Caudate, putamen, and globus pallidus volume in schizophrenia: A quantitative MRI study

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Abstract

Basal ganglia structures have been reported to be abnormal in schizophrenia. However, while component structures of the basal ganglia are functionally differentiated, there have been no evaluations of their separate magnetic resonance imaging (MRI) volumes with small voxel (1.5 mm³) spoiled gradient-recalled acquisition in steady state techniques and multi-plane assessments. We examined MRI scans from 15 male, right-handed, neuroleptic-medicated schizophrenic patients and 15 age-, handedness-, and gender-matched normal volunteers. Compared with normal subjects, schizophrenic patients showed enlarged volumes: 14.2% for total basal ganglia, 27.4% for globus pallidus, 15.9% for putamen, and 9.5% for caudate. Increased volumes, especially of the caudate, were associated with poorer neuropsychological test performance on finger tapping and Hebb's Recurring Digits. These findings indicate abnormalities throughout all basal ganglia structures in at least a subgroup of schizophrenic patients.

Keywords: Basal ganglia; Magnetic resonance imaging; Neuropsychology

1. Introduction

Basal ganglia structures have become an important focus of attention for both basic neuroscience studies and clinical neuroscience investigations related to schizophrenia. Although there have been several important magnetic resonance imaging (MRI) studies (see below), separate quantification of the volumes of caudate, putamen, and globus pallidus (GP) has not been done with very high resolution techniques and only one study has provided complete data on volumes (Elkashef et al., 1994) — despite the clear recent neuroscience evi-
idence for differentiation of the functional roles of these structures.

More specifically, the input stages of the basal ganglia, primarily the caudate nucleus and putamen, receive excitatory glutamatergic projections from multiple zones, including sensorimotor, cingulate, prefrontal, and insular cortices as well as amygdala (see reviews by Alexander and Crutcher, 1990; Graybiel, 1990). These multiple inputs have led to the characterization of the basal ganglia as a “multilaned throughway for separate streams of influence over the thalamus and motor structures...” (Goldman-Rakic and Selemon, 1990). The output nuclei of this multilaned throughway consist primarily of the internal segment of the GP and the substantia nigra pars reticulata. Their neurons, via γ-aminobutyric acid (GABA), exert a tonic inhibitory effect on their target thalamic nuclei, including the ventral anterior, ventral lateral, and mediodorsal groups. Input-output coupling in the basal ganglia is (1) by a direct pathway that inhibits output neurons (via GABA and Substance P) and (2) by an indirect pathway: → the external segment of the GP → glutamatergic subthalamic nucleus neurons → neurons in the output nuclei. Modulatory dopaminergic projections from the substantia nigra pars compacta (and also A8) are to the caudate and putamen (striatum) but not to the GP.

The basal ganglia are also now thought to participate in extensive parallel processing in different functional domains (as well as having parallel processing within each domain). Each functional domain is characterized by output links to appropriate frontal cortex zones for skeletonmotor (primary and supplementary motor cortex), oculomotor (frontal eye fields), cognitive (dorsolateral and lateral orbital prefrontal cortex), and limbic processing (anterior cingulate and medial orbitofrontal cortex), as reviewed by Chevalier and Deniau (1990) and by Goldman-Rakic and Selemon (1990). It is thus clear that the earlier focus on the basal ganglia as primarily involved in motor functions was too narrow and has been expanded to include important cognitive, oculomotor, and limbic processing as well — all of which may be important in disorders such as schizophrenia.

Within the field of schizophrenia, extensive dopaminergic input to the striatum, as well as the therapeutic effectiveness of neuroleptics acting on dopamine receptors, stimulates numerous PET functional imaging studies of this region which suggest dopamine receptor abnormalities (for a review and discussion, see Seeman et al., 1993).

Carlsson and Carlsson (1990), drawing on the intimate interrelationships between glutamatergic and dopaminergic synapses in the basal ganglia, as well as on data collected from animal pharmacological studies, suggest that a primary abnormality of schizophrenia may involve glutamatergic neurotransmission, especially that acting on the basal ganglia by the circuitry described above. Modulatory neurotransmitters such as dopamine may thus act to ameliorate this primary abnormality, especially through their basal ganglia effects. Other neural models of schizophrenic pathology have emphasized basal ganglia control over “gating” of sensory stimuli, such as those important for startle, through basal ganglia connections with thalamus and brainstem (e.g., Swerdlow and Koob, 1987; Potkin et al., 1993).

Finally, the phenomenology of schizophrenia includes types of movement disorder associated with basal ganglia dysfunction. Unusual posturing, grimacing, and other dyskinesias were observed in schizophrenic patients long before the era of neuroleptic therapy and are, in fact, richly illustrated in Kraepelin’s (1919/1971) classic photographs of schizophrenic patients.

Thus, the presence and nature of structural abnormalities in the basal ganglia are of great interest in the investigation of schizophrenia, and two reports in this field have been especially seminal. The study by Jernigan et al. (1991) was the first to present MRI data indicating enlargement of the lenticular nuclei (putamen + GP) in living schizophrenic patients, with a 13% increase in age- and head size-corrected volumes compared with those in normal volunteers; caudate volume was not altered in their samples. Larger lenticular volumes were associated with an earlier onset of schizophrenia, suggesting the possibility of a progressive enlargement. Their MRI technology did not, however, allow direct measurement of total volume. They used 5-mm axial slices with 2.5-mm
gaps. In the same year, however, a post-mortem study on older schizophrenic subjects (mean age = 62 years) by Heckers et al. (1991) found that schizophrenic patients had, compared with age-matched control subjects, a bilateral 9% increase in the volume of striatum (caudate + putamen + nucleus accumbens) and a bilateral 14% increase in the volume of the GP.

