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Structural analysis of the basal ganglia in schizophrenia

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Abstract

Increases in the total volume of basal ganglia structures have been reported in schizophrenia. However, patterns of basal ganglia shape change, which can reveal localized changes in substructure volumes, have not been investigated. In this study, the total volume and shape of several basal ganglia structures were compared in subjects with and without schizophrenia.

T_1-weighted magnetic resonance scans were collected in 54 schizophrenia and 70 comparison subjects. High-dimensional (large-deformation) brain mapping was used to assess the shape and volume of several basal ganglia structures. The relationships of shape and volume measures with psychopathology, cognition and motor function were also assessed.

Left and right volumes of the caudate and putamen, as well as the right globus pallidus volume, were significantly increased in subjects with schizophrenia as compared to comparison subjects after total brain volume was included as a covariate. Significant differences in shape accompanied these volume changes in the caudate, putamen and globus pallidus, after their total volumes were included as covariates. There were few significant correlations between volume or shape measures and either cognitive function or clinical symptoms, other than a positive correlation between an attention/vigilance cognitive dimension and the volume of the caudate and putamen, and a negative correlation between nucleus accumbens volume and delusions.

In conclusion, basal ganglia volumes relative to total brain volume were larger in schizophrenia subjects than healthy comparison subjects. Specific patterns of shape change accompanied these volume differences.

Keywords: Schizophrenia; Basal ganglia; Caudate; Putamen; Globus pallidus; Nucleus accumbens; Structural neuroimaging; High-dimensional brain mapping; Shape analysis

1. Introduction

The basal ganglia are a collection of nuclei deep within the cerebrum. These nuclei include the caudate, the nucleus accumbens and the putamen – which are collectively called the *striatum*, and also the globus pallidus, the subthalamic nucleus and the substantia nigra. Through their extensive cortical connections, the basal ganglia can influence both motor and cognitive functions (Parent and Hazrati, 1995; DeLong, 2000). There has been increasing evidence for the involvement of the basal ganglia in cognitive and behavioral syndromes (Levy et al., 1997; Mendez et al., 1989). Also, emotional and cognitive dysfunction has been

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observed in basal ganglia-related movement disorders (Zgaljardic et al., 2003; Joel, 2001).

Abnormal activity of the basal ganglia has been reported in subjects with schizophrenia at rest and during various cognitive tasks by several investigators (Manoach et al., 2000; Menon et al., 2001). However, structural imaging studies of the basal ganglia in schizophrenia have yielded less consistent results. Most investigators report enlargement of the volumes of various basal ganglia (Staal et al., 2000; McCarley et al., 1999; Breier et al., 1992), although normal (Gunduz et al., 2002) or even decreased volumes (Corson et al., 1999; Keshavan et al., 1998) have also been reported. Basal ganglia enlargement, when found, has usually been interpreted to be the result of exposure to antipsychotic medications.

In contrast to volume studies, there have been few studies of basal ganglia shape or conformation in schizophrenia (however see Shihabuddin et al., 1998). Shape assessment can be used to demonstrate subtle abnormalities in the contouring of a structure that reflect localized changes in regional subvolumes (Csernansky et al., 1998, 2002). Also, comparing the shape of a structure can allow for better discrimination between normal and pathologic conditions than that observed by comparing the volume alone (Csernansky et al., 2002, 2004). We have previously used large-deformation high-dimensional brain mapping (HDBM-LD; Haller et al., 1997; Wang et al., 2001) to characterize the shape of the hippocampus (Csernansky et al., 2002) and thalamus (Csernansky et al., 2004) in patients with schizophrenia.

In the present study, we used HDBM-LD to compare the shape, as well as the symmetry and volume, of several basal ganglia structures in 54 schizophrenia subjects and 70 healthy subjects. The relationships between the neuroanatomical measures (i.e. volume and shape) and selected clinical and cognitive features of the subjects were assessed in an exploratory analysis.

2. Methods

2.1. Subjects

The demographic and clinical characteristics of the 54 schizophrenia and 70 comparison subjects are summarized in Table 1. The majority of these subjects were included in prior studies of hippocampal and thalamic shape (Csernansky et al., 2002, 2004). All subjects were diagnosed using DSM-IV criteria on the basis of a consensus between a research psychiatrist who conducted a semi-structured interview and a trained research assistant who used the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995). The healthy comparison subjects had no prior history of mental illness, nor any first-degree relative with a psychotic disorder. Subjects were excluded if they had neurologic disorders,

Table 1
Demographic and clinical characteristics of schizophrenia and healthy comparison subjects

Characteristic	Schiz $n=54$	Control $N=70$
Age (yrs)	37.6 (12.3)	39.1 (14.3)
Gender – *n* (%)		
Male	32 (59.3)	35 (50.0)
Female	22 (40.7)	35 (50.0)
Race – *n* (%)		
Caucasian	22 (40.7)	41 (58.6)
African American	30 (55.6)	28 (40.0)
Other	2 (3.7)	1 (1.4)
Handedness – *n* (%)		
Right	48 (88.9)	65 (92.9)
Left	6 (11.1)	5 (7.1)
Parental SES[a]	4.1 (0.9)	3.6 (1.0)
Illness duration (yrs)	12.9 (12.5)	n/a
Neuroleptic (*n*)		
Risperidone	21	0
Olanzapine	13	0
Haloperidol	7	0
Clozapine	2	0
Thiotixene	1	0
Fluphenazine	1	0
Risperidone or haloperidol[b]	5	0
Quetiapine and fluphenazine	2	0
Risperidone and haloperidol	1	0
None	1	70
Anticholinergic (*n*)		
Benztropine	17	0
Trihexphenidyl	1	0
SAPS[c]		
Total	18.9 (17.2)	n/a
Delusions	9.6 (10.5)	n/a
Hallucinations	4.1 (5.7)	n/a
Disorganized behavior	1.3 (2.3)	n/a
SANS[d]		
Total	21.9 (14.5)	n/a
Affect	8.5 (6.3)	n/a
Alogia	4.0 (3.4)	n/a
Avolition/apathy	4.3 (3.2)	n/a
Anhedonia/asociality	4.9 (4.0)	n/a
Attention	2.1 (2.1)	n/a
ESRS[e]		
Dyskinesia	1.39 (2.04)	n/a
Parkinsonism	1.28 (2.60)	n/a
Dystonia	1.07 (2.26)	n/a

