Shape of Caudate Nucleus and Its Cognitive Correlates in Neuroleptic-Naive Schizotypal Personality Disorder

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Background: *We measured the shape of the head of the caudate nucleus with a new approach based on magnetic resonance imaging (MRI) in schizotypal personality disorder (SPD) subjects in whom we previously reported decreased caudate nucleus volume. We believe MRI shape analysis complements traditional MRI volume measurements.*

Methods: *Magnetic resonance imaging scans were used to measure the shape of the caudate nucleus in 15 right-handed male subjects with SPD, who had no prior neuroleptic exposure, and in 14 matched normal comparison subjects. With MRI processing tools, we measured the head of the caudate nucleus using a shape index, which measured how much a given shape deviates from a sphere.*

Results: *In relation to comparison subjects, neuroleptic never-medicated SPD subjects had significantly higher (more "edgy") head of the caudate shape index scores, lateralized to the right side. Additionally, for SPD subjects, higher right and left head of the caudate SI scores correlated significantly with poorer neuropsychological performance on tasks of visuospatial memory and auditory/verbal working memory, respectively.*

Conclusions: *These data confirm the value of measuring shape, as well as volume, of brain regions of interest and support the association of intrinsic pathology in the caudate nucleus, unrelated to neuroleptic medication, with cognitive abnormalities in the schizophrenia spectrum.*

Key Words: Schizotypal personality disorder, basal ganglia, caudate nucleus, prefrontal cortex, structural magnetic resonance imaging, shape analysis

We have chosen to study the caudate nucleus in schizotypal personality disorder (SPD) because of its central role in frontal–striatal brain circuitry and its possible dysfunction in schizophrenia and schizophrenia spectrum disorders. The role of this circuitry in cognition, as well as in motor functioning, is now well accepted. Discrete motor and cognitive circuits anatomically link the prefrontal cortex to the basal ganglia in what has been proposed to be parallel, segregated feedback loops with the striatal nuclei (caudate, putamen, and nucleus accumbens) serving as the basal ganglia "input nuclei" from the cortex for this circuitry (Alexander et al 1986, 1990). Abnormalities in any of the core components of the frontal basal ganglia–thalamo–cortical circuits might therefore functionally "disconnect" the feedback loops, resulting in behavioral syndromes that resemble damage to the prefrontal cortex itself (see for example, Bhatia and Marsden 1994; Calabresi et al 1997; Cummings 1993; Kawagoe et al 1998; Levitt et al 2002). Three prefrontal circuits, important for higher cognitive and limbic functions, originate, respectively, in the dorsolateral prefrontal cortex (DLPFC), the lateral orbitofrontal cortex, and in the anterior cingulate gyrus (Alexander et al 1986, 1990). The head of the caudate nucleus, the major recipient of "cognitive" PFC input (Levy et al 1997), and the nucleus accumbens, the major recipient of "limbic," or anterior cingulate gyrus PFC input, are of particular interest as the primary targets for these higher cognitive circuits, whereas the putamen is the primary target for sensorimotor cortex (Alexander et al 1990). The striatum, which is believed to mediate procedural, nondeclarative memory (Mesulam 2000), however, is also postulated to be involved in working memory (Levy et al 1997; Manoach et al 2000) because of the heavy connection to the caudate nucleus from the DLPFC. Finally, functional (Buchsbaum et al 1992; Cohen et al 1997; Holcomb et al 1996), structural (Breier et al 1992; Hokama et al 1995; Jernigan et al 1991), and postmortem studies (Beckmann and Lauer 1997; Heckers et al 1991), though not all (Bogerts et al 1985), have pointed to abnormalities in the caudate nucleus in schizophrenia; and in SPD, structural (Levitt et al 2002; Shihabuddin et al 2001) and functional studies (Shihabuddin et al 2001) have implicated the striatum.

We previously reported, using magnetic resonance imaging (MRI), significant reductions in left and right absolute (13.1%, 13.2%) and relative (9.0%, 9.3%) volume of the caudate nucleus in never-medicated SPD subjects (Levitt et al 2002). Furthermore, we reported a bilateral inverse correlation between the volume of the caudate nucleus in our SPD subjects with the severity of perseveration in a spatial working memory task and a left-lateralized inverse correlation between the left caudate nucleus with the severity of perseveration in a verbal fluency working memory task. Exploratory analyses examining the head of the caudate nucleus

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alone yielded similar results. We chose to study the caudate nucleus in SPD to avoid the confounding effect of neuroleptic medications and chronicity on the size of basal ganglia structures (Levitt et al 2002). Additionally, we studied SPD subjects because genetic studies support the concept that SPD might be in the schizophrenia spectrum (Kendler et al 1993; Siever et al 1993), and hence brain structural pathology and its clinical correlates in SPD might have relevance for schizophrenia. Lastly, SPD itself is a disabling disorder, requiring treatment and understanding.