Since the MRI report of Jernigan et al. (1991), Breier et al. (1992) found a 10% increase in left caudate volume in schizophrenic patients. Buchanan et al. (1993) used the same patients and MRI scans, but they compared deficit and nondeficit patient subgroups. They reported that while there was no difference in left caudate volume, there was a trend for the deficit subgroup to have a larger right caudate than nondeficit patients (8% increase vs. 2% volume decrease, respectively, compared with normal volunteers). Region of interest (ROI) evaluations were exclusively on coronal slices. Although none of the studies thus far cited included putamen and GP measurements, bilaterally increased putamen volume in males (10%) has been reported in a study using thick (1-cm) slices and planimetric measurements on film (Swayze et al., 1992). This study also reported a trend for bilateral caudate enlargement (11%), as did an earlier first episode study (DeLisi et al., 1991). Elkashef et al. (1994) recently reported volume increases of putamen and GP using 5-mm axial slices, and they found a trend for caudate enlargement using 3-mm slices in a subset of the Breier et al. (1992) patient group.

With respect to the onset time and cause of increased volumes, Chakos et al. (1994) have noted, compared with normal volunteers, caudate enlargement in first episode schizophrenic patients and a further increase in caudate volume in 18-month follow-up scans. The degree of schizophrenic volume increase was correlated with a longer time to remission and a larger cumulative neuroleptic dosage, raising the possibility of a neuroleptic-induced effect.

As this survey of MRI studies of basal ganglia in schizophrenic and normal comparison groups indicates, no studies have used the power afforded by the most recent MRI technology, which includes the precision available in 1.5 mm³ voxels and three-dimensional reconstruction/slicing techniques, to allow comparison of ROI definitions in multiple planes. Use of these advanced techniques to provide quantification of the volumes of caudate, putamen, and GP as separate ROIs seems an important consideration in view of the evidence for different functional roles. Also, there has been little use of clinical scale measurements and neuropsychological assessment in conjunction with volumetric MRI measurements so as to permit delineation of the functional cognitive abnormalities that might be associated with basal ganglia structural abnormalities in schizophrenic patients. Finally, the reports of no enlargement in a number of MRI studies (e.g., Kelsoe et al., 1988; Mion et al., 1991; Young et al., 1991), while perhaps attributable to subject population differences, also emphasize the need for a study done with the most sensitive and accurate technology (Kikinis et al., 1992).

We thus examined volumes of caudate, putamen, and GP using the latest generation of MRI technology in conjunction with clinical scale and neuropsychological assessment of a group of chronic schizophrenic patients. We here report that, compared with the age-matched normal comparison group, schizophrenic patients showed an increase in all basal ganglia volumes, most prominently in the GP (27%), but also in the putamen (16%) and in the caudate (10%).

2. Methods

2.1. Subjects

MR scans from 15 schizophrenic and 15 control subjects, all right-handed males, were obtained from a previous study, which provides further details about the subjects and MRI methodology (see Shenton et al., 1992). Schizophrenic subjects were recruited from the Brockton Veterans Affairs Medical Center; 13 were hospitalized and 2 were in VA foster homes. They had a mean age of onset of 22.3 years (SD = 2.8), mean duration of illness of 15.7 years (SD = 8.8), and a mean time hospitalized of 7.1 years (SD = 4.6). Patient diagnoses were made in accord with DSM-III-R criteria (American Psychiatric Association, 1987) on the basis of chart review and information obtained from ad-
ministration of the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott, 1978).

All schizophrenic subjects were receiving neuroleptic medication (chlorpromazine-equivalent mean = 881 mg/day, SD = 683). Available medical records and data from the subjects indicated that neuroleptic medication had been prescribed throughout the entire course of illness, although they did not permit a reconstruction of a complete medication history. Comparison subjects were recruited through newspaper advertisements. All subjects were between the ages of 20 and 55 years with no history of electroconvulsive shock treatment, neurologic illness, or steroid use, and no lifetime history of drug/alcohol addiction or abuse (as defined in DSM-III-R) within the last 5 years. Comparison subjects were also excluded if they had a history of psychiatric illness in themselves or in their first-degree relatives. All subjects gave informed consent before participation in the study.

There was careful age matching in the two groups, with each pair matched to within 2 years, save for one difference of 3 years; mean age for the schizophrenic patients was 37.6 years (SD = 9.3), while that for the normal volunteers was 37.9 years (SD = 9.8). There were no statistically significant differences between the two groups in height, weight, head circumference, socioeconomic status (SES) of family of origin, or scores on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Information subscale (Wechsler, 1981). There was a difference between groups in educational level. However, matching on educational level may lead to groups that are unmatched in premorbid ability levels due to the fact that schizophrenic subjects may start to show symptoms at the time when they would normally be finishing high school and going on to college. We therefore matched subjects on parental SES level and WAIS-R Information subscale score, both of which are likely to correspond better with premorbid functioning.

2.2. Clinical evaluations

Three instruments were used to assess type and severity of symptoms: The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1981), and the Thought Disorder Index (TDI; Johnston and Holzman, 1979). The average score on the TDI was 60; normal subjects score < 5. On the basis of the Andreasen classification, 11 of the 15 patients were characterized as having mainly positive symptoms, and four patients were characterized as having mixed symptoms. None of the patients had predominantly negative symptoms, but some negative symptoms were present (mean SANS score = 9.1).

2.3. Movement disorder evaluation

Nine of the 15 schizophrenic subjects had formal motor evaluations on the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976), the Simpson-Angus rating scale (Simpson and Angus, 1970) for extrapyramidal symptoms, and the Brande et al. (1983) akathisia scale.

2.4. Neuropsychological evaluation

For comparative purposes, we examined performance in this study with the same battery of neuropsychological tests of memory, attention, and abstraction that we found previously to be correlated with volumetric variations in gray matter temporal and frontal lobe structures in the schizophrenic patients (see Nestor et al., 1993, 1994). These measures included: (1) verbal memory, as assessed by the Verbal Paired Associates subtest of the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) (correlated with left temporal lobe ROI volume reductions [Nestor et al., 1993]); (2) abstraction/categorization, as assessed by both the Similarities subtest of the WAIS-R (Wechsler, 1981) and the number of categories achieved on the Wisconsin Card Sorting Test (WCST; Heaton, 1981) (both previously found to be correlated with bilateral temporal lobe ROI volume reductions [Nestor et al., 1993]); and (3) attention-related processes of temporary storage, as assessed by Hebb's Recurring Digits (Hebb, 1961), and switching, as assessed by Trail-Making Test B and Alternating Semantic Categories (Reitan and Wolfson, 1985) (both previously found to be correlated with variations in volumes of bilateral frontal lobe ROIs [Nestor et al., 1994]).