Values are means (standard deviation) unless stated otherwise.
n/a=not applicable.
[a] Socioeconomic status. Higher values indicate lower socioeconomic status.
[b] Investigators were blinded to subjects' neuroleptic regimen.
[c] Scale for the Assessment of Positive Symptoms.
[d] Scale for the Assessment of Negative Symptoms.
[e] Extrapyramidal Symptom Rating Scale.

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unstable medical disorders, head injury with loss of consciousness, or if they met DSM-IV criteria for substance abuse or dependence during the 3 months preceding the study. A distant lifetime history of substance abuse or dependence was reported by 14 schizophrenic subjects and 7 comparison subjects. Handedness was evaluated in all subjects (Oldfield, 1971).

All schizophrenic subjects were clinically stable; the global severity of their symptoms had remained unchanged for at least 2 weeks. 19 of the schizophrenia subjects had one or more extrapyramidal motor symptoms (dyskinesia, dystonia or parkinsonism) ranging in severity from borderline to moderately severe. In the subjects who were receiving antipsychotic drugs, their most recent (last 4 weeks) drug treatment was categorized as either typical or atypical. Atypical antipsychotic drugs included risperidone, olanzapine, clozapine and quetiapine. Typical antipsychotic drugs included haloperidol, thiothixene, and fluphenazine. The median duration of treatment was 12 weeks (range 1 to 520 weeks) with atypical drugs and 78 weeks (range 2 to 468 weeks) with typical drugs.

2.2. Rating of clinical function

The severity of psychopathology was assessed in the schizophrenia subjects using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen et al., 1995; Andreasen and Olsen, 1982).

To investigate relationships between neuroanatomical variables and specific domains of cognitive function, a principal component analysis was applied to data from a battery of neuropsychological tests. The principal axis method was used to extract the components, followed by a Varimax (orthogonal) rotation. Significant test items and corresponding factor loadings are presented in Table 2. This PCA identified some factors that were similar to, although not identical to, cognitive domains previously reported in groups of schizophrenic patients (Nuechterlein et al., 2004).

Extrapyramidal motor symptoms of schizophrenia subjects were evaluated by a psychiatrist using the Extrapyramidal Symptom Rating Scale (ESRS) (Gharabawi et al., 2005). From the ESRS, performance on the clinical global impression of severity of dyskinesia, parkinsonism and dystonia were used to assess correlations between motor symptoms and neuroanatomical measures.

2.3. Image acquisition and preprocessing

Magnetic resonance (MR) scans were collected using a turbo-fast low-angle shot (turbo-FLASH) sequence (TR = 20, TE = 5.4, flip angle = 30 degrees, number of acquisitions = 1, matrix = 256 × 256, scanning time = 13.5 minutes) that acquired three-dimensional datasets with 1 mm × 1 mm × 1 mm isotropic voxels across the entire cranium (Vankatesan and Haacke, 1997). Raw MR data were reformatted for analysis using Analyze software (Rochester, Minn.), and signed 16-bit MR datasets were compressed to unsigned 8-bit MR datasets by linearly rescaling voxel intensities such that voxels with intensity levels at two standard deviations above the mean of white matter (corpus callosum) were mapped to 255, and voxels with intensity levels at two standard deviations below the mean of CSF (lateral ventricle) were mapped to 0. The white matter and CSF means and standard deviations were obtained by sampling voxels from these respective regions.

Landmarks were placed in all scans at the external boundaries of the brain, and at points where the anterior and posterior commissures intersect the midsagittal plane (Haller et al., 1997). Additional landmarks were also placed at selected points throughout structures of interest as previously described (Wang et al., in press). These landmarks provided starting values for HDBM-LD (see below).

2.4. Large-deformation high-dimensional brain mapping (HDBM-LD)

An MR scan collected from a healthy comparison subject not otherwise included in the study was used to construct the neuroanatomical template. The basal ganglia in the right hemisphere were manually outlined in this scan by expert raters (MG, LW) according to a priori neuroanatomical guidelines. Target scans were landmarked at defined positions within the basal ganglia-thalamus complex that corresponded to landmarks placed in the template scan.

Transformation of the template onto the target MR scans occurred in a two-step process. First, it was coarsely aligned to the left and right sides of each target scan by using the landmarks, and then a probabilistic, large-deformation transformation was applied to it (Miller et al., 1997). During this transformation, the movement and deformation of template voxels were constrained by assigning them the physical properties of a fluid. The reliability and validity of high-dimensional brain mapping for segmenting subcortical structures with respect to expert manual outlining has been previously demonstrated (Haller et al., 1997). To check the validity of high-dimensional brain mapping as used in this study, we compared the segmentations generated by this process to those manually outlined by experts (M.G., L.W.) in the MR scans of a randomly selected subgroup of 10

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Table 2
Rotational factor pattern from principal component analysis of neuropsychological tests administered to schizophrenic patients ($N=54$)