In the study reported here, we measured the shape of the head of the caudate nucleus because shape measures might provide a further index of brain abnormalities that is not evident from volume measures alone. Of note, the shape of the caudate nucleus might be distorted in developmental disorders, such as schizophrenia, because midline and medial C-shaped structures in the brain are thought to be sensitive to developmental forces and tensions (Van Essen 1997; Van Essen and Drury 1997). For example, the cavum septum pellucidum (Kwon et al 1998; Nopoulos et al 1996), the corpus callosum, and the hippocampus (Csernansky et al 1998; Frumin et al 2002; Shenton et al 2002; Thompson et al 2000) each have been reported to have distorted shapes in schizophrenia. Furthermore, the quantitative analysis of shape, we believe, provides a complementary approach to the quantitative analysis of volume of structural brain abnormalities in neuropsychiatric disorders, because shape changes might occur with little or no change in volume. As suggested by prior shape studies of the hippocampus in adult schizophrenia (Csernansky et al 1998; Shenton et al 2002; Wang et al 2001), quantitative shape analyses might be more sensitive than volumetric measures for detecting small changes in volume or volume changes that might be restricted to subregions of brain structures. Here, we use an approach that is conceptually less complex than prior methods (e.g., Csernansky et al 1998; Shenton et al 2002; Thompson et al 2000; Wang et al 2001) for measuring the shape of brain structures and have been able to detect group differences that complement our prior volumetric findings. In essence, our shape measure uses the surface area–volume ratio to generate a quantitative index of how much a given shape differs from a sphere.

We studied the head of the caudate for our shape analysis because 1) the head of the caudate represents a good candidate region of interest (ROI) for correlations with "prefrontal" neuropsychological measures because of its close anatomic linkage to prefrontal cortex; and 2) it is the most accessible part of the caudate for our shape index (SI) measure (see Methods and Materials section). As we define it here, the head of the caudate includes much of the nucleus accumbens and represents approximately 77% of the total caudate nucleus by volume (Levitt et al 2002) and presumably that proportion of neurons as well. We hypothesized that in neuroleptic-naive SPD subjects, compared with normal comparison subjects, the head of the caudate nucleus, which was smaller in volume, would differ in shape, with the SI being higher, representing a less spherical, or more "edgy" form. Furthermore, we hypothesized that higher SI caudate nucleus head scores would correlate with poorer "frontal" neuropsychological functioning (as we had previously shown for our volumetric measures) and with more abulia, or negative symptoms. We predicted our SI would be higher in SPD, based on our prior finding of reduced volume in the caudate nucleus in SPD. On a cellular level, this finding is perhaps consistent with tissue loss, as has been proposed for schizophrenia by Selemon et al (1998), because of reduced neuropil (a reduction in structures such as neuronal and or glial processes). We hypothesized that this potential reduction in neuropil in the caudate nucleus might result in a less full shape, with shrinkage of the form and consequently a less spherical, or more edgy, shape, yielding a higher SI.

Methods and Materials

Subjects

The subjects consisted of 15 neuroleptic-naive male SPD subjects and 14 normal comparison male subjects, all right-handed, all of whom underwent MRI scanning. Subjects were recruited and diagnosed as described in detail in our previous studies (Dickey et al 2000). Briefly, SPD subjects were recruited from newspaper advertisements in the local community. The advertisement solicited individuals with unusual thinking and other features of SPD. An initial telephone screen was used to rule out subjects not meeting study criteria. A total of 303 right-handed males were screened, with 84 male subjects remaining after screening. Inclusion criteria were 1) age between 18 and 55 years; 2) English as the primary language; 3) no history of neurologic disorder (including head trauma with loss of consciousness longer than 2 min); 4) no history of electroconvulsive therapy, no drug or alcohol dependence ever or abuse in the last year; and 5) no current use of psychotropic medications and no use of medications that might affect MRI, such as steroids. Videotaped interviews of these subjects with the Stuctured Clinical Interview for DSM-IV–Patient Edition (SCID; First et al 1995) and the personality disorders version of the SCID (SCID-II; First et al 1997) were conducted by either a research psychiatrist or a research psychologist (CCD or MMV). Interrater reliability, established by a second research psychologist (LJS) who reviewed the videotapes for a diagnosis of SPD was, as previously reported, high ($\kappa = .89$, $n = 25$).

