An MRI Study of Basal Ganglia Volumes in First-Episode Schizophrenia Patients Treated With Risperidone

Donna J. Lang, B.Sc.
Lili C. Kopala, M.D.
Robert A. Vandrope, M.D.
Qing Rui, M.B.
Geoffrey N. Smith, Ph.D.
Vina M. Goghari
William G. Honer, M.D.

Objective: The basal ganglia may contribute to extrapyramidal movement disorders, affective disturbances, and cognitive deficits in schizophrenia. Basal ganglia volumes are putatively affected by antipsychotic medications. The purpose of this study was to determine the long-term effects of risperidone treatment in a cohort of first-episode patients with schizophrenia.

Method: The subjects were 30 patients with first-episode schizophrenia, 12 patients chronically treated with typical antipsychotics, and 23 healthy comparison subjects. They were scanned by magnetic resonance imaging at baseline. The first-episode patients received 1 year of continuous risperidone treatment, after which they and the comparison subjects were rescanned. Caudate, putamen, and globus pallidus volumes were determined from coronal images.

Results: The baseline caudate, putamen, and globus pallidus volumes were significantly larger in the chronically treated patients than in the untreated first-episode patients and comparison subjects. These volumes did not differ between the first-episode patients and healthy comparison subjects. Basal ganglia volumes were unchanged after 1 year of exposure to risperidone. Extrapyramidal movement disorders were present in the majority of chronically treated patients and more than one-third of the never-medicated first-episode patients at baseline.

Conclusions: This group of first-episode patients did not exhibit abnormalities of basal ganglia volumes, nor were basal ganglia volumes affected by exposure to risperidone. Movement disorders were observed in both first-episode and chronically treated patients, suggesting effects of both illness and medications.

Diseases that affect the basal ganglia, such as Huntington's disease and Parkinson's disease, are associated with affective disturbances and psychosis (1, 2). Involuntary movements, affective disturbance, and catatonia in schizophrenia are phenotypically similar to symptoms found in basal ganglia disorders, suggesting the possibility of basal ganglia pathology in schizophrenia. Postmortem studies suggest both abnormally high and abnormally low basal ganglia volumes in schizophrenia (3, 4), and some (5, 6) but not all (7) magnetic resonance imaging (MRI) studies have shown low caudate volumes in antipsychotic-naive patients.

Several longitudinal MRI studies of basal ganglia volumes in schizophrenia during treatment with typical or atypical antipsychotics have been described. Chronic exposure to typical antipsychotic medications was associated with basal ganglia enlargement in patients who were previously drug naive (8, 9), and volume decreased when patients were switched to clozapine or other atypical antipsychotic (8, 10, 11).

The effects of treatment with atypical antipsychotics on basal ganglia volumes in a drug-naive population are unclear. We performed a longitudinal study of basal ganglia volumes in patients with first-episode schizophrenia, measuring volumes before and after treatment with risperidone. Comparison groups included patients treated chronically with typical antipsychotics and healthy subjects. The hypotheses were that 1) basal ganglia volumes in first-episode patients would be smaller than those in healthy subjects, 2) basal ganglia volumes in patients treated chronically with typical antipsychotics would be larger than the baseline values for the first-episode patients, and 3) there would be a decrease in volumes following risperidone treatment.

Method

Subjects

Demographic characteristics of the 30 first-episode, 12 chronic, and 23 healthy subjects appear in Table 1. The ratings of socioeconomic status were based on the Canadian National Occupational Classification system (12). The ratings of parental socioeconomic status reflected the higher-rated parent. Diagnoses were made according to the DSM-IV criteria, with information obtained from the Structured Clinical Interview for DSM-IV. All first-episode and chronically treated patients were diagnosed with schizophrenia, except for one first-episode subject diagnosed with schizoaffective disorder.