Neuropsychological tests	Cognitive Factor						
	1	2	3	4	5	6	7
Phonological Verbal Fluency	0.16	0.23	0.13	−0.05	0.03	**0.86**	0.11
Categorical Verbal Fluency (animals)	0.12	0.32	−0.17	**0.46**	0.15	**0.67**	0.11
Trails B	**0.78**	0.24	0.16	0.33	0.07	0.14	0.06
WAIS-III Picture Completion	0.21	0.28	**0.72**	0.15	−0.17	0.15	0.28
WAIS-III Vocabulary	0.16	**0.79**	0.28	0.16	0.01	0.35	0.05
WAIS-III Digit Symbol	**0.42**	−0.00	0.27	**0.48**	−0.08	**0.54**	0.04
WAIS-III Similarities	0.11	**0.49**	0.62	0.05	0.17	0.38	−0.09
WAIS-III Block Design	**0.66**	0.34	**0.53**	−0.01	0.02	0.19	0.09
WAIS-III Arithmetic	**0.42**	0.39	**0.46**	0.07	**0.51**	−0.21	−0.01
WAIS-III Matrix Reasoning	**0.66**	0.04	**0.56**	0.11	0.13	0.14	−0.02
WAIS-III Digit Span	0.37	**0.75**	0.02	−0.05	0.27	−0.05	0.21
WAIS-III Information	0.14	**0.74**	0.39	−0.04	0.02	0.28	−0.08
WAIS-III Picture Arrangement	**0.82**	−0.05	0.09	0.13	0.13	0.33	−0.01
WAIS-III Comprehension	0.02	**0.89**	−0.04	0.27	0.10	0.09	0.01
BVRT (immediate recall)	**0.66**	0.04	0.23	0.01	0.26	0.07	**0.41**
WMS-III Logical Memory	0.05	0.29	−0.11	0.34	**0.66**	0.07	0.37
WMS-III Faces	0.15	0.01	0.14	0.02	−0.01	0.02	**0.80**
WMS-III Verbal Pairs	0.09	0.08	0.16	−0.10	**0.76**	0.20	**0.45**
WMS-III Family Pictures	0.16	0.09	−0.00	**0.46**	0.20	0.20	**0.65**
WMS-III Letter Number Sequencing	**0.68**	0.51	−0.03	0.02	0.20	−0.04	0.21
WMS-III Spatial Span	**0.72**	0.34	0.28	0.27	0.09	−0.06	0.28
WMS-III Word Lists	0.27	0.05	−0.04	0.10	**0.75**	−0.02	−0.26
CPT-IP (overall d-prime)	0.25	−0.04	**0.80**	0.22	0.05	−0.10	0.13
WCST Categories Completed	0.29	0.09	0.05	**0.82**	0.05	0.05	0.19
WCST Perseverative Errors	0.03	0.13	0.36	**0.80**	0.09	0.05	−0.03

WAIS-III = Wechsler Adult Intelligence Scale – Third Edition; BVRT = Benton Visual Retention Test; CPT-IP = Continuous Performance Test, identical pairs version; WMS-III = Wechsler Memory Scale – Third Edition; WCST = Wisconsin Card Sorting Test.
Factor loadings greater than .40 are in bold.

subjects. Values estimating the overlap of caudate, putamen and globus pallidus contours produced by HDBM versus manual outlining averages exceeded 80% in all subjects, which is comparable to the accuracy of repeated attempts at manual outlining of these structures by the same expert. The values estimating overlap of the nucleus accumbens contours produced by HDBM versus manual outlining approached but did not exceed 80% in all subjects. Total cerebral volumes were derived using elastic-based transformations of the template scan (Miller et al., 1997) so that comparisons of structural volume could be performed using total cerebral volume as a covariate.

To quantify the shape and volume of individual structures, a triangulated surface was first superimposed onto each structure outlined in the template scan. These surfaces were then carried along as the template scan was transformed to match left and right sides of each of the target scans. Volumes of the selected basal ganglia were calculated by computing the volumes enclosed by the transformed surfaces. To compare structural shapes between subject groups, vector fields were derived from the displacements of the triangulated surface points during the transformations. The pooled covariance of the vector fields yielded eigenvalues and a complete orthonormal set of eigenvectors representing shape variation for the population under study via singular value decomposition (Joshi et al., 1997). Coefficients (eigenscores) associated with these eigenvalues and eigenvectors were then calculated for each structures in each hemisphere in every subject. Eigenscores based on the fewest number of eigenvectors needed to explain ~75% of the total variance (i.e. 10) were then used for statistical analysis.

2.5. Statistical analysis

All statistical analyses were performed using SAS 9.0 software. Structural volumes were analyzed using one-way analysis of variance with diagnostic group as an independent variable. Group comparisons of individual structural volumes were repeated using cerebral volume as a covariate, since cerebral volume ($F=4.59$, $df=1$, 122, $p<0.05$; see Table 3) but not intracranial volume

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Table 3
Cerebral and basal ganglia volumes in schizophrenic subjects ($n=54$) and healthy comparison subjects ($N=70$)

Brain structure	Side	SCHIZ Total (mm^3) $N=54$	SCHIZ[a] Typical neuroleptic (mm^3) $N=9$	SCHIZ[a] Atypical neuroleptic (mm^3) $N=35$	Control (mm^3) $N=70$
Caudate	Left	3408 (382)	3384 (549)	3396 (342)	3345 (406)
	Right	3336 (394)	3342 (645)	3350 (341)	3279 (416)
Nucleus accumb.	Left	409 (85)	416 (77)	405 (94)	420 (62)
	Right	409 (79)	396 (64)	407 (87)	416 (68)
Putamen	Left	4679 (577)	4671 (710)	4648 (577)	4701 (510)
	Right	4576 (584)	4566 (759)	4550 (558)	4568 (483)
Globus pallidus	Left	1564 (207)	1559 (218)	1553 (208)	1606 (175)
	Right	1590 (206)	1584 (253)	1584 (196)	1596 (174)
Cerebrum[b]	Total	952,636 (120,789)	943,223 (124,758)	954,746 (123,843)	996,853 (108,321)

Values are displayed as volumes (standard deviation).