In addition, given the relationship of basal ganglia to motor control, we examined the rela-
tionship of basal ganglia structures to motor speed and dexterity, as assessed by the Finger Tapping Test (Reitan and Wolfson, 1985). Our previous work demonstrated performance on this test was not correlated with either frontal or temporal lobe volumes in patients with schizophrenia.

**Verbal associative memory and learning.** The Verbal Paired Associates subtest of the WMS-R presented subjects with eight word pairs, half of which were highly associated (e.g., baby-cries) and half which had a low association (e.g., school-grocery).

**Abstraction and categorization.** The Similarities subtest of the WAIS-R required the subject to determine how various pairs of words (e.g., dog/lion, fly/tree) were alike. The WCST involved sorting 128 response cards, each of which has a geometric figure that may vary along three dimensions (color, form, and number). The task was to sort the cards according to a specific principle (color, form, or number), which the subject had to deduce on the basis of performance feedback.

**Attention-related processes of temporary memory storage.** Temporary storage was measured by Hebb’s Recurring Digits, which may be viewed as a modified digit span test. The subject’s immediate digit span (maximum number of digits recalled) was established. Subjects were then asked to repeat sets of orally presented strings of digits, each of which was one digit longer than their immediate digit span. Without the subjects’ knowledge, the same string of numbers was repeated on every third trial. Twenty-four trials were presented, eight of which were repeating strings. The percentage of numbers recalled in the correct sequence for each of the eight recurring trials was used as an index of temporary storage.

**Attention switching.** Two measures were used: The Trail-Making Test B, a timed pencil-and-paper task, required that subjects connect alternating numbered and lettered circles in sequence (e.g., 1, A, 2, B, 3, C...). For the Alternating Semantic Categories, subjects were given 60 s to say as many names as possible while alternating between exemplars in two distinct categories (i.e., boys’ names and fruits; e.g., Paul-Orange, Bob-Apple).

**Motor functions.** The Finger Tapping Test provided a relatively pure measure of motor speed and dexterity. Subjects pressed a lever with their index finger as rapidly as possible, and the number of taps was recorded. There were five 10-s trials for each hand.

2.5. MRI methodology

All MR scans were acquired at the Brigham and Women’s Hospital on a 1.5-Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, WI). The MR methodology has been described in detail (see Shenton et al., 1992) and is therefore more briefly described here. For the measurement of specific ROIs, a three-dimensional Fourier transform spoiled gradient-recalled acquisition in steady state (SPGR) was used to obtain scans throughout the entire brain which were reformatted into 124 contiguous 1.5-mm coronal slices. This protocol creates images with excellent gray/white matter contrast. The SPGR images were obtained with the following parameters: echo time (TE) = 5 ms, repetition time (TR) = 35 ms, one repetition, nutation angle = 45°, field of view = 24 cm, acquisition matrix = 256 × 256 × 124, voxel dimensions = 0.9375 × 0.9375 × 1.5 mm.

For the measurement of the intracranial contents (e.g., whole gray matter, white matter, and cerebrospinal fluid [CSF]), 108 (54 for each echo) contiguous double-echo, spin-echo 3-mm axial slices were obtained throughout the extent of the brain. Imaging parameters were: TE = 30 and 80 ms, TR = 3000 ms, field of view = 24 cm, acquisition matrix = 256 × 256, voxel dimensions = 0.9375 × 0.9375 × 3 mm. The data for whole brain volume have been presented elsewhere (see Shenton et al., 1992). No gross abnormalities were observed in any of the scans (normal subjects or schizophrenic patients) when they were evaluated by a clinical neuroradiologist.

2.6. Image processing

The image-processing stages were slightly different for the whole brain than for the individual ROI measurements (e.g., basal ganglia ROI). The semiautomated image-processing procedures for the measurement of intracranial content (used to compute the relative volume measurements) were based on the 3-mm double-echo axial scans and are described elsewhere (see Cline et al., 1987,
The algorithms used for postprocessing of MR images are part of the MRX software package, a joint project of GE Medical Systems, Schenectady, NY, and the Surgical Planning Laboratory of the Brigham and Women's Hospital. They were also used for SPGR image evaluation and included: (1) a preprocessing filter; (2) a non-parametric clustering algorithm for classifying voxels as to tissue type (i.e., CSF, gray and white matter) on the basis of double-echo intensity information; (3) a connectivity algorithm for linking regions of similar tissue type; (4) voxel summation for computing volumes; and (5) three-dimensional reconstructions for ROI visualization.

The postprocessing steps for basal ganglia ROI volume measurements were done on the SPGR images. The first step was to filter the images to reduce noise. Then, after separation of brain and surrounding CSF from skull and tissue bridges, the images were segmented into CSF, gray matter, and white matter on the basis of operator-selected sample points and a nonparametric clustering algorithm. Finally, this segmentation was used as the basis for operator outlining of the basal ganglia ROI, as defined below, on a slice-by-slice basis, with continuous cross-reference of coronal (best for dorsoventral margins) and axial (best for anterior-posterior and some mediolateral margins) slices on the computer workstation screen. The slice editor of the MRX image-processing program contained algorithms to perform manual drawing of ROI, connectivity, island removal, erosion and dilation of tissue classes; a color editor to assign colors to different ROIs; and a magnifier to magnify the image to a user-chosen level of magnification. An especially useful feature is the capability for virtual reslicing of the slice series so that the user may operate on any plane or thickness, with preservation of ROI boundaries defined in another plane (see Metcalf, 1995), allowing the "best view" of any anatomical structure to be used for editing and definition of ROIs.

A dividing cubes algorithm was used to reconstruct the segmented ROIs to allow for a three-dimensional view of each tissue class (Cline et al., 1988, 1990). Finally, the voxels for each tissue class were summed to compute the volume for each slice and the cumulative volume.

