquel E. Gur, MD, PhD, Neuropsychiatry, University of Pennsylvania, 10th Floor, Gates Bldg, Philadelphia, PA 19104 (e-mail: raquel@bbl.psych.upenn.edu).

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Correction

Error in Figure. In the original article by Gur et al titled “Reduced Dorsal and Orbital Prefrontal Gray Matter Volumes in Schizophrenia,” published in the August issue of the ARCHIVES (2000;57:761-768), the color contents of Figure 2 on page 766 were accidentally omitted when the figure was printed. Figure 2 is reprinted correctly here in black and white. The journal regrets the error.

Figure 2. Means (± SEM) for gray matter volume of healthy men and women and patients with schizophrenia for lateral and medial aspects of dorsal and orbital prefrontal cortex. HC indicates healthy controls (37 men and 44 women); SCH, patients with schizophrenia (40 men and 30 women).