[a] Only those schizophrenic subjects on typical ($N=9$) or atypical ($n=35$) neuroleptic monotherapy at the time of assessment were included in this analysis. Subjects on multiple neuroleptics or on neuroleptics blinded to investigators were not included in the analysis.

[b] The *cerebrum* is comprised largely of the cerebral hemispheres and the structures within. (The *cranium* comprises of the cerebrum and other structures in the intracranial cavity, including the brain stem and the cerebellum).

($F=3.7$, $df=1, 122$, $p=0.06$) showed significant group differences in volume.

To compare the shape of the basal ganglia between groups, the first 10 eigenvectors representing variation in the shape of each structure were selected a priori. These eigenvectors were then used in a one-way multiple analysis of variance, with diagnostic group as an independent variable, to test the hypothesis there was a significant group effect on shape. Then, to identify the eigenvectors that contributed most to group discrimination, a logistic backward regression was performed using a significant likelihood ratio statistic for discrimination. The eigenvectors selected by the logistic regression model were later used in a "leave-one-out" discrimination function analysis to determine the percentage of correctly classified subjects in each group.

To visualize the physical pattern of basal ganglia shape difference between groups, we reconstructed maps of the composite surfaces of individual structures in the schizophrenia and comparison subjects at every point on the graphical surfaces for each of the structures. The displacements were calculated at each surface point as the difference between the means of the group vectors in magnitude.

Bivariate correlations between volume measures and clinical measures of psychopathology, motor function, and performance on the various cognitive domains were examined in the schizophrenia subjects on an exploratory basis, using non-parametric statistics. To examine the relationship between shape and clinical measures, the canonical variate discriminating groups was determined separately for each of the basal ganglia structures using its shape eigenvectors. Correlations between these canonical variables and clinical measures were determined using bivariate statistics.

3. Results

3.1. Combined basal ganglia volumes

Mean combined volume of all basal ganglia structures that were assessed was 19,972 mm^3 (SD=2284) in the schizophrenic subjects and 19,930 mm^3 (SD=2061) in the comparison subjects. The volume difference between groups was not statistically significant. After covarying the combined basal ganglia volumes for total cerebral volume, the effect of diagnosis became significant ($F=7.58$, $df=1, 122$, $p<0.007$).

3.2. Caudate volume and shape

The effect of diagnosis on left and right caudate volumes was not significant (Table 3). After covarying caudate volumes for total cerebral volumes, the effect of diagnosis became significant on the left ($F=10.76$, $df=1, 122$, $p<0.002$; see Fig. 1A) and right ($F=7.51$, $df=1, 122$, $p<0.01$; see Fig. 1B). In both cases the schizophrenia subjects had larger caudate volumes relative to total cerebral volumes than the comparison subjects. This result was not affected by covarying caudate volumes for age, gender, race, handedness, type of antipsychotic drug treatment (i.e., atypical versus typical), or a lifetime history of substance abuse/dependence.

Using the first 10 eigenvectors representing the shape of the left and right caudate nucleus, a MANOVA revealed a trend towards a significant group effect (Wilks' Lambda=0.86, $p=0.07$). The group effect became highly significant after including caudate volume as a covariate in the analysis (Wilks' Lambda=0.79, $p=0.002$). Eigenvectors 3 and 8 maximally discriminated the 2 subject groups. In a "leave one out" discriminant function

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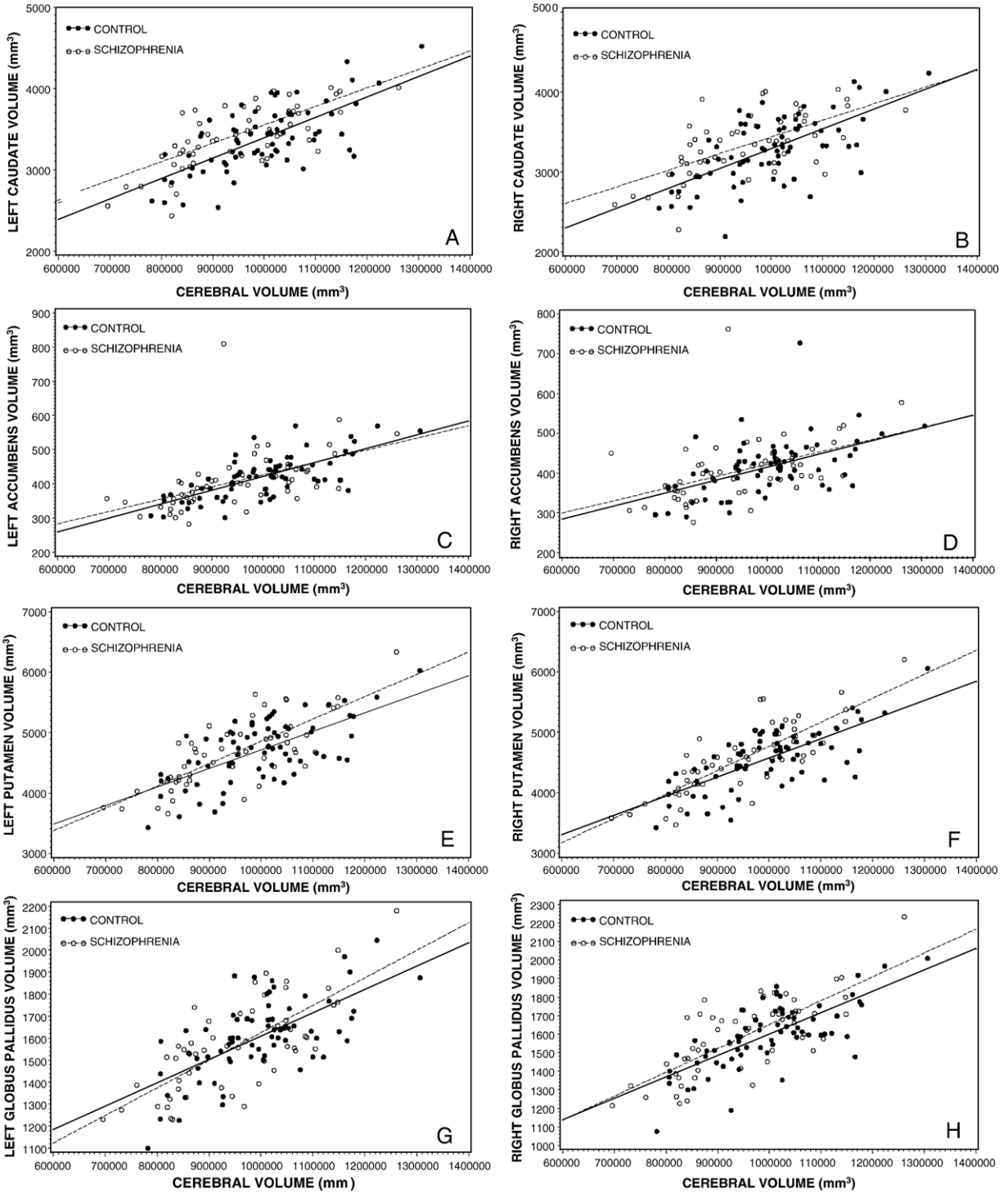