From the 84 subjects who passed the phone screen, 30 met DSM-IV criteria for SPD, but 15 of these subjects were not included (nine were lost to follow-up, three were claustrophobic and could not go in the MRI scanner, two exceeded the weight limit for the MRI scanner, and one SPD subject was removed due to technical problems with the MRI scan). Of note, the subjects who were not scanned did not differ from those who were scanned on demographic characteristics (i.e., age, education, estimated intelligence quotient (IQ), parental or personal socioeconomic status). The SPD subjects met criteria for a number of comorbid personality and Axis I disorders, including paranoid ($n = 6$) and borderline ($n = 5$) personality disorders and depression ($n = 2$), dysthymia, panic disorder, alcohol abuse, and polysubstance abuse ($n = 1$; all substance abuse took place more than 2 years before testing). For further information about subject characteristics, the reader is referred to our previous studies (Dickey et al 2000).

Through newspaper advertising, comparison subjects were recruited from the community, and they also underwent SCID and SCID-II interviews. Additionally, they were required not to have a personal or family history (in first-degree relatives) of major mental illness or a personal history of personality disorder. There were no significant group differences in demographic characteristics between SPD and comparison subjects in mean age (38.5 [SD 11.0] vs. 38.0 [10.5] years), number of years of education completed, estimated IQ, or parental socioeconomic status, though personal socioeconomic status did differ (see Table 1).

All subjects, who were the same subjects used for our MRI caudate volumetric measurements, underwent a standard neuro-

Table 1. Demographic Characteristics for Schizotypal Personality Disorder (SPD) and Normal Comparison Subjects

	SPD Subjects (n = 15)		Comparison Subjects (n = 14)		Student t Test (Two-Tailed)		
Characteristic	Mean	SD	Mean	SD	t	df	p
Age (years)	38.5	11.0	38.0	10.5	.13	27	.90
Education (years)	15.2	3.2	14.9	1.7	.28	27	.78
Estimated IQ[a]	108.93	12.9	116.31	14.4	−.14	26	.16
Parental SES[a,b]	3.5	1.3	3.6	1.1	−.18	26	.86
SES[b]	3.1	1.2	4.2	.7	−3.1	27	<.01
Finger Tapping with Left Hand[c,d]	45.4	9.5	48.7	6.7	−.96	24	.35
Finger Tapping with Right Hand[c,d]	50.2	11.0	54.4	5.6	−1.1	24	.27

IQ, intelligence quotient; SES, socioeconomic status.
[a]Based on 15 SPD subjects and 13 normal comparison subjects.
[b]Higher numbers represent higher SES.
[c]Taps per 10-sec period.
[d]Based on 15 SPD subjects and 11 normal comparison subjects.

psychological test battery in our laboratory, as previously described (Voglmaier et al 2000). Schizotypal personality disorder subjects also were assessed with the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1981, 1984). For this study, we aimed to examine the relationship of SI with performance on neuropsychological measures of cognitive and noncognitive, motor abilities. We thus included neuropsychological measures of 1) immediate and delayed visual memory, as assessed by the Rey-Osterreith Complex Figure Test (Lezak 1995); 2) response inhibition and shifting attention set as assessed by the object alternation and delayed alternation delayed response tasks (Seidman et al 1995); and 3) digit span exercises involving immediate storage and sequencing of aurally presented numbers, as assessed by Serial Digits Learning (Benton et al 1983). In addition, we used a simple, noncognitive measure of motor speed and dexterity, known as the Finger Tapping Test (Lezak 1995) as a neuropsychological control test. Written informed consent was obtained from all subjects after they received a complete description of our study.

MRI Methods

Magnetic resonance images were acquired with a 1.5-Tesla General Electric Scanner (GE Medical Systems, Milwaukee, Wisconsin). This methodology has been described previously in detail (Dickey et al 2000; Gerig et al 1992). Briefly, a three-dimensional Fourier transform spoiled gradient-recalled acquisition sequence was used to delineate caudate ROIs, which yielded a series of contiguous 1.5-mm coronal images throughout the brain. The parameters used were as follows: echo time = 5 msec, repetition time = 35 msec, one repetition, nutation angle = 45°, field of view = 24 cm, acquisition matrix = 256 × 256 × 124, voxel dimensions = .9375 × .9375 × 1.5 mm. Because our shape measure was independent of size, we did not require the use of a separate pulse sequence to assess intracranial contents. Magnetic resonance imaging caudate nucleus measurements were all performed blind to diagnostic status.