First-episode patients were included if lifetime exposure to antipsychotic medication did not exceed 8 weeks of treatment in...
the year of the baseline scan or 4 weeks of continuous treatment immediately before scanning. The first-episode patients’ total lifetime exposure to antipsychotics was less than 12 weeks. The chronically treated patients had received 12 or more weeks of continuous treatment with typical antipsychotic medication immediately before the baseline scan. The dose of antipsychotic medication was converted to chlorpromazine equivalents. The mean dose for the chronically treated patients was 276.1 mg/day of chlorpromazine units. The 23 healthy comparison subjects were recruited from hospital staff and the local community.

The exclusion criteria were a history of significant head injury or loss of consciousness exceeding 5 minutes, a history of facial or nasal trauma, a history of DSM-IV substance abuse or seizure disorder, and a family history of psychotic disorders. Written consent was obtained from all participants. The study was approved by the Dalhousie University Research Ethics Committee.

### Treatment and Clinical Measures

Ratings of psychiatric and extrapyramidal signs and symptoms were completed by research clinicians. Afterward, 24 of the first-episode patients were treated with risperidone (dose range = 1–6 mg/day, mean = 2.7 mg/day). Risperidone was the first atypical antipsychotic available in Canada for use with first-episode patients, and Canadian practice guidelines recommended using atypical antipsychotics for this patient group. Risperidone was routinely offered as first-line treatment during the time of enrollment in this study (1995–1998). Of the six patients not treated with risperidone, four refused all treatment, one was treated with olanzapine, and one participated in a controlled trial. Of the 24 patients taking risperidone, 15 were treated continuously for a minimum of 6 months, and these patients were used to study the effects of risperidone on basal ganglia structures. At baseline, one first-episode subject and two of the chronic subjects were receiving concomitant medications (lorazepam, 3 mg/day; benz-

### TABLE 1. Characteristics of Healthy Subjects, Patients With First-Episode Schizophrenia Treated With Risperidone, and Patients With Chronic Schizophrenia Previously Treated With Typical Antipsychotics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Subjects (N=23)</th>
<th>First-Episode Schizophrenia Patients (N=30)a</th>
<th>Chronic Schizophrenia Patients (N=12)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>22</td>
<td>26</td>
<td>11</td>
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<tr>
<td>African American</td>
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<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mean socioeconomic statusc</td>
<td>High 11</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Parent with higher rating</td>
<td>High 13</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mean currently in schoolde</td>
<td>5</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.7</td>
<td>7.2</td>
<td>22.9</td>
</tr>
<tr>
<td>Patients’ lifetime exposure to antipsychotic medication at baseline</td>
<td>Duration (weeks)</td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Dose (mg/day chlorpromazine equivalents) (13)</td>
<td>Total 36.5</td>
<td>66.9</td>
<td>—</td>
</tr>
<tr>
<td>Risperidone</td>
<td>—</td>
<td>—</td>
<td>2.5–6.0</td>
</tr>
<tr>
<td>Clozapine</td>
<td>—</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Extrapyramidal Symptom Rating Scale scores</td>
<td>Baseline 2.0</td>
<td>2.2</td>
<td>0–6</td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale scores</td>
<td>Baseline 100.9</td>
<td>18.0</td>
<td>70–141</td>
</tr>
</tbody>
</table>

*a lifetime antipsychotic medication did not exceed 8 weeks during the year of the study or 4 weeks of continuous treatment immediately before the study.*

*b typical antipsychotics had been received for 12 or more weeks immediately before the study.*

*c based on Canadian National Occupational Classification (12). High=professional or managerial work, moderate=skilled clerical or technical work, low=manual labor or untrained clerical work. Data were not available in all cases.*

*d currently enrolled in elementary or high school or in the process of obtaining an undergraduate degree.*
tropine, 2.0 mg/day; and fluvoxamine, 300 mg/day, respectively). At follow-up, one first-episode patient was receiving concomitant medication (sertraline, 25 mg/day). Of the nine patients treated with risperidone initially but excluded from the follow-up study, four did not receive a second MRI (two moved, two refused scan) and five were not taking risperidone at the time of the second scan (three changed medication, two later refused medication).