Fig. 1. Volumes of basal ganglia structures in relation to cerebral volume in schizophrenia subjects ($N=54$) and healthy comparison subjects ($N=70$). Solid line (and filled circle) represent comparison subjects; and dashed line (and open circle) represent schizophrenia subjects. Volumes are given in mm^3. A) Left caudate, B) right caudate, C) left nucleus accumbens, D) right nucleus accumbens, E) left putamen, F) right putamen, G) left globus pallidus, and H) right globus pallidus.

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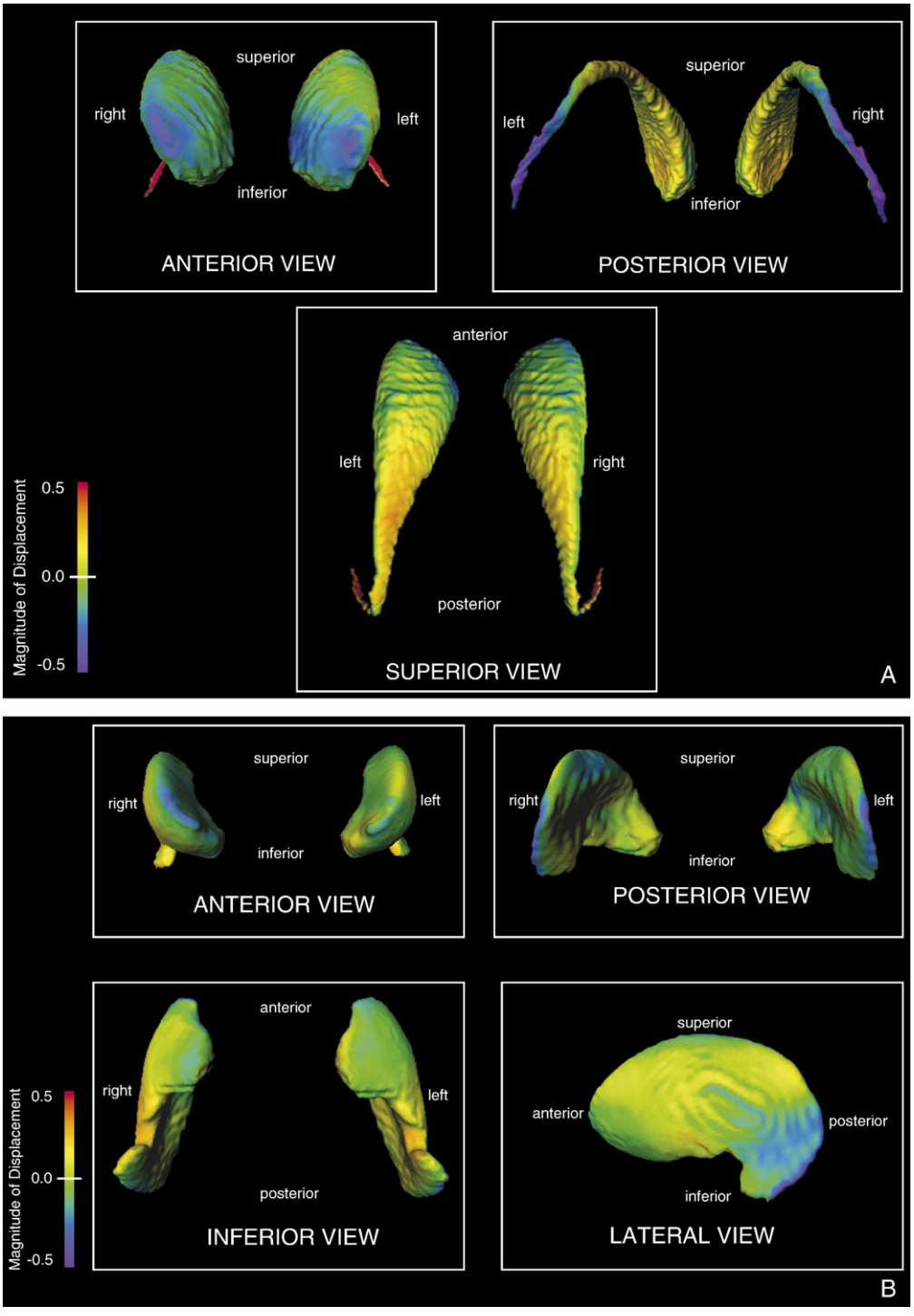

Fig. 2. Surface maps depicting basal ganglia shape difference in schizophrenia subjects ($N=54$) and healthy comparison subjects ($N=70$). Blue-to-purple shading denotes regions of inward deformity of the basal ganglia surfaces in schizophrenia versus comparison subjects. Red-to-orange shading denotes regions of outward deformity. A) Caudate, B) putamen, C) globus pallidus, and D) composite basal ganglia which shows the caudate, the putamen, the globus pallidus and the nucleus accumbens. Right-sided structures are labeled as C (caudate), A (nucleus accumbens), P (putamen), and G (globus pallidus).

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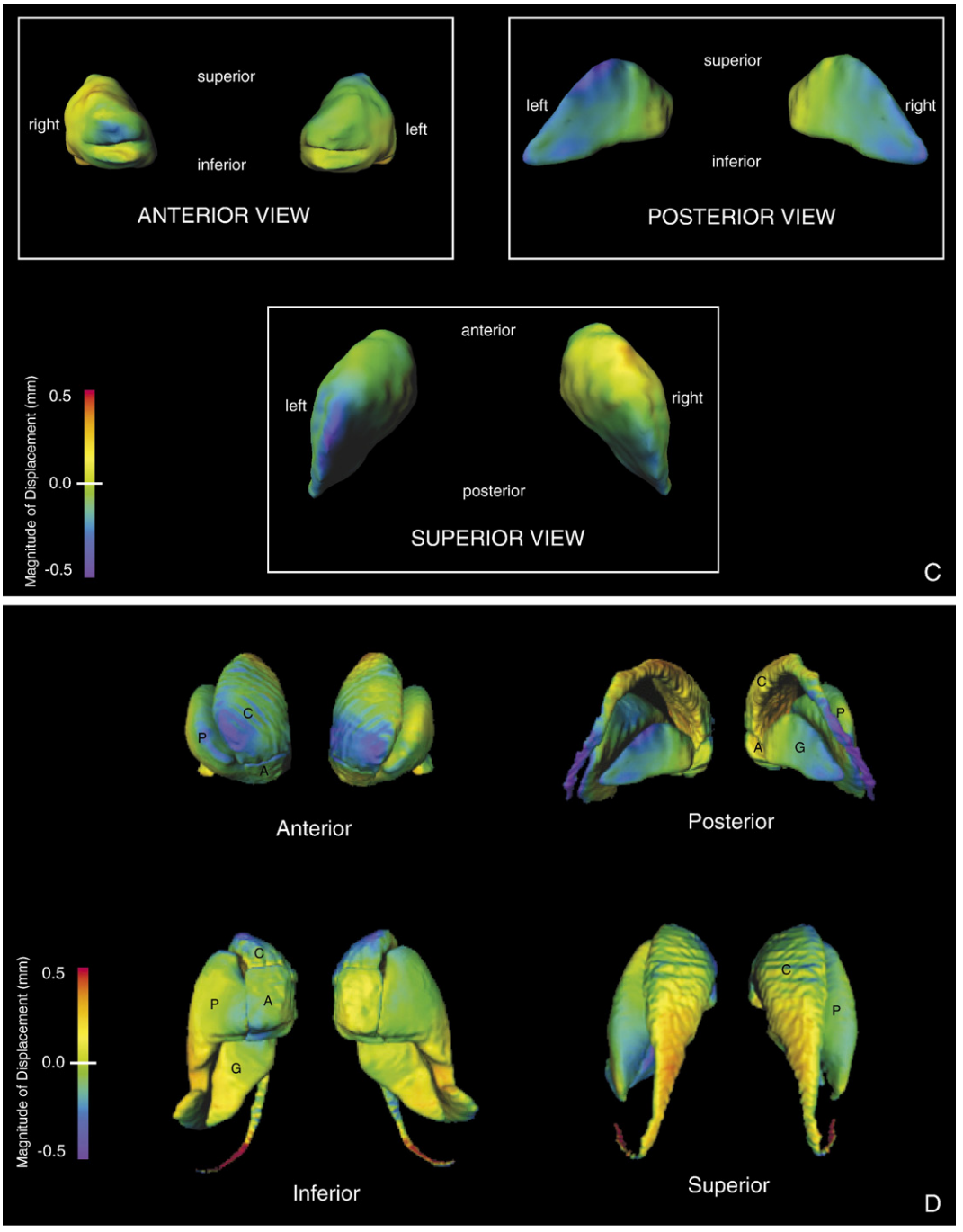

Fig. 2 (*continued*).

analysis using these eigenvectors, 32 (59.3%) schizophrenic and 42 (60.0%) comparison subjects were correctly classified. When total caudate volume was included in the analysis, 33 (61.1%) schizophrenic and 47 (67.1%) comparison subjects were correctly classified. Visual representations of the group difference in caudate shape is shown in Fig. 2A.

3.3. Nucleus accumbens volume and shape

The group effect on nucleus accumbens volumes was nonsignificant before and after adding total cerebral volume as a covariate. (Table 3; Fig. 1C and D). This finding was not altered by adding age, gender, race, handedness, type of antipsychotic drug or a

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lifetime history of substance abuse/dependence as covariates.

Using the first 10 eigenvectors representing the shape of the left and right nucleus accumbens, a MANOVA suggested no significant difference in the shape of the nucleus accumbens between the groups and this result was not altered by adding total cerebral volume as a covariate.