The caudate nucleus was measured bilaterally on all slices with three orthogonal views in which it appeared, as previously described by us in detail (Levitt et al 2002). Briefly, the head, body, and tail of the caudate were measured to the point where the tail bordered the lateral aspect of the atrium of the lateral ventricles (see Figure 1). To separate the anterior caudate and putamen, we drew a vertical line from the most ventral point of the internal capsule inferiorly to the external capsule, including most of the nucleus accumbens (ventral striatum), and forming the lateral bound of the caudate nucleus. We parcellated the caudate nucleus into its head and body, using the interventricular foramen of Monroe, bilaterally, as the dividing landmark, which was defined as the most posterior coronal slice in which the anterior column of the fornix was present. Interrater reliability, as previously reported (Levitt et al 2002), was high for whole left and right caudate nucleus volume ($r_I > .98$); it was also high for left and right anterior ($r_I > .82$; $r_I > .87$) and left and right posterior ($r_I > .94$; $r_I > .92$) caudate nucleus ROIs. Interrater intraclass correlation coefficients (ICCs) reliability for left and right anterior caudate nucleus surface area measurements, the ROIs used in our SI measure, were high as well ($r_I > .87$; $r_I > .95$). All ICCs, for both our volumetric and shape measures, were based on 10 cases delineated by three raters, tracing every other slice. To generate continuous surface area measurements, for our reliability, we omitted the skipped slice.

There have been many approaches to shape characterization, which has resulted in a specialized area of computer science expertise (recently review by Shenton et al [2002]). Quantitative descriptions of shape have included approaches such as the generation of skeletons or a medial axis to characterize features of a shape (Golland et al 1999). Other physically based approaches have shape depictions, such as thin-plate splines and

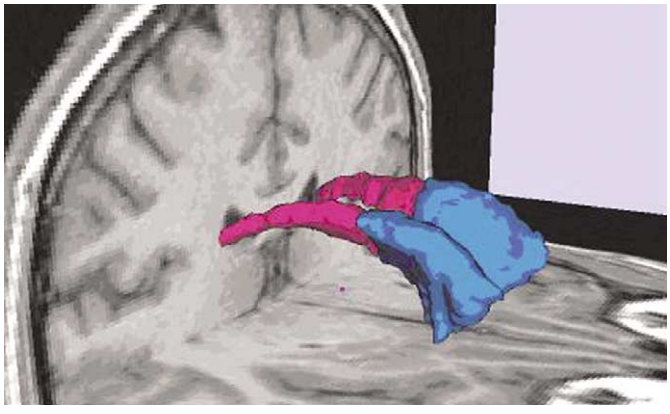

Figure 1. A Three-dimensional rendering of left and right head of the caudate nucleus (shaded blue) and left and right posterior caudate nucleus (shaded red) superimposed on magnetic resonance imaging coronal and axial slices in a normal subject. Adapted from Levitt et al (2002).

Table 2. Shape Index Scores for Basic Three-Dimensional Forms

Type of Polyhedron	Number of Faces	Shape Index $A^3/(36\pi V^2) - 1$
Tetraheder	4	2.31
Cube	6	.91
Octaheder	8	.65
Sphere	Infinite	.00

fiducials, or those based on surfaces and contours of objects (Blum 1967; Bookstein 1989; Cootes and Taylor 1995). In general, the more sophisticated the methods, the more parameters are used to describe the shape. Although these parameters can be used successfully in a statistical classification framework for shape analysis, the more parameters, the larger the sample size that is required to gain descriptive power of shape discrimination. For this reason, we used an alternative approach to measure shape that is based on a single scalar value and that has a simple, more intuitive, geometric interpretation. The proposed scalar shape measure is derived from a surface area–volume ratio and describes deviation from a sphere.

