

ARCHIVAL REPORT

Basal Ganglia Shape Abnormalities in the Unaffected Siblings of Schizophrenia Patients

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Background: Abnormalities of basal ganglia structure in schizophrenia have been attributed to the effects of antipsychotic drugs. Our aim was to test the hypothesis that abnormalities of basal ganglia structure are intrinsic features of schizophrenia by assessing basal ganglia volume and shape in the unaffected siblings of schizophrenia subjects.

Method: The study involved 25 pairs of schizophrenia subjects and their unaffected siblings and 40 pairs of healthy control subjects and their siblings. Large-deformation, high-dimensional brain mapping was used to obtain surface representations of the caudate, putamen, and globus pallidus. Surfaces were derived from transformations of anatomic templates, and shapes were analyzed using reduced-dimensional measures of surface variability (i.e., principal components and canonical analysis). Canonical functions were derived using schizophrenia and control groups and were then used to compare shapes in the sibling groups. To visualize shape differences, maps of the estimated surface displacement between groups were created.

Results: In the caudate, putamen, and globus pallidus, the degree of shape abnormality observed in the siblings of the schizophrenia subjects was intermediate between the schizophrenia and control subjects. In the schizophrenia subjects, significant correlations were observed between measures of caudate, putamen, and globus pallidus structure and the selected measures of lifetime psychopathology.

Conclusions: Attenuated abnormalities of basal ganglia structure are present in the unaffected siblings of schizophrenia subjects. This finding implies that basal ganglia structural abnormalities observed in subjects with schizophrenia are at least in part an intrinsic feature of the illness.

Key Words: Basal ganglia, caudate, globus pallidus, putamen, schizophrenia, siblings

Evidence from family, twin, and adoption studies suggest that genetic factors play an important role in the pathogenesis of schizophrenia (1,2). Consistent with the involvement of genetic factors in schizophrenia, cognitive (3,4), neurologic (5,6) and neurobiological (7,8) abnormalities have been found in the unaffected relatives of schizophrenia subjects, generally in attenuated form.

A number of lines of research suggest that basal ganglia abnormalities might also have genetic associations in schizophrenia. The basal ganglia play important roles in the regulation of both motor and nonmotor functions (9–11), and motor abnormalities can occur in neuroleptic-naïve schizophrenia patients (12). Basal ganglia dysfunction, assessed with functional magnetic resonance imaging (MRI), has been reported in schizophrenia patients and their unaffected siblings (13–15). The caudate is also involved in smooth pursuit and saccadic eye movement (16,17), which have been shown to be abnormal in individuals with schizophrenia and their relatives (18,19).

Enlargement of basal ganglia volume in schizophrenia has been reported (20–22); however, these findings have been generally attributed to treatment with older generation (“typical”

antipsychotic medications that act primarily as antagonists at D2-type dopamine receptors in the basal ganglia (23,24). Volumetric abnormalities in various brain areas have been reported in nonpsychotic first-degree relatives of schizophrenia patients (25–27), but there have been relatively few studies of basal ganglia structure in this population. Reduced volume of the right putamen has been reported in the unaffected siblings of subjects with schizophrenia (28). Other authors, however, did not find a significant difference in basal ganglia structures between the siblings of schizophrenia subjects and control subjects (21,29).

We have previously used large-deformation high-dimensional brain mapping (HDBM-LD) (30,31) to characterize shape deformities of the hippocampus (32) and thalamus (33) in unaffected siblings of schizophrenia subjects. Shape analysis has been shown to be complementary to volumetry in discriminating between normal and neuropsychiatric conditions (34,35). Recently, we used shape analysis to characterize basal ganglia structure in subjects with schizophrenia (36). Abnormal shape of the caudate has also been reported in antipsychotic-naïve subjects with schizotypal personality disorder (37), which is genetically linked to schizophrenia.

The objective of our current study was to test the hypothesis that abnormalities of basal ganglia structure are present in the unaffected siblings of individuals with schizophrenia. This hypothesis is based on the premise that genetic factors that influence the pathogenesis of schizophrenia could also alter the neurodevelopment of these structures. Schizophrenia subjects recruited for this study were generally treated with atypical antipsychotic drugs, but their siblings had not and were still within the age of risk for developing the disorder. Therefore, at least in siblings, we were able to assess basal ganglia structure as it is related to schizophrenia without the confounding effects of treatment factors. In addition to antipsychotic medications, recreational drugs are commonly used by schizophrenia patients and may also influence subcortical brain structure (38,39). Thus,

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we also explored the impact of significant substance use on basal ganglia structure. Finally, we investigated correlations between neuroanatomic measures and the severity of psychopathology on an exploratory basis.

Methods and Materials

Subjects

Four groups of subjects were recruited for this study by advertising in local area psychiatric clinics and in the community: schizophrenia probands (SCZ; $n = 25$), unaffected siblings of schizophrenia probands (SCZ-SIB; $n = 25$), healthy control subjects (CON; $n = 40$), and siblings of healthy control subjects (CON-SIB; $n = 40$). Siblings were full-siblings, based on self-report. From an initial group of 216 potential subjects that fit inclusion criteria (discussed later), the final group of study

subjects were selected from those who had an MR scan of acceptable quality and whose sibling also completed MR scanning. This cohort of subjects was the same as that used in our previous report on the thalamus (33).

