ORIGINAL ARTICLE

Smaller Neocortical Gray Matter and Larger Sulcal Cerebrospinal Fluid Volumes in Neuroleptic-Naive Women With Schizotypal Personality Disorder

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Context: Structural brain abnormalities, including larger cerebrospinal fluid (CSF) volumes, have been observed in men diagnosed as having schizotypal personality disorder (SPD).

Objectives: To determine whether women with SPD have abnormalities similar to those of men with SPD and to elucidate specific SPD regional volume deficits and symptom correlations.

Design: Naturalistic study.

Setting and Participants: Thirty neuroleptic-naive women with SPD and 29 female control subjects, both recruited from the community. Participants were group matched for age, parental socioeconomic status, handedness, and IQ.

Interventions: A new segmentation method was applied to magnetic resonance images to automatically parcel the images into CSF, gray matter, and white matter. The neocortex was manually separated from subcortical and other nonneocortical structures. Voxel-based morphometry was applied to determine global and regional volume deficits.

Main Outcome Measures: Left and right neocortical gray matter, white matter, and CSF relative volumes as well as clinical symptoms from the Structured Interview for Schizotypy and the Schizotypal Personality Questionnaire–Brief Version.

Results: Smaller left (3.84%) and right (3.83%) neocortical gray matter relative volumes associated with larger left (9.66%) and right (9.61%) sulcal CSF relative volumes were found in women with SPD compared with controls. Voxel-based morphometry showed that the neocortical deficits in SPD were especially prominent in the left superior and middle temporal gyri, left inferior parietal region with postcentral gyrus, and right superior frontal and inferior parietal gyri. In the SPD group, larger lateral ventricle volumes correlated with more severe symptoms on the Structured Interview for Schizotypy and the Schizotypal Personality Questionnaire–Brief Version.

Conclusions: The smaller neocortical gray matter volume and larger sulcal CSF volume provide evidence of the brain basis of this personality disorder and emphasize the communality of brain abnormalities in the schizophrenia spectrum.

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SCHIZOTYPAL PERSONALITY DISorder (SPD) is genetically related to schizophrenia[1,2] and shows similar psychophysiologic, neurochemical, and cognitive functional abnormalities.[3,4] Moreover, data from neuroimaging studies confirm pathological similarities between SPD and schizophrenia,[4,5] such as in the superior temporal gyrus,[6-10] basal ganglia,[11,12] and thalamus.[13] Finally, smaller volumes have been reported in the frontal lobe in schizophrenia[14-17] and in individuals with schizotypal features,[18] although not all studies agree.[1,2,4]

These findings suggest focal, regional volume deficits in schizophrenia spectrum disorders that are not confined to a single area but are more widespread, although some areas may be more affected than others.[19] Some structural neuroimaging studies[20-24] in schizophrenia show smaller overall cortical gray matter volume relative to controls, with accompanying larger cerebrospinal fluid (CSF) or ventricle volumes,[20,21,24] whereas some studies show negative findings, including a postmortem study[25] and some imaging studies.[26,27] Studies with nonpsychotic first-degree relatives of patients with schizophrenia have also reported smaller cortical gray matter and larger sulcal CSF[20,28] or ventricle[20,29,30] volumes compared with control subjects. To reconcile these different findings, it seems essential

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that studies control for potential confounders that likely affect cerebral cortical volume, such as demographic variables[31-33] (including age, sex, and handedness), and especially factors associated with chronic serious mental illness, such as recurrent hospitalizations and neuroleptic medication use.[34-38]

With respect to the control of potential confounding variables, SPD is a schizophrenia spectrum disorder that is genetically related to schizophrenia,[2] but because the subjects are not psychotic, they usually do not receive neuroleptic medications or require recurrent hospitalizations. Consequently, individuals with SPD may afford a clearer representation of the underlying brain abnormalities in schizophrenia spectrum disorders.

In a previous study[39] of men with SPD, the Clinical Neuroscience Laboratory (VA Boston Healthcare System and Harvard Medical School) reported a significantly larger CSF volume not attributable to ventricular volume (eg, sulcal CSF) and a trend-level smaller cortical gray matter volume. Because sex may affect regional cerebral cortical volumes differently in healthy individuals[40] and in individuals with schizophrenia[41-43] or SPD,[9] and the clinical course of SPD may be milder in women, the present study examines brain volumes in neuroleptic-naive women with SPD compared with female controls using a newly developed and sensitive magnetic resonance imaging (MRI) segmentation method.[44,45] Moreover, in the present study we focus on neocortical rather than total cortical gray matter to allow more precise delineation of brain abnormalities[44,45] and to determine whether the strong evidence for neocortical abnormalities in schizophrenia[20,21,46] was also observed in SPD, a schizophrenia spectrum disorder.

We hypothesized that neuroleptic-naive women with SPD would show smaller neocortical gray matter volume but larger sulcal CSF and lateral ventricle volumes than female control subjects group matched for age, sex, handedness, parental socioeconomic status, and IQ. Clinical correlates of neocortical gray matter, sulcal CSF, and lateral ventricle volumes in women with SPD were also examined. We further used voxel-based morphometry (VBM) to evaluate whether there were specific regional neocortical gray matter differences in subjects with SPD and controls.

METHODS

PARTICIPANTS

From January 1, 1997, through December 31, 2005, 30 neuroleptic-naive women diagnosed as having SPD and 29 female control subjects were recruited from the community through advertisements on the transit system, in newspapers, and on fliers. Subjects with SPD from the community were recruited via the following advertisement: "Sixth Sense/Very Shy: A study at Harvard Medical School seeks right-handed people who believe they have ESP, telepathy, or a "sixth sense"; often mistake noises for voices; sense the presence of others when alone; have extreme social anxiety (or discomfort) in social situations involving unfamiliar people; and have few friends."

Recruitment of female participants began several years after that of male participants, accounting for the timing of this article. Of the 962 individuals who responded to the SPD advertisement, 421 female participants underwent an extensive telephone screening process that used the following inclusion criteria: (1) age between 18 and 55 years; (2) right-handed; (3) English as the primary language; (4) no history of neurologic disorder with loss of consciousness longer than 2 minutes; (5) no history of electroconvulsive therapy, drug or alcohol dependence in the past 5 years, or abuse in the past year; and (6) no history of using neuroleptics ever or psychotropic medications in the past year. The SPD advertisement tapped the *DSM-IV* diagnostic criteria for SPD,[6] which include (1) ideas of reference, (2) odd beliefs and superstitions or "sixth sense," (3) abnormal perceptual experiences, (4) odd and vague speech, (5) suspiciousness, (6) constricted affect, (7) odd and peculiar appearance or behavior, (8) no close friends, and (9) extreme social anxiety.

Of the 421 subjects, 92 met the telephone inclusion criteria, including positive responses to at least 3 of the previously mentioned SPD criteria on screening questions. The *Structured Clinical Interview for* DSM-IV–*Patient Edition* (SCID)[47] and its personality disorder version (SCID-II)[48] were then used to make *DSM-IV* diagnoses and to exclude Axis I psychotic and bipolar disorders from both groups and Axis I and II diagnoses from controls. A recently published article[3] describes in detail the clinical and demographic characteristics of subjects with SPD so recruited.

Interviews were conducted by either a licensed psychiatrist or a licensed psychologist. Interrater reliability for the diagnosis of SPD was high ($\kappa = 0.89$; $n = 25$).[6] Women with SPD in the present study were included after diagnosis reliability testing using the same interviewers as in the present study. Interviewers were trained to detect nuances of behavior and history and to ask follow-up questions to establish the correct diagnosis. In the rare instances in which the first interviewer was uncertain about the diagnosis, a second licensed psychiatrist or psychologist interviewed the subject, and a consensus was obtained. All 30 subjects with SPD who underwent MRI and other parts of the protocol met the full *DSM-IV* SPD diagnostic criteria (having ≥5 of the 9 characteristics). Subjects with SPD also met the criteria for other comorbid personality and Axis I disorders, including paranoid (n=9), borderline (n=7), and narcissistic (n=3) personality disorders; depression (n=6); dysthymia (n=2); panic disorder (n=2); and phobic disorder (n=1).

Female controls were recruited from the community via a different advertisement and similarly underwent the SCID and SCID II. Controls had the additional inclusion requirement of no family history of psychotic or bipolar illness and no personal history of an Axis I or personality disorder diagnosis. Controls were group matched for demographic variables, including age and parental socioeconomic status, with subjects with SPD. The project was approved by our institutional review boards at Harvard Medical School and at VA Boston Healthcare System, and after a full description of the study to the participants, written informed consent was obtained.

CLINICAL MEASURES

Clinical symptoms were measured using the Structured Interview for Schizotypy (SIS)[49,50] and the Schizotypal Personality Questionnaire–Brief Version (SPQ-B).[51] Use of the SIS began in the middle of female recruitment; therefore, only 15 of the 30 women with SPD completed the SIS. Data were acquired on 9 factors from the SIS (magical thinking, ideas of reference, illusions, suspiciousness, psychotic-like phenomena, restricted emotion, social isolation/introversion, schizotypal social anxiety, and anger to slights) and 3 factors from the SPQ-B (cognitive-perceptual, interpersonal, and disorganized).

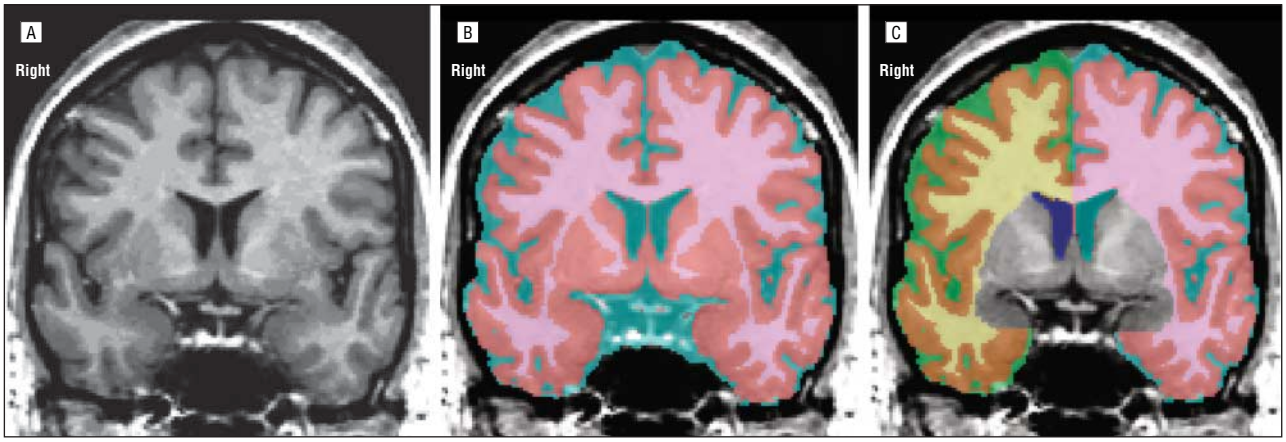

Figure 1. Spoiled gradient recalled images. A, Gray scale image of a woman with schizotypal personality disorder. B, The same image with automatically segmented tissue types overlaid. Cerebrospinal fluid is color coded as turquoise, gray matter as red-brown, and white matter as pink. C, The same image with the neocortex and ventricle extracted by manual exclusion of nonneocortical structures from the automatically segmented image. Cerebrospinal fluid is color coded as green, gray matter as brown, and white matter as yellow on the right; color codes on the left are as in part B. The lateral ventricle is color coded as dark blue on the right and as dark green on the left. The region of interest definition illustrated in part C was used for the statistical analysis.

MRI ACQUISITION, POSTPROCESSING, AND AUTOMATED SEGMENTATION METHOD

All the participants underwent MRI using a 1.5-T system (1.5T Signa; GE Medical Systems, Milwaukee, Wis). The acquisition protocol involved 2 MRI pulse sequences, as described elsewhere.[12] Several steps were taken to process the images on computer workstations (Sun Microsystems, Mountain View, Calif). First, a preprocessing filter was used to reduce noise. Next, T2 information from the double-echo spin-echo axial slices was coregistered with data from the spoiled gradient recalled (SPGR) images by reformatting the axial voxels into the voxel dimensions corresponding to those in the coronal SPGR images.[52] Third, a recently developed segmentation method[45] was applied to the MRIs to partition the images into the 3 major tissue classes: gray matter, white matter, and CSF. The method is based on use of an expectation maximization algorithm, which simultaneously estimates the inhomogeneities in the images and segments the images into the 3 major tissue classes. The algorithm analyzes SPGR and T2-weighted MRIs[45] and uses spatial priors[53] to increase the accuracy of the approach. Spatial priors capture the probability of a certain tissue class being present at a certain location in the 3-dimensional volume. Compared with other state-of-the-art algorithms,[44] this method produces highly accurate segmentations of the 3 major tissue classes because it combines previous information, image inhomogeneity correction, and dual-channel analysis. The final step measured the volume of the different tissue classes using medical imaging software (3D-Slicer; an Open Source development project begun at the MIT Artificial Intelligence Laboratory and the Surgical Planning Laboratory at Brigham and Women's Hospital).[54] The voxel volumes of gray and white matter and CSF were summed, yielding the total intracranial contents (ICC).

NEOCORTEX SEPARATION METHOD FROM THE SEGMENTED BRAIN

To exclude nonneocortical tissues from the whole segmented brain, the exclusion region of interest (ROI) was manually drawn on each coronal slice of the nonrealigned SPGR image to remove the basal ganglia, thalamus, brainstem, cerebellum, and medial temporal structures (amygdala-hippocampus complex).[7,12,39,55] First, the exclusion ROI was drawn on the coronal slices from anterior to posterior starting with the first slice in which the basal ganglia appeared. The whole basal ganglia were drawn, and as soon as the temporal stem appeared, the medial temporal structures (hippocampus and amygdala) were also added to the exclusion ROI. Progressing posteriorly, the brainstem, the third and fourth ventricles, and the entire infratentorial structure (eg, the cerebellum) were added to the exclusion ROI. Then, the expectation maximization atlas segmentation, the exclusion ROI, and the ICC mask were merged into a single image, resulting in neocortical gray matter, white matter, and CSF. This ROI delineation included all 6 layers of the neocortex and excluded the major portion of nonneocortical cortex, including limbic cortical areas (except for the piriform cortex) and most of the paralimbic cortex, except for portions of the cingulate, insula, and temporal pole (see the publication by Mesulam[56] for an anatomical description). For simplicity, we labeled this ROI as neocortical gray matter because the included regions of non–6-layer cortex compose less than 5% of the neocortical gray matter volume.

The merged image was then realigned and resampled with the reference line connecting 2 points of the anterior and posterior commissures, resulting in reformatted images 0.9375 mm thick. **Figure 1**A illustrates an SPGR image of a woman with SPD, and Figure 1B illustrates the segmentation results on the image in Figure 1A. Figure 1C illustrates the results of applying the exclusion ROI to the segmented image so as to include only neocortical structures. Finally, the realigned neocortical brain images were overlaid on the corresponding realigned SPGR images for further manual division of the left and right neocortices. Also, lateral ventricle volume was delineated (Figure 1C) to examine whether any CSF volume change found would be attributable to lateral ventricle or sulcal CSF. The lateral ventricles were manually separated from sulcal CSF space on each slice. Then sulcal CSF was measured from the CSF volumes by excluding the ventricle volumes. Interrater reliabilities (based on intraclass correlation coefficients) among 3 raters (M.K., M.N., and Adam Cohen, BA) on 5 MRIs for separation of the neocortex from other tissue were high on the left (r=0.999) and right (r=0.998) neocortices and also on left (r=0.987) and right (r=0.989) lateral ventricles and on ICC (r=0.999).

VBM ANALYSIS

Voxel-based analysis of gray matter volume differences between women with SPD and controls was conducted using optimized VBM[57] and SPM2 software (Institute of Neurology, Uni-

Table 1. Demographic Characteristics of the 59 Study Participants*

	Subjects With Schizotypal Personality Disorder (n = 30)	Control Subjects (n = 29)	t_{57} (2 Tailed)	*P* Value
Age, y	29.8 (9.4)	30.9 (10.5)	−0.4	.67
Education, y	15.6 (2.1)	16.3 (1.6)	−1.6	.12
IQ	116.0 (10.2)	117.4 (10.2)	−0.5	.60
Socioeconomic status†				
Parental	4.1 (1.0)	4.2 (0.8)	−0.7	.47
Participant's own	2.9 (1.3)	3.8 (1.4)	−2.6	.01
Edinburgh Handedness Inventory‡	64.1 (24.1)	65.7 (28.4)	−0.2	.82

*Data are given as mean (SD) unless otherwise indicated.
†Higher numbers represent higher socioeconomic status, based on the Hollingshead 2-factor index of socioeconomic status.
‡Edinburgh Handedness Inventory: (right hand − left hand) × 100/(right hand + left hand).

versity College London, London, England).[58] Because the structural SPGR images used in this study differed from the SPM T1 template, we created a study-specific template by averaging all spatially normalized SPGR images into the Montreal Neurological Institute (McGill University, Montreal, Quebec) T1 template using a nonlinear spatial transformation function.

Spatial normalization was conducted by applying nonlinear spatial transformations (derived from all SPGR images to the new group template) to segmented gray matter images (see the "Methods" section for a description of segmentation). Spatially normalized gray matter maps that were resampled to a voxel size of $1\times1\times1$ mm^3 were modulated by the jacobian determinant of spatial normalization transformation to preserve volume changes minimized during the nonlinear transformation. These modulated segmentations were smoothed using an isotropic gaussian kernel with 8-mm full-width half-maximum to accommodate misregistration errors and subtle anatomical variations. Significant differences in the adjusted regional volume were obtained using *t* statistics at every voxel in the gray matter from subjects with SPD and controls. Clusters consisting of a minimum of 1000 contiguous voxels with the threshold of uncorrected $P<.005$ were considered significantly different between groups.

STATISTICAL ANALYSIS

Statistical analyses for MRI structural measures were performed on relative brain volumes to correct for variations in head size. Relative volumes were obtained by dividing absolute volumes by ICC and multiplying by 100. (Using absolute, rather than relative, volumes or covarying by ICC [also by ICC and age] in these analyses did not affect the statistical conclusions.)

The effects of group (subjects with SPD vs controls) difference were examined using repeated-measures analyses of variance with group as the between-group factor and laterality (left vs right) as the within-group factor. Planned contrasts consisting of unpaired *t* tests for normally distributed groups (neocortical gray matter, white matter, and sulcal CSF volumes) were subsequently performed. For nonnormally distributed volumes (lateral ventricle volumes, Shapiro-Wilks test: left [$W_{30}=0.78$; $P=.01$ in women with SPD; $W_{29}=0.85$; $P=.01$ in controls] and right [$W_{30}=0.69$; $P=.01$ in women with SPD; $W_{29}=0.96$; $P=.27$ in controls]), the Mann-Whitney test was applied.

To evaluate the association between relative volumes of gray matter and CSF, Pearson product moment correlations were performed. Spearman correlations were derived for correlations with lateral ventricle volumes because of the nonnormality of this sample.

RESULTS

There were no significant group differences in demographic characteristics, including age, IQ, parental socioeconomic status, and handedness (**Table 1**). The groups differed in participant socioeconomic status ($t_{57}=-2.6$; $P=.01$), consistent with other SPD studies.[3] There was no significant difference between the 2 groups in ICC ($t_{57}=-1.1$; $P=.26$) (**Table 2**).

NEOCORTEX AND CSF VOLUME MEASURES

A repeated-measures analysis of variance of neocortical gray matter relative volumes revealed a significant main effect of group (SPD vs control) ($F_{1,57}=6.13$; $P=.02$) (Table 2). There was no significant main effect of laterality (left vs right hemisphere) ($F_{1,57}=0.03$; $P=.87$) and no interaction between group and laterality ($F_{1,57}<0.001$; $P>.99$). Planned follow-up contrasts applying *t* tests showed that left ($t_{57}=-2.39$; $P=.02$; effect size=−0.62; 3.84% smaller) and right ($t_{57}=-2.53$, $P=.01$; effect size=−0.66; 3.83% smaller) neocortical gray matter relative volumes were significantly smaller in subjects with SPD than in controls (**Figure 2** and Table 2). There was no difference in asymmetry between groups ($t_{57}=0.03$; $P=.82$). In contrast to gray matter, white matter relative volumes revealed no significant differences between groups (Table 2).

A repeated-measures analysis of variance of relative volume of sulcal CSF revealed a significant main effect for group ($F_{1,57}=7.98$; $P=.01$) and no significant effect for laterality, with no interaction between laterality and group (Table 2). Planned follow-up *t* tests showed that the sulcal CSF relative volumes were larger in subjects with SPD than in controls on the left ($t_{57}=2.53$; $P=.01$; effect size=0.66; 9.66% larger) and right ($t_{57}=2.79$; $P=.007$; effect size=0.73; 9.61% larger) (**Figure 3** and Table 2).

To determine whether the difference in sulcal CSF volume was paralleled by SPD-control differences in the lateral ventricles, nonparametric (Mann-Whitney) tests for lateral ventricle relative volumes were also performed and showed no significant difference on either the left ($U=-1.5$; $P=.10$) or right ($U=-0.6$; $P=.55$) ventricle

Table 2. Volumes of Neocortical Gray Matter, White Matter, and Cerebrospinal Fluid

Region and Volume Type*	Subjects With Schizotypal Personality Disorder (n = 30)	Control Subjects (n = 29)	t_{57} or U†	*P* Value	Effect Size	Partial η^2‡	% Difference§
Total intracranial contents, mL	1312.2 (79.7)	1340.1 (108.1)	−1.1	.26	−0.29	NA	2.08
Neocortical gray matter volume, mL‖							
Left	252.5 (23.5)	267.5 (20.7)	−2.4	.02	−0.62	0.196	3.84
Right	252.7 (23.9)	267.6 (19.0)	−2.5	.01	−0.66	0.207	3.83
White matter volume, mL¶							
Left	182.4 (20.3)	186.5 (20.5)	−0.1	.96	−0.01	0.002	0.09
Right	182.5 (18.5)	186.6 (20.0)	−0.1	.96	−0.01	0.002	0.08
Sulcal CSF volume, mL#							
Left	68.7 (9.1)	63.5 (12.3)	2.5	.01	0.66	0.113	9.66
Right	68.9 (8.5)	63.7 (11.8)	2.8	<.01	0.73	0.121	9.61
Lateral ventricle volume, mL**							
Left	6.77 (2.8)	6.29 (3.2)	−1.5	.10	0.24	NA	9.80
Right	6.27 (2.5)	6.00 (2.5)	−0.6	.55	0.22	NA	8.33

Abbreviations: CSF, cerebrospinal fluid; NA, not available.
*To facilitate comparisons with other data sets, mean (SD) absolute volumes are given in the table, whereas the volumes used for statistical comparisons (unpaired *t* tests, Mann-Whitney tests, and analysis of variance [ANOVA]) are relative volumes.
†Two-tailed *t* tests were performed for relative volume comparisons on neocortical gray matter, white matter, and sulcal CSF, and Mann-Whitney tests were performed for relative volume comparisons on the lateral ventricles.
‡Calculated from ANOVA.
§Calculated using the following formula: [100 × (volume of control subjects – volume of subjects with schizotypal personality disorder)/volume of control subjects].
‖Repeated-measures ANOVA with group (women with schizotypal personality disorder vs control subjects) as the between-subjects factor and laterality (left vs right) as the within-subjects factor revealed a main effect for group ($F_{1,57}$ = 6.13; *P* = .02).
¶Repeated-measures ANOVA revealed no significant main effect for group ($F_{1,57}$ = 0.1; *P* = .73).
#Repeated-measures ANOVA revealed a significant main effect for group ($F_{1,57}$ = 7.98; *P* = .007).
**Repeated-measures ANOVA was not performed because the group volumes were not normally distributed.

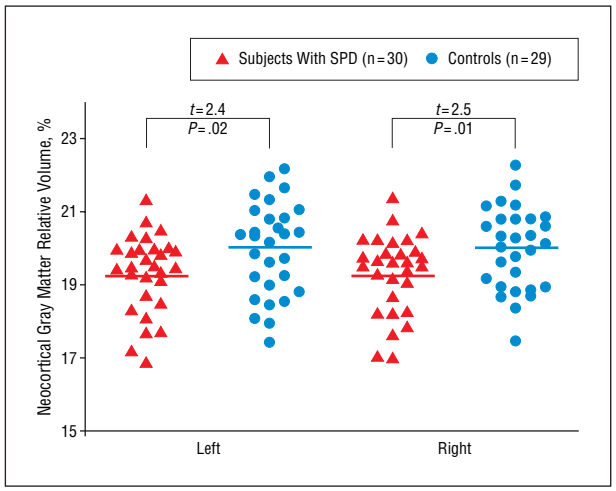

Figure 2. Neocortical gray matter relative volumes for women with schizotypal personality disorder (SPD) and female control subjects. Horizontal lines indicate means, and *t* values are from *t* test comparing groups.

(Table 2). The scatterplots of the lateral ventricles showed 1 SPD outlier each on the left and right, but even with this outlier removed, the SPD-control group differences were not significant.

To determine whether smaller neocortical gray matter volumes were associated with larger volumes of the surrounding sulcal CSF, we performed a correlation analysis, finding that total neocortical gray matter relative volumes were significantly negatively correlated with the relative volumes of the total sulcal CSF surrounding the neocortex in the SPD group (r=–0.36; P=.048) (**Figure 4**). In contrast, the control group showed no such significant correlation between total sulcal CSF and total neocortical gray matter relative volumes (r=0.18; P=.36). A comparison of SPD and control correlation coefficients using the Fisher z transformation showed that these r values were significantly different (z=–2.03; P=.02). We also performed a similar correlation in the SPD group between relative volumes of the lateral ventricles and neocortical gray matter, finding that there was no significant correlation (r=–0.08; P=.68).

We did not find any differences in neocortical gray matter, sulcal CSF, or lateral ventricle volumes between subjects with SPD without depression and those who were comorbid for depression. In addition, 6 subjects with SPD had first-degree relatives with psychosis, although there was no significant volume difference in neocortical gray matter, white matter, and sulcal CSF between groups with and without a family history.

GRAY MATTER REGIONS SHOWING MORE PRONOUNCED VOLUME DEFICITS IN WOMEN WITH SPD VS CONTROLS: VBM ANALYSIS

Optimized VBM analysis showed greater deficits in subjects with SPD compared with controls on the left side in the superior (Brodmann area [BA] 22) and middle (BA 21) temporal gyri and the inferior parietal (BA 40) region with postcentral gyrus (BA 13) and on the right side in the superior frontal (BA 6) and inferior parietal (BA 40) gyri (**Figure 5** and **Table 3**). In contrast, no area showed a deficit in controls compared with subjects with SPD.

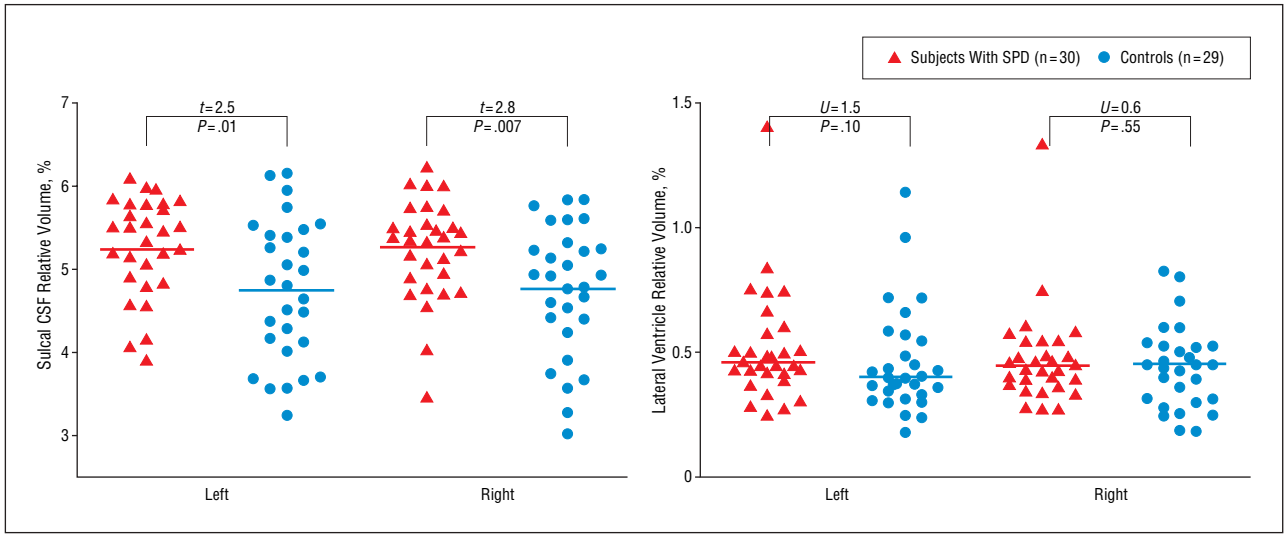

Figure 3. Sulcal cerebrospinal fluid (CSF) (A) and lateral ventricle (B) relative volumes for women with schizotypal personality disorder (SPD) and female control subjects. Horizontal lines indicate means, and *t* (or *U*) values are from the *t* (or Mann-Whitney) test comparing groups.