2.7. Overview of ROI definition

Crosby et al. (1962), Carpenter (1978), and Duvernoy (1991) were used as primary anatomical references. Throughout the development of the ROIs, we were quite conscious of partial volume (PV) constraints on reliability: when voxels include more than one tissue component, such as both gray and white matter, reliability is greatly reduced. Our rule was that if reliable tracing of the boundaries of a portion of a ROI could not be performed, this portion was excluded from analysis (such as most of the tail of the caudate — see ROI descriptions below). The basic definitions of landmarks used for the basal ganglia ROI (caudate, putamen, and GP) are described below, and a more detailed description is available in the Appendix, which illustrates the entire extent of ROIs on coronal slices for one case.

Caudate nucleus. This ROI included the head and body of the caudate and the tail portion as it curved ventrally abutting the lateral portion of the atrium of the ventricle (Figs. 1a and 1b). Tracing of the tail portion stopped when it turned to course anteriorly, since, even with our small voxels, PV effects rendered more extensive tracing unreliable. The caudate ROI also included most of the nucleus accumbens; the accumbens is ontogenetically and phylogenetically related to the caudate-putamen and cannot be reliably differentiated on MR images.

Putamen. This included its ventral extension, termed the peduncle of the lentiform nucleus (see Fig. 1).

Globus pallidus. The medial and lateral GP are separated by a very thin white matter layer (medial medullary lamina) which, because of its thinness
and consequent PV effects, is lumped together with medial and lateral GP to form the GP ROI (see Fig. 1).

2.8. Reliability

Anterior-posterior boundaries. Each of three raters was within ± one 1.5-mm slice for all three ROIs.

Intrarater reliability. H.H. measured all cases. Reliability was assessed by duplicate measurements, 6 months apart, by H.H. on the entire data set of two randomly selected cases. There was an excellent agreement for caudate (4.4% and 4.3% volume differences on the two cases for the two measurements), putamen (2.0% and 3.2% differences), and GP (0.5% difference for both cases).

Segmentation reliability. The excellent reliability measurements for the segmentation of total gray matter, white matter, and CSF on the double-echo/spin-echo images have been described elsewhere (Kikinis et al., 1992; Shenton et al., 1992).

2.9. Statistical analyses

Volumetric analyses were corrected for intracranial volume to control for variations in head size. As described elsewhere (Shenton et al., 1992), there were no group differences between the normal volunteers and the schizophrenic patients on total intracranial contents, total CSF, total gray matter, or total white matter. All tests for statistical significance of ROI volume differences were performed on corrected (relative) volumes (ROI volume/intracranial contents); the results of statistical significance tests for absolute volumes are also reported where these substantially differed from tests on relative volumes. For comparative purposes, we also present absolute volume data. Laterality and region effects for basal ganglia ROIs were examined by a mixed-model analysis of variance with one between factor, group (schizophrenic vs. normal), and two within factors, laterality (left vs. right), and region (caudate, putamen, GP). This analysis was followed by planned comparisons with statistical significance set at $P < 0.05$. Based on the literature, we used one-tailed $t$ tests for comparisons because we hypothesized that schizophrenic patients would show an increase in basal ganglia volume. Although the normal volunteers and schizophrenic patients were closely matched (see below), we conservatively used unpaired $t$ tests.

As age can affect volumetric measures, even within a restricted age range (Zipursky et al., 1992), age comparability of normal and schizophrenic groups is important. This is especially critical for basal ganglia measurements, since one hypothesis derived from the literature is that normal subjects will show a trend for age-related reduction in relative volume whereas schizophrenic patients will show volume increases — increases related to the disease process and/or to neuroleptic medication, and hence be progressive with time. We emphasize the scrupulous age matching of our two groups as a critical control for age confounds. (Since the two groups are predicted to show different age-basal ganglia volume relationships, a covariance control is not appropriate.)

For correlations among neuroanatomical, neuropsychological, and clinical/motor measures within groups, the nonparametric Spearman’s rho ($r$) and two-tailed significance tests were used. For these correlations, relative ROI volumes were always used to correct for head-size differences. Because of the multiple correlations performed, the analyses of the relationship between basal ganglia ROI and the neuropsychological and clinical/motor measures are to be regarded as exploratory and in need of confirmation in another study.

3. Results

3.1. Basal ganglia

Basal ganglia volumes. The total volume of the basal ganglia was increased by 14.2% in the schizophrenic group compared with the normal comparison group, a statistically significant increase ($P < 0.007$, see Table 1). The analysis of variance also showed a significant laterality effect, with larger left-sided structures ($F = 5.563; df = 1, 28; P = 0.0256$). This laterality effect did not differ in the two groups (laterality $\times$ group interaction: $P = 0.238$). There was a significant region $\times$ laterality interaction ($F = 5.586; df = 2, 56; P = 0.007$),
indicating that the three basal ganglia structures differed in the degree of lateralization, with the putamen being most lateralized. Schizophrenic patients and normal volunteers did not, however, differ in the degree of region x laterality interaction (region x laterality x group: *P* = 0.872). Since the two groups did not differ in laterality effects, subsequent volumetric data presentations are based on combined left and right structures.

Table 1 shows that the schizophrenic group, compared with the normal comparison group, had a volume increase of 9.5% in the caudate, 15.9% in the putamen, and 27.4% in the GP. When relative volumes were analyzed, *t* tests revealed that the GP and the putamen were statistically different in schizophrenic patients and normal volunteers (*Ps* < 0.003); caudate volumes differed at the trend level when relative volumes were used; but when absolute volumes were used in the comparison, the *P* value was 0.02 (*t* = 2.24). These volume differences were sufficiently great to be visible in three-dimensional reconstructions. Fig. 2 provides color-coded three-dimensional volume renderings of caudate (red), putamen (green), and GP (violet) for the schizophrenic subject (viewer left) and the control subject (viewer right) whose total basal ganglia volumes fell just above and closest to their respective group means. There was no region x group interaction (*F* = 1.408; *df* = 2, 56; *P* = 0.253), indicating that the degree of regional volume differences (i.e., 9.5%, 15.9%, versus 27.4%) did not reach statistical significance.

Fig. 3 illustrates the mean volume differences in a bar graph and provides the individual volume values for each member of the schizophrenic and normal groups for the caudate, putamen, and GP. The individual values show that the group mean differences are not the result of outliers, but stem from an overall population shift in values. Particularly remarkable are the population differences on the putamen and GP volumes, where all members of the schizophrenic group have values above both the mean and median of the normal group.

Correlations between basal ganglia volume ROIs for normal volunteers and schizophrenic patients. With respect to correlations between the volumes of basal ganglia ROIs, our hypothesis was that the same abnormal process acted on all these structures to increase volume relative to normal values.
We reasoned that evidence for this common abnormal process would consist of higher correlations between volumes in schizophrenic patients relative to those found in normal subjects, since a common abnormal process would leave a "footprint" in a joint and hence correlated change in the different basal ganglia structures. In contrast, in normal subjects, multiple independent processes would be acting to control volume and hence intercorrelations would be less. To correct for total intracranial volume differences, we used relative volumes and Spearman rank-order correlations to control for nonnormality of statistical distributions. Table 2 shows the matrix of intercorrelations between the basal ganglia ROIs for the schizophrenic and normal groups (the correlations

Fig. 2. Color-coded three-dimensional volume renderings of caudate (red), putamen (green), and globus pallidus (violet) for the schizophrenic subject (viewer left) and the normal subject (viewer right) whose total basal ganglia volumes fell just above and closest to their respective group means. Note the visually greater volumes in the schizophrenic subject.
between left and right sides of the same structure are omitted since our hypothesis addresses between- and not within-structure correlations. There was a statistical trend for the correlation coefficients for the schizophrenic group to be larger than those of the normal group ($P = 0.07$, Wilcoxon matched-pairs signed rank test, a non-parametric test that uses the ranks of the

Table 2
Spearman correlation coefficients between relative volumes of basal ganglia components for the schizophrenic group (boldfaced type) and for the normal group ($P$ values are below the $r$ values, in parentheses)

<table>
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<tr>
<th></th>
<th>Caudate</th>
<th>Putamen</th>
<th>Globus pallidus</th>
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<tr>
<td></td>
<td>Left Right</td>
<td>Left Right</td>
<td>Left Right</td>
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<tr>
<td>Caudate</td>
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<td>Left</td>
<td>—</td>
<td>—</td>
<td>0.46</td>
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<tr>
<td>Right</td>
<td>—</td>
<td>0.69</td>
<td>0.61</td>
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<tr>
<td></td>
<td>(0.076)</td>
<td>(0.020)</td>
<td>(0.094)</td>
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<tr>
<td>Putamen</td>
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<tr>
<td>Left</td>
<td>0.47</td>
<td>0.54</td>
<td>0.19</td>
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<tr>
<td></td>
<td>(0.076)</td>
<td>(0.040)</td>
<td>(0.506)</td>
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<tr>
<td>Right</td>
<td>0.40</td>
<td>0.48</td>
<td>0.39</td>
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<tr>
<td></td>
<td>(0.138)</td>
<td>(0.069)</td>
<td>(0.165)</td>
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<tr>
<td>Globus pallidus</td>
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<tr>
<td>Left</td>
<td>0.14</td>
<td>0.28</td>
<td>0.51</td>
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<td>(0.627)</td>
<td>(0.317)</td>
<td>(0.051)</td>
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<tr>
<td>Right</td>
<td>0.03</td>
<td>0.18</td>
<td>0.64</td>
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<td></td>
<td>(0.920)</td>
<td>(0.512)</td>
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magnitude of the differences between correlation coefficients for the same structures in the two groups).

**Basal ganglia volume correlations with prefrontal and temporal lobe volume measures.** Because of their neuroanatomical interconnectivity, we further examined the correlations of basal ganglia ROIs with the volumes of left and right prefrontal gray and white matter and of amygdala/anterior hippocampus (ROIs that had been previously measured for these subjects [Shenton et al., 1992; Wible et al., 1994]). As just discussed, we reasoned that a common process acting in the same direction would increase the magnitude of positive correlation coefficients, whereas a common process acting to increase basal ganglia volume and to decrease prefrontal and amygdala volume would increase the magnitude of negative correlation coefficients. Separate processes acting on prefrontal/amygdalar and basal ganglia structures would likely decrease the absolute magnitude of the correlations. For the prefrontal-basal ganglia volume correlations in normal subjects, the largest values were between left prefrontal gray and right putamen (0.51, \( P = 0.052 \)) and right caudate (0.41, \( P = 0.13 \)); the magnitude of these and other correlations was generally slightly reduced in the schizophrenic group, but not to a statistically significant degree (\( P > 0.2 \), Wilcoxon matched-pairs signed rank test). Neither normal nor schizophrenic subjects showed large-magnitude correlations between amygdala/anterior hippocampus ROIs (boundaries described in Shenton et al., 1992) and any basal ganglion structure (maximal \( r = 0.35, P > 0.2 \)).

**Basal ganglia volume correlations with demographic and clinical data.** We next analyzed the relationship between relative basal ganglia volumes and age of subjects in the two groups. As expected, age and relative volumes showed an inverse relationship in the normal group. Spearman correlation coefficients were \(-0.722\) for caudate (\( P < 0.01 \)) and \(-0.698\) (\( P < 0.01 \)) for putamen, with GP showing a lesser correlation (\( r = -0.335, P < 0.30 \)). In marked contrast, there were no strong correlations with age in the schizophrenic group, with \( r \) values being \(-0.115\), \(-0.315\), and \(0.095\) for caudate, putamen, and GP, respectively (all \( P > 0.20 \)). Neither estimated verbal IQ nor parental SES showed large-magnitude correlations with relative ROI volumes in either the schizophrenic group or the normal group (\( rs < 0.30, P > 0.20 \)).

Since results from a first episode study (Chakos et al., 1994) have suggested that volumetric increases in schizophrenic patients might be secondary to neuroleptic medication, we examined the correlation between relative ROI volumes and several measures relevant to this variable, although the absence of detailed medication history precluded our using actual dosage, which would have been a more direct and desirable variable. There were no large-magnitude correlations with either current chlorpromazine-equivalent neuroleptic dosage level or several measures of disease duration and severity: duration of illness, age of onset, or percentage and absolute time hospitalized since onset. The maximum \( r \) value was only \(-0.279\) (with the set of \( r \) values having \( P > 0.2 \)).

We next turned to an exploratory analysis of the relationship between relative basal ganglia volumes in the schizophrenic group and clinical symptomatology, as measured by the TDI and by the SANS and SAPS scales; these measures were available for correlation in 13 patients. There were no large-magnitude correlations with the TDI (total thought disorder) or with the global and subscale scores of the SANS. For both the TDI and the SANS, the largest correlations were with caudate volume. For the TDI, the correlation was only \( r = -0.281 \) (\( P > 0.2 \)), while the largest SANS correlation (with total score) was only \( r = -0.206 \) (\( P > 0.3 \)). There were larger magnitude correlations between the SANS bizarre behavior subscale score and the relative volumes of the GP (\( r = -0.633, P < 0.03 \)) and putamen (\( r = -0.591, P < 0.05 \)). The caudate showed a lesser correlation (\( r = -0.483, P = 0.09 \)). The negative sign of these correlations indicates that increased volume was associated with less bizarre behavior.

**Basal ganglia volume correlations with measurement of motor function.** With respect to motor abnormalities, there were no large-magnitude correlations between the Simpson-Angus scores, expressed either as a sum of items or as individual
items, and the basal ganglia ROI relative volumes. The maximal Spearman's rho was 0.358 ($P = 0.34$). However, there was a large magnitude inverse correlation between the Simpson-Angus total score and the relative volume of the left amygdala/anterior hippocampus ($r = -0.749$, $P = 0.02$). Only two patients, however, had abnormal (nonzero) AIMS scores. The patient scoring 5 had the largest putamen volume in the group, and the patient with a score of 2 had a volume in the upper third of the group. (In fact, the Spearman's $r$ for the total [relative] basal ganglia volume-total AIMS score was 0.667 [$P = 0.05$], although we consider the correlation unreliable because of the presence of abnormal AIMS values in only two subjects.) There were no large-magnitude correlations between the akathisia scale and basal ganglia volumes (e.g., when the correlations for left and right caudate, putamen, GP, and left and right total basal ganglia were examined, the maximal value was $r = -0.35$ [all $P$s $> 0.35$]).

3.2. Neuropsychological test results

An overview of the neuropsychological results suggests that the strongest correlations were found between basal ganglia volume ROI and relatively pure tests of motor speed and dexterity. There was also evidence suggesting that basal ganglia pathology influenced attentional processes. By contrast, performance on tests of memory and abstraction/categorization did not correlate with basal ganglia volumes. Since there was the possibility of lateralized effects, in addition to examining the total relative volumes of basal ganglia ROI, we also examined the left and right ROI volumes of caudate, putamen, and GP; these $r$ values are included in this report.

With respect to motor speed and dexterity, poor right-hand performance on the Finger Tapping Test correlated significantly with increased volume in both left caudate ($r = -0.62$, $n = 14$, $P = 0.013$) and right caudate ($r = -0.67$, $n = 14$, $P < 0.01$) while poor left-hand performance correlated with increased volume in right GP ($r = -0.53$, $n = 14$, $P = 0.053$). Thus, poorer performance was associated with abnormally enlarged basal ganglia ROI volumes. Attention-related processes of temporary storage, as assessed by Hebb's Recurring Digits, were negatively correlated with right caudate volume ($r = -0.62$, $n = 13$, $P = 0.025$) and, to a lesser extent, with left caudate volume ($r = -0.53$, $n = 13$, $P = 0.063$). The negative correlation indicates that poorer performance on this test was associated with an abnormally enlarged caudate. Other basal ganglia structures did not correlate so highly. Left and right putamen correlations were $-0.42$ and $-0.44$, respectively ($P$s $> 0.15$), while left and right GP correlations were $-0.27$ and $-0.28$, respectively ($P$s $> 0.30$).

Tests of attention-related processes of rapid switching or shifting showed lesser correlations with basal ganglia structures. Attention switching, as assessed by Trails B, had the largest correlation with right GP ($r = -0.42$, $n = 14$, $P = 0.135$) and left GP ($r = 0.38$, $n = 14$, $P = 0.183$); other correlations had absolute values $< 0.18$ ($P$s $> 0.50$). Attention switching, as assessed by Alternating Semantic Categories, had low magnitude $r$ values, with the largest being $r = 0.19$ ($P > 0.50$).

Performance on tests of memory and abstraction/categorical thinking, which had correlated significantly with volumetric reductions in bilateral temporal lobe structures, did not strongly correlate with volumes of basal ganglia ROIs. Specifically, performance on the Verbal Paired Associates subtest from the WMS-R had negative $r$ values whose absolute magnitude was small ($< 0.30$, $P < 0.276$, $n = 15$). Abstraction/categorization, as assessed by the number of categories achieved on the WCST, had small magnitude $r$ values, both positive and negative, with the absolute magnitude of the $r$ values being $< 0.25$ ($P$s $> 0.40$). Abstraction/categorization, as assessed by the Similarities subtest of the WAIS-R, had the largest correlation with left GP volume ($r = -0.42$, $n = 15$, $P = 0.125$); however, other $r$ values were all of small magnitude, with absolute values $< 0.28$ ($P$s $> 0.30$).

4. Discussion

This study is, to our knowledge, the first to use small voxel (1.5 mm$^3$) SPGR acquisitions and advanced image-processing techniques to define the
volume of each major component of the basal ganglia in schizophrenic patients and matched normal volunteers. The small voxels minimized PV errors, and the image-processing techniques included a slice editor that enabled the simultaneous use of multiple planes of section to assist in the precise bounding of ROIs. These features likely were key in our obtaining a high reliability of ROI definition and, by reducing variability due to measurement error, in obtaining statistically significant schizophrenic-normal differences. The present study confirms previous reports of basal ganglia enlargement in schizophrenic patients, as cited in the Introduction.

