

Increase in Caudate Nuclei Volumes of First-Episode Schizophrenic Patients Taking Antipsychotic Drugs

Miranda H. Chakos, M.D., Jeffrey A. Lieberman, M.D., Robert M. Bilder, Ph.D., Michael Borenstein, Ph.D., Gail Lerner, M.S., Bernhard Bogerts, M.D., Houwei Wu, M.D., Bruce Kinon, M.D., and Manzar Ashtari, Ph.D.

***Objective:** This study examined the pathomorphology of the caudate nuclei in first-episode schizophrenic patients with minimal previous neuroleptic exposure. **Method:** Magnetic resonance imaging (MRI) of the brain was used to examine longitudinally the caudate pathomorphology in 29 first-episode schizophrenic patients and 10 healthy comparison subjects. MRI scans were obtained after the subjects entered the study and at 18-month follow-up. The patients were treated with standardized neuroleptic regimens during the 18-month period. Volumetric assessments of the cerebral cortex, lateral ventricles, and caudate nuclei were performed on T₁-weighted coronal brain sections. In addition, the patients were systematically evaluated for psychopathology at baseline and during treatment. **Results:** Caudate volumes increased 5.7% in the patients during the 18-month treatment interval, whereas they decreased 1.6% in the comparison subjects over the same time period. Greater amounts of antipsychotic medication received by patients before the first scan and younger age at the time of the first scan were associated with larger increases in caudate volume. **Conclusions:** Caudate enlargement occurs early in the course of treatment in young first-episode schizophrenic patients. This may be a result of an interaction between neuroleptic treatment and the plasticity of dopaminergic neuronal systems in young patients.*

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Post-mortem and in vivo imaging studies conducted over the last three decades have made substantial progress in identifying the neuropathology of schizophrenia. Abnormalities reflected by volume, shape, cytoarchitecture, and histology have been described in specific brain structures, including the ventricular system, cerebral cortex, hippocampus, cingulate gyrus, entorhinal cortex, and parahippocampal gyrus (1-3). Current research efforts are attempting to

link these neuropathologic findings to pathogenic processes and the clinical dimensions of the disease. Two questions that have not been resolved, however, are 1) whether some of the neuropathologic findings associated with schizophrenia are a consequence of the disease or of the substantial treatment that most patients receive in the course of their illness and 2) whether the neuropathologic process is, in some regions, progressive.

Since the major pharmacologic action of antipsychotic drugs is in the dopamine neurons that project to the basal ganglia nuclei—including the caudate nucleus, globus pallidus, and putamen—and produce extrapyramidal side effects as a consequence of this action, if drugs can affect brain morphology, these structures might be particularly susceptible. In this context, recent post-mortem and magnetic resonance imaging (MRI) studies that have reported increased striatal and lenticular nuclei volumes in schizophrenic patients (4-8) are of interest. These findings are in contrast to the usual pattern of neuropathology in schizophrenia, in which reduction in the size of soft-tissue brain structures and enlargement of fluid-containing structures are characteristically seen (1, 2). In a post-mortem study, Heckers et al. (5) reported significant increases in left striatal

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volumes and a trend toward increases in right striatal volumes of brains of schizophrenic patients in comparison with brains of age- and gender-matched control subjects. MRI studies of subcortical structures have found increased lenticular nuclei volumes (6) and putamen and caudate enlargement (7, 8) in young but chronic, medicated schizophrenic patients compared with age- and gender-matched normal control subjects. These findings of striatal enlargement have been interpreted as a feature of schizophrenia that is caused by a disturbance in neurodevelopmental pruning of subcortical structures in patients with the disease, particularly those with early onset of illness (6, 9). Alternatively, treatment with neuroleptic drugs and resultant dopamine blockade could result in disinhibition of the striatum, with consequent activation and (analogous to muscle cells after activation) hypertrophy of striatal synaptic and/or cellular elements. Various forms of activity-dependent synaptic plasticity have been described in many neural systems (10). Since cross-sectional studies reporting caudate enlargement have examined heterogeneous groups of chronically medicated patients, it is not clear whether the observed enlargement reflects a preexisting abnormality or is an effect of drug treatment. To address this question we examined the caudate nuclei in MRI scans acquired in a longitudinal prospective study of first-episode schizophrenic patients who were in the early phases of treatment.

