ORIGINAL ARTICLE

Structural Brain Differences Between Never-Treated Patients With Schizophrenia, With and Without Dyskinesia, and Normal Control Subjects

A Magnetic Resonance Imaging Study

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Background: In south India, abnormal movements indistinguishable from tardive dyskinesia have been observed in chronically ill patients with schizophrenia who have never received antipsychotic medication. The present study, using magnetic resonance imaging, examines brain structure in such patients, in those without dyskinesia, and in normal control subjects.

Methods: Chronically ill patients with schizophrenia with and without dyskinesia and controls were identified in villages south of Chennai, India (each group, n=31). Patients' mental state was assessed by the Positive and Negative Syndrome Scale for schizophrenia, dyskinesia by the Abnormal Involuntary Movements Scale, and parkinsonism by the Simpson and Angus scale. In patients and controls, magnetic resonance imaging measured the volume of the caudate and lentiform nuclei and the lateral ventricle-hemisphere ratio.

Results: The left lentiform nucleus was significantly (11%) larger in patients with dyskinesia compared with controls, and the right lateral ventricle-hemisphere ratio was significantly (33%) larger in patients without dyskinesia compared with controls. In all 3 groups, there were significant positive correlations between age and ventricle-hemisphere ratio. In controls, but not in patients, there were significant negative correlations between age and the volume of the caudate and lentiform nuclei.

Conclusions: Never-treated patients with dyskinesia may have striatal pathologic conditions and may represent a subgroup of patients with schizophrenia; in those without abnormal movements, cortical atrophy is more apparent. The schizophrenic process may interfere with normal age-related anatomical changes in the basal ganglia.

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IN SOUTH INDIA, abnormal movements indistinguishable from tardive dyskinesia (TD) are not uncommon in chronically ill patients with schizophrenia who have never received antipsychotic medication.[1,2] We sought to determine whether there are any differences in brain structure between 2 patient groups with and without dyskinesia, and how the 2 groups compare with normal subjects. For the past 20 years, using computed tomography or magnetic resonance imaging (MRI), researchers on TD have measured cerebral atrophy and the size of the basal ganglia in treated patients, with inconsistent results.[3-14] For example, studies have shown no differences between patients with and without TD in the size of the caudate[3,4,7,10,12] or lentiform nucleus[9,10,12,13]; other studies in patients with TD have found a larger caudate nucleus[14]; and others have found a smaller caudate[5,9,13] or lentiform nucleus.[5] In 5 reports[15-19] of drug-naive first-episode patients, 3 found a reduction in volume of the caudate nucleus in patients compared with control subjects[16,17,19]; the other 2 found no differences.[15,18] In 2 of the studies, there were no differences in the size of the lentiform nucleus.[17,18]

In the present MRI study, we report on the volume of the caudate and lentiform nuclei and the lateral ventricle-hemisphere ratio in never-treated chronically ill patients with and without dyskinesia, and in normal control subjects.

RESULTS

Thirty-one patients with dyskinesia (18 men and 13 women) were identified, with the same number and sex distribution of patients without dyskinesia and of controls. There were no significant differences between patients with and without dyskinesia in age, age at onset of illness, and severity of mental state, as assessed by the PANSS total score and subscales, nor between patients with dyskinesia and controls in age (**Table 1**). Patients with

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SUBJECTS AND METHODS

SUBJECTS

Patients were identified predominantly in and around the village of Thiroporur, 40 km south of Madras (Chennai), in south India. Here there is an outreach center run by SCARF (Schizophrenia Research Foundation, Chennai, India), a nongovernmental organization specializing in research and community care of patients with schizophrenia. Community mental health workers, trained to recognize major mental illness, bring to the center individuals from villages within a 20-km radius for assessment and treatment.

Patients were recruited if they fulfilled *DSM-IV*[20] criteria for schizophrenia and had never received antipsychotic medication. The diagnosis was made through mental state examination results (see "Assessment") and a history obtained from patients and relatives. The diagnosis was made by 1 of 2 psychiatrists (R.T. or R.P.), each of whom has postgraduate qualifications in psychiatry and has been practicing clinicians for more than 15 years. Patients were excluded if there was a history of seizures. No patients were abusing street drugs. Two male patients used alcohol once or twice monthly. No patient had ever received psychotropic medication. Analgesics and antipyretics were taken as needed for short periods.

The study was approved by the ethical review board at SCARF. Written consent was inappropriate as almost all subjects were illiterate. All patients gave informed oral consent, witnessed by their next of kin, who also gave informed oral assent, and a SCARF staff member. The oral consent was recorded in the patient's case record. Because almost all patients and their family members had to travel a long distance from their homes to the city for MRI, a detailed oral explanation of the study and the procedures involved was provided to them before obtaining their consent.

ASSESSMENT

Mental state was assessed by the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.[21] The ratings were made by 2 psychiatrists (R.T. and R.P.) fluent in English and Tamil (the local language) and trained in the use of the PANSS. The interrater reliability of the 2 psychiatrists in a previous unpublished study was high ($\kappa = 0.86$). One psychiatrist (R.G.M.) examined each patient for evidence of dyskinesia, using the Abnormal Involuntary Movements Scale,[22] and of parkinsonism, using the Simpson and Angus scale.[23] A patient was said to have probable dyskinesia if he or she fulfilled Schooler and Kane criteria,[24] namely, movements were "mild" in at least 2 of 7 individual areas rated or "moderate" in at least 1 area.

For each patient thus identified, another patient who did not have dyskinesia was recruited and matched for sex, age (within 5 years), and age at onset of illness (also within 5 years). Also recruited for each patient with dyskinesia was a normal control subject in the same village, matched for sex and age (within 5 years). In addition to the controls themselves, at least 1 other member of their families was interviewed to exclude a history of psychiatric disorder in the controls, using *DSM-IV* criteria. All subjects were villagers of low socioeconomic class.

MRI SCANNING

Magnetic resonance imaging scans were carried out using a scanner with uniform protocol and software (MR Vectra II, version 4.10, O.5T; GE Medical Systems, Milwaukee, Wis). One neuroradiologist (S.D.J.), blinded to subject

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dyskinesia had higher scores on the Simpson and Angus parkinsonism scale than did patients without dyskinesia.

Three patients with dyskinesia and 1 patient without dyskinesia refused to be scanned. Through a miscommunication between the clinicians and the radiologist, the latter failed to measure ventricle and hemisphere volumes in the first 16 patients, 5 with dyskinesia and 11 without dyskinesia. Therefore, the number of matched pairs was substantially less in the comparisons of ventricle and hemisphere volumes and basal ganglia-hemisphere ratios.

There were 2 statistically significant between-group differences in brain structure (**Table 2**). First, the absolute size of the lentiform nucleus was largest in patients with dyskinesia, followed by patients without dyskinesia, and then controls. The difference between patients with dyskinesia and controls was statistically significant for the left lentiform nucleus, with the former 11% larger than the latter. Second, the lateral ventricle-hemisphere ratio was largest in patients without dyskinesia, followed by patients with dyskinesia, and then controls. The difference between patients without dyskinesia and controls was statistically significant on the right side, with the former 33% larger than the latter.

We then considered hemisphere size in comparing the size of the left lentiform nucleus in the patients with dyskinesia and controls by using the lentiform-hemisphere ratio. There were only 23 matched pairs in whom both the lentiform nucleus and hemisphere measurements were available. In this smaller group, the mean absolute value of the lentiform nucleus was not significantly higher in the patients with dyskinesia (mean [SD], 3.37 [0.60] vs 3.10 [0.79] mL), nor was the lentiform-hemisphere ratio greater.

In the dyskinesia group, the scores on the PANSS subscales and parkinsonism scale did not correlate significantly with the size of the left lentiform nucleus. In the group without dyskinesia, the scores on the PANSS subscales and parkinsonism scale did not correlate significantly with the lateral ventricle-hemisphere ratio.

When within-group correlations were calculated between age, the size of the caudate and lentiform nuclei, and the ventricle-hemisphere ratio, in all 3 groups there were significant positive correlations between age and ventricle-hemisphere ratio (Pearson r range, 0.44-0.73). In the controls, but not in the patients, there were significant negative correlations between age and the size of the caudate and lentiform nuclei (r range, –0.48 to –0.49).

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and dyskinesia status, made all the measurements. The subject's head was positioned in a head coil fixation device, centered at the orbitomeatal line with no angulation. A spin echo sequence was used to obtain T2-weighted images in the axial plane.

For a volumetric study of the basal ganglia, lateral ventricles, and cerebral hemispheres at the level of the caudate nucleus, a fast inversion recovery sequence was used. Transaxial images were obtained using the following sequence: repetition time, 5000 milliseconds; echo time, 13 milliseconds; inversion time, 600 milliseconds; number of excitations, 2; matrix size, 192×256; slice thickness, 3 mm; number of contiguous slices with no gap, 24; field of view, 30 cm; and imaging options, rectangular-pixel, no phase wrap saturation–head first. All the axial images were aligned along the canthomeatal orientation.

The head of the caudate nucleus was defined in the transaxial plane as the mass of grey matter bounded inferolaterally by the anterior limb of the internal capsule, superolaterally by the external capsule, and medially by the lateral walls of the lateral ventricles. The superior extent of the caudate nucleus was defined up to the confluence of anterior and posterior horns of the lateral ventricles.

The lentiform nucleus was defined as the grey matter bounded by the internal and external capsules. Region tracing for the superior extent of the lentiform nucleus (putamen) was done until the thalamus disappeared and the body and the tail of the caudate nucleus became continuous. The third ventricle was used to identify the inferior extent of the lentiform nucleus.

All measurements were in cubic centimeters. The caudate nucleus and the lentiform nucleus were separately defined on the left and right side for each subject for volumetric measurements.

An image was displayed on the screen from the set of inversion recovery sequences. The area of interest (ie, caudate nucleus or lentiform nucleus) was defined by 2 sets of fixed intensities within a cursor-defined region. A minimal pixel intensity of 50 and a maximum pixel intensity of 150 were given. The cursor was positioned over the area of interest (caudate or lentiform nucleus) and its size adjusted. Trace function was used to draw the area of interest. The area in square centimeters was posted on the screen. A manual mode was used to collect data from each image within the selected range for the accurate definition of the area of interest. This was repeated separately for the caudate nucleus and lentiform nucleus on either side. The volume was calculated by the MRI software by summing the areas.

Cerebral hemisphere volume and the lateral ventricular volumes were measured in 2 contiguous sections. The inferior section was selected where both Monro foramina were seen. The sulcal spaces were excluded for volume measurements.

Not all scan measurements were available on all patients and control subjects (see the "Results" section).

STATISTICAL ANALYSIS

As a result of the methods used, we recruited 3 sets of matched pairs: patients with and without dyskinesia, patients with dyskinesia and controls, and patients without dyskinesia and controls. Between-group differences in the size of brain structures were measured by paired *t* tests. We compared not only differences in absolute size of the caudate and lentiform nuclei but also the caudate-hemisphere volume and lentiform-hemisphere volume ratios.

Within-group correlations between age and the size of different brain structures were measured by Pearson product moment correlation coefficient. As there were many correlations, we used the Scheffé multiple comparison test to assess the level of significance. A 5% level of significance was used. All tests were 2-tailed.

In the patients, there were no significant correlations between duration of illness and size of the caudate and lentiform nuclei, or between duration of illness and ventricle-hemisphere ratio.

COMMENT

We recruited to our study chronically ill, never-treated patients with schizophrenia. They were, on average, middle-aged and had been ill for about 10 years. The late age at onset of illness reflects the difficulty with our rural Indian patients in retrospectively assessing the exact age at onset. We considered this to be the first appearance of positive schizophrenic symptoms, as estimated by the patient or family, and obviously not first contact with psychiatric services or hospital admission. The apparent late onset of illness raises the possibility that some of our patients had an organic psychotic illness. However, we excluded from the study patients who had a history of seizures or alcohol or other drug abuse.

We are confident that the patients, although ill for many years, had not been exposed to antipsychotic medication. The SCARF team has been working in the Thiropuror area for more than 6 years, and the health workers drawn from the villages know the families well, especially details about health conditions and treatment. Also, there are no mental health services in this region except for the outreach program of SCARF. Antipsychotics are not available in any of the local stores; therefore, it is improbable that any of these patients would have received any antipsychotic medication.

We are also satisfied that the abnormal movements rated were indistinguishable from TD. The rater (R.G.M.) has had extensive experience in the use of the Abnormal Involuntary Movements Scale[2] in TD and has made more than 1500 ratings using this scale.

There are, however, limitations to our study. Patients who were eventually recruited to the study had first to agree to come with outreach workers to the SCARF center for assessment. They had to agree to be examined by clinicians and then travel with their relatives to the city (up to 100 km) for an MRI scan. All this demanded a high degree of cooperation from the patients and their families. We cannot be certain, therefore, that those patients are representative of the large numbers of never-treated patients in and around Thiropuror.

Another limitation is that the diagnosis of schizophrenia was made on clinical grounds, albeit by experi-

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Table 1. Demographic and Clinical Data*

	Patients With Dyskinesia (n = 31)	Patients Without Dyskinesia (n = 31)	Control Subjects (n = 31)
Mean (SD) [range] age, y	43 (16) [18-70]	44 (15) [17-70]	43 (16) [17-73]
Mean (SD) [range] age at onset of illness, y	32 (12) [15-60]	35 (13) [16-67]	. . .
Mean (SD) PANSS[21] score			
Positive scale	19 (9)	19 (6)	. . .
Negative scale	17 (11)	17 (9)	. . .
General psychopathology scale	29 (10)	28 (9)	. . .
Total	65 (19)	64 (14)	. . .
Mean (SD) dyskinesia AIMS[22] score	7.1 (2.9)†	0.5 (0.9)†	. . .
Mean (SD) parkinsonism score[23]	2.13 (2.5)‡	0.68 (1.1)‡	. . .

*PANSS indicates Positive and Negative Syndrome Scale; AIMS, Abnormal Involuntary Movements Scale; and ellipses, data not applicable.
†Mean difference (95% confidence interval): 6.58 (5.42-7.75), $t_{30} = 11.59$, $P < .001$.
‡Mean difference (95% confidence interval): 1.45 (0.41-2.49), $t_{30} = 2.86$, $P = .007$.

Table 2. Magnetic Resonance Imaging Measurements*

	No.	Patients With Dyskinesia	No.	Patients Without Dyskinesia	No.	Control Subjects
Caudate nucleus						
Left	28	1.13 (0.31)	30	1.12 (0.30)	31	1.27 (0.37)
Right	28	1.07 (0.35)	30	1.08 (0.30)	31	1.16 (0.39)
Lentiform nucleus						
Left	28	3.44 (0.59)†	30	3.23 (1.20)	31	3.10 (0.73)†
Right	28	3.28 (0.64)	30	3.23 (0.77)	31	3.02 (0.86)
Hemisphere						
Left	23	22.34 (7.56)	19	22.85 (9.14)	31	21.80 (6.06)
Right	23	22.02 (7.83)	19	23.04 (9.29)	31	21.72 (6.35)
Ventricle						
Left	23	1.67 (0.65)	19	1.93 (0.85)	31	1.51 (0.77)
Right	23	1.56 (0.84)	19	1.77 (0.66)	31	1.36 (0.61)
Ventricle-hemisphere ratio						
Left	23	0.08 (0.03)	19	0.09 (0.04)	31	0.07 (0.03)
Right	23	0.08 (0.05)	19	0.08 (0.03)‡	31	0.06 (0.02)‡

*Values are given as mean (SD) milliliters unless otherwise indicated.
†Mean difference (95% confidence interval): 0.37 (0.04-0.70), $t_{27} = 2.32$, $P = .02$.
‡Mean difference (95% confidence interval): 0.02 (0.01-0.03), $t_{18} = 2.76$, $P = .01$.

enced clinicians, using the PANSS assessment and history from the patients and their families. A structured diagnostic interview was not carried out.

There were several radiological limitations. First, the imager had a low field-strength. Second, through a miscommunication, ventricle and hemisphere volumes were not measured in the first 16 patients. Third, one radiologist alone was responsible for all MRI measurements. Fourth, there was only partial coverage of the brain for the hemisphere values.

Compared with normal subjects, never-treated patients with dyskinesia had a larger lentiform nucleus, especially on the left side, and never-treated patients without dyskinesia had a larger lateral ventricle-hemisphere ratio, especially on the right side. This suggests that the patients with dyskinesia may have striatal pathologic conditions and may represent a subgroup of schizophrenia. In those without abnormal movements, cortical atrophy was more apparent. However, these results should be interpreted with caution. When we attempted to consider the effect of hemisphere volume, the number of matched pairs fell to 23. In this smaller group, although the difference in mean absolute lentiform nucleus volume between the patients with dyskinesia and the controls was the same as in the total group, the difference was no longer statistically significant, nor was the difference in mean lentiform-hemisphere ratio. Another note of caution is that the significant differences were between patients and controls; there were no statistically significant differences between patients with and without dyskinesia.

Our findings suggest that the structure in the basal ganglia of patients with dyskinesia that differs from that of controls is the lentiform nucleus, not the caudate nucleus. As stated in the introduction, most studies of TD in treated patients and of spontaneous dyskinesia in first-episode patients have found differences in the caudate nucleus rather than the lentiform nucleus. However, differences in the lentiform nucleus have also been seen in studies in which patients not classified by TD status have been compared with normal controls.[25,26] For example, one study[25] found an increased lentiform nucleus in patients with chronic schizophrenia compared with controls; as in our study, the increase was greater on the left side. This study also found that the earlier the age of

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onset of illness, the greater was the increase in lentiform nucleus volume. The authors speculated that an increased lentiform nucleus volume in patients with schizophrenia could be related to the failure of late processes of maturation that normally would result in its volume reduction.

Longitudinal studies of drug-naive, then treated patients, or comparisons of drug-naive and treated patients, suggest that antipsychotic medication may enlarge the basal ganglia.[15,16,27,28] Our study suggests that chronically ill patients who have never received medication may also have an enlarged lentiform nucleus.

In the controls, there was an association between age and the size of the basal ganglia and the ventricle-hemisphere ratio: the older the person, the smaller the basal ganglia and the larger the ventricle-hemisphere ratio. These age-related changes have been described previously in controls.[29,30] In the patients, the relationship between age and the ventricle-hemisphere ratio held; this also has been demonstrated previously.[31] However, there was no relationship between age and the size of the basal ganglia. This suggests that the schizophrenic process interferes with normal age-related anatomical changes in the basal ganglia. One possible explanation is that age and illness duration have opposing effects on basal ganglia volumes (ie, increased lentiform nucleus volume with longer duration of illness). However, we found no correlation between duration of illness and size of the basal ganglia.

We are further examining the differences between the never-treated patients with and without movement disorders. It has recently been shown that there may be a dopamine D_3 receptor gene variation in patients with schizophrenia with TD.[32] This does not seem to be the case in our patients with spontaneous dyskinesia.[33]

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REFERENCES

1. McCreadie RG, Thara R, Kamath S, Padmavathy R, Latha S, Mathrubootham N, Menon MS. Abnormal movements in never-medicated Indian patients with schizophrenia. *Br J Psychiatry*. 1996;168:221-226.
2. McCreadie RG, Latha S, Thara R, Padmavathi R, Ayankaran JR. Poor memory, negative symptoms and abnormal movements in never-treated Indian patients with schizophrenia. *Br J Psychiatry*. 1997;171:360-363.
3. Gelenberg AJ. Computerized tomography in patients with tardive dyskinesia. *Am J Psychiatry*. 1976;133:578-579.
4. Jeste DV, Wagner RL, Weinberger DR, Rieth KG, Wyatt RJ. Evaluation of CT scans in tardive dyskinesia. *Am J Psychiatry*. 1980;137:247-248.
5. Bartels M, Themelis J. Computerized tomography in tardive dyskinesia: evidence of structural abnormalities in the basal ganglia system. *Arch Psychiatr Nervenkr*. 1983;233:371-379.
6. Brainin M, Reisner T, Zeitlhofer J. Tardive dyskinesia: clinical correlation with computed tomography in patients aged less than 60 years. *J Neurol Neurosurg Psychiatry*. 1983;46:1037-1040.
7. Swayze VW 2nd, Yates WR, Andreasen NC, Alliger RJ. CT abnormalities in tardive dyskinesia. *Psychiatry Res*. 1988;26:51-58.
8. Hoffman WF, Casey DE. Computed tomographic evaluation of patients with tardive dyskinesia. *Schizophr Res*. 1991;5:1-12.
9. Mion CC, Andreasen NC, Arndt S, Swayze VW 2nd, Cohen GA. MRI abnormalities in tardive dyskinesia. *Psychiatry Res*. 1991;40:157-166.
10. Harvey I, Ron MA, Murray R, Lewis S, Barker G, McManus D. MRI in schizophrenia: basal ganglia and white matter T1 times. *Psychol Med*. 1991;21:587-598.
11. Ueyama K, Fukuzako H, Takeuchi K, Hirakawa K, Fukuzako T, Hokazono Y, Takigawa M, Matsumoto K. Brain atrophy and intellectual impairment in tardive dyskinesia. *Jpn J Psychiatr Neurol*. 1993;47:99-104.
12. Elkashef AM, Buchanan RW, Gellad F, Munson RC. Basal ganglia pathology in schizophrenia and tardive dyskinesia: an MRI quantitative study. *Am J Psychiatry*. 1994;151:752-755.
13. Dalgalarrendo P, Gattaz WF. Basal ganglia abnormalities in tardive dyskinesia: possible relationship with duration of neuroleptic treatment. *Eur Arch Psychiatry Clin Neurosci*. 1994;244:272-277.
14. Brown KW, White T, Wardlaw JM, Walker N, Foley D. Caudate nucleus morphology in tardive dyskinesia. *Br J Psychiatry*. 1996;169:631-636.
15. Chakos MH, Lieberman JA, Bilder RM, Borenstein M, Lermer G, Bogerts B, Wu H, Kinon B, Ashtari M. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *Am J Psychiatry*. 1994;151:1430-1436.
16. Shihabuddin L, Buchsbaum MS, Hazlett EA, Haznedar M, Harvey P, Newman A, Schnur DB, Spiegel-Cohen J, Wei T, Machac J, Knesaurek K, Vallabhajosula S, Biren MA, Ciaravolo TM, Luu-Hsia C. Dorsal striatal size, shape, and metabolic rate in never-medicated and previously medicated schizophrenics performing a verbal learning task. *Arch Gen Psychiatry*. 1998;55:235-243.
17. Keshavan MS, Rosenberg D, Sweeney JA, Pettegrew JW. Decreased caudate volume in neuroleptic-naive psychotic patients. *Am J Psychiatry*. 1998;155:774-778.
18. Gur RE, Maany V, Mozley PD, Swanson C, Bilker W, Gur RC. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. *Am J Psychiatr*. 1998;155:1711-1717.
19. Corson PW, Nopoulos P, Andreasen NC, Heckel D, Arndt S. Caudate size in first-episode neuroleptic-naive schizophrenic patients measured using an artificial neural network. *Biol Psychiatry*. 1999;46:712-720.
20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
21. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261-276.
22. Abnormal Involuntary Movements Scale (AIMS). In: Guy W, ed. *ECDEU Assessment Manual for Pharmacology*. Rockville, Md: US Dept of Health, Education, and Welfare; 1976:534-537.
23. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl*. 1970;212:11-19.
24. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. *Arch Gen Psychiatry*. 1982;39:486-487.
25. Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Braff DL. Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. *Arch Gen Psychiatry*. 1991;48:881-890.
26. Swayze V, Andreasen N, Alliger R, Yuