Impact of Normal Sexual Dimorphisms on Sex Differences in Structural Brain Abnormalities in Schizophrenia Assessed by Magnetic Resonance Imaging

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Background: Previous studies suggest that the impact of early insults predisposing to schizophrenia may have differential consequences by sex. We hypothesized that brain regions found to be structurally different in normal men and women (sexual dimorphisms) and abnormal in schizophrenia would show significant sex differences in brain abnormalities, particularly in the cortex, in schizophrenia.

Methods: Forty outpatients diagnosed as having schizophrenia by *DSM-III-R* were systematically sampled to be comparable within sex with 48 normal comparison subjects on the basis of age, ethnicity, parental socioeconomic status, and handedness. A comprehensive assessment of the entire brain was based on T1-weighted 3-dimensional images acquired from a 1.5-T magnet. Multivariate general linear models for correlated data were used to test for sex-specific effects regarding 22 hypothesized cortical, subcortical, and cerebrospinal fluid brain volumes, adjusted for age and total cerebrum size. Sex × group interactions were also tested on asymmetries of the planum temporale, Heschl's gyrus, and superior temporal gyrus, additionally controlled for handedness.

Results: Normal patterns of sexual dimorphisms were disrupted in schizophrenia. Sex-specific effects were primarily evident in the cortex, particularly in the frontomedial cortex, basal forebrain, cingulate and paracingulate gyri, posterior supramarginal gyrus, and planum temporale. Normal asymmetry of the planum was also disrupted differentially in men and women with schizophrenia. There were no significant differential sex effects in subcortical gray matter regions or cerebrospinal fluid.

Conclusion: Factors that produce normal sexual dimorphisms may be associated with modulating insults producing schizophrenia, particularly in the cortex.

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NUMEROUS STUDIES have demonstrated sex differences in the phenomenology and genetic transmission of schizophrenia (see review by Goldstein and Lewine[1]). Although one's sex modifies the phenotypic expression of schizophrenia, there is some debate about whether these differences have etiologic implications.[1] Recent research has begun to examine whether sex differences in brain abnormalities in schizophrenia contribute to explaining the heterogeneous phenotypic illness expression. This is a reasonable expectation, since other neurodevelopmental disorders have shown sex-mediated neurobehavioral and neuroanatomic consequences.[2] One question of interest has been whether sex differences in schizophrenia are similar, but exaggerated, normal sex differences in the brain, or whether one's sex is a risk factor for the illness per se, since there is a slightly but significantly higher incidence among men.[3,4]

Relatively few previous studies have been designed to test for sex differences in structural brain abnormalities in schizophrenia, and there was a tendency among them to find greater abnormalities among the men.[5] Magnetic resonance (MR) imaging and postmortem studies showed that men had larger lateral and third ventricles[6,7] and anterior temporal horn,[8] and smaller medial temporal volume, eg, hippocampus and amygdala,[8,9] Heschl's gyrus,[10,11] superior temporal gyrus,[9,10] and overall frontal[12] and temporal[13] lobe volumes (findings not wholly consistent).[14,15] In addition, more left-lateralized abnormalities among men were reported,[7,8,13] such as smaller volumes of the left planum temporale (PT),[16-19] left Heschl's gyrus,[16] left superior temporal gyrus,[20] and left hippocampus.[8,21] Other abnormalities more likely to be found in men with schizophrenia, eg, greater sulcal volume[22] and smaller thalamic size,[6] suggested somewhat more pervasive brain damage in men than women.[5]

SUBJECTS AND METHODS

SUBJECTS

Cases were recruited from 3 public psychiatric hospitals in the Boston, Mass, area serving primarily psychotic patients.[56-58] The sample included subjects described previously for the cortex[59] and for subcortical regions and cerebrospinal fluid (CSF).[60] Inclusion criteria for recruitment consisted of subjects between the ages of 23 and 68 years at MR imaging, who had at least an eighth-grade education, English as their first language, and an estimated IQ of 70 or more. Exclusion criteria for subjects were substance abuse within the past 6 months; history of head injury with documented cognitive sequelae or loss of consciousness for longer than 5 minutes; neurologic disease or damage; mental retardation; and medical illnesses that significantly impair neurocognitive function. (Only 3 subjects had past substance dependence, and analyses were run with and without them.) Written informed consent was obtained after a complete description of the study was given to the subjects.

Normal comparison subjects were recruited through advertisements in the catchment areas and notices posted on bulletin boards at the hospitals from which the patients were ascertained. They were selected to be proportionately comparable to patients on age, sex, ethnicity, parental socioeconomic status, and handedness. They were screened for current psychopathology by means of a short form of the Minnesota Multiphasic Personality Inventory[61] and family history of psychoses or psychiatric hospitalizations. We excluded potential controls if they had current psychopathology or lifetime history of any psychosis, family history of psychosis, or psychiatric hospitalization, or if any Minnesota Multiphasic Personality Inventory clinical or validity scale score, except Masculinity-Femininity, was above 70.

The case sample consisted of probands with a *DSM-III-R* diagnosis of schizophrenia (n=40), based on the Schedule for Affective Disorders and Schizophrenia[62] and a systematic review of the medical record. Interviews were obtained by masters-level interviewers with extensive diagnostic interviewing experience. Senior investigators (J.M.G. and L.J.S.) reviewed the interview and medical record to determine the consensus, best-estimate, lifetime diagnosis. Blindness of assessments was maintained among MR imaging data and psychiatric status and subject's sex.

Cases had an average age at MR imaging of 45 years and parental education of 12 years (**Table 1**). They were primarily Caucasian, from middle to lower-middle socioeconomic backgrounds, with an average of some college education. Measures of premorbid and current IQ were in the average range. There were no significant differences in age, parental education, ethnicity, parental socioeconomic status, single word reading ability, or handedness by sex. There was a small, but significant, sex difference in IQ and patient education, ie, lower among men, which is typical of schizophrenia.

Patients primarily had undifferentiated or paranoid subtypes (Table 1). All cases were clinically stable, and only 5 of 40 were ascertained as inpatients. They were rated as having mild to moderate negative and positive symptoms, on the basis of the Schedules for Positive and Negative Symptoms[63,64] (Table 1). The patients were a chronically disabled group, as seen in Table 1, and their conditions were maintained with an average chlorpromazine-equivalent neuroleptic daily dose of 600 to 700 mg, not significantly different by sex.