METHOD

This study used MRI and clinical data from a longitudinal prospective study of first-episode schizophrenic patients and normal comparison subjects to examine changes in caudate volumes over time. The subjects included in the study were a subgroup of the subjects for whom brain morphology studies of medial temporal lobe structures and the ventricular system have previously been reported (11-13). We selected subjects who had baseline and 18-month follow-up MRIs suitable for examination of the caudate. Detailed descriptions of the methods of the parent study have been previously reported (12, 14, 15). Patients admitted to the hospital for a first episode of psychosis who had had fewer than 12 weeks of lifetime exposure to neuroleptics or none at all underwent a structured interview with the Schedule for Affective Disorders and Schizophrenia (SADS) (16). Eligible patients were between the ages of 16 and 40 years and had diagnoses of schizophrenia, schizophreniform disorder, or schizoaffective disorder, mainly schizophrenic, according to the Research Diagnostic Criteria (17). They had no prior psychotic episodes, no history of current substance abuse, and no neuromedical illness that could influence the diagnosis or the major variables assessed in the study. Patients with prior neuroleptic exposure had at least a 2-week medication washout period before entering the study. All patients were acutely psychotic with severe psychopathology at the time of entry into the study.

Comparison subjects were recruited through advertisements in the local media and, if eligible, were offered \$50 to undergo MRI. The volunteers were screened for medical and psychiatric illness and history of drug abuse. They were then given the Structured Clinical Interview for DSM-III-R (18) and a physical examination with laboratory testing. Volunteers with significant findings were excluded from participation.

Measurements of the caudate nuclei were performed on two MRI scans of 29 first-episode patients (21 with schizophrenia and eight with schizoaffective disorder) and 10 healthy comparison subjects. Twenty-one of the 29 primarily schizophrenic patients had had no prior exposure to neuroleptic treatment at the time they entered the

study. The remaining eight patients had had fewer than 12 weeks of lifetime treatment exposure. Seventeen patients were male, and 12 were female; 13 were white, eight black, four Hispanic, and four Asian. The mean age of the patients was 25.2 years ($SD=6.3$), and the mean age at onset of illness was 24.4 years ($SD=6.6$).

Eight of the comparison subjects were male, and two were female; all of them were white. Their mean age was 30.5 years ($SD=4.9$).

Patients underwent the first MRI of the brain (scan 1) when they entered the study or following initiation of neuroleptic treatment; they underwent scan 2 at 18-month follow-up. Scan 1 was done as soon as a patient could tolerate the procedure and allow images of adequate quality to be obtained. When necessary, chloral hydrate (500-1000 mg p.o.) or amobarbital sodium (250-500 mg p.o. or i.m.) was used to sedate patients for the procedure. Comparison subjects had MRI scans at approximately the same intervals within the same time period.

MRIs were acquired on a Siemens Magnetom operating at 1.0 T with a 3-dimensional gradient-echo sequence FLASH (fast low-angle shots) (flip angle=50°, TR=40 msec, TE=15 msec) acquiring 63 contiguous 3.1-mm T₁-weighted slices in the coronal plane (19). Patients' and comparison subjects' MRIs were transferred from a VAX 11/750 onto a Sun SPARC 10 workstation operating from a Sun 670 server for morphometric analysis. Quantitative assessments of volumes of the caudate nuclei, cortex, and lateral ventricles were performed with the use of a semiautomated computer mensuration system, the validity and interrater reliability of which had been established previously through phantom and in vivo studies (19).

The manual function of the computerized mensuration system was used to measure the caudate in order to demarcate precisely the boundaries of adjacent gray matter structures. The caudate nucleus was selected for measurement because its anatomic boundaries could be more precisely delineated than those of the globus pallidum and putamen. The caudate nucleus was measured in coronal sections, with the cisterna pontis as the posterior landmark; measurement was continued anteriorly until the caudate head was no longer visible. At the slice anterior to the section where the anterior commissure crosses the midline, the nucleus accumbens was separated from the caudate by a line combining the most basal extents of the lateral ventricle and the internal capsule. All caudate measurements were performed by a single operator (M.H.C.) under blind conditions and with the scans randomly ordered. The reliability coefficient on test-retest measurements of the caudate nuclei of all patients and comparison subjects was 0.89.