The magnitude of the schizophrenic group’s mean volume increases was 9.5% in the caudate, 15.9% in the putamen, 27.4% in the GP, and 14.2% overall. All volume increases were statistically significant when relative volumes were used for tests, save for a trend level in caudate, where the increase was statistically significant when absolute volumes were used. Our interpretation of the caudate findings is that a volume increase is likely present, but of lesser magnitude than in putamen and GP; thus, statistical significance is less robust in the present group of 15 subjects.

There was considerable group separation on putamen and GP volumes, with the lowest schizophrenic volume for the putamen and GP being larger than the mean and medial normal values. The finding of a 27% enlargement in the GP suggests that this structure should be of particular interest to MRI studies of schizophrenic patients, especially those, such as first episode studies, looking for the presence of change in volume over time. We note that the volumes of both normal subjects and schizophrenic patients reported in the present study closely approximate those of post-mortem measurements (Heckers et al., 1991).

There was a trend ($P = 0.07$) for correlations between volumes of the caudate, putamen, and GP to be higher in the schizophrenic than in the normal group, thus providing some supporting evidence for our hypothesis of a similar pathologic process (or processes) acting on each of these three basal ganglia structures. Further neuropathologic studies will be needed to determine which neural elements (somata, dendrites, and/or neuropil) are primarily involved in this volume increase.

From a functional point of view, the new evidence for a very strong change in the output elements of the basal ganglia (GP) indicates that the abnormal process is neither confined to basal ganglia regions innervated by glutamatergic cortical and amygdalar input (striatum) nor to regions receiving dopaminergic input and having a high concentration of dopamine receptors (also the striatum).

Neuropsychological evaluation indicated the most prominent clinical associate of enlarged basal ganglia was lessened speed and dexterity of motor performance. Performance inversely correlated with volume, which was abnormally increased. Poor right-hand performance on the Finger Tapping Test correlated significantly with increased volume in both left caudate ($r = -0.62$) and right caudate ($r = -0.67$) while poor left-hand performance was associated with increased volume in right GP ($r = -0.53, n = 14, P = 0.053$).

Consistent with basal ganglia involvement in nonmotor processing, a correlation was also observed between attention-related processes of temporary memory storage. As assessed by Hebb’s Recurring Digits, performance was significantly and inversely correlated with right caudate volume ($r = -0.62$); and, at a trend level, with left caudate volume ($r = -0.53$). We note that volumes of prefrontal lobe structures, assessed in this same subject group, also showed correlations with Hebb’s Recurring Digits and with other relatively pure neuropsychological tests of working memory (Trails B and Alternating Semantic Categories). Thus, there was partial overlap of basal ganglia and prefrontal MRI volume correlations with neuropsychological performance. In contrast, performance on tests of memory and abstraction/categorization (including the total score on the TDI), which strongly correlated with temporal lobe volumes (Nestor et al., 1993), did not correlate with basal ganglia volumes. The different degree of commonality with prefrontal and temporal lobe neuropsychological correlations appears reasonable in terms of relative density of prefrontal and temporal lobe neuroanatomical intercon-
nections with basal ganglia. Our neuropsychological tests were selected to include measures thought most likely to correlate with frontal and temporal lobe abnormalities. Measures of procedural memory (Schwartz et al., 1992) and of memory related to visuospatial/oculomotor tasks, such as saccades (Park and Holzman, 1992), would appear useful in future studies of basal ganglia-functional correlations, given the evidence for a basal ganglia role in these functions.

With respect to the AIMS scores, our data suggest further work may be useful but are not conclusive in themselves. Only two subjects showed abnormal scores, although the degree of abnormality correlated remarkably well with extreme putamen volumes. A possible confounding factor is that involuntary movements may interfere with MRIs and hence subjects with such movement disorders may not be selected for study or may not be successful in completing the MRI (as happened with one subject in our pool). Other potential confounds include possible masking by continued antipsychotic administration and fluctuation of abnormal movements over time. Basal ganglia evaluation of more schizophrenic subjects, including unmedicated patients and perhaps patients selected to have AIMS abnormalities, is needed. There was no evidence for an association between extrapyramidal movement disorder, as assessed by the Simpson-Angus scale, and abnormal basal ganglia volumes. However, the presence of neuroleptic medication may have obscured any correlations that might be observable in a nevermedicated population. We note that Elkashef et al. (1994) failed to find any association between tardive dyskinesia and basal ganglia volume (including that of the putamen).

With respect to the overall paucity of correlations between basal ganglia volumes and SAPS or SANS measures, it should be kept in mind that most of the correlations in the literature (usually with caudate volume, see Introduction) were with negative (deficit) symptoms and that our subjects had predominantly positive symptoms. The strong inverse correlation between the SAPS bizarre behavior score and GP volume is, nonetheless, interesting, although caution is needed in interpretation because of the small number of subjects and the large number of correlations performed. The inverse correlation indicates that the abnormal increase in volume was associated with a decrease in bizarre behavior. Although needing confirmation in a subsequent study, this association may indicate a suppressive effect on motor activity by this abnormality of the output part of the circuit of the basal ganglia. This point also underscores the usefulness of determining whether any startle gating abnormalities might be associated with basal ganglia enlargement. Another possible explanation is that increased neuroleptic dosage might both decrease bizarre behavior and increase GP volume.

It is important to note that the generalizability of our basal ganglia findings to other groups of schizophrenic patients, such as those with severe deficit and negative symptoms, remains an open question. Also unknown is whether the findings might appear in other psychiatric disorders, such as mood disorders with psychotic features, as suggested in a recent study by Aylward et al. (1994). Finally, we emphasize that the relatively small number of subjects limited power to detect true differences and true correlations with smaller effect sizes, and that negative results in this article should be viewed with this point in mind. Also the patient group’s restricted range in certain variables, such as in age of onset, may have lessened the ability to detect correlations.

From a neuropathological standpoint, the basal ganglia remain a fascinating enigma, being enlarged in schizophrenic patients while other brain regions are reduced in volume. Neuroleptic dosage studies in animals show that neuroleptics induce plastic changes, including enlargement of neural elements, that may be reversible at the ultrastructural level, but thus far have not examined whole structure volumetric changes (Benes et al., 1983, 1985; Klintzova et al., 1989; Meshul and Casey, 1989). Such animal studies, as well as follow-up studies of first episode patients (e.g., Chakos et al., 1994), may help answer the question of whether the enlargement is neuroleptic-related, partly or completely. Studies at the in vivo MRI level cannot offer insight as to which neuronal or glial structures are altered, but the large-scale involvement of the GP, a structure not heavily innervated
by cortical glutamatergic or brainstem dopaminergic projections, suggests to us that these elements are not likely to be directly causative (although their abnormalities may cause a chain of events that eventuates in enlargement) and also emphasizes the need for study of this structure in first episode test-retest studies (Chakos et al. [1994] examined only caudate). While such mechanisms are speculative, the evidence for control of neuropeptide gene expression (transcription) by striatal inputs and several neurotransmitters (Graybiel, 1990) suggests that similar control of expression of other genes, including those possibly related to abnormal enlargement, is a possibility. A developmental origin of basal ganglia volume alteration also remains a possibility; for example, Loopuijt and Villablanca (1993) have recently reported caudate enlargement secondary to lesions of frontal or parietal cortex in fetal kittens.

Appendix

Definition of ROIs for caudate, putamen, and GP. Although both coronal and axial formats were
used in the manually guided delineation of gray matter, we here describe the ROIs primarily in terms of the coronal images. This description will facilitate the reader’s cross-referencing with standard anatomical texts. To give the reader a sense of the distance between landmarks, we describe the ROIs as they would be encountered going anterior to posterior on a set of 1.5-mm coronal images that encompass the basal ganglia structures (n = 42 slices) obtained from a typical normal

Fig. 5. Basal ganglia area. See text for description.
brain. Fig. 4 shows the ROIs for this case on a single complete coronal slice to orient the reader to Fig. 5 (panels A and B), which display only the basal ganglia area. The caudate is outlined in yellow, the putamen in red, and the GP in green. Fig. 5 (panels A and B) will be referred to extensively as the reference images for the ROIs defined below. All references to slice numbers are to the numbered slices on Fig. 5.

Description of ROI on coronal slices, with anterior to posterior progression. As can be seen in Fig. 5, the coronal slices are examined sequentially until the caudate gray matter (head portion) appears (subsequently referred to as the “first slice”). This is bounded by frontal lobe white matter, with a small portion of the lateral ventricle also appearing medial to the caudate (see the first five coronal slices in Fig. 5). For the most anterior segment of caudate, a small portion may appear superior to the lateral ventricle, but it may not be included because of unreliability attributable to PV; the caudate must initially appear with a volume of at
least one voxel and with gray matter intensity comparable to cortex (to rule out PV effects). The caudate cross-section enlarges during succeeding slices, being bounded medially (and with more posterior slices, superiorly) by the lateral ventricle and elsewhere by frontal white matter. About 7.5 mm posterior to the appearance of the caudate (first slice), the putamen appears, ventrolateral to the caudate and separated from it by the anterior limb of the internal capsule (slice 6 in Fig. 5). The caudate and putamen have small bands of gray matter streaming between and bridging these two structures; because of PV effects, however, these are not included in the ROIs, which are defined by the bounds of the main compact masses of gray in these two structures. The putamen is bounded laterally and ventrally by the external capsule.

Progressing posteriorly, these relationships are maintained until about 12 mm posterior to the first slice, at which point the caudate and putamen gray matter masses appear to become linked by another gray matter mass at their most ventral point: this is the nucleus accumbens (slices 9–10, Fig. 5). It is impossible to differentiate accumbens gray from caudate gray, and thus they are grouped together in our ROI labeled “caudate.” Progressing posteriorly, the separation of caudate/accumbens from the putamen is accomplished by drawing a vertical line from the most ventral extension of the internal capsule, with caudate being lateral to this line (see slices 11–13, Fig. 5). At this point, the body of the caudate has assumed a position directly lateral to the lateral ventricle. Also, the ventromedial portion of the accumbens/caudate is bounded by the white matter of the diagonal band of Broca/medial olfactory stria, as well as the ventral portion of the cingulate gyrus, which has assumed a position just ventral to the lateral ventricle at this point.

About 18 mm posterior to the first slice (slice 13), the accumbens becomes separated from the more dorsal caudate, and almost immediately (within 1 slice more posteriorly) ends. This small separated portion of the accumbens is not included in the caudate ROI. About 19.5 mm posterior to the first slice (slice 14), the GP appears, just medial to the ventral portion of putamen, with two structures separated by the lateral medullary lamina. Other bounds for the GP are the internal capsule (dorsally and medially) and the substantia innominata ventrally. For reference, we note that the anterior commissure appears 24 mm posterior to the first slice (see slice 17). By about 31 mm posterior to the first slice (slice 22), the GP has reached its maximal cross-sectional area, while the putamen has reduced its mediolateral extent, and the ventral portion of the putamen has become contiguous with a gray matter extension, called the peduncle of the lentiform nucleus, included with the putamen ROI in our classification. The GP then decreases in volume, ending about 43.5 mm posterior to the first slice (slice 30). In this same slice, the caudate has assumed a nearly circular cross-sectional area and is positioned at the very lateral-most extent of the lateral ventricles. As one proceeds further posteriorly, the putamen shrinks to a slender fusiform structure, ending 48 mm posterior to the first slice (slice 33). It should be noted that the posterior extent of both putamen and GP is best determined from axial slices and three-dimensional reconstructions, as was done for this description. By about 58.5 mm posterior to the first slice (slice 40), the ventricular atrium (nearly vertical connection between lateral and temporal horns) is present without PV effects, and the tail of the caudate has moved ventrally to course along the lateral margin of the atrium, before turning anteriorly. As noted, PV effects meant that this anterior-coursing portion of the tail could not be reliably outlined, and so it is not included in the ROI.

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