CORRELATIONS OF RELATIVE VOLUMES WITH CLINICAL SYMPTOMS

In subjects with SPD, more severe SIS symptoms were associated with larger lateral ventricle relative volumes but not with neocortical gray matter or sulcal CSF relative volumes (**Figure 6**). Specifically, we found that schizotypal social anxiety scores (n=15; ρ=0.70; *P*=.003; effect size=1.83), anger to slights scores (n=15; ρ=0.61; *P*=.02; effect size=1.43), and restricted emotion scores (n=15; ρ=0.60; *P*=.02; effect size=1.40) were significantly positively correlated with total relative volumes of the lateral ventricles. Because there were 9 SIS factors and Bonferroni correction would have meant that only the single *P*=.003 (which was below .0056 [.05/9]) for social anxiety would have been significant, correlation analyses with the SPQ-B were performed to determine whether the association between more severe symptoms and larger lateral ventricles could also be found in this different schizotypal symptom scale (Figure 6). On the SPQ-B, lateral ventricle volumes were significantly positively correlated with cognitive-perceptual factor scores (n=21; ρ=0.62; *P*=.003) and interpersonal factor scores (n=21; ρ=0.59; *P*=.005).

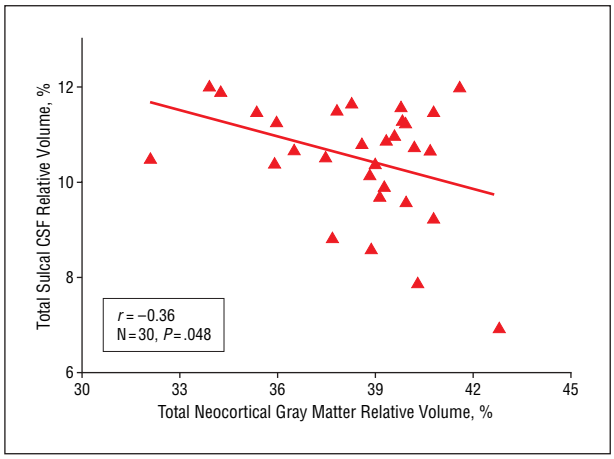

Figure 4. Inverse correlation between relative volumes of neocortical gray matter and surrounding sulcal cerebrospinal fluid (CSF) in women with schizotypal personality disorder. *r*=Pearson correlation coefficient. The least squares line was added for ease of interpretation.

COMMENT

There are 4 major findings in this study. First, left and right neocortical gray matter relative volumes in neuroleptic-naive women with SPD were significantly smaller than those in demographically matched controls by 3.84% and 3.83%, respectively, but no difference was found in white matter volumes in subjects with SPD compared with controls. Second, left and right sulcal CSF relative volumes surrounding the neocortex in women with SPD were significantly larger than those in controls by 9.66% and 9.61%, respectively. In addition, the larger sulcal CSF relative volumes were associated with smaller neocortical gray matter relative volumes in this sample of women with SPD but not in controls. Third, VBM analyses showed that the neocortical deficits in SPD were most prominent in the left superior and middle temporal gyri, left inferior parietal region with postcentral gyrus, and right superior frontal and inferior parietal gyri. Fourth, although we found no group difference in lateral ventricle volume, we did find that larger lateral ventricle relative volumes correlated with more severe symptoms (social anxiety, anger to slights, and restricted emotion scores on the SIS and interpersonal and cognitive-perceptual scores on the SPQ-B) in women with SPD.

These findings are especially noteworthy because, to our knowledge, this is the first study to report statistically significantly smaller neocortical gray matter volume in association with larger sulcal CSF relative volume in a neuroleptic-naive group of women with SPD. These results are highly consistent with previous findings[39] in a smaller sample of 16 men with SPD compared with 14 male controls of larger CSF volumes, not attributable to enlarged lateral ventricle volumes, together with trend level smaller total cortical gray matter volumes. This study used a simi-

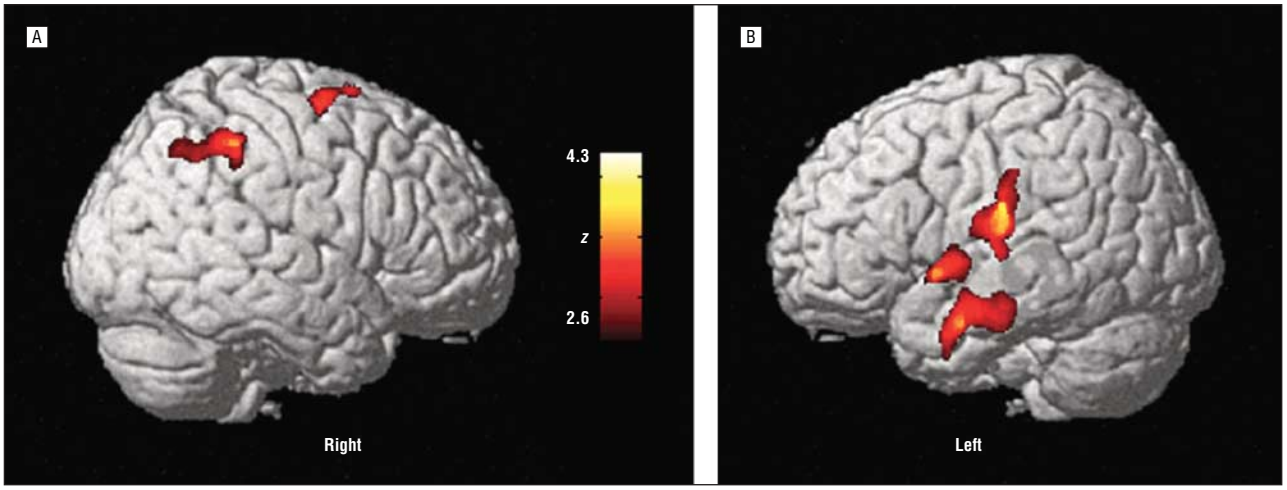

Figure 5. Regions of reduced regional gray matter volume in subjects with schizotypal personality disorder compared with control subjects analyzed using optimized voxel-based morphometry. The left superior and middle temporal gyri, the tempoparietal region, and the right superior frontal gyrus with the inferior parietal region showed deficits in subjects with schizotypal personality disorder (see Table 3 for specific coordinates). The scale shows the color codes of *z* values (standard normal deviates) corresponding to the *t* statistics of the volume deficits for subjects with schizotypal personality disorder.

Table 3. Areas of Reduced Regional Gray Matter Volume in Subjects With Schizotypal Personality Disorder Compared With Control Subjects

	Control-Schizophrenia*		
Anatomical Location	Talairach Coordinates (x, y, z)	*z* Score	Cluster Size†
Left superior temporal gyrus (BA 22)	–57, 1, –1	3.57	1267
Left middle temporal gyrus (BA 21)‡	–67, –20, –17	4.30	2647
Left inferior parietal gyrus/parietal (postcentral) gyrus (BA 40/BA 13)	–49, –18, 21	3.30	3032
Right inferior parietal gyrus (BA 40)	58, –39, 47	3.84	1725
Right superior frontal gyrus (BA 6)	17, –1, 60	3.26	1254

*Areas of reduced gray matter volume in patients with schizophrenia compared with controls. The table shows regions that survived correction for spatial extent with corresponding *z* scores for different anatomical locations. An 8-mm smoothing kernel was used. The threshold was 0.005 ($t = 2.67$). There was no area of reduced volume in controls compared with patients with schizophrenia.

†The number of voxels in each cluster.

‡The region extends toward the upper part of the left inferior temporal gyrus as shown in coordinates 65, –10, –19.

lar, although not identical, exclusion of subcortical structures and found that SPD cortical gray matter volumes were 7.1% smaller (trend level significance, $P = .07$; effect size = 0.78) and CSF volumes not attributable to the lateral ventricle were larger ($P = .01$; effect size = 0.54).[39] The present data for women with SPD (Table 2) show similar effect sizes for neocortical gray matter (effect size = 0.62 on the left and 0.66 on the right) and sulcal CSF volume (effect size = 0.66 on the left and 0.73 on the right). It is likely that the present statistically significant results in neocortical gray matter are due to the larger sample size (30 women with SPD and 29 female controls). The slightly larger effect size and greater percentage reduction in neocortical gray matter volumes in men vs women with SPD may reflect sex differences.

We think it is likely that the larger sulcal CSF volume reported herein was due to the smaller volume of underlying gray matter, as evinced by their significant correlation. Also note that the lateral ventricle volume difference measured herein (0.48 mL on the left and 0.27 mL on the right) was too small to account for the difference in cortical gray matter volume (15 mL on the left and 14.9 mL on the right).

Findings of smaller total neocortical gray matter volume in women with SPD in the present study and previous findings in men with SPD together suggest that cortical brain abnormalities in SPD are widespread but are greater in some regions than others. For example, in women with SPD, our laboratory found a 21% smaller Heschl gyrus volume,[8] a much larger difference than the 3.8% smaller neocortical gray matter volume reported herein. In addition, in men with SPD, our laboratory reported 9% reductions in left superior temporal gray matter volumes.[6] The left temporal neocortical deficits are consistent with a previous study of subjects with SPD[10] and our study of first-episode schizophrenia[59] and hence are consistent with a model of temporal neocortical abnormalities across the schizophrenia spectrum. The frontal region, on the other hand, was reported to be preserved in SPD.[60] With respect to this discrepancy, we echo the previous conclusion[61] that SPM findings need to be confirmed with specific ROI analysis and note that the right superior frontal gyrus deficit and bilateral inferior parietal regions have not yet been examined using ROI analysis in SPD.

These findings of smaller neocortical gray matter volume and larger CSF volume in subjects with SPD are similar to those of neuroimaging studies of patients with schizophrenia[20-24,62] and their nonpsychotic siblings[20,30] and support the hypothesis of a shared genetic diathesis between SPD and schizophrenia.[63] The present SPD findings in neuroleptic-naive individuals seem particularly important for understanding the underlying brain mor-

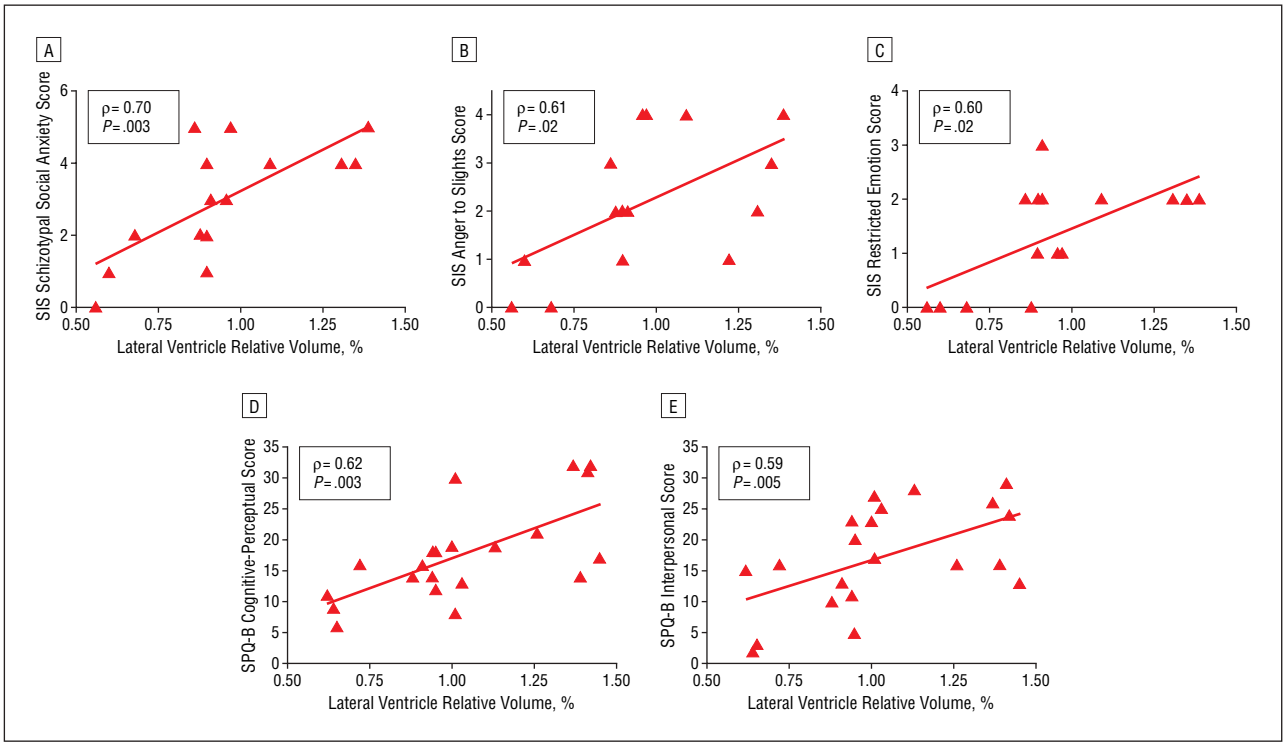

Figure 6. Positive correlations between lateral ventricle relative volumes and symptom scores on the Structured Interview for Schizotypy (SIS) (A, B, and C) and on the Schizotypal Personality Questionnaire–Brief Version (SPQ-B) (D and E). The Spearman ρ was used because of the smaller sample size and nonnormality of ventricles. Least squares lines were added for ease of interpretation.

phologic features in schizophrenia spectrum disorders, given the potential confounding effects of neuroleptic medications on ROI volumes.[37]

A variety of possible causes for the deficits in gray matter volume have been reported, with deficits in neural development appearing especially important.[5] In general, MRI abnormalities in SPD seem less severe than those in schizophrenia,[4,5] including cavum septi pellucidum abnormalities, which are developmental in origin.[64] As a measure of relative severity, it will be important to evaluate patients with schizophrenia using the same global ROI measures as in this study, particularly given that preliminary neocortical gray matter data from this group suggest a 5.6% control-schizophrenia difference compared with the 3.8% control-SPD difference.[65] A growing number of studies in schizophrenia indicate significant postonset progression of MRI gray matter volume loss that parallels worsening symptoms and functional measures.[66,67] In contrast, this progression of severity seems to be absent clinically in SPD,[3] and there is no evidence of progression of MRI abnormalities in SPD, although there has been no systematic longitudinal study.[4,5]

Approximately 75% of neuroimaging studies assessing ventricular volumes have reported enlarged lateral ventricles in patients with schizophrenia.[68] Because lateral ventricular enlargement may indicate tissue loss in surrounding brain regions,[69] these findings have generated great interest. The present study showed no significant difference in lateral ventricle volumes between subjects with SPD and controls, which is consistent with other findings in the literature for subjects with SPD.[39,70,71]

The present results, however, showed that specific psychopathologic symptoms in SPD, as measured with the SIS and SPQ-B, were not associated with measures of gray matter volumes but were associated with lateral ventricle volumes. Two domains, although controversial,[63] have been suggested for the characterization of SPD symptoms, and both were correlated with ventricular volumes in the present study: the cognitive-perceptual[72] (or positive[63]) domain and the social-interpersonal[72] (or negative[49]) domain. However, not all laboratories have found such correlations. For example, Siever et al,[70] in a computed tomography study, reported that in subjects with SPD, there were no significant correlations between clinical symptoms and ventricle volumes. There were, however, methodological differences between that study and the present study. Siever et al[70] included clinic-based men who were not neuroleptic naive. In the schizophrenia literature, ventricular volumes have been found to correlate with the severity of symptoms. For example, Shenton et al[68] reported that thought disorder correlated with left to right ventricle-brain ratio. In a recent longitudinal study, Lieberman et al[36] found that a greater improvement in negative symptoms was correlated with a lower increase in lateral ventricle volumes.

We believe that a strength of the present study is that it represents, to our knowledge, the largest study of women with SPD evaluating total gray matter volume and total sulcal CSF volume. Furthermore, possible confounding variables, including neuroleptic treatment,[34-37] age,[31,32] sex,[31,33,73] handedness,[33] and other demographic factors (eg, parental socioeconomic status), that could affect the size of the gray matter or other compartments in the brain

were carefully controlled. We believe that a second positive attribute is the use of a new and sensitive expectation maximization segmentation method[44,45] to evaluate the neocortex more accurately. The increased sensitivity and accuracy of this new segmentation method, together with the larger sample size, provided enough statistical power to show the association between smaller gray matter volumes and larger sulcal CSF volumes in women with SPD. However, there were several potential limitations. First, as in almost all SPD studies,[3,74-76] there was diagnostic comorbidity, especially with depression and with paranoid and borderline personality disorders, each of which might affect the results. Although we did not find that the subgroup with comorbid depression had different volumetric values than the nondepressed subjects with SPD, other comorbid disorders might have contributed to the results. Because alcohol consumption may be a potential confounder of MRI brain measures,[77,78] even if subjects do not receive a diagnosis of alcohol dependence or abuse, we note that our clinical study of a larger female SPD cohort found no more alcohol use in SPD than the low level in controls.[3]

In conclusion, the findings of smaller neocortical gray matter volume and larger sulcal CSF volume in women with SPD were congruent with previous findings in men with SPD and add to a growing number of studies reporting the existence of MRI brain abnormalities in SPD. Furthermore, because similar findings have also been reported in patients with schizophrenia and their unaffected siblings, we believe that the present findings support the hypothesis that SPD is in the schizophrenia spectrum and shares a genetic diathesis with schizophrenia that is expressed in similar brain abnormalities.

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