Cortical volumes were determined by the sums of the volumes of cortical regions (the occipitoparietal, sensorimotor, premotor, prefrontal, and temporal regions). The regional volumes included cortical gray and hemispheric white matter, but not subcortical structures; basal ganglia, thalamus, and ventricle volumes were excluded. Each region was measured separately in each hemisphere, with the interhemispheric fissure as a medial boundary. In the sensorimotor region, the temporal lobe, basal ganglia, and thalamus were excluded by a line from the most superior extent of the insular cisterns to the sulcus of the corpus callosum. In the premotor region, the basal ganglia were excluded by a line from the most superior extent of the insular cisterns to the sulcus between the corpus callosum and the cingulate gyrus. In the temporal region, the temporal stem was separated from the basal ganglia by a line from the most inferior part of the insular cisterns to the most lateral extent of the basal cisterns above the hippocampus. (Full delineation criteria for cortical regions have been described by Bilder et al. [20].)

Lateral ventricular volumes were computed by adding the volumes of the frontal horn, body, and occipital horn of the lateral ventricles. (The methods of ventricular measurement have been reported by Degreef et al. [13].) All cortical and ventricular volume measurements were made by a single operator (H.W.), using automated functions on the computer-based mensuration system under blind conditions and with the scans randomly ordered. The test-retest reliability was 0.90 for cortical measurements and 0.99 for ventricular system measurements.

The patients had baseline evaluations of psychopathology, extrapyramidal side effect status, and involuntary movements that included use of the SADS—Change Version (SADS-C) with psychotic and disorganization items, a modified Scale for the Assessment of

TABLE 1. Morphologic Measures of Brain Structures of First-Episode Schizophrenic Patients and Normal Comparison Subjects at Baseline MRI (Scan 1) and at 18-Month Follow-Up (Scan 2)

Measure	Schizophrenic Patients							
	Total Group (N=29)		Treatment-Naive Subgroup (N=21)		Previously Treated Subgroup (N=8)		Comparison Subjects (N=10)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Caudate volume (cc) ^a								
Scan 1	5.58	0.86	5.50	8.45	5.77	9.17	5.59	0.94
Scan 2	5.90	0.88	5.84	8.13	6.07	1.08	5.50	0.89
Cortical volume (cc) ^b								
Scan 1	780.63	162.40	—	—	—	—	849.22	321.15
Scan 2	805.81	126.89	—	—	—	—	831.38	315.70
Lateral ventricular volume (cc) ^c								
Scan 1	16.24	6.79	—	—	—	—	13.38	5.49
Scan 2	15.59	7.65	—	—	—	—	13.21	6.68

^aTotal group of patients versus comparison subjects: nonsignificant effect of group ($F=0.40$, $df=1$, 37 , $p=0.53$); significant Group by Time interaction ($F=6.01$, $df=1$, 37 , $p<0.02$). Treatment-naive subgroup versus comparison subjects: nonsignificant effect of group ($F=0.17$, $df=1$, 29 , $p=0.69$); significant Group by Time interaction ($F=5.19$, $df=1$, 29 , $p=0.03$). Previously treated subgroup versus comparison subjects: nonsignificant effect of group ($F=0.75$, $df=1$, 16 , $p=0.40$); nearly significant Group by Time interaction ($F=4.13$, $df=1$, 16 , $p<0.06$).

^bTotal group of patients versus comparison subjects: nonsignificant effect of group ($F=0.43$, $df=1$, 37 , $p=0.52$); nonsignificant Group by Time interaction ($F=1.47$, $df=1$, 37 , $p=0.23$).

^cTotal group of patients versus comparison subjects: nonsignificant effect of group ($F=1.30$, $df=1$, 37 , $p=0.26$); nonsignificant Group by Time interaction ($F=0.05$, $df=1$, 37 , $p=0.83$).

Negative Symptoms (21), a modified Simpson-Angus Rating Scale (22), and a modified Simpson Dyskinesia Scale (23). After baseline assessment, patients were treated openly in accordance with a standardized treatment algorithm (13, 14). They initially received fluphenazine, which was increased to 20 mg/day for 6 weeks. If they achieved remission or showed continuing improvement, they remained on this regimen. Remission was operationally defined as a rating of no more than 3 on any of the positive psychotic items on the SADS-C with psychotic and disorganization items, a Clinical Global Impression (CGI) severity rating of 3 (mild) or less, and a CGI improvement rating of 2 (much improved) or 1 (very much improved). If not improved in 6 weeks, patients progressed through the treatment algorithm, receiving full trials of up to three different neuroleptics. All study patients were followed as outpatients by research psychiatrists. They were evaluated biweekly with the SADS-C with psychotic and disorganization items, the Scale for the Assessment of Negative Symptoms, the Simpson-Angus Rating Scale, and the CGI for 12 weeks and every 4 weeks thereafter. Evaluations with the Simpson Dyskinesia Scale were completed every 8 weeks. The general strategy of maintenance treatment was to reduce the daily dose of antipsychotic medication gradually to the lowest effective level.

RESULTS

Our analysis focused on changes in caudate volume in the first-episode patients and the effect of patient group versus comparison subject group on caudate change. The size of our comparison group remained small and limited our capacity to match for age and gender. Taking into account the small size of this group, we focused our primary analyses on the within-subject effect of time in the patients. We subsequently examined the between-group effect and the interaction of group and time with respect to caudate volume.

All 29 patients had a remission of their illness with treatment. The median time to remission was 11 weeks.

The patients had a significant mean increase of 0.32 cc (SD=0.47) in total caudate volume from scan 1 to scan 2 (paired $t=-3.68$, $df=28$, $p=0.001$) but no signifi-

cant change in their ventricular and cortical volumes (table 1). To examine whether the apparent change in caudate volume noted in the patients was a discrete process or secondary to a more generalized process in the brain, analyses of covariance were performed. The change in caudate volume in the patients during the 18-month interval of treatment remained significant when we covaried height ($F=11.68$, $df=1$, 27 , $p=0.002$) and total cortical volume ($F=11.08$, $df=1$, 27 , $p=0.003$).

Between-Group Effects

The morphologic variables for the patients and comparison subjects are presented in table 1. There was no main effect of group on caudate volume for the whole group of patients and the comparison subjects. However, the Group by Time interaction was significant, and it remained significant when we covaried height ($F=5.47$, $df=1$, 36 , $p<0.03$) and cortical volume ($F=4.60$, $df=1$, 36 , $p<0.04$). The mean total caudate volume for the 29 patients increased 0.32 cc (SD=0.47) (paired $t=3.68$, $df=28$, $p=0.001$), while the mean caudate volume for the normal comparison subjects was reduced by 0.09 cc (SD=0.04) (paired $t=0.69$, $df=9$, $p=0.51$).

Right caudate volumes were larger than left caudate volumes (main effect of hemisphere: $F=9.56$, $df=1$, 37 , $p=0.004$) (table 2). This effect was not limited to either patients or comparison subjects (Group by Hemisphere interaction: $F=0.14$, $df=1$, 37 , $p=0.71$). Nor did the asymmetry change over time (Hemisphere by Time interaction: $F=0.09$, $df=1$, 37 , $p=0.79$; Group by Hemisphere by Time interaction: $F=0.08$, $df=1$, 37 , $p=0.77$). When age was used as a covariate, the Group by Time interaction did not reach conventional levels of statistical significance ($F=3.33$, $df=1$, 36 , $p<0.08$). There was a negative association between caudate volume change

TABLE 2. Caudate Volumes of First-Episode Schizophrenic Patients and Normal Comparison Subjects at Baseline MRI (Scan 1) and at 18-Month Follow-Up (Scan 2)

Measure	Caudate Volume (cc)			
	Schizophrenic Patients (N=29)		Comparison Subjects (N=10)	
	Mean	SD	Mean	SD
Scan 1				
Right hemisphere	2.81	0.45	2.82	0.45
Left hemisphere	2.77	0.42	2.77	0.48
Total	5.58	0.86	5.59	0.94
Scan 2				
Right hemisphere	2.98	0.44	2.77	0.47
Left hemisphere	2.92	0.45	2.73	0.42
Total	5.90	0.88	5.50	0.89

score and age among both the patients and the comparison subjects (figure 1). In patients this negative association appeared to be caused by greater increases in volumes in young patients, while in comparison subjects it was largely due to reduction in the caudate volumes of the older subjects. Since the group of comparison subjects was relatively small, nonparametric statistics were also used to confirm that the between-group difference in caudate change was not a spurious effect of a few outlying values. A Mann-Whitney U test performed on the rank-ordered change scores again revealed a significant difference between the two groups ($U=76.00$, $z=-2.22$, $p<0.03$).