For shape analyses, we calculated SI scores using the following approach. With our image processing tool developed at the Brigham and Women's Hospital (available at http://www.slicer.org; Gering et al 2001), we generated a three-dimensional rendering of the head of the caudate nucleus for each subject. Using this three-dimensional shape, we then calculated surface area (SA) and volume (Vol) for this ROI. Our SI index is based on a ratio between the surface area of the model and its volume. The sphere is the shape that minimizes the surface area for a given volume. All other shapes will have a larger surface-to-volume ratio. Because the volume of the model is increasing with the power of 3 with size (radius in the case of a sphere), whereas the surface area is increasing with the power of 2, a straightforward ratio SA/Vol will vary with size. Because we are interested in shape only, we need to compensate for this, giving the following family of shape indices: $(SA^3/Vol^2)^{\alpha}$. The choice of α in the expression is not critical because it will not alter the order of the shape values. For this reason we will, in the following, use $\alpha = 1$. To make the shape index surface area more intuitive, we normalize the ratio with the ratio of the sphere, giving the following expression: $(SA^3/Vol^2)/(SA_{sphere}^3/Vol_{sphere}^2)$. This ratio is exactly 1 for a sphere, and larger for all other shapes. We finally subtracted 1 from this number, so that a sphere would yield an SI of 0. Inserting the expressions of the surface area and volume for a sphere, we get the following formula of our shape index, SI: $([SA]^3[4/3\pi r^3]^2)/([Vol]^2[4\ \pi r^2]^3) - 1$, which can be further simplified to $(SA)^3/36\pi\ (Vol)^2 - 1$. To appreciate further how our shape index would perform when applied to basic three-dimensional forms, we include the resulting SI scores in Table 2 for the following forms with progressively increasing number of faces: the tetraheder (four), the cube (eight), the octaheder (eight), and the sphere (infinite).

Statistical Analyses

Statistical analyses were performed with MRI structural SI measures. The effect of laterality on the head of the caudate nucleus was examined by a mixed-model, repeated measures analysis of covariance (ANCOVA), with age as a covariate, group (SPD vs. comparisons) as the between-subjects factor, and laterality (left vs. right) as the within-subject factor. When a main effect was found, follow-up planned Student *t* tests were used, with significance set at $p < .05$ (two-tailed), to test group mean SI differences. Because of our relatively small sample size ($n = 15$) and to avoid being unduly influenced by outliers, we used nonparametric Spearman ρ (r) tests, with two-tailed p values, for all within-group correlations between caudate ROI relative volumes and measures of cognition and psychopathology.

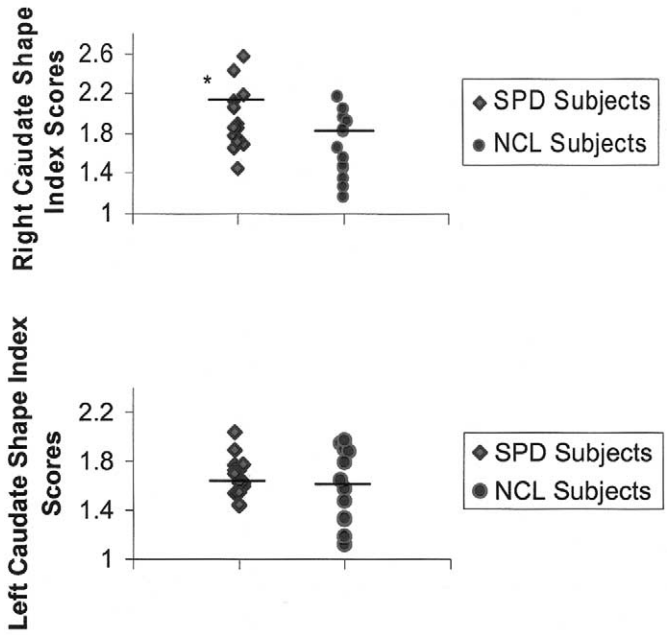

Figure 2. Scatterplots of right and left caudate shape index scores in schizotypal personality disorder (SPD) and normal subjects. Horizontal lines represent means. * $p = .01$. Diamonds indicate SPD subjects; circles are normal subjects.

Results

Head of Caudate Nucleus SI Scores

Repeated measures ANCOVA, using head of the caudate SI scores with age as a covariate, revealed no main effect for diagnosis [$F(1,26) = 1.728$, $p = .2$] but a main effect for side [$F(1,26) = 5.465$, $p = .027$] and a significant interaction between side and diagnosis [$F(1,26) = 7.90$, $p = .009$] was revealed. When we additionally covaried for total, right, or left relative head of the caudate volume, our interaction between side and diagnosis results remained unchanged ($p \leq .029$). The mean (SD) right and left head of the caudate SI scores for SPD, versus normal comparison subjects, were 1.91 (.31) versus 1.68 (.31) and 1.67 (.16) versus 1.64 (.31), respectively. Follow-up planned *t* tests revealed a significant group difference for the right [$t(27) = 2.06$, $p = .049$] but not left [$t(19.33) = .27$, $p = .79$] head of the caudate SI scores, suggesting that the main effect for side reflected greater SI for right than left for both groups (see Figure 2). In percentage terms, we found that the right and left head of the caudate nucleus SI in our SPD subjects, compared with normal comparison subjects, was increased by 14.3% and 1.8%, respectively.

Correlations between Head of the Caudate Nucleus SI Scores and Measures of Psychopathology in SPD Subjects

We found that right SI scores in SPD subjects inversely correlated with both immediate and delayed recall on the Rey-Osterreith Complex Figure Test (Spearman $r = -.57$, $n = 15$, $p = .028$; Spearman $r = -.54$, $n = 15$, $p = .039$). That is, the larger the right head of the caudate SI, the lower, or worse, the

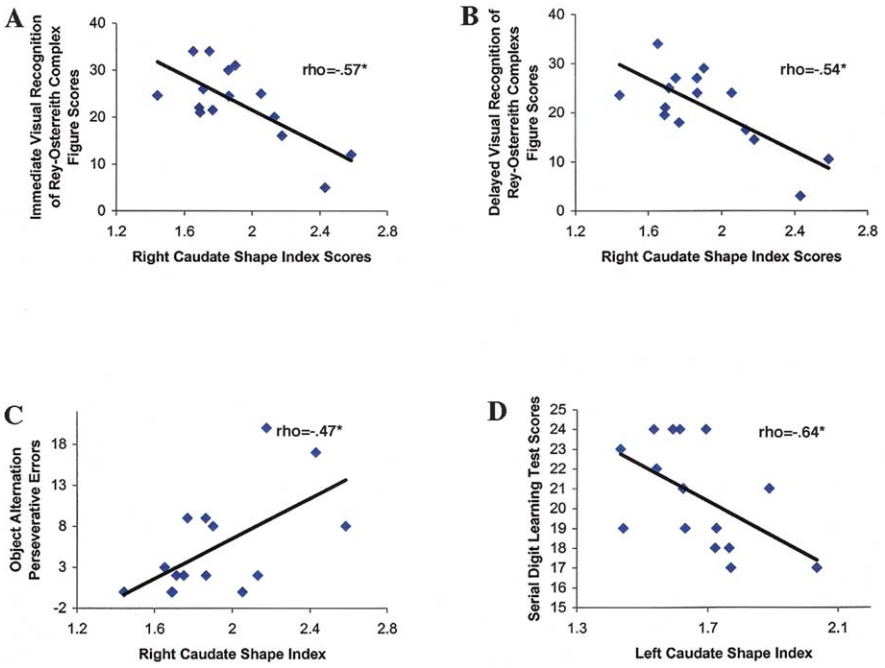

Figure 3. Scatterplots between immediate (**A**) and delayed (**B**) recall of Rey-Osterreith Complex figures, object alternation perseverative errors (**C**), and serial digit learning test scores (**D**) and right and left caudate shape index scores. * $p \leq .05$. Although we used Spearman ρ for testing statistical significance because of our small sample size, we have plotted a least-squares line for the convenience of the reader. SPD, schizotypal personality disorder.

scores on immediate and delayed recall were. Of note, right and left SI scores in SPD did not correlate significantly with the original copy scores from the Rey-Osterreith Figure itself (Spearman $r = -.21$, $n = 15$, $p > .44$; Spearman $r = -.12$, $n = 15$, $p > .67$). Additionally, we found that right SI scores in SPD subjects positively correlated with number of perseverative errors on an object alternation delayed response task (Spearman $r = .56$, $n = 15$, $p = .029$; see Figure 3). That is, the larger the right head of the caudate SI, the more perseverative errors on the delayed response task there were.

Furthermore, we found that left SI scores in SPD subjects inversely correlated with serial digit learning scores on the Serial Digit Learning Test (Spearman $r = -.64$, $n = 15$, $p = .011$) and positively correlated with number of trials necessary to achieve learning of the task on this test (Spearman $r = .56$, $n = 15$, $p = .03$; see Figure 3). That is, the larger the left head of the caudate SI, the lower, or worse, the Learning Test scores were, and the slower to learn, or greater the number of trials required for learning to occur. In contrast to the SPD subjects, correlations for normal control subjects with neuropsychological measures were nonsignificant; however, due to small sample sizes ($n = 9$ or 10), these findings are difficult to interpret.

We did not find significant correlations with clinical measures in SPD for overall SANS or SAPS scores or for the Thought Disorder Index (TDI) measure of formal thought disorder.

Finally, as an index of motor speed and dexterity we measured left and right hand finger tapping. We found no group differences between SPD and normal comparison subjects for left or for right hand finger tapping (see Table 1). Furthermore, we found that right- and left-hand finger tapping in SPD or in normal control subjects did not significantly correlate with our measures of left or right SI (Spearman r, $n = 15$, $.39 \leq p < .89$; Spearman r, $n = 11$, $.78 \leq p < .98$).

Discussion

To our knowledge, the findings in our study represent the first report on the quantitative assessment of shape in the caudate nucleus in SPD or in schizophrenia. There were two major findings. First, in neuroleptic, never-medicated SPD subjects we found a significantly higher head of the caudate nucleus SI for SPD subjects, lateralized to the right side. Second, we found lateralized significant correlations between higher (more abnormal) head of the caudate SI scores in SPD subjects and poorer performance on neuropsychological measures assessing cognitive but not noncognitive, motor functioning. That is, right and left head of the caudate SI scores in SPD subjects correlated with reduced performance in visuospatial and verbal cognitive domains, respectively. We found significant correlations between more abnormal right head of the caudate SI scores and poorer declarative/episodic memory for visual material. Specifically, we showed that higher right head of the caudate SI scores correlated with reduced immediate and delayed recall of complex figures (Rey-Osterreith Complex Figure Test), but not with figure copying itself. In addition, higher right head of the caudate scores correlated with reduced scores on a measure sensitive to working memory executive division operations of response inhibition, shifting attention, and ignoring of irrelevant spatial cues (object alternation delayed response task). We also found that left head of the caudate SI scores inversely correlated with impaired auditory/verbal working memory performance on the Serial Digit Learning Test. Specifically, we found that higher left head of the caudate SI scores inversely correlated with poorer performance on the Serial Digit Learning Test and positively correlated with number of trials required for learning. By contrast, as expected, noncognitive mea-

sures of motor speed and dexterity and copying of the Rey-Osterreith figure itself failed to correlate with caudate SI.

These data confirm the value of measuring the shape, as well as the volume, of cognitively relevant brain regions of interest (ROIs) mediating higher cognitive functions in neuropsychiatric conditions and offer further support for intrinsic pathology in the caudate nucleus in the schizophrenia spectrum. Our failure to correlate our measures of shape with clinical measures, despite showing neuropsychological correlations, is consistent with our prior correlative findings for caudate nucleus volumetric measures (Levitt et al 2002). We believe that abulia, the difficulty in initiating thought and action described in clinical reports of isolated caudate stroke (Bhatia and Marsden 1994), might not be sufficiently quantitatively captured by our clinical measures (e.g., negative symptoms), making such correlations difficult to achieve in studies with relatively small samples. Again, similar to our SPD caudate volumetric data (Levitt et al 2002), no correlations with motor performance and caudate SI were found, offering additional support that caudate nucleus abnormalities reflect cognitive and not merely motor dysfunction.

Recently, greater interest in the field of neuroimaging has emerged in the quantitative measurement of shape of specific brain structures (Csernansky et al 1998; Frumin et al 2002; Shenton et al 2002; Thompson et al 2000; Wang et al 2001). Shape has been described as a sensitive index of developmental disturbance. For example, tension effects during neural development and growth might distort the shape of midline and medial structures, such as the cavum septum pellucidum, the hippocampus, and the corpus callosum (Csernansky et al 1998; Frumin et al 2002; Kwon et al 1998; Nopoulos et al 1996; Shenton et al 2002; Van Essen 1997). We believe our results highlight the potential usefulness of the quantitative assessment of shape with MRI in the study of neuropsychiatric disorders. As indicated by our data, shape and volume can be thought of as independent structural parameters that might yield complementary information. For example, in our previous study of these same subjects (Levitt et al 2002), our volumetric data revealed a bilateral decrease in volume of the caudate nucleus for our SPD sample, whereas the SI scores in this report yielded a group difference, which lateralized to the right.

Two important advantages of our shape analysis, in comparison both with volumetric and with other shape analyses, are these: first, it automatically normalizes for head size because it is independent of the radius or size of a given shape; second, it does not require realignment or coregistration of brains. Hence, our shape analysis method avoids the difficult problem in structural MRI studies of head size correction; and it avoids the additional step, with attendant potential errors, of coregistration of brains into normalized space, as required in other more complex shape analyses. A third advantage is that our shape measure is based on a single scalar value that has an intuitive geometric interpretation.