MR IMAGING PARAMETERS AND SEGMENTATION PROCEDURES

The MR images were acquired at the NMR Center of the Massachusetts General Hospital, Boston, with a 1.5-T scanner (Signa; General Electric Co, Milwaukee, Wis). Contiguous 3.1-mm coronal spoiled gradient echo images of the entire brain were obtained by means of the following parameters: repetition time, 40 milliseconds; echo time, 8 milliseconds; flip angle, 50°; field of view, 30 cm; matrix, 256 × 256; and averages, 1. The MR images were processed and analyzed at the Massachusetts General Hospital Center for Morphometric Analysis. Images were positionally normalized by imposing a standard 3-dimensional coordinate system on each 3-dimensional MR image with the use of the midpoints of the decussations of the anterior and posterior commissures, and the midsagittal plane at the level of the posterior commissure, as points of reference for rotation and (nondeformation) transformation.[40,67] Scans were then resliced into the normalized 3.1-mm coronal scans. Positional normalization overcomes potential problems caused by variation in head position across subjects during scanning.

Each slice of the T1-weighted, positionally normalized 3-dimensional coronal scans was segmented into gray and white matter and ventricular structures by

However, recent work with the use of more refined measures of the cortex have reported smaller volumes among women as well as men, depending on the cortical region assessed. Some have reported smaller volumes of heteromodal association areas among women with schizophrenia (eg, dorsolateral prefrontal cortex and superior temporal gyrus[23] and orbital prefrontal cortex[24]). However, others found smaller volumes of superior temporal gyrus in men[10,20,25] and similar abnormalities in men and women in dorsolateral prefrontal cortex.[24] A recent study,[24] which involved a large sample and refined segmentation of prefrontal regions, demonstrated different differences between men and women with schizophrenia compared with their normal counterparts, depending on the particular prefrontal

region assessed. The inconsistencies across studies may be, in part, due to methodologic and sample size differences and to a relative dearth of conceptual models tested in studies of sex differences.

In this study, we propose a heuristic framework for examining sex effects in schizophrenia that we will begin to test indirectly. Our initial premise, based on numerous studies, is that the risk for schizophrenia is initiated during prenatal (especially second and third trimesters) and perinatal development.[26-31] Furthermore, animal studies have demonstrated that the critical early period of the sexual differentiation of the brain, so-called organizational effects of gonadal hormones, also occurs in second- and third-trimester and early postnatal development (for review see

means of a semiautomated intensity contour mapping algorithm and signal intensity histogram distributions. This technique, described in previous reports[40,59,67-69] and illustrated in **Figure 1**, yields separate compartments of neocortex, subcortical gray nuclei, white matter, and ventricular system subdivisions, generally corresponding to the natural tissue boundaries distinguished by signal intensities in the T1-weighted images. The neocortex, defined by the gray-white matter segmentation procedure, was subdivided into bilateral parcellation units, based on the system described by Caviness et al[67] and applied by Goldstein et al[59] to patients with schizophrenia. This is a comprehensive system for neocortical subdivision, designed to approximate architectonic and functional subdivisions, and based on specific topographic anatomic landmarks present in virtually all brains (see detailed anatomic definitions[67,68] and Figure 1). The diencephalon was partitioned into dorsal thalamus and epithalamus above and hypothalamus and subthalamus below by a transaxial plane positioned on the z-axis at the level of the anterior commissure–posterior commissure line, which approximates the diencephalic fissure.[70] The dorsal thalamus was further subdivided along the y-axis into anterior, medial, lateral-anterior, lateral-posterior, and posterior topographic parcellation units, described by Makris et al[70] and applied to schizophrenia by Seidman et al.[60] Volumes, measured in cubic centimeters, were calculated for each brain region by multiplying the slice thickness by the region's area measurements on each slice, and summing all slices on which the region appeared. Very good interrater and intrarater reliability of the cortical, subcortical, and CSF regions has been established in previous studies.[59,67,69] Furthermore, the concurrent, discriminant, and predictive validity of these techniques has been demonstrated in numerous studies of normal subjects and various patient populations.[40,59,69,71-73]

STATISTICAL ANALYSES

Significant interaction effects of sex and group (ie, patients with schizophrenia vs normal control subjects) were hypothesized for cortical regions: middle, medial, and orbital prefrontal cortices; basal forebrain; cingulate and paracingulate gyri; parahippocampal gyrus; posterior parietal cortex (operationalized as supramarginal and angular gyri); and Heschl's gyrus. Subcortical and CSF regions included the hippocampus, amygdala, medial dorsal thalamic nuclei, and basal ganglia. Lateral and third ventricles were also included in the analyses, since earlier studies found significant sex differences (see introduction). We tested the hypothesis that significant sex $\times$ group interactions would be more likely in hypothesized cortical than subcortical or CSF regions. To conduct this 2-group comparison, a normalized summary measure, the absolute value of the t statistic, was calculated for sex $\times$ group interactions for each brain area. This estimated the mean magnitude of a different difference in volumes for female and male cases compared with their normal counterparts. A permutation test[74] was conducted to examine whether the distribution of these 22 standardized scores significantly differed on the basis of the dichotomous grouping. Specifically, a t statistic was calculated by means of the observed 22 scores; the magnitude of this test was compared with 20000 iterations in which the brain regions were randomly regrouped. Under the null hypothesis that there was no difference in the significance of sex $\times$ group effects for the cortical vs subcortical distinction, the observed t statistic was not expected to be extreme when compared with the permutation distribution. We have applied this method successfully to our normal control sample.[36]

Multivariate general linear models for correlated data were also used for cortical and subcortical or CSF regions separately; controlled for age, given a large age range; and total cerebral volume, given that men have larger cerebrums than women. The model was appropriate because tests of normality showed that the brain volumes were, in general, normally distributed. Significance levels were based on P values of .05 or less. Effect sizes,[75] based on volume differences relative to cerebrum size, were estimated as follows: adjusted mean female brain volume minus adjusted mean male brain volume, divided by the pooled SD of male and female volumes. Effect sizes are unaffected by sample size and thus can be compared across studies.

In a separate general linear model for analyses of asymmetries, we tested sex $\times$ group interaction effects on asymmetries of Heschl's gyrus, superior temporal gyrus, PT, and Broca's area, additionally controlled for handedness and handedness $\times$ group interaction effects. The subject had to score 5 of 6 items on the Annett scale, including writing hand, to be considered right- or left-handed. Asymmetries were measured[76] with the use of 2 times left hemisphere volume minus right hemisphere volume divided by left plus right hemisphere volumes. Thus, a positive value represented greater left-sided volume; a negative value, greater right-sided volume; and around 0, symmetry.

Kawata[32]). We thus hypothesized that the organizational effects of gonadal hormones, occurring during the same developmental period as risk factors for schizophrenia, would modify brain abnormalities differentially in males and females who later developed schizophrenia. We hypothesized that the cortex would be more vulnerable to sex-specific brain abnormalities, since animal studies have shown that the cortex has a high density of gonadal hormone receptors only during these early critical periods of development, which then primarily recede postnatally.[33-35] This is an extension of previous findings by our group,[36] in which sex differences in brain volumes in normal adults (subsequently referred to as normal sexual dimorphisms) were more often found in homologous regions in humans that were implicated in animal studies to have a high density of gonadal hormone receptors in these early periods of development compared with regions that had not been so identified. The largest sex differences were in the cortex.[36]

Those findings on normal sexual dimorphisms were consistent with a number of previous imaging and postmortem studies of normal subjects. Compared with men, relative to cerebrum size, women have been found to have relatively larger volumes of Broca's area,[36,37] superior temporal cortex,[36-39] hippocampus,[36,40-42] caudate,[40,42] thalamic nuclei,[42] anterior cingulate gyrus,[36,43] dorsolateral[36,38] and orbital prefrontal[36] cortices, inferior parietal lobe,[36,44] and overall cortical gray matter volume.[36,45] Cell packing density, or number of neurons per unit volume, in the PT was

Table 1. Sociodemographic and Clinical Characteristics of the Men and Women*

	Subjects With Schizophrenia		Normal Control Subjects	
	Women (n = 13)	Men (n = 27)	Women (n = 21)	Men (n = 27)
Age at MR imaging	41.4 ± 7.0	46.6 ± 11.4	39.0 ± 9.9	41.6 ± 11.6
Ethnicity, No. (%) white	12 (92)	25 (93)	20 (95)	24 (89)
Handedness, No. (%) right	10 (77)	21 (78)	18 (86)	26 (96)
Parental SES†	3.0 ± 1.3	3.1 ± 1.1	2.5 ± 0.9	2.6 ± 1.0
Parental education, y	12.4 ± 3.2	11.7 ± 2.8	12.2 ± 2.2	12.1 ± 2.5
Education, y				
Mean ± SD	13.7 ± 2.4	12.4 ± 2.4	14.9 ± 2.3	14.7 ± 2.3
Range	10-18	8-18	11-18	9-18
WRAT reading‡	105.8 ± 9.8	100.6 ± 18.7	105.8 ± 11.9	104.6 ± 11.7
IQ estimate§				
Mean ± SD	106.8 ± 14.0	95 ± 15.7	111.5 ± 14.7	113.4 ± 11.9
Range	86-125	71-132	83-131	89-134
DSM-III-R schizophrenia, No. (%)				
Undifferentiated	4 (31)	14 (52)	. . .	. . .
Paranoid	8 (62)	9 (33)	. . .	. . .
Disorganized	0	4 (15)	. . .	. . .
Catatonic	1 (8)	0 (0)	. . .	. . .
Age at onset, y				
Mean ± SD	25.2 ± 6.7	22.7 ± 5.1	. . .	. . .
Range	16-38	14-36	. . .	. . .
Duration of illness, y	14.1 ± 8.1	18.7 ± 10.4	. . .	. . .
No. of hospitalizations	5.6 ± 4.2	7.7 ± 5.8	. . .	. . .
Chlorpromazine equivalents, mg	689.9 ± 387	617.4 ± 513	. . .	. . .
Positive and negative symptom ratings[63,64]				
Delusions	1.8 ± 2.3	2.2 ± 1.8	. . .	. . .
Bizarre behavior	0.3 ± 0.7	0.6 ± 1.1	. . .	. . .
Formal thought disorder	1.0 ± 1.1	2.1 ± 1.4	. . .	. . .
Hallucinations	1.1 ± 1.7	2.1 ± 1.7	. . .	. . .
Affective flattening	1.8 ± 1.4	1.5 ± 1.1	. . .	. . .
Alogia	1.0 ± 1.0	1.5 ± 1.3	. . .	. . .
Avolition	1.6 ± 1.3	1.3 ± 1.3	. . .	. . .
Anhedonia	2.0 ± 1.3	1.9 ± 1.4	. . .	. . .

*MR indicates magnetic resonance; SES, socioeconomic status; and WRAT, Wide Range Achievement Test–Revised.[65] On the basis of *t* tests or χ^2 tests, there were no statistically significant differences for these characteristics between the sexes within group or between group within sex, except for patient education and IQ estimate (and within patients, diagnostic subtype). Although there was a large range in reading ability, particularly among male patients, sex differences in brain volume abnormalities did not change when controlled for reading. There were also more male left-handed patients; however, analyses controlled for handedness did not change the results.

†Parental SES was measured on the basis of the Hollingshead and Redlich 2-factor scale of mother's and father's education and occupational status. The scale ranges from social class 1 (highest SES) to social class 5 (lowest SES).

‡Single oral word reading ability, measured with the reading test on the WRAT, has been used as an estimate of premorbid IQ.

§IQ estimate was derived from the vocabulary and block design age-scaled scores from the Wechsler Adult Intelligence Scale–Revised short form,[66] as typically reported in other studies.

also greater in women than men.[46] Compared with women, men have been found to have larger volumes, relative to cerebrum size, in the amygdala,[36,41] hypothalamus,[36,47,48] paracingulate gyrus,[36,43] medial prefrontal cortex,[36] and CSF (lateral ventricles[49,50] or sulcal volume[45]). Abnormalities in these brain regions have been implicated in schizophrenia, thus suggesting that normally sexually dimorphic brain regions may be particularly affected in schizophrenia. Thus, we hypothesize that factors affecting normal sexual dimorphisms have implications for understanding brain abnormalities in schizophrenia.

This study will analyze regions that have been found in animal studies to have a high density of sex steroid receptors prenatally and perinatally[33,34,51,52] and found to be abnormal in schizophrenia, which include middle frontal gyrus; frontomedial and fronto-orbital cortices; basal forebrain; anterior, posterior, and paracingulate gyri; insula; parahippocampal gyrus; posterior parietal cortex (an-

gular and supramarginal gyri); primary auditory cortex (Heschl's gyrus); and subcortical regions: amygdala, hippocampus, dorsal medial thalamic nuclei, and the caudate, putamen, and globus pallidus. We hypothesized that significant sex-specific effects in schizophrenia (ie, disturbed normal sexual dimorphisms) would be more likely in cortical than subcortical regions. In exploratory analyses, we were also interested in testing whether sex differences in normal asymmetries, reported in Heschl's gyrus, superior temporal gyrus, PT, and Broca's area,[10,53-55] would be disturbed in schizophrenia.
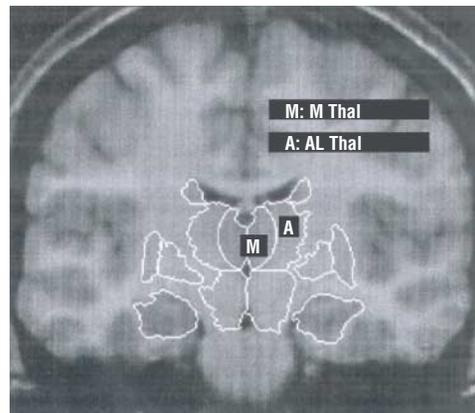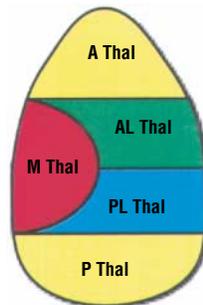
RESULTS

Consistent with numerous studies, the total cerebrum was larger in men than women within both groups, and not significantly different between the sexes across groups. In contrast, the total cortex, relative to cerebrum size, was larger
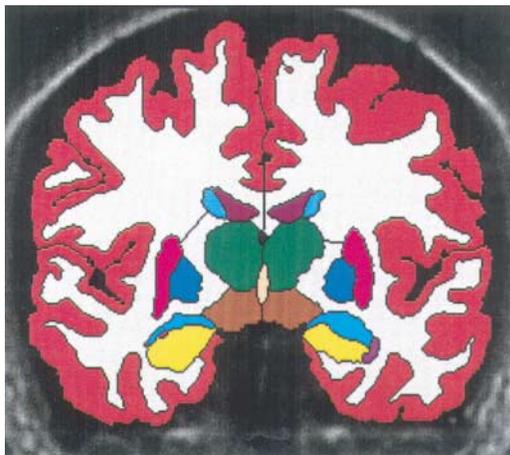
General Segmentation: Sample Coronal Slice
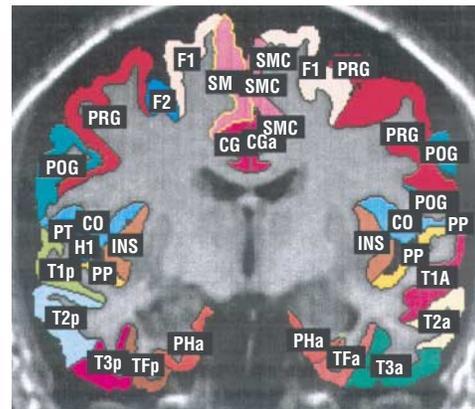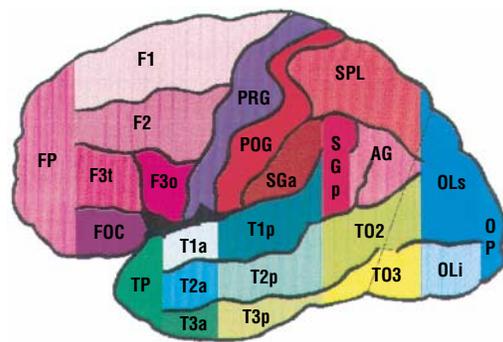
Cortical Parcellation: General Scheme and Sample Coronal Result

Thalamic Parcellation: General Scheme and Sample Coronal Result

Figure 1. Segmentation and parcellation. Cortical abbreviations: AG indicates angular gyrus; BF, basal forebrain; CGa, cingulate gyrus, anterior division; CGp, cingulate gyrus, posterior division; CN, cuneus; CO, central operculum; F1, superior frontal gyrus; F2, middle frontal gyrus; F3t, inferior frontal gyrus, pars triangularis; F3o, inferior frontal gyrus, pars opercularis; FMC, frontomedial cortex; FOC, fronto-orbital cortex; FP, frontal pole; H1, Heschl's gyrus; INS, insula; JPL, juxtaparacentral lobule; OLi, occipital lateral gyri, inferior division; OLs, occipital lateral gyri, superior division; OP, occipital pole; PAC, paracingulate cortex; PCN, precuneus; PHa, parahippocampal gyrus, anterior division; POG, postcentral gyrus; PP, planum polare; PRG, precentral gyrus; PT, planum temporale; SC, subcallosal cortex; SGa, supramarginal gyrus, anterior division; SGp, supramarginal gyrus, posterior division; SMC, supplementary motor cortex; SPL, superior parietal lobule; T1, superior temporal gyrus; T1a, superior temporal gyrus, anterior division; T1p, superior temporal gyrus, posterior division; T2a, middle temporal gyrus, anterior division; T2p, middle temporal gyrus, posterior division; T3a, inferior temporal gyrus, anterior division; T3p, inferior temporal gyrus, posterior division; TFa, temporal fusiform gyrus, anterior division; TFp, temporal fusiform gyrus, posterior division; T02, middle temporal gyrus, temporo-occipital division; T03, inferior temporal gyrus, temporo-occipital division; and TP, temporal pole. Subcortical abbreviations: A Thal indicates anterior thalamic division; AL Thal, anterior lateral thalamic division; M Thal, medial dorsal thalamic division; PL Thal, posterior lateral thalamic division; P Thal, posterior thalamic division; and VentDC, ventral diencephalon. Regarding correction for head tilt, the interpolation used in the positional normalization step is trilinear. Reformatting may cause "interpolation error," ie, attenuation of high spatial frequency in the processed image data. However, measurement of brain regions requires "secondary" segmentation definitions that require the use of anatomically specified "cutting lines." To standardize these anatomic definitions, which are dependent on the orientation of the brain within the data matrix, we force the image data into a common orientation. The "loss" of precision due to interpolation error is less than the "gain" of reliability and reduction of systematic volumetric variability caused by the use of a standard orientation.

Table 2. Brain Volumes, Adjusted for Cerebrum Size, in Men and Women With Schizophrenia and Normal Control Subjects: Sex × Group Interactions and Effect Sizes*

Cortical Brain Regions† (Approximate Brodmann Areas)	Adjusted Volumes, Mean (SD), cm³						
	Normal Control Subjects			Subjects With Schizophrenia			
	Female (n = 21)	Male (n = 27)	Effect Sizes†	Female (n = 13)	Male (n = 27)	Effect Sizes‡	Sex × Group t Test
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		
Total cerebrum volume	86.83 (0.94)	87.03 (0.81)	−0.24	86.98 (0.63)	87.10 (0.97)	−0.14	−0.08
Total cortex volume	53.71 (2.38)	52.15 (2.58)	0.60	52.21 (2.37)	51.41 (1.87)	0.39	−0.59
Posterior cingulate gyrus (23, 32, 26, 29, 30)	1.09 (0.17)	1.01 (0.16)	0.51	1.05 (0.12)	1.13 (0.15)	−0.53	−2.42
Posterior supramarginal gyrus (40)	1.08 (0.35)	0.92 (0.29)	0.51	0.84 (0.23)	0.98 (0.30)	−0.51	−2.25
Basal forebrain	0.27 (0.07)	0.25 (0.08)	0.26	0.22 (0.07)	0.27 (0.08)	−0.68	−2.14
Right planum temporale (42, 40; posterior 22)	0.21 (0.04)	0.21 (0.04)	0.04	0.24 (0.06)	0.19 (0.05)	0.85	1.95
Paracingulate (32)	1.15 (0.11)	1.15 (0.13)	0.05	1.17 (0.11)	1.06 (0.12)	0.84	1.86
Anterior cingulate gyrus (33, 24)	1.21 (0.26)	1.09 (0.19)	0.53	1.02 (0.18)	1.08 (0.26)	−0.26	−1.61
Frontomedial (11, 12)	0.41 (0.09)	0.45 (0.09)	−0.44	0.41 (0.09)	0.39 (0.07)	0.28	1.56
Fronto-orbital (47)	1.35 (0.21)	1.20 (0.18)	0.71	1.24 (0.20)	1.22 (0.19)	0.11	−1.41
Right Heschl's gyrus (41)	0.13 (0.03)	0.13 (0.04)	−0.19	0.13 (0.04)	0.11 (0.03)	0.47	1.33
Angular gyrus (39)	1.01 (0.35)	1.16 (0.36)	−0.39	1.15 (0.30)	1.06 (0.36)	0.26	1.31
Right pars opercularis (44)	0.34 (0.11)	0.32 (0.12)	0.22	0.36 (0.08)	0.28 (0.10)	0.80	1.27
Insula (13, 14, 15, 16)	1.38 (0.12)	1.35 (0.11)	0.24	1.34 (0.08)	1.27 (0.10)	0.72	1.21
Parahippocampal gyrus (anterior 28, 34; posterior 27, 35)	0.84 (0.12)	0.80 (0.10)	0.30	0.80 (0.17)	0.80 (0.11)	0.03	−0.42
Superior temporal gyrus (22)	1.04 (0.13)	1.06 (0.12)	−0.19	1.06 (0.22)	1.06 (0.13)	−0.03	0.33
Middle frontal (6, 8, 9, 46)	2.33 (0.39)	2.18 (0.28)	0.46	2.28 (0.28)	2.09 (0.34)	0.60	0.23
Subcortical/CSF brain regions							
Right amygdala	0.18 (0.03)	0.19 (0.03)	−0.15	0.19 (0.02)	0.21 (0.03)	−0.73	−1.05
Medial dorsal thalamus	0.40 (0.05)	0.38 (0.04)	0.24	0.38 (0.04)	0.39 (0.05)	−0.25	−0.98
Putamen	0.92 (0.11)	0.89 (0.09)	0.26	0.95 (0.11)	0.96 (0.09)	−0.10	−0.70
Third ventricle	0.06 (0.02)	0.08 (0.03)	−0.81	0.09 (0.04)	0.10 (0.04)	−0.25	0.58
Caudate	0.62 (0.07)	0.59 (0.09)	0.42	0.63 (0.06)	0.62 (0.07)	0.19	−0.55
Lateral ventricle	1.30 (0.38)	1.63 (0.57)	−0.63	1.78 (0.63)	2.18 (0.88)	−0.47	−0.51
Pallidum	0.33 (0.03)	0.34 (0.04)	−0.04	0.37 (0.03)	0.38 (0.05)	−0.23	−0.33
Left hippocampus	0.39 (0.04)	0.38 (0.05)	0.23	0.36 (0.05)	0.38 (0.05)	−0.05	−0.19

*Permutation test: P = .004; SE (P) = .0005; 95% confidence interval, .0034-.0052. Overall F test from general linear models for correlated data for sex × group × area interaction in the cortex: $F_{12,87}$ = 2.59, P = .005; for subcortical regions: F = 0.30, P = .95. CSF indicates cerebrospinal fluid.

†The order of the brain regions listed, beginning with posterior cingulate gyrus, is based on the size of the significance of the interaction effects of sex and group (ie, largest effects first).

‡Effect size = [(adjusted mean female brain volume – adjusted mean male brain volume)/pooled SD of male and female volumes]; brain volumes adjusted for total cerebral volume; total cerebrum is adjusted for whole brain volume. Thus, a positive effect size represents larger volumes in women and a negative effect size represents larger volumes in men in normal control subjects or patients with schizophrenia.

in women than men, again regardless of group status (**Table 2**). Overall cortical gray matter in female and male cases compared with their normal counterparts was smaller, with women showing a larger, but nonsignificant, effect size than the men (**Table 3**, effect sizes).

We tested the hypothesis that significant sex × group interactions would be more likely in hypothesized cortical than subcortical or CSF regions. The permutation test[74] (see "Subjects and Methods" section for explanation) showed that only 86 of 20000 iterations yielded a more extreme value than the observed data (P = .004; SE [P] = .0005; 95% confidence interval, .003-.005). Thus, there was a significantly greater likelihood of the presence of a sex × group interaction effect for the cortical regions than the subcortical or CSF regions, which was consistent with the significant overall F test resulting from the general linear model for correlated data for the cortex only (sex × area × group interaction: $F_{12,87}$ = 2.59, P = .005; see Table 3).

As seen in Tables 2 and 3, in which the order of the brain regions was based on the size (ie, largest effects first)

of the significance of the sex × group interaction effects, male patients compared with male comparison subjects had smaller volumes of frontomedial and middle frontal cortices, paracingulate gyrus, insula, Heschl's gyrus, and Broca's area, and larger volumes of the posterior cingulate gyrus and basal forebrain than in female patients compared with their normal counterparts. Female cases compared with female normal subjects had smaller volumes of fronto-orbital cortex, basal forebrain, anterior cingulate gyrus, and posterior supramarginal gyrus, and larger volumes of the angular gyrus and right PT than in men compared with their normal counterparts. The univariate t tests for sex-specific effects were significant (at $P \le .05$) for the cingulate and paracingulate gyri, frontomedial cortex, basal forebrain, posterior supramarginal gyrus, and PT (Table 2). There were no significant sex differences in volumetric abnormalities in the hypothesized subcortical or CSF regions. Sex effects for cortical and subcortical regions are illustrated in **Figure 2**.

In addition, there were no significant sex differences in asymmetries, except for the PT. Consistent

Table 3. Brain Volumes, Unadjusted for Cerebrum Size, in Men and Women With Schizophrenia and Normal Control Subjects: Sex × Group Interactions and Effect Sizes*

| | Unadjusted Volumes, Mean (SD), cm³ | | | | | |
| | Women | | | Men | | |
Cortical Brain Regions† (Approximate Brodmann Areas)	Normal Control Subjects (n = 21) Mean (SD)	Subjects With Schizophrenia (n = 13) Mean (SD)	Effect Sizes†	Normal Control Subjects (n = 27) Mean (SD)	Subjects With Schizophrenia (n = 27) Mean (SD)	Effect Sizes‡
Total cerebrum volume	1021.76 (89.48)	1040.61 (84.39)	−0.19	1113.10 (92.46)	1103.30 (91.61)	−0.08
Total cortex volume	548.81 (54.75)	543.18 (48.83)	0.61	580.10 (52.45)	567.06 (49.40)	0.33
Posterior cingulate gyrus (23, 32, 26, 29, 30)	11.17 (2.00)	10.95 (1.67)	0.28	11.21 (1.91)	12.45 (2.08)	−0.72
Posterior supramarginal gyrus (40)	11.09 (3.78)	8.65 (2.27)	0.74	10.18 (3.29)	10.86 (3.53)	−0.23
Basal forebrain	2.80 (0.73)	2.27 (0.68)	0.78	2.81 (0.85)	3.01 (0.86)	−0.24
Right planum temporale (42, 40; posterior 22)	2.14 (0.47)	2.47 (0.64)	−0.60	2.30 (0.50)	2.13 (0.59)	0.34
Paracingulate (32)	11.79 (1.79)	12.19 (1.83)	−0.15	12.78 (2.02)	11.74 (1.97)	0.63
Anterior cingulate gyrus (33, 24)	12.37 (3.00)	10.54 (1.85)	0.78	12.05 (2.10)	11.82 (2.85)	0.05
Frontomedial (11, 12)	4.21 (1.13)	4.31 (0.91)	−0.06	4.98 (1.01)	4.33 (0.80)	0.66
Fronto-orbital (47)	13.76 (2.37)	12.90 (2.22)	0.51	13.35 (2.13)	13.47 (2.36)	−0.10
Right Heschl's gyrus (41)	1.31 (0.35)	1.31 (0.37)	0.04	1.49 (0.48)	1.22 (0.34)	0.61
Angular gyrus (39)	10.27 (3.52)	11.86 (2.89)	−0.40	12.94 (4.41)	11.81 (4.59)	0.27
Right pars opercularis (44)	3.49 (1.12)	3.75 (0.84)	−0.19	3.50 (1.21)	3.09 (1.14)	0.34
Insula (13, 14, 15, 16)	14.11 (1.79)	13.91 (1.20)	0.41	15.05 (1.66)	13.94 (1.31)	0.77
Parahippocampal gyrus (anterior 28, 34; posterior 27, 35)	8.52 (1.22)	8.30 (1.81)	0.28	8.95 (1.35)	8.75 (1.39)	0.11
Superior temporal gyrus (22)	10.60 (1.62)	11.00 (2.35)	−0.13	11.83 (1.84)	11.72 (1.59)	−0.03
Middle frontal (6, 8, 9, 46)	23.82 (4.45)	23.79 (3.67)	0.14	24.35 (4.32)	23.13 (4.78)	0.30
Subcortical/CSF brain regions						
Right amygdala	1.83 (0.22)	1.99 (0.30)	−0.40	2.06 (0.36)	2.33 (0.29)	−0.83
Medial dorsal thalamus	4.03 (0.57)	3.94 (0.56)	0.37	4.26 (0.57)	4.29 (0.65)	−0.11
Putamen	9.35 (1.30)	9.88 (1.16)	−0.34	9.89 (1.23)	10.57 (0.98)	−0.74
Third ventricle	0.74 (0.21)	1.09 (0.44)	−0.95	1.04 (0.29)	1.28 (0.48)	−0.57
Caudate	6.37 (0.89)	6.55 (0.76)	−0.12	6.56 (1.20)	6.80 (0.86)	−0.35
Lateral ventricle	13.28 (4.18)	18.44 (6.12)	−0.90	17.92 (5.97)	24.05 (9.90)	−0.70
Pallidum	3.40 (0.36)	3.87 (0.34)	−1.12	3.73 (0.57)	4.21 (0.43)	−0.96
Left hippocampus	4.00 (0.33)	3.70 (0.64)	0.76	4.24 (0.49)	3.93 (0.54)	0.50

*Permutation test: $P = .004$, SE (P) = .0005, 95% confidence interval, .003-.005. Overall F test from general linear models for correlated data for sex × group × area interaction in the cortex: $F_{12,87} = 2.59$; $P = .005$; for subcortical regions: $F = 0.30$, $P = .95$. CSF indicates cerebrospinal fluid.

†The order of the brain regions listed, beginnning with posterior cingulate gyrus, is based on the size of the significance of the interaction effects of sex and group (ie, largest effects first).

‡Effect size[75] = [(adjusted mean normal comparison brain volume − adjusted mean schizophrenia brain volume)/pooled SD of normal comparison and schizophrenia volumes]; brain volumes adjusted for total cerebral volume; total cerebrum is adjusted for whole brain volume. Thus, a positive effect size represents larger volumes in normal subjects and a negative effect size represents larger volumes in schizophrenia in men or women.

with previous studies, normal men and women showed larger left- than right-sided PT volumes (mean ± SD, 0.20 ± 0.26 vs 0.17 ± 0.26, respectively; $t_{46} = 0.37$; $P = .71$). Male patients had smaller volumes on the right, resulting in greater leftward PT asymmetry, than male normal subjects (0.25 ± 0.23 vs 0.20 ± 0.26; $t_{52} = −0.85$; $P = .40$). The right side was larger among female patients, resulting in greater symmetry, than female normal subjects (0.06 ± 0.22 vs 0.17 ± 0.26; $t_{32} = 1.23$; $P = .23$). The sex × group interaction effect on PT was significant at $P \leq .05$ (see Table 2).

COMMENT

Our findings show sex-specific effects in schizophrenia in cortical regions found to be normally sexually dimorphic and abnormal in schizophrenia. There were no significant differential sex effects in subcortical gray matter regions or CSF, even though some of these regions have been shown to be normally sexually dimorphic. This suggests that sex-specific effects in schizophrenia may be confined primarily to the cortex.

The findings are consistent with, and extend, recent work demonstrating sex differences in these brain regions.[11,24,43,77] This includes the same direction of the effects, such as smaller volumes of the anterior cingulate gyrus in female patients[43,78] and Heschl's gyrus in male patients[11] and larger volumes of the inferior parietal lobe[79] and right PT[77] in female patients. Consistent with recent work,[24] the middle frontal gyrus was smaller in cases of both sexes, even though we found a larger effect size, although nonsignificant, among the men. Furthermore, abnormal asymmetry of the PT in males is consistent with numerous imaging[17,25,53,77,80] and postmortem[19,20] studies, and in females, with right-sided abnormalities.[53,77]

The main limitation of this study is the relatively small sample size, particularly the women; thus, replication is necessary. However, we would argue that the
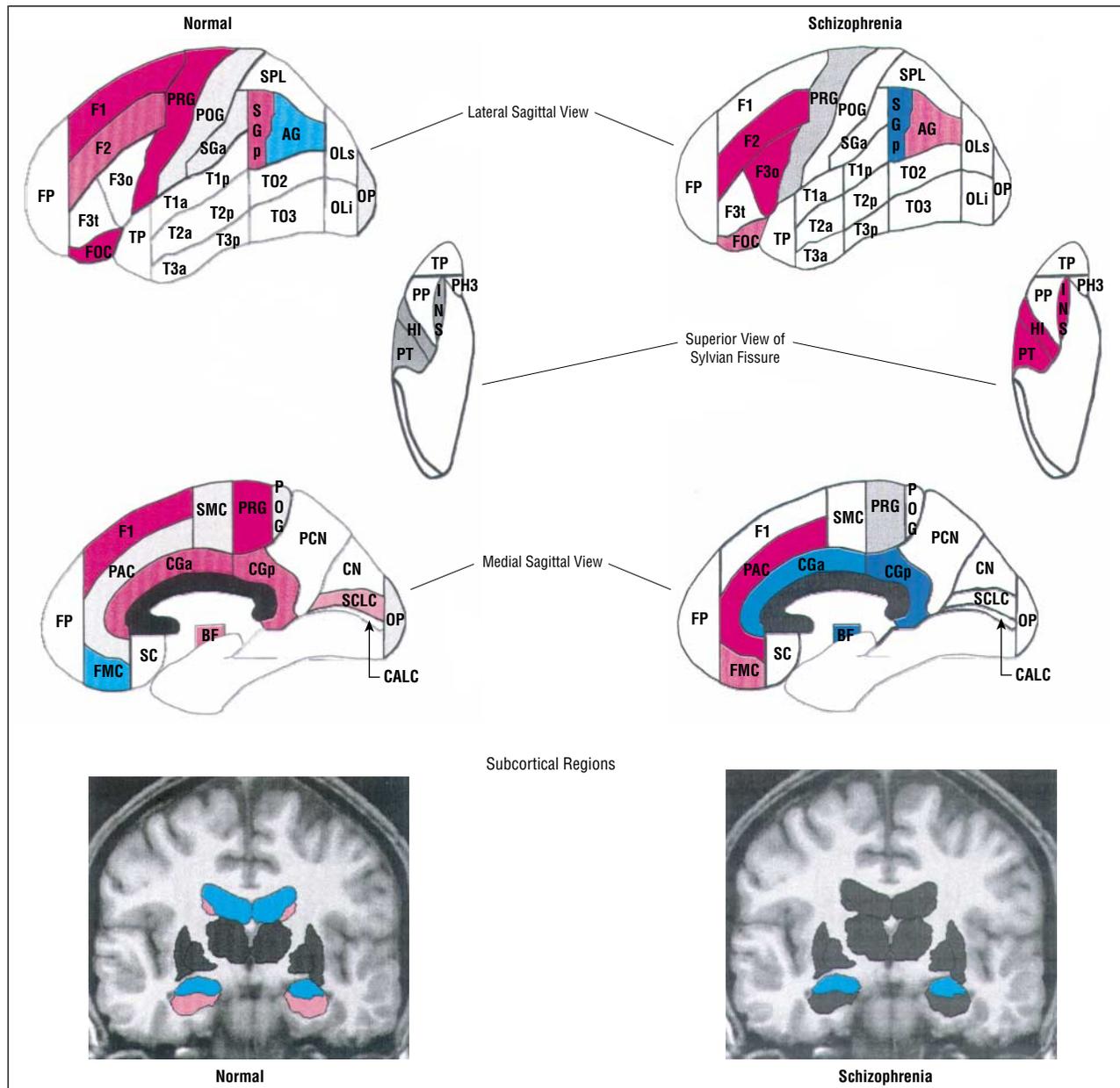
Figure 2. Sex × group interaction effects in subjects with schizophrenia vs normal control subjects: cortical normal sexual dimorphisms disrupted. Sample sizes were as follows: normal men (n=27), normal women (n=21), men with schizophrenia (n=27), women with schizophrenia (n=13). Permutation test of significant sex × group interactions in cortical vs subcortical/cerebrospinal fluid regions, demonstrating significant sex × group effects only in the cortex: P=.004; SE (P)=.0005; 95% confidence interval, .003-.005). Overall F test from general linear models for correlated data for sex × group × area interaction in the cortex: $F_{12,87}$=2.59, P=.005; for subcortical regions: F=0.30, P=.95. The color coding of the brain regions refers to the following: pink and red indicate that women have relatively larger volumes (ie, relative to cerebrum size) than men; light and dark blue indicate that men have relatively larger volumes than women. The darker the red or blue coloring, the larger the t value (seen in Table 3). The gray color indicates that men and women were approximately equivalent in relative volume size. See legend to Figure 1 for explanation of abbreviations.

question of adequate statistical power, and thus the validity of our negative results, is addressed by the significant overall test of the cortical sex × group interaction effects, sex differences in effect sizes, and consistency of findings with previous studies, even the variable direction of the sex effects. We would argue that low statistical power does not explain the lack of significant sex differences in hippocampal, basal ganglia, and ventricular volumes, for which there was adequate power to test for interaction effects.[60] Furthermore, although 3-mm scans were analyzed in this study compared with recent

acquisitions of 1.5 mm, our findings are consistent with studies using 1.5 mm. Finally, we had the unique advantage of simultaneously analyzing, within the same person, a large number of brain regions, in particular, across the entire cortex, allowing for tests of the specificity of abnormalities across the cerebrum in men and women. We have extended previous work by providing a heuristic model for examining sex differences across the entire brain.

Sex-specific effects in the cortex are interesting, since we found significant normal sexual dimorphisms in these cortical regions.[36] This suggests that factors that contrib-

ute to producing normal sexual dimorphisms may be the same factors that modulate brain abnormalities in schizophrenia. The impact of sex steroid hormones on brain development, particularly during late gestation and early postnatal sexual differentiation of the brain,[33,81] may contribute to understanding the mechanisms responsible for these sex-specific cortical effects, since this is the same developmental timing implicated in schizophrenia and the initiation of cortical differentiation. Potential mechanisms[32] include epigenetic hormonal factors (eg, secretion of testicular testosterone), sex-specific genetic programs affecting early sexual brain differentiation, regulation of apoptosis by androgens, and the colocalization of gonadal receptors with neurotransmitters, such as the monoamines and γ-aminobutyric acid, and nerve growth factors.

We are not proposing that the fetal or early postnatal periods are the only periods that may contribute to understanding sex effects in schizophrenia, since, for example, "activational effects" of circulating hormones, occurring later in development, eg, during puberty, may or may not potentiate neural circuits laid down during early development.[32] This may be particularly important for the cortex, since it fully develops later than do subcortical regions. It is interesting that the sex-specific abnormalities for the dorsolateral and orbital prefrontal cortices were not as large as for other hypothesized cortical regions. Animal studies have shown that the level of sex steroid receptors in these two regions does not recede as dramatically as that in other cortical regions postnatally.[33,34] This suggests that there may be relatively greater continuing hormonal effects on these brain regions influencing plasticity than on other cortical regions.

It is difficult to hypothesize the directions of the sex effects across the entire brain, since they may depend differentially on the timing of the insult, the interconnections between brain regions, and their differential plasticity to early insults (affected by circulating hormones[82,83]). Variation in the sex effects may also be due to tissue differences across brain regions and the fact that the modulations of the impact of early brain insults by differential gonadal hormone mechanisms may be nonlinear, ie, modified only given a particular level or threshold of hormonal exposure in a particular brain region or specific nuclei within it. Although this is not a study of developmental mechanisms, the results suggest potential hypotheses about sex effects, timing of insults, and consequences for brain morphologic features that can be tested in animal models in future studies. Thus, an understanding of sex-specific brain abnormalities in schizophrenia may lead to etiologic clues, in addition to understanding the normal properties of the male and female brain in the face of disease.

Finally, sex differences in cortical abnormalities must be related to cognitive and symptomatologic differences between men and women with schizophrenia.[24,45,77,78,84-86] For example, Heschl's gyrus, PT, and Broca's area are brain regions involved in, among other things, primary auditory processing, language comprehension, and verbal learning, respectively. We and others have showed some preservation of function in language and verbal memory in women with schizophrenia,[7,56] which may be related to sex

differences in brain abnormalities.[24,45,77,85] Our future work will relate volumetric sex differences reported in this study to sex differences in cognitive function.

In summary, we report herein that sex-specific volumetric brain abnormalities are primarily in the cortex. These brain regions are normally sexually dimorphic and abnormal in schizophrenia. This finding suggests that factors that produce normal sex differences in brain morphologic features may be modulating insults producing schizophrenia. Furthermore, the specificity for the cortex may implicate fetal or early postnatal timing, since this is similar to the timing of risk factors for schizophrenia, the beginnings of sexual differentiation of the brain, and the initiation of cortical differentiation.

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levels. Rather, we suggest that a dimensional look at pathology is emerging from our ideas about developmental and evolutionary heterogeneity and variation gone haywire to produce illness and pathology. The retiring shy child has a greater risk for panic disorder or social phobia than his more outgoing brother, even before he is ill. How does the temperamentally difficult child yield to or overcome his or her status as a case, joining the ranks of the variant normal child. These are the questions for the 21st century. The new techniques available to scientists certainly are rife with potential for learning new things about development. However, the questions to be asked should derive from sophisticated clinicians who know what children do and say at each epoch in their development.

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Correction

Error in Table. In the Original Article by Goldstein et al titled "Impact of Normal Sexual Dimorphisms on Sex Differences in Structural Brain Abnormalities in Schizophrenia Assessed by Magnetic Resonance Imaging," published in the February issue of the ARCHIVES (2002;59:154-164), an error occurred in the last row of Table 2. For male subjects with schizophrenia, the mean (SD) adjusted volume of the left hippocampus should have read 0.36 (0.05) cm^3.