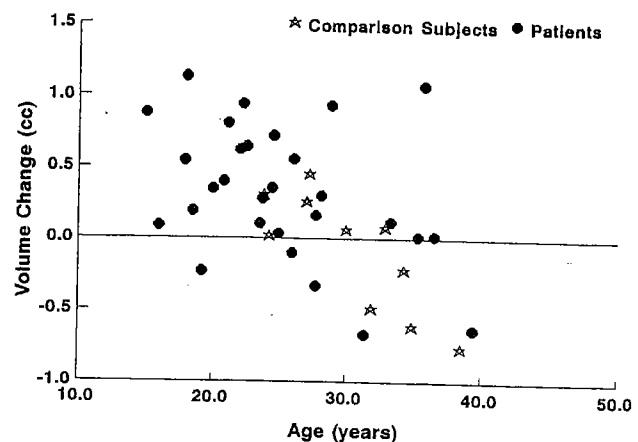
Clinical Correlates

The amount of time that patients were treated with medication prior to scans was not associated with caudate volume change scores. However, a higher daily dose received prior to scan 1 was associated with larger increases in caudate volume ($r=0.41$, $N=29$, $p<0.02$) (figure 2), while an average dose received between scan 1 and scan 2 was not. Younger age at onset of illness was associated with a higher daily dose of medication prior to scan 1 ($r=-0.50$, $N=28$, $p=0.003$) and greater caudate volume change scores ($r=-0.38$, $N=28$, $p=0.02$).

The effects of age and gender on changes in caudate volume in the patients were also examined. The Gender by Time interaction demonstrated that gender was not related to changes in caudate size ($F=0.97$, $df=1, 27$, $p=0.33$). When we examined caudate change within the patient group and covaried age at the time of scanning, there was no longer a significant effect of time ($F=0.03$, $df=1, 27$, $p=0.87$).

Weeks to remission and level of remission achieved; baseline psychopathology as reflected by scores on the SADS-C with psychotic and disorganization items, the Scale for the Assessment of Negative Symptoms, and the CGI; and development of tardive dyskinesia and acute parkinsonism were not correlated with caudate volumes or caudate volume change scores.

FIGURE 1. Change at 18-Month Follow-Up in Caudate Volume of First-Episode Schizophrenic Patients and Normal Comparison Subjects by Age at the First MRI Scan^a



^aFor comparison subjects, $r=-0.82$, $N=10$, $p=0.002$; for patients, $r=-0.39$, $N=29$, $p<0.02$.

DISCUSSION

These findings indicate that the caudate nuclei enlarge in the early stages of treatment of young first-episode schizophrenic patients. The change in caudate volume in the patients was in contrast to the lack of change in the healthy comparison subjects, who had scans over the same time interval and received no treatment. The small number of comparison subjects (and their unequal age and gender distribution) limits definitive comparisons with the patients. Nevertheless, the observed changes in caudate volumes were significant within the patient group as well as between patients and comparison subjects. The increase in caudate volume remained significant when cortical volume and height were covaried and occurred primarily in younger patients. This direction of change is in contrast to the normal developmental trend of the caudate, which is to decline in volume with increasing age (24), and to what would be the expected pattern of morphologic change of the caudate in the course of schizophrenia if it involved a degenerative process (25).

An increase in striatal volumes of early-onset, first-episode schizophrenic patients could occur through at least two mechanisms. It is possible that degenerative changes in these patients could provoke regenerative collateral sprouting (26) with resultant volume increases. If enlargement was produced by such degenerative changes, we might expect that enlargement would be associated with measures of severity of illness, including psychopathology scores, time to remission, and level of remission. In our group of patients there was no association between caudate volume or caudate volume change scores and measures of severity of illness, with the exception of age at onset of illness.

An alternative explanation for the increase in young first-episode patients' caudate nuclei volumes during