A potential limitation of our method is that it is a global measure of shape. Hence, we are also developing and using other shape measures, with greater localization capabilities (Levitt et al, unpublished data), and believe it will be of interest to complement and compare our results for the caudate nucleus with the results of these alternative shape measures. A further limitation of our SI measure is that a number of different shapes that deviate from a sphere might have the same SI score. This, however, can also be said of volumetric measures because diminished volume can be achieved in a number of different ways (e.g., a given ROI could be equally smaller because of reductions in different subcomponents of the overall ROI). Furthermore, although it is true that a number of different shapes might have the same SI scores, if an SI score is different for a given shape, this implies that the shape differs; thus in a group sense, our SPD subjects, whose SI scores were different form normal control subjects on the right side, clearly had different caudate shapes compared with normal control subjects. Hence, we believe that our SI retains value as a discriminator between groups.

Our findings are important because they support our previous report (Levitt et al 2002) of abnormalities in the caudate nucleus in neuroleptic-naive schizophrenia spectrum subjects, further suggesting that these abnormalities might be intrinsic to the disorder itself, rather than being secondary to the effects of neuroleptic medications. In any study of basal ganglia structures, neuroleptic medication is an important confound, which makes neuroletic-naive SPD subjects such an appealing sample for such studies. Numerous prior postmortem, animal, and MRI studies have supported the effects of neuroleptic medications on the size of the caudate nucleus (Beckmann and Lauer 1997; Benes et al 1985; Chakos et al 1994; Corson et al 1999; Heckers et al 1991; Hokama et al 1995; Keshavan et al 1994; Konradi and Heckers 2001; Lauer and Beckmann 1997). In our view, quantitative shape analysis provides an additional approach to volumetric analysis for studying the effect of neuroleptic medication on basal ganglia structures. We are currently following first-episode psychotic subjects longitudinally and will measure both the shape and volume of the caudate nucleus in these subjects.

Additionally, not only does our shape analysis reveal a group difference between SPD and control subjects, but we also found that our SI scores yielded meaningful correlations with cognitive functioning. We are encouraged that our neuropsychological correlates support that a shape abnormality in the head of the caudate nucleus in SPD predicts poorer neuropsychological functioning. Furthermore, our data support that right and left head of the caudate shape abnormalities predict visuospatial and verbal impairments, respectively, corresponding to material specific patterns of neuropsychological lateralization. This is consistent with the primarily ipsilateral anatomic connection between prefrontal cortex and the basal ganglia. Our data also are consistent with a recent review of positron emission tomography and functional MRI studies that suggests that prefrontal activation tends to be right lateralized during episodic memory retrieval, in contrast to left lateralized prefrontal activation during semantic memory retrieval (Cabeza and Nyberg 2000). In addition, SI scores correlated strongly in the expected direction with two of our measures (the object alternation delayed response task and Serial Digits Learning) that are thought to be highly sensitive to prefrontally mediated working memory executive functions. This fits well with current conceptualizations that frontal–striatal circuits help mediate working memory. As pointed out in the Introduction, there is a heavy afferent input to the striatum from the DLPFC, and functional neuroimaging studies in humans and nonhuman primates support that frontal–striatal circuits are involved in mediating working memory (Levy et al 1997; Manoach et al 2000). Our data offer strong support for this view.

A limitation of this study is that our sample size is relatively small and, hence, the conclusions need to be considered preliminary, and the findings will require replication in a larger sample of SPD subjects.

A further potential methodologic limitation of our study again relates to the small sample size and the number of correlations with psychopathologic measures that we have performed. We have attempted to address this issue by basing our correlations on a priori

hypotheses. We hypothesized that basal ganglia abnormalities in shape would be associated with impairment in performance of working memory and other frontally mediated neuropsychological traits, as suggested by our previous study (Levitt et al 2002). We believe that our neuropsychological correlates do help to validate the finding of abnormality in shape that we report here. Future studies, however, involving larger samples of subjects, would be needed to confirm the findings in this report.

In sum, our finding of an abnormal shape of the caudate nucleus, lateralized to the right, and its associated neuropsychological correlates in neuroleptic-naive SPD subjects offers further support for an intrinsic abnormality in the striatum in schizophrenia spectrum conditions. Our findings also support that the caudate nucleus, as part of the frontal–striatal circuitry, helps to mediate cognitive functioning and that abnormalities in frontal–basal ganglia circuits might yield important insights into the pathophysiology of disorders of cognition and behavior, such as SPD. Lastly, our findings suggest that the quantitative assessment of shape with the use of advanced MRI techniques offers an important complement to quantitative volumetric MRI studies in neuropsychiatric disorders.

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