Extrapyramidal signs and symptoms were rated at baseline, at the time of the follow-up scan, and whenever medication was changed. The ratings were obtained by using the Extrapyramidal Symptom Rating Scale (15). Interrater reliability, as reflected by intraclass correlation coefficients (ICCs), was high (ICC=0.84). Psychiatric symptoms were assessed by using the Positive and Negative Syndrome Scale (16). Ratings were made at baseline, with changes in medications, and at follow-up.

MRI Measurements

The subjects were scanned with a Siemens Magneton Vision 1.5-T MRI scanner. A coronal inversion recovery sequence was obtained for each subject. The inversion recovery sequence was obtained as follows: TR/TE=2000/20 msec, field of view=200 cm, and matrix size=168×256, pixel size=1.0×0.78 mm. A total of 18 slices, 4 mm thick with a 1-mm interslice gap, were available. Follow-up scans were acquired a mean of 1.06 years after baseline (SD=0.41). Repeat scans were not available for the chronically treated group. Digitized slices were measured by using a Macintosh G3/350 Mz computer. Additional T2-weighted axial images of the entire brain were acquired to facilitate assessment of total intracranial volume. The axial T2-weighted images were highly sensitive to focal pathology and provided good demarcation of the CSF-containing spaces. Inversion recovery sequences (cortical T1) were obtained for anatomical detail and superior differentiation of gray and white tissue. The white-to-gray pixel intensity ratio in these scans was 1.42, compared with a value of 0.89 obtained by using a spoiled gradient recall acquisition sequence obtained on a 1.5-T GE scanner of similar quality.

Basal ganglia measurements were made by a single rater (D.J.L.) blind to diagnosis, time of scan, and gender. Total intracranial volumes were measured by two raters (D.J.L., V.M.G.). The films were visually inspected for motion artifact, tilt, rotation, and slice matching at follow-up. One subject was excluded because of head tilt. Slice-to-slice matching of the baseline and follow-up scans was assessed by comparison of the placements of the anterior commissure slice and of the first frontal horn slice. This approach was used in a serial scan follow-up study of lesions in multiple sclerosis (17).

All regions of interest were manually selected with interactive shareware (NIH Image, version 1.61 ppc) (18). The basal ganglia measures began two slices anterior and ended two slices posterior to the anterior commissure slice in every subject (five slices in each). The slices were determined a priori on the basis of the clarity of edge detection and unequivocal presentation of basal ganglia regions according to Duvernoy’s MRI atlas (19). All basal ganglia measurements were the mean of four independent trials.

The caudate, putamen, and globus pallidus were manually selected on each slice. The most anterior slice showed the head of the caudate-putamen complex; however, these nuclei could not be separated at this level. The total bilateral caudate-putamen complex on this slice was therefore divided into two halves. The nucleus accumens was included in the total caudate volume. Interrater reliability was assessed in a randomly selected subset of 10 scans (caudate, ICC=0.99; putamen, ICC=0.97; globus pallidus, ICC=0.96; intracranial volume, ICC=0.99).

Data Analysis

Continuous demographic variables were analyzed by omnibus analysis of variance (ANOVA). A single ANOVA was performed with age entered as a dependent measure and group (first-episode, chronic, healthy) entered as a main effect. Differences in gender, socioeconomic status, and ethnicity were analyzed by using chi-square goodness-of-fit tests. Measures of total intracranial volume and baseline regional brain volumes were analyzed by an omnibus analysis of covariance (ANCOVA). For analysis of total intracranial volume, group and gender were entered as main effects, with age entered as a covariate. For regional brain volumes, total (left plus right) caudate, putamen, and globus pallidus volumes were entered as dependent measures, with group entered as a main effect and total intracranial volume entered as a covariate. Post hoc analyses of significant main effects were performed by using Bonferroni inequality/Dunn’s tests for comparisons of groups (with significance set to p<0.05) and paired t tests for comparisons of baseline and follow-up volumes. Scores on the Positive and Negative Syndrome Scale and the Extrapyramidal Symptom Rating Scale at week 12 of the medication trial were used as outcome measures. Medication doses and extrapyramidal symptom scores in the first-episode and chronic patients were compared by using unpaired Student t tests. The difference between baseline and follow-up extrapyramidal symptom scores for the risperidone-treated patients was assessed by a paired t test.

Results

Demographic characteristics are given in Table 1. Age was significantly different between groups (F=5.91, df=2, 62, p=0.005), as post hoc analysis showed that the chronically treated patients were significantly older than the first-episode patients. Gender, ethnicity, and parental socioeconomic status did not differ significantly between groups (gender: χ²=1.81, df=2, p=0.40; ethnicity: χ²=1.27, df=2, p=0.53; parental socioeconomic status: χ²=6.24, df=4, p=0.18). Both the first-episode and chronic patients had lower socioeconomic status than the healthy subjects (χ²= 43.22, df=6, p<0.0001).

Basal Ganglia Volumes

Individual volumes of the regions of interest at baseline are shown in Figure 1, and follow-up values appear in Figure 2 for the subjects with both baseline and follow-up values. The men had larger intracranial volumes than the women (F=37.63, df=1, 61, p=0.0001), but no significant differences were found between groups (F=0.42, df=2, 61, p=0.66), and no effect of age was found (F=0.41, df=1, 61, p=0.52). All subsequent regional ANCOVAs included total intracranial volume as a covariate.

A significant group effect on volume was observed for the caudate (F=3.18, df=2, 61, p<0.05), putamen (F=3.41, df=2, 61, p=0.04), and globus pallidus (F=11.87, df=2, 61, p=0.0001). Post hoc analyses revealed significantly larger caudate, putamen, and globus pallidus in the chronically treated patients than in the first-episode group (Figure 1). Post hoc analysis also revealed that the globus pallidus volumes of the chronically treated patients were significantly larger than those of the healthy comparison
subjects. The caudate, putamen, and globus pallidus baseline volumes in the first-episode patients and healthy subjects did not differ significantly, nor did the volumes in the never-medicated first-episode patients and those in the first-episode patients exposed to less than 12 weeks of medication before scanning (p>0.10 for all regions).

Only the first-episode patients and healthy comparison subjects were included in the risperidone follow-up analyses (Figure 2). No significant group changes in total caudate, putamen, or globus pallidus volumes were observed at follow-up in either the first-episode patients or the healthy comparison subjects (p>0.20 for all comparisons).

**Clinical Measures and Exploratory Analyses**

Baseline scores on the Extrapyramidal Symptom Rating Scale were available for 23 never-treated first-episode patients and 11 chronically treated patients (Table 1). Ten of the never-treated first-episode patients had preexisting movement disorders, and 10 of the chronically treated patients had movement disorders at baseline. The chronically treated patients had significantly higher scores on the Extrapyramidal Symptom Rating Scale than the never-medicated patients (t=3.38, df=32, p=0.002). ANOVA did
not reveal differences in baseline basal ganglia volumes between the never-medicated patients with extrapyramidal symptoms (i.e., those who had scores higher than 0 on the Extrapyramidal Symptom Rating Scale) and those without such symptoms (i.e., had scores of 0) (in all cases, \(F<1.50, df=1, 21, p>0.10\)). Fourteen first-episode patients treated with risperidone were rated for extrapyramidal symptoms again after 1 year of treatment (mean dose=2.7 mg/day, SD=1.4). Their total scores after treatment were not different from the initial scores (\(t=0.20, df=12, p=0.84\)). After treatment, the extrapyramidal symptom scores were lower in four patients (as in the patients in our prior study [20]), slightly higher in two patients, and unchanged in the remaining eight patients. Exploratory correlational analyses of extrapyramidal symptoms and baseline basal ganglia volumes in the chronically treated patients did not reveal statistically significant relationships between basal ganglia volumes and total length of antipsychotic exposure, total lifetime dose (converted to chlorpromazine units), or the product of exposure length and dose. However, a positive correlation between globus pallidus volume and total length of antipsychotic exposure approached significance in the chronically treated subjects (\(r=0.56, df=11, p=0.06\)).

Before the start of any antipsychotic drug treatment, scores on the Positive and Negative Syndrome Scale were collected for 24 first-episode patients. These scores were used in the subsequent analyses of symptom scores. As shown in Table 1, the first-episode patients had higher baseline scores on the Positive and Negative Syndrome Scale than the chronically medicated patients (\(t=4.76, df=33, p<0.0001\)). Scores were also collected for 14 first-episode patients after 12 weeks of continuous risperidone treatment. Their scores were significantly reduced after 12 weeks of risperidone treatment (\(t=8.39, df=13, p<0.001\)). The 12-week scores on the Positive and Negative Syndrome Scale for the risperidone-treated patients did not differ significantly from the scores for the patients chronically treated with typical antipsychotics (\(t=1.10, df=23, p>0.20\)).

**Discussion**

Three main findings emerged from this study. First, we replicated the observation of higher basal ganglia volumes in patients chronically treated with typical antipsychotic medication. Second, contrary to our hypothesis, we found no baseline differences in basal ganglia volumes between patients with first-episode schizophrenia and healthy comparison subjects. Third, we did not detect significant changes in basal ganglia volumes in first-episode patients after a mean of 1.06 years of exposure to risperidone.

In studies of nonhuman basal ganglia tissues (21, 22), haloperidol treatment increased the number of neurons immunoreactive for the Fos-like protein in the caudate nucleus and putamen. A study of rats (23) demonstrated basal ganglia enlargement after 1 to 6 months of haloperidol administration. Rat studies (24, 25) have also demonstrated increased neuronal soma volumes in the prefrontal cortex and striatum after exposure to haloperidol. These investigations suggest neuronal activation in the striatum after exposure to typical antipsychotics. In addition, functional brain studies of humans (26, 27) have demonstrated haloperidol-induced increases in deoxyglucose metabolism in basal ganglia regions. Both increased neuronal activation and increased neuronal metabolism may contribute to basal ganglia enlargement after exposure to typical antipsychotics.

The globus pallidus was approximately 25% larger in the chronically treated patients than in the healthy comparison subjects or the first-episode patients. In comparison, the caudate and putamen were larger by approximately 7% and 8%, respectively. Similar magnitudes of pallidal enlargement in patients treated with typical antipsychotics were seen in two previous studies (28, 29), and Chakos et al. (14) reported a significant correlation between basal ganglia volume and fluphenazine dose in first-episode schizophrenia. Basal ganglia enlargement may occur relatively rapidly and reach a plateau in the early phases of antipsychotic treatment, and even low-dose exposure to a typical agent may result in hypertrophy (9).

Our data did not demonstrate abnormalities of basal ganglia volumes in the early phases of illness. Corson et al. (5) reported low caudate volumes in never-medicated patients with schizophrenia, but Gur et al. (28) found no differences between drug-naive patients and healthy comparison subjects. Normal brain development involves volumetric changes during adolescence (30). Both age and gender in normal comparison subjects may require careful matching to determine true differences in subregional brain volumes.

The first-episode patients in this study did not exhibit basal ganglia enlargement after a mean of 1.06 years of continuous risperidone treatment. Studies comparing the effects of typical and atypical antipsychotics suggest that the basal ganglia enlargement induced by typical antipsychotics is reversible (8, 10, 11) and that differences in the pharmacology of these medications may be related to volume changes.

Risperidone's dopamine D2 occupancy rates are dose dependent, and optimal doses (D2 occupancy of 65%–80%) range from 2 to 5 mg/day (31). The doses in this study (1–6 mg/day) were mostly within the optimal range. At doses above 6 mg/day, risperidone induces extrapyramidal symptoms without additional improvement in psychotic symptoms (31, 32). Similarly, optimal doses of haloperidol also have 65%–80% D2 basal ganglia occupancy rates (33), and at recommended clinical doses (i.e., at recommended D2 occupancy levels) haloperidol can increase basal ganglia volumes (8). These results suggest that the mechanism underlying basal ganglia enlargement cannot be attributed to D2 blockade alone.

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Conversely, the evidence that any atypical antipsychotic causes a reduction in basal ganglia volumes below pretreatment levels remains questionable. Some groups have speculated that clozapine reduces basal ganglia volumes in animals (34) and humans (8, 10, 11). The clozapine trials with human subjects were confounded by switches from typical antipsychotics, and the animal study was based on D2 receptor autoradiography, which may not be optimal for accurate volume estimation. The current data do not support the hypothesis of basal ganglia reduction from a never-treated baseline, at least for risperidone.

We and others (20, 35–37) have documented preexisting movement disorders in some drug-naïve patients. Preexisting movement disorders in schizophrenia may be masked by antipsychotic drug effects, particularly those of typical antipsychotic medications. In the present study, 10 of 11 of the chronically treated patients had extrapyramidal symptoms. Of the first-episode patients in this study, 10 of 23 had extrapyramidal symptoms at baseline. This is a higher proportion than we reported previously (20) and suggests a subtle underlying basal ganglia dysfunction in schizophrenia. Overall, the patients experienced improvement of extrapyramidal symptoms with risperidone.

The finding of no difference in basal ganglia volumes between the first-episode patients with and without extrapyramidal symptoms is in contrast to the higher basal ganglia volumes in the chronically treated patients with extrapyramidal symptoms. Enlargement of basal ganglia structures following treatment with typical antipsychotics may be closely related to the likelihood of movement disorders with traditional antipsychotic medications. The relationship of extrapyramidal symptoms and pretreatment basal ganglia volumes remains unclear.

There are several limitations to the present study. First, the results may have been influenced by the MRI acquisition protocol, slice thickness, the presence of interslice gaps, and the clarity of the white-to-gray tissue contrast. Typically, volumes acquired from two-dimensional and three-dimensional MRIs produce lower basal ganglia volumes than are found in postmortem studies (3, 4, 38). The volumes and error variances obtained in the present study are similar to values determined by imaging protocols with thinner coronal slices (5, 8, 14, 39). Interstudy comparisons do not indicate that slice thickness affects the accuracy or reliability of basal ganglia volume acquisition. Both accuracy and reliability of basal ganglia volumes are most affected by measurement methods. Our measurement protocols were clearly defined and highly reliable (ICC > 0.90 for all regions). Second, subtle differences in basal ganglia morphology are difficult to identify in small study groups. The present study had a relatively small number of subjects because of the inherent difficulty in obtaining appropriate subjects and keeping subjects involved during follow-up. Third, if progressive changes in the basal ganglia are occurring over the early years of illness, we may not have detected differences between the healthy volunteers and patients with schizophrenia in the relatively short follow-up period of 1 year. However, as already noted, studies of nonhuman subjects suggest that changes related to treatment with typical antipsychotics occur relatively rapidly.

There are several implications of the present results. Typical antipsychotics are associated with extrapyramidal symptoms, which appear to be related to enlargement of the basal ganglia. While motor disturbances may also be present in never-medicated patients with schizophrenia, the structural correlates are less clear. Last, the effects of risperidone on basal ganglia structures appear to be different from those of typical antipsychotics. These observations suggest there may be lasting advantages to the use of risperidone (and possibly other atypical antipsychotics) in first-episode schizophrenia.

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