The demographic and clinical profiles of the subject groups are summarized in Table 1. All subjects were diagnosed using DSM-IV criteria on the basis of a consensus between a research psychiatrist and a trained research assistant who used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (40). Subjects were excluded if they had neurologic disorders, unstable medical disorders, head injury with loss of consciousness, or if they met DSM-IV criteria for current substance abuse or dependence (i.e., during the month preceding assessment). Handedness was determined in all subjects as the hand used for writing. The cumulative amount of alcohol con-

Table 1. Demographic, Clinical, and Pharmacologic Profiles

Characteristics/Profiles	SCZ ($n = 25$)	SCZ-SIB ($n = 25$)	CON-SIB ($n = 40$)	CON ($n = 40$)	F or χ^2	p
Age (yrs)	22.6 (3.2)	22.3 (3.5)	20.0 (3.5)	21.2 (3.6)	3.68	.01
Gender (%)					$\chi^2 = 18.4$.0004
Female	20.0	60.0	72.5	45.0		
Male	80.0	40.0	27.5	55.0		
Race (%)					$\chi^2 = 3.4$.75
African American	32.0	32.0	20.0	20.0		
Caucasian	68.0	68.0	77.5	77.5		
Other	0	0	2.5	2.5		
Handedness (%)					$\chi^2 = 1.5$.69
Right	84.0	92.0	92.5	87.5		
Left	16.0	8.0	7.5	12.5		
Parental Socioeconomic Status ^a	2.9 (1.2)	2.9 (1.0)	3.1 (.9)	2.9 (1.0)	.4	.8
Illness duration (yrs)	4.6 (4.4)	n/a	n/a	n/a	—	—
Current Antipsychotic (AP) (%) ^b						
Atypical	87.0	0	0	0	—	—
Typical	4.3	0	0	0	—	—
Atypical and Typical	8.7	0	0	0	—	—
Lifetime Typical AP Use (%) ^c	30.4	0	0	0	—	—
Duration of Typical AP Use (months) ^d	11.0 (7.0)	n/a	n/a	n/a	—	—
Lifetime Substance Dependence (%)						
Alcohol	28.0	12.0	0	5.0	$\chi^2 = 15.7$.001
Sedative/Hypnotic	0	0	0	0	—	—
Cannabis	36.0	12.0	10.0	2.5	$\chi^2 = 15.9$.001
Stimulant	0	4.0	2.5	0	$\chi^2 = 2.3$.52
Opioid	0	0	0	0	—	—
Cocaine	0	4.0	2.5	0	$\chi^2 = 2.3$.52
Hallucinogen	0	4.0	2.5	0	$\chi^2 = 2.3$.52
Total Alcohol Consumption in Last 2 yrs (kg)	9.1 (14.8)	7.6 (13.0)	3.5 (6.7)	5.2 (8.9)	1.72	.17
Current Axis I Diagnosis (%)						
Psychotic Disorder	100	0	0	0	$\chi^2 > 100$	<.0001
Mood Disorder	8.0	0	7.5	0	$\chi^2 = 5.2$.16
Anxiety Disorder	16.0	16.0	10.0	2.5	$\chi^2 = 4.5$.21
Lifetime Axis I Diagnosis (%)						
Psychotic Disorder	100	0	0	0	$\chi^2 > 100$	<.0001
Mood Disorder	52.0	52.0	35.0	2.5	$\chi^2 = 25.5$	<.0001
Anxiety Disorder	20.0	24.0	15.0	5.0	$\chi^2 = 5.3$.15

CON, control subjects; n/a = not applicable; SCZ, schizophrenia subjects; SIB, siblings.

Values are mean (SD) unless stated otherwise.

F values were calculated using one-way analysis of variance across all groups. The χ^2 value is the result of a chi-square comparison.

^aRange is 1 to 5, with higher values indicating lower socioeconomic status. Minor differences in how the siblings reported their parental information account for the small differences in parental socioeconomic status.

^bAtypical antipsychotics used (number of subjects) were risperidone (8), aripiprazole (5), olanzapine (5), clozapine (3), ziprasidone (3), and quetiapine (2). Typical antipsychotics used were haloperidol (1), thiothixene (1), and loxapine (1). Two schizophrenia subjects were receiving an unknown study medication and were not used in calculating percentages.

^cRefers to lifetime use of scheduled typical antipsychotic for >1 week. Typical antipsychotics used on an "as needed" basis were not included.

^dOnly patients with lifetime use of typical antipsychotics were used in calculating the mean.

sumed during the 2 years preceding participation in the study was measured using structured questionnaires adapted from Skinner (1982) (41).

The SCZ subjects were clinically stable; global severity of their symptoms had remained unchanged for at least 2 weeks before the participation in the study. The majority of SCZ were currently on atypical antipsychotic drugs; only three SCZ subjects were currently treated with typical antipsychotics (see Table 1). Also, a lifetime history of scheduled typical antipsychotic drug use was reported by seven SCZ subjects. The CON subjects had no lifetime history of Axis I psychotic or major mood disorders (i.e., major depression or bipolar disorder) or any first-degree relative with a psychotic disorder. SCZ-SIB were excluded if they had present or past Axis I psychotic disorders. The CON-SIB subjects were included as an additional comparison group because a lifetime history of Axis I major mood disorders was not an exclusion criteria for SCZ-SIB subjects. The CON-SIB were thus ascertained in a manner identical to SCZ-SIB: they were excluded if they had lifetime Axis I psychotic disorders but not major mood disorders.

Assessment of Psychotic Symptoms

Measures of specific domains of psychopathology were derived in two ways. First, measures of lifetime history of psychopathology were derived for delusions, hallucinations, thought disorganization, and negative symptoms using selected item scores extracted from the SCID-I. Scores for these domains of lifetime symptomatology were calculated as the sum of the corresponding item scores from the SCID-I (where absent = 1, subthreshold = 2, and present = 3). Second, measures of current psychopathology were derived from the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (42), the Structured Interview for Prodromal Syndromes (SIPS) (43) and the Chapman Psychosis Proneness Scales (CPPS) (44). The domains for current symptomatology consisted of positive symptoms, negative symptoms, and thought disorganization and were composed of the same items as in Delawalla *et al.* (45) but slightly modified as in Harms *et al.* (33) on the basis of analyses of internal consistency in our larger subject sample (see Supplement 1).

Image Acquisition and Preprocessing

Magnetic resonance scans of the whole brain were collected on a Siemens Magnetom Vision (Siemens, Erlangen, Germany) 1.5-T imaging system using a three-dimensional FLASH sequence (repetitions time = 20, echo time = 5.4, flip angle = 30°, number of acquisitions = 1, voxel size = 1 × 1 × 1 mm³, scanning time = 13.5 min). Signal intensity differences across subjects were normalized by linear rescaling, using the intensity of the corpus callosum and the third ventricles as reference structures (46).

Large-Deformation High-Dimensional Brain Mapping

An MR scan collected from a healthy comparison subject, not included in the study, was used to construct a neuroanatomic template as in prior studies (39,46). In the construction of this template, the right hemisphere caudate, putamen, and globus pallidus were manually outlined by expert consensus using atlas (47) guidelines, supervised by a neuroradiologist with extensive neuroanatomic research experience (46). A set of landmarks were developed for placement within the basal ganglia–thalamus complex in MR scans of the template and each study subject (46). Transformation of the template MR scan onto the MR scan of

study subjects (“subject scan”) occurred in a two-step process. First, the template scan was coarsely aligned to the left and right sides of each subject scan using the landmarks. Second, HDBM-LD was used to determine the transformation between template and subject scan (48). During this transformation, the movement and deformation of template voxels were constrained by assigning them the physical properties of a fluid. The validity of HDBM-LD as used in this study has been demonstrated previously (46).

To derive a surface for each individual basal ganglia structure, a triangulated graph was first superimposed onto the surface of each structure outlined in the right hemisphere of the template scan. These surfaces were then carried along as the template scan was transformed to match the left and right sides of each of the subject scans. Volumes of the selected basal ganglia were calculated by computing the volumes enclosed by the transformed surfaces.

Measurements of total cerebral volume (excluding the ventricles, brainstem, and cerebellum) were obtained from Freesurfer, a semiautomated software package for segmentation and cortical surface reconstruction (49).

Data Analysis

Principal components analysis was used to reduce the high dimensionality of the surfaces of each structure, yielding an orthonormal set of principal components (PC) representing shape variation for each structure in the population under study (50). Each surface was projected into the space defined by the first 15 PCs for that structure, yielding 15 PC scores for each surface, which accounted for more than 90% of total shape variance (across subjects and hemispheres).

To examine whether there were overall differences in the shapes of the basal ganglia structures across groups or hemisphere, multivariate analysis of variance (MANOVA) was applied to the PC scores of each basal ganglia structure (using all four subject groups). The 30 PC scores representing the left and right surfaces from each subject were entered as dependent variables, with hemisphere treated as a repeated factor and gender included as a covariate. Next, to test for an ordered variation in shape across the subject groups, we computed a single set of 15 PC scores for each structure of each subject by averaging corresponding PC scores from the left and right hemisphere. We then performed canonical analysis using a general linear model with the averaged PC scores as dependent variables and group and gender as predictor variables. The canonical analysis was designed to score the SCZ-SIB and CON-SIB along the dimension that “maximized” the difference between SCZ and CON. Thus, the canonical weighting coefficients were obtained from the contrast between SCZ and CON (33). A canonical score was obtained for each structure and subject by applying these weighting coefficients to the original dependent variables (i.e., PC scores).

Group differences in cerebral volume, basal ganglia volume, and canonical scores were assessed using mixed-model methods that explicitly estimated the covariance (correlation) in the residuals attributable to the sibling relationships. For basal ganglia volume, the mixed-model additionally included the correlation across hemispheres as part of the covariance structure. Gender was included as a covariate for all analyses of volume and canonical scores.

Model validity for the volumes and canonical scores was assessed by computing externally Studentized residuals. Only the residuals from the volume of the putamen showed statistical

evidence for a departure from normality (Shapiro-Wilk, $p = .0004$; otherwise $p > .08$). However, the skewness (.59) and kurtosis (.74) of that residual distribution was nonextreme. Three observations for putamen volume had a Studentized residual > 3 (but < 4). However, visual examination of these revealed no odd appearing surfaces or segmentations. Notably, F tests are robust for moderate departures from normality given a reasonable sample size (51), and thus we proceeded with statistical inference and testing under the mixed model for all structures.

Results

Volume Analyses

Volume measures for the basal ganglia and cerebrum and post hoc comparisons are summarized in Table 2. Volumes were compared across the four subject groups using a mixed linear model that specified group, hemisphere (for basal ganglia only), the interaction of group with hemisphere, and gender as fixed effects. Using this model, there was a significant effect of group status on cerebral volume [$F(3,46) = 6.3, p = .001$] and caudate volume [$F(3,50) = 3.77, p = .016$]. There was a significant effect of hemisphere on caudate volume (left $>$ right, $F(1,54) = 8.6, p = .005$], but no effect of group by hemisphere interaction [$F(3,63) = .9, p = .43$]. The significant effect for the caudate disappeared after including cerebral volume as an additional covariate [$F(3,46) = 1.10, p = .36$].

Mixed-model analysis indicated no main effect of group for the volume of the putamen [$F(3,58) = .4, p = .75$] or the globus pallidus [$F(3,55) = .3, p = .86$], even after covarying for cerebral volume (both $p > .4$). There was a significant effect of hemisphere on putamen volume [left $>$ right, $F(1,58) = 5.7, p = .02$], but no effect of group by hemisphere interaction [$F(3,58) = .2, p = .89$]. For the globus pallidus, there was neither a significant effect of hemisphere on volume [$F(1,64) = .1, p = .76$] nor an effect of group by hemisphere interaction [$F(3,58) = 1.1, p = .35$].

Substance and Alcohol Effects on Volumes

When either 1) lifetime history of alcohol and cannabis dependence or 2) total grams of alcohol consumed over the previous 2 years were included as covariates in the mixed-model analysis (but not cerebral volume), the main effect of group on

caudate volume remained significant [$F(3,50) = 3.2, p = .03$ and $F(3,50) = 3.9, p = .01$, respectively]. None of the substance use variables themselves had a significant effect on the volume of any basal ganglia structure. However, there was a trend toward significance of the effect of cannabis dependence on globus pallidus volume [$F(1,94) = 3.7, p = .06$].

Shape Analyses

Caudate Shape. Using all four subject groups, MANOVA applied to the PC scores for the caudate (covarying for gender) showed a significant group effect on shape [$\lambda = .52, F(45,331) = 1.8, p = .002$]. Differences between groups based on the canonical shape score are shown in Figure 1A.

A visual representation of caudate shape in SCZ and SCZ-SIB compared with CON is shown in Figure 2A. The most prominent shape patterns in the caudate of SCZ and SCZ-SIB were 1) an inward deformation in a large region of the caudate head anteriorly and anterodorsally and 2) an inward deformation along a large segment of the posterior side of the tail, with a reciprocal outward deformation on the anterior side of the tail. The noted shape abnormalities were observed bilaterally and more prominently in SCZ than SCZ-SIB.

Putamen Shape. MANOVA applied to PC scores for the putamen showed a significant group effect on shape [$\lambda = .58, F(45,331) = 1.5, p = .03$]. Figure 1B shows significant canonical shape score differences.

A visual representation of the shape of the putamen in SCZ and SCZ-SIB compared with CON is shown in Figure 2B. The most prominent shape patterns in the putamen of SCZ and SCZ-SIB were 1) an inward deformation in a moderate-sized region in the anterior edge of the putamen, which extends more medially on the left in SCZ, and 2) inward deformation along the posterior edges of the putamen, more notable on the left. Shape abnormalities are more prominent in SCZ than SCZ-SIB.

Globus Pallidus Shape. MANOVA applied to PC scores for the globus pallidus showed a near-significant group effect on shape [$\lambda = .60, F(45,331) = 1.4, p = .06$]. Figure 1C shows significant canonical shape score differences.

A visual representation of the shape of the globus pallidus in SCZ and SCZ-SIB compared with CON is shown in Figure 2C. The most prominent shape patterns in the globus pallidus of SCZ

Table 2. Adjusted Volumes of Basal Ganglia Structures and the Cerebrum

Brain Structure	Side	SCZ		SCZ-SIB		CON-SIB		CON	
		Gender	Gender + Cerebral volume	Gender	Gender + Cerebral volume	Gender	Gender + Cerebral Volume	Gender	Gender + Cerebral Volume
Caudate ^a	Left	3.39 (.07)	3.55 (.06)	3.33 (.07)	3.41 (.06)	3.62 (.06)	3.53 (.04)	3.56 (.06)	3.50 (.05)
	Right	3.34 (.07)	3.50 (.05)	3.32 (.07)	3.40 (.06)	3.55 (.06)	3.46 (.05)	3.53 (.06)	3.46 (.05)
Putamen	Left	5.45 (.10)	5.65 (.09)	5.48 (.10)	5.58 (.10)	5.59 (.08)	5.47 (.07)	5.56 (.08)	5.47 (.07)
	Right	5.38 (.11)	5.58 (.11)	5.41 (.11)	5.50 (.11)	5.52 (.08)	5.40 (.07)	5.44 (.08)	5.36 (.07)
Globus Pallidus	Left	1.71 (.03)	1.76 (.03)	1.74 (.04)	1.77 (.04)	1.77 (.02)	1.74 (.02)	1.74 (.03)	1.72 (.02)
	Right	1.72 (.04)	1.77 (.04)	1.75 (.05)	1.77 (.04)	1.73 (.02)	1.70 (.03)	1.74 (.03)	1.73 (.03)
Cerebrum ^a	Total	916 (19.9)	n/a	952 (15.6)	n/a	1024 (14.3)	n/a	1011 (14.4)	n/a

CON, control subjects; n/a = not applicable; SCZ, schizophrenia subjects; SIB, siblings.

Values are given in cm^3 and are the least square means (standard errors) adjusted for the indicated effects.

^aThe caudate and cerebrum showed significant main effects across the four groups when adjusted for gender alone (see volume analyses results). For the caudate, post hoc analyses showed significant differences between 1) SCZ and CON [$F(1,69) = 4.7; p = .03$], 2) SCZ-SIB and CON [$F(1,66) = 6.0; p = .02$], 3) SCZ and CON-SIB [$F(1,76) = 6.2; p = .02$], and 4) SCZ-SIB and CON-SIB [$F(1,64) = 8.6; p = .005$]. For the cerebrum, post hoc analyses showed significant differences between the same groups: 1) SCZ and CON [$F(1,50) = 15.1; p = .0003$], 2) SCZ-SIB and CON [$F(1,57) = 7.5; p = .008$], 3) SCZ and CON-SIB [$F(1,54) = 18.4; p < 0.0001$], and 4) SCZ-SIB and CON-SIB [$F(1,56) = 11.6; p = .001$]. The SCZ vs. SCZ-SIB differences for the cerebrum almost reached significance [$F(1,27) = 4.2; p = .051$].

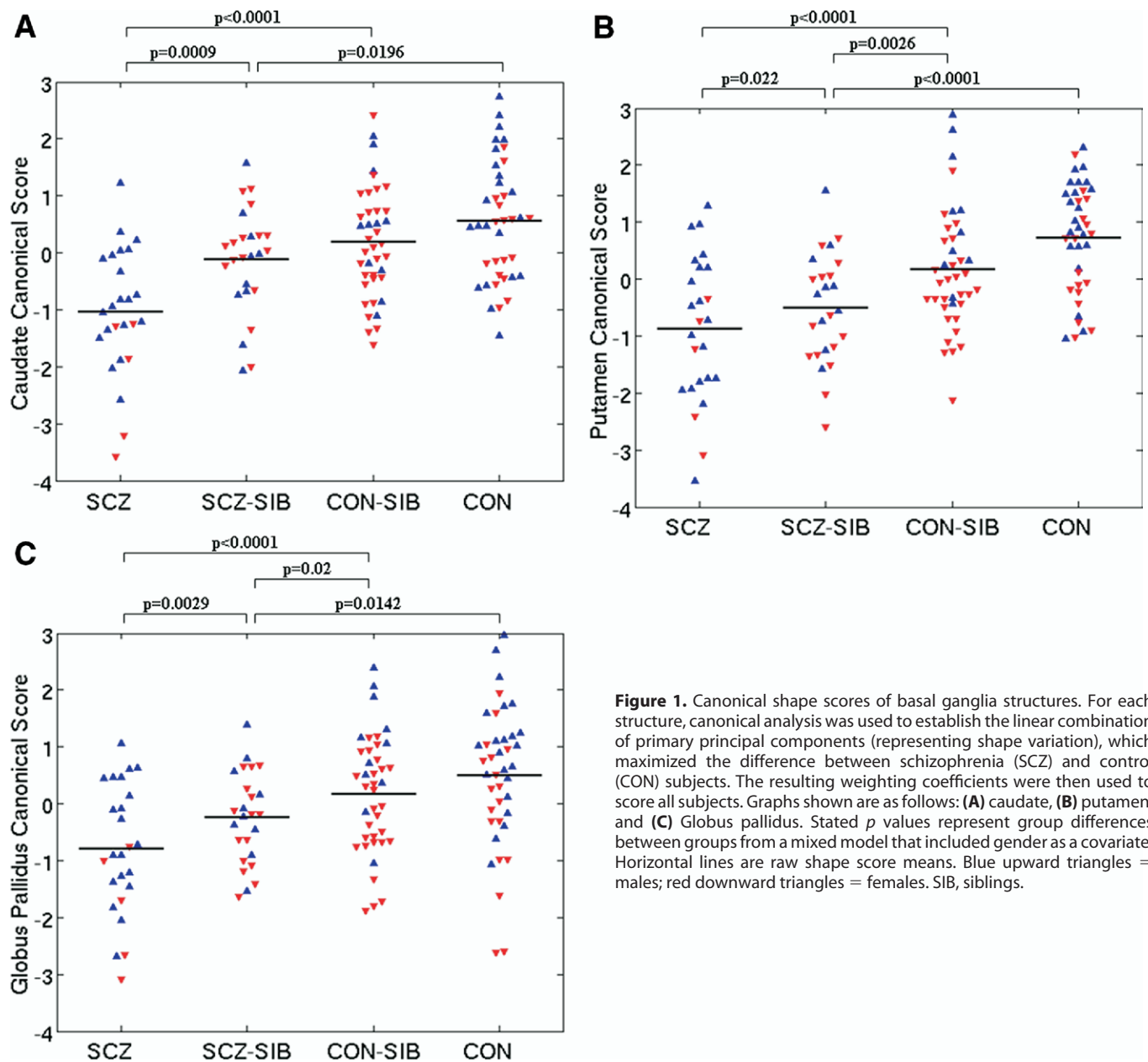


Figure 1. Canonical shape scores of basal ganglia structures. For each structure, canonical analysis was used to establish the linear combination of primary principal components (representing shape variation), which maximized the difference between schizophrenia (SCZ) and control (CON) subjects. The resulting weighting coefficients were then used to score all subjects. Graphs shown are as follows: **(A)** caudate, **(B)** putamen, and **(C)** Globus pallidus. Stated *p* values represent group differences between groups from a mixed model that included gender as a covariate. Horizontal lines are raw shape score means. Blue upward triangles = males; red downward triangles = females. SIB, siblings.

and SCZ-SIB were 1) an inward deformation in a moderate-sized region dorsally on the right and anterodorsally on the left in SCZ (in SCZ-SIB, a smaller region was inwardly deformed anterior-dorsally on the left) and 2) a small inward deformation posteromedially in SCZ, not notable in SCZ-SIB.

Substance and Alcohol Effects on Shapes

When comparing canonical shape scores between groups, the inclusion of either: 1) a lifetime history of alcohol and cannabis dependence or 2) total grams of alcohol consumed over the previous 2 years as additional covariates did not alter the results (Table 3). Further, none of these three covariates had a significant relationship with the canonical shape scores of any of the basal ganglia structures.

Shape and Volume Relationships to Clinical Symptoms

Using lifetime psychopathology measures derived from the SCID, significant correlations were observed in SCZ subjects

between the severity of hallucinations and the volume of the caudate (Spearman's $r = -.62$, $p = .001$) and globus pallidus ($r = -.39$, $p = .05$); a trend toward significance was also found for the putamen ($r = -.38$, $p = .059$). After covarying for cerebral volume, the correlation between lifetime hallucination severity and caudate volume was still nearly significant ($r = -.40$, $p = .054$). There was also a near-significant correlation between the lifetime severity of negative symptoms and putamen volume ($r = .39$, $p = .054$), which became significant after covarying for cerebral volume ($r = .45$, $p = .03$). Finally, there was a significant relationship between hallucination severity and caudate shape scores ($r = -.49$, $p = .01$). Similar analyses performed in SCZ-SIB (who had little variability in their lifetime psychopathology scores) did not show any significant relationships.

Using current psychopathology measures obtained from standardized tests in SCZ, a significant correlation was observed between the severity of thought disorganization and the caudate

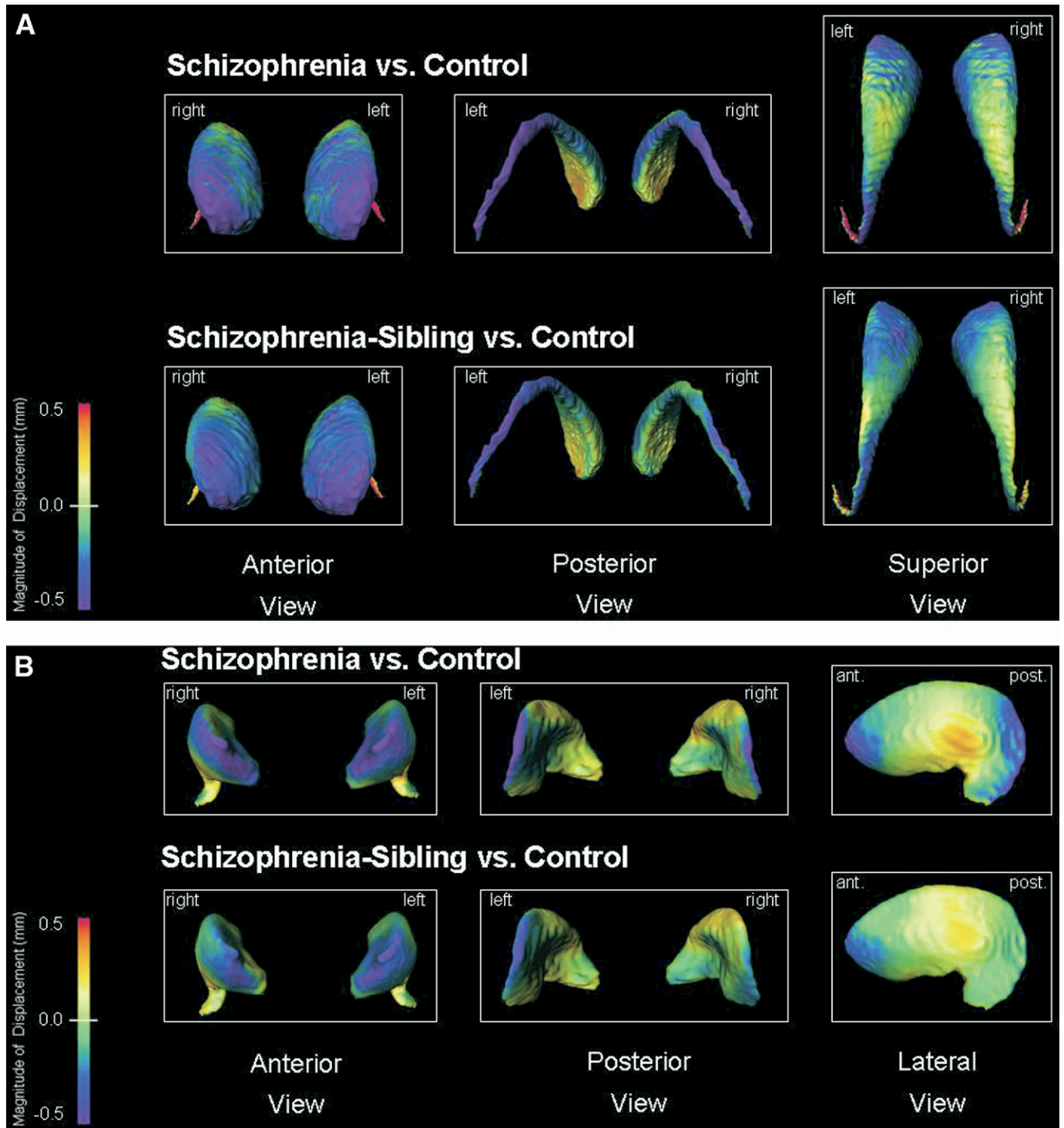


Figure 2. Basal ganglia surface map abnormalities in schizophrenia subjects (SCZ) and their unaffected siblings (SCZ-SIB). Structures shown are as follows: **(A)** caudate, **(B)** putamen, and **(C)** globus pallidus. Figures represent mean estimated displacement between subject groups, controlling for gender. Surface displacement maps were obtained by first computing for every structure and subject the surface-normal component of the displacement of each surface point of that structure relative to the average surface of all 130 subjects. The least square mean of these displacements for each group (and surface point) was then computed, controlling for gender. Finally, the difference of these least square means between the two selected subject groups was displayed as a color map (overlaid on the mean surface of the control [CON] subjects). Purple-to-blue shading denotes regions of inward deformation compared with CON. Red-to-orange shading denotes regions of outward deformation compared to CON. For the SCZ versus CON maps in the caudate, the largest inward deformation was .8 mm bilaterally in its anterior, whereas for the SCZ-SIB versus CON maps the inward deformation in this area was .6 mm bilaterally. For the SCZ versus CON maps in the putamen, the inward deformation was .7 mm bilaterally in its anterior, whereas the largest inward deformation was .8 mm posteriorly on the left side only. All other maximum deformations were approximately .5 mm or smaller and thus were well captured by the indicated color scale. The lateral view of the putamen showed a similar surface pattern on both left and right sides.

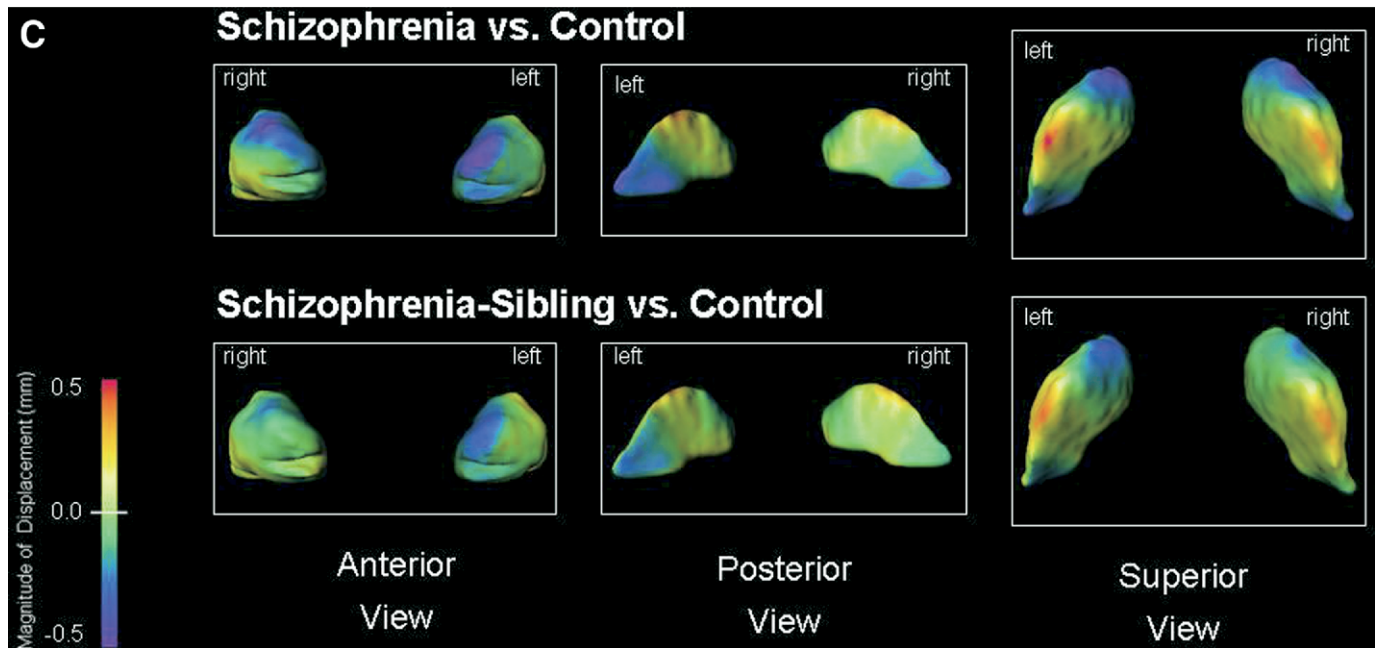


Figure 2. (Continued)

shape score ($r = -.39, p = .05$). No other significant relationships between basal ganglia shape measures or volumes and the severity of current psychopathology were found in SCZ or SCZ-SIB subjects. There was also no significant relationship between the duration of illness of SCZ and either the canonical shape score or volume of any basal ganglia structure.

Discussion

In this study, we did not find significant differences in basal ganglia volumes across the four subject groups after controlling

for cerebral volume. However, when caudate volumes were not adjusted for cerebral volume, they were smaller in SCZ and SCZ-SIB than in control subjects. Our failure to find a relative increase in basal ganglia volume measures in SCZ differs from the results of other studies. This may be because few of our SCZ were currently receiving typical antipsychotic drugs, which has been linked to such increases in other studies (52,53). In turn, and more consistent with our results, the use of atypical antipsychotic drugs have not usually been associated with alterations in basal ganglia size (54,55).

Table 3. Statistical Significance of Basal Ganglia Shape Score Differences Between Groups

Subject Groups Compared	Structure	Gender	Covariates Included in Mixed Model Analysis	
			Gender + History of Alcohol and Cannabis Dep.	Gender + 2 yr Amount of Alcohol
SCZ vs. SCZ-SIB	Caudate	.0009	.0017	.0006
	Putamen	.022	.023	.02
	Globus pallidus	.0029	.0031	.0029
SCZ vs. CON-SIB	Caudate	<.0001	<.0001	<.0001
	Putamen	<.0001	<.0001	<.0001
	Globus pallidus	<.0001	<.0001	<.0001
SCZ-SIB vs. CON	Caudate	.0196	.032	.034
	Putamen	<.0001	<.0001	<.0001
	Globus pallidus	.0142	.012	.017
SCZ-SIB vs. CON-SIB	Caudate	ns	ns	ns
	Putamen	.0026	.0023	.0036
	Globus pallidus	.02	.016	.025
CON vs. CON-SIB	Caudate	ns	ns	ns
	Putamen	ns	ns	ns
	Globus pallidus	ns	ns	ns

CON, control subjects; Dep., dependency; ns, not statistically significant ($p > .05$); SCZ, schizophrenia subjects; SIB, siblings.

Values are p values generated by comparing univariate canonical shape scores and including as covariates: gender or gender and either 1) lifetime history of alcohol and cannabis dependence or 2) 2-year cumulative amount of alcohol consumed. Shape scores were derived from canonical analysis of shape principal components in SCZ and CON. Notably, the multivariate analysis of variance contrast between the SCZ and CON groups was significant in all three basal ganglia structures [caudate: $F(15,111) = 2.5, p = .003$; putamen: $F(15,111) = 2.0, p = .02$; globus pallidus: $F(15,111) = 2.8, p = .001$], thus providing a basis for the canonical analysis comparing canonical scores of the SCZ-SIB and CON-SIB to the other groups. This analysis strategy maximized the power to detect differences between groups (as defined by the SCZ vs. CON difference).

Despite the absence of volume differences between groups, we found significant shape abnormalities of every basal ganglia structure in SCZ. We also found that the unaffected siblings of these subjects demonstrate deformities in the shape, but of lesser in magnitude, of the basal ganglia in regions similar to those found in their affected siblings. The most notable shape found in SCZ and SCZ-SIB was an inward deformity on the anterior surface of the caudate and putamen. This pattern of structural change may have functional consequences because of topographic projections from these anterior basal ganglia regions to areas of the prefrontal, orbitofrontal, and limbic cortices (56–58). Several other regional abnormalities were also observed in the basal ganglia of both SCZ and SCZ-SIB. Structural deficits noted in posteromedial regions of the globus pallidus or the posterior edge of the putamen, for example, could be involved in neurologic “soft signs” sometimes observed in schizophrenia patients and their unaffected relatives (5,6) because of the roles of these regions in motor coordination (59).

Our findings of similar basal ganglia structural abnormalities in SCZ-SIB may indicate that such changes are related to genetic influences that predispose individuals to develop schizophrenia (60). However, these structural changes could also be traits that cosegregate with the disorder in families but are not directly relevant to the psychopathology of schizophrenia. Although not directly addressed by our data, basal ganglia abnormalities may have some relation to premorbid behavioral symptoms or cognitive deficits that have been found in the relatives of patients with schizophrenia (61,62).

Structural deficits of the caudate and putamen in SCZ from this study are highly similar but appear more pronounced than those observed in our prior study of a nonoverlapping group of subjects with schizophrenia (36). The subjects in our prior study were older and had a longer duration of illness and therefore were probably exposed to larger cumulative amounts of typical antipsychotics than subjects in this study. The effect of typical antipsychotics, which are known to increase basal ganglia size (63,64), could have minimized a potentially greater basal ganglia structural deficit. As mentioned earlier, the large majority of SCZ subjects in this study were receiving atypical antipsychotic drugs.

The abnormalities in basal ganglia shape observed may not necessarily imply volume changes in exact proximity to the areas of surface change. Abnormalities could lie deeper within the basal ganglia, which could be clarified by postmortem neuropathologic studies. Such studies would provide insights into the microscopic nature of surface shape abnormalities; for example, whether they represent changes in parenchymal volume (i.e., neuropil, somal, or both) or physiologic compensations (e.g., dendritic, vascular, or osmotic) to altered activity (65). Postmortem studies in schizophrenia have previously demonstrated reductions in neuropil volume in the cerebral cortex and the hippocampus with a corresponding increase in neuronal density (66).

The canonical shape scores of SCZ-SIB were intermediate between those of SCZ and CON in all three of the basal ganglia structures, indicating that SCZ-SIB have attenuated forms of the structural abnormalities observed in SCZ. Statistically significant differences in canonical scores were not observed between CON and CON-SIB subjects for any of the three structures. This is of particular interest because CON and CON-SIB had different recruitment criteria, the latter group being allowed to have a history of major mood disorder (i.e., major depression or bipolar disorder). This suggests that the presence of major mood disorder

has little association with schizophrenia-like basal ganglia structural abnormalities.

We found an inverse relationship between the lifetime severity of hallucinations and caudate volume in SCZ subjects. Similar inverse relationships were also observed between a “schizophrenia-like” caudate canonical shape score and hallucination severity, as well as a similar, but less significant, correlation between hallucination severity and the volume of both the globus pallidus and putamen. Thus, abnormalities of basal ganglia structure, perhaps especially of the caudate, may be associated with impaired sensory perception and manifested as hallucinations. We also found a near-significant relationship between the lifetime severity of negative symptoms and putamen volume, which could suggest unique role for this structure in alogia, avolition, or affective blunting. Notably, prominent correlations were not found between the neuroanatomic measures and current severity of psychopathology, except for a relationship between a schizophrenia-like caudate shape and thought disorganization. Because psychosis severity often fluctuates within a short period, it may be difficult to correlate the current severity of such pathology with neuroanatomic measures (66,67). Rather, structural changes may be more closely related to lifetime measures of psychopathology severity.

Both schizophrenia patients and their unaffected siblings have been reported to have increased substance use compared with the general population (68,69). It is therefore plausible that some of the structural abnormalities observed in this study might have been influenced by substance use. However, after volume and shape results were controlled for lifetime substance dependence and the amount of alcohol used, there were no significant changes from our original findings, and these covariates themselves were not significant predictors of either volume or canonical scores. We were not able to evaluate the effects of milder degrees of substance use (i.e., those not meeting criteria for DSM-IV substance dependence) or the cumulative amounts of other drugs, which could potentially influence our results. Future studies designed to study specific associations between various degrees of substance use and brain structure are critical for validating structural findings in psychiatric disorders, due to their high comorbidity with drug use (70).

Additional studies could provide insight into the role of specific genotypes in the development of basal ganglia structural findings in schizophrenia. For example, a coding polymorphism (rs6280/Ser9Gly) has been reported at the gene for the dopamine D3 receptor (71), which is highly expressed specifically in limbic regions of the basal ganglia (72–74). However, little is known about the associations between such polymorphisms and structural abnormalities in schizophrenia. Valine substituted polymorphisms at the gene for catechol-O-methyltransferase (COMT), which degrades extracellular dopamine, have been related to smaller anterior cingulate gray matter in high-risk relatives of schizophrenia subjects (75). Distinct patterns of shape abnormality may serve as potential endophenotypes by fulfilling at least some criteria proposed by Gottesman and Gould in 2003 (60). In the case of the measures studied here, the structural abnormalities were similarly present in affected and unaffected family members. Furthermore, there did not appear to be a strong relationship with “current” illness severity, suggesting “state-independence.” However, the specificity of the noted neuroanatomic findings to schizophrenia, observed in this and our previous study (36), requires further research.

Structural studies of the basal ganglia in various diagnostic populations could help to gain a better understanding the

relation between structure and clinical symptoms. We hope to follow the unaffected siblings of schizophrenia subjects included in this study prospectively to determine whether the structural differences observed predict the future appearance of schizophrenia psychopathology.

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