3.4. Putamen volume and shape

The effect of diagnosis on left and right putamen volumes was not significant (Table 3). After covarying putamen volumes for total cerebral volumes, the effect of diagnosis became significant on the left ($F=3.30$, $df=1$, 122, $p<0.01$; Fig. 1E) and the right ($F=7.01$, $df=1$, 122, $p<0.01$; Fig. 1F). This result was not altered by adding age, gender, race, handedness, type of antipsychotic drug or a lifetime history of substance abuse/dependence as covariates.

Using the first 10 eigenvectors representing the shape of the left and right putamen, there was significant group effect (Wilks' Lambda=0.83, $p=0.02$). The group effect became more significant after including caudate volume as a covariate in the analysis (Wilks' Lambda=0.77, $p=0.0012$). Eigenvectors 2, 4 and 8 maximally discriminated the subject groups. In a "leave one out" discriminant function analysis using these eigenvectors, 29 (53.7%) of the schizophrenia subjects and 40 (57.1%) of the comparison subjects were correctly classified. When total putamen volume was include in the analysis, 34 (63.0%) of the schizophrenic subjects and 44 (63.0%) of the comparison subjects were correctly classified. Visual representations of the group difference in putamen shape is shown in Fig. 2B.

3.5. Globus pallidus volume and shape

The group effect on left and right globus pallidus volumes was not significant (Table 3), and after covarying globus pallidus volumes for total cerebral volumes, the group effect remained non-significant on the left ($F=0.15$, $df=1$, 122, $p<0.7$; Fig. 1G), but became significant on the right ($F=4.14$, $df=1$, 122, $p<0.05$; Fig. 1H). This result was not altered by adding age, gender, race, handedness, type of antipsychotic drug or a lifetime history of substance abuse/dependence as covariates.

Using the first 10 eigenvectors representing the shape of the left and right globus pallidus, the group effect almost reached significance (Wilks' Lambda=0.86, $p=0.06$) between the two subject groups. The group effect reached statistical significance after globus pallidus volume was included as a covariate in the analysis (Wilks' Lambda=0.82, $p=0.013$). Eigenvector 3 maximally discriminated the subject groups, and in a "leave one out" discriminant function analysis using these eigenvectors, 26 (48.2%) of the schizophrenia subjects and 40 (57.1%) of the comparison subjects were correctly classified. When total globus pallidus volume was included in the analysis, 31 (57.4%) of the schizophrenia subjects and 42 (60.0%) of the comparison subjects were correctly classified. Visual representations of the group difference in globus pallidus shape is shown in Fig. 2C.

3.6. Typical and atypical antipsychotic drug effects

Table 3 shows the mean volumes of the basal ganglia structures in the schizophrenia subjects exposed to typical and atypical antipsychotic drugs. A one-way ANOVA comparing the two treatment groups did not show any significant volume differences for any basal ganglia structure on either side. Comparing schizophrenia subjects exposed to atypical antipsychotic drugs ($N=35$) to comparison subjects ($N=70$) also did not reveal significant volume differences for any basal ganglia structure. Similar comparisons were not carried out with subjects on typical antipsychotics, due to the low number of subjects in this group ($N=9$).

3.7. Group discrimination using combined basal ganglia shape information

Visual representation of the group difference in the shape of the entire basal ganglia complex is displayed in Fig. 2D. However, use of the combination of eigenvectors that maximally discriminated the groups for each of the basal ganglia in which a significant group effect was found did not improve the proportion of subjects correctly classified, over and above the proportion of subjects correctly classified when each of the structures were analyzed separately.

3.8. Cognitive and clinical relationships

Correlation analysis of cognitive factors showed a significant relationship between scores on cognitive factor 3 and both total caudate ($r=0.41$, $p=0.02$) and total putamen volumes ($r=0.35$, $p<0.05$) in schizophrenic subjects (p values uncorrected for multiple comparisons). When left and right volumes were investigated separately to determine relationship with this cognitive factor, significant correlations were found between

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cognitive factor 3 and caudate volumes bilaterally (right, $r=0.47$, $p=0.005$; left, $r=0.39$, $p=0.05$) and the right putamen volume ($r=0.38$, $p=0.03$). There were no significant relationships observed between any cognitive factor and the shape discriminant canonical variate for any structure.

When the relationships between basal ganglia volume and shape variables and SAPS and SANS scores were investigated, significant correlations were found between smaller total nucleus accumbens volume and increased total SAPS scores ($r=-0.29$, $p=0.037$). Separate analysis of the left and right volumes showed a correlation between the right nucleus accumbens volume and the total SAPS scores ($r=-0.31$, $p=0.02$), and with its delusion component ($r=-0.29$, $p=0.03$).

There were no significant correlations between volume or shape variables and extrapyramidal motor symptoms. There were no significant differences in basal ganglia volume or shape between schizophrenic subjects treated recently with typical antipsychotic drugs and those treated recently with atypical antipsychotic drugs. The duration of illness in the schizophrenic subjects also did not correlate significantly with and volume or shape measure.

4. Discussion

Our results suggest that the volumes of some basal ganglia structures (i.e., caudate, putamen and perhaps also the globus pallidus) are abnormally large relative to total cerebral volume in schizophrenia subjects. Further, these differences in relative volumes were associated with significant differences in the shape of these structures. This finding suggests that differences in basal ganglia volumes are not due to uniform changes throughout the structure. Rather, the shape changes we observed suggest that specific subregions within these complex nuclei are altered in individuals with schizophrenia.

Most investigators report that treatment with antipsychotic drugs (Gur et al., 1998; Andersson et al., 2002) is the cause of basal ganglia volume enlargement in schizophrenia. It has also been suggested that basal ganglia structures may have been spared from a pathological process that affected other structures of the cerebrum, especially the cerebral cortex (Swayze et al., 1992). Regarding the effects of antipsychotic drugs on the basal ganglia, typical antipsychotic drugs have been most often associated with volume increases. In contrast, second generation (atypical) neuroleptics have been described as devoid of these effects (Lang et al., 2004; Andersson et al., 2002). Also, treatment-naïve schizophrenia patients have been reported to have normal (Gur et al., 1998) or even decreased basal ganglia volumes (Corson et al., 1999; Keshavan et al., 1998). In our study, there were no differences in basal ganglia volumes between schizophrenic subjects who were receiving typical versus atypical antipsychotic drugs. However, we were only able to make this comparison based only on the type of drugs used at the time of assessment. The influence of other antipsychotic drugs used in the past cannot be excluded. Furthermore, there were relatively few subjects who were receiving typical drugs ($n=9$) as compared to atypical drugs ($n=35$), which limits statistical power to examine the differential effects of different types of antipsychotic medication. Therefore, with our sample of subjects, we could not adequately address the question of differential antipsychotic drug effects on basal ganglia volume.

Another limitation of our study was that we were not able to completely exclude the possible confounding effects of prior use of other medications or recreational substances. Varying degrees of exposure to substances over a lifetime may have affected the structure of the basal ganglia in both groups. Nonetheless, the structural differences that we observed between schizophrenic and comparison subjects were not altered after controlling for the presence of a lifetime history of substance abuse or dependence.

The basis of the observed shape differences between groups appeared to be uneven changes in the surface of individual basal ganglia, perhaps reflecting localized changes in substructure volumes. In the case of the caudate nucleus, there was a suggestion of localized volume loss in the anterior pole and anterior deflection of the tail. The anatomical distinctions observed are notable, in that the anterior pole of the caudate has reciprocal connections to prefrontal and limbic cortices (Parent and Hazrati, 1995; Lehericy et al., 2004; DeLong, 2000). In the putamen, more irregular shape changes were observed; however, it is notable that the anterior-lateral regions of the putamen with prominent connections to non-motor cortical areas (Lehericy et al., 2004) were affected. As discussed above, the structures of the basal ganglia may be affected differently by the presence of the disease state and by treatment (typical versus atypical drugs); thus, it may not be surprising that we observed a complex pattern of basal ganglia shape changes. Neuronal loss within the basal ganglia in schizophrenia has not been reported, and so is unlikely to be the basis for the observed changes in shape. Rather, it seems more plausible to suggest that basal ganglia shape changes could result from changes in the position of underlying

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neurons and their processes. Also, the ventral deflection of the tail of the caudate could be secondary to structural changes in the underlying thalamus (Csernansky et al., 2004).

In considering the patterns of shape change observed, it is also interesting to consider the patterns of neurotransmitter receptors that are differentially distributed in the basal ganglia. Opposite directional gradients have been reported for dopamine receptors in the basal ganglia, with a greater density of D_1 receptors ventrally, and a greater density of $D_{2/3}$ receptors dorso-posteriorly (Rosa-Neto et al., 2004; Hall et al., 1994). Therefore, antipsychotic drugs that block $D_{2/3}$ receptors, might be expected to have disproportionate effects on dorso-posterior regions of the basal ganglia.

In our study, larger volumes of the caudate and putamen were correlated with greater performance on the third cognitive factor in schizophrenic subjects. Inspection of the cognitive measures loading on this factor, particularly performance on the continuous performance test, suggests that this dimension may be related to attention/vigilance (Nuechterlein et al., 2004). It is notable, however, that the WAIS Picture Completion task which also loaded highly on this factor, has not been linked to the attention/vigilance dimension in previous reports, but to reasoning and problem solving (Nuechterlein et al., 2004). Attention tasks are well known to be severely impaired in schizophrenia (Suwa et al., 2004). In particular, right hemispheric involvement has been reported in attention and vigilance (Pardo et al., 1991), and in our study, correlations between structural volumes and the attention cognitive factor were more substantial for the right-sided structures. We would caution that these findings are not conclusive in establishing a relationship between basal ganglia structural measures and cognitive function, especially considering that changes in such structures could have resulted from confounding from antipsychotic treatment. Furthermore, the cognitive battery used in this study was not specifically designed to measure basal ganglia functions, and overall, we found little evidence for a relationship between the structural measures and cognitive function. Future research using more focused cognitive batteries is needed to help elucidate whether there is a systematic relationship between either volume or shape changes in the basal ganglia in schizophrenia and specific aspects of cognitive function that may be supported by these structures (e.g., set switching).

In our exploratory analysis of correlations between structural and clinical measures, the right nucleus accumbens volume was inversely correlated with the severity of positive symptoms (and delusions alone). While the nucleus accumbens has traditionally been associated with reward, pleasure and addiction, an important role for this structure in the pathophysiology of schizophrenia has been suggested (Gray, 1998; Grace, 2000). Of course, our finding was the result of an exploratory analysis (uncorrected for multiple comparisons), and the precision of mapping the nucleus accumbens was not as strong as the other basal ganglia structures in this study. Thus, this observation must be considered highly preliminary.

As mentioned above, a limitation of our study was our inability to assess the impact of antipsychotic drug treatment other than the most recent on the neuroanatomical measures collected in our study. To determine the relationship between alterations of the basal ganglia in subjects with schizophrenia, the disease process and treatment, siblings of schizophrenia patients that later become ill or treatment naïve patients would need to be studied. The elucidation of abnormalities in neuroanatomical volume and shape in schizophrenia using MR imaging and computational anatomy may one day be useful for improving clinical diagnosis and selecting treatment. However, before such measures can be used for clinical purposes, the causes and consequences of such structural abnormalities must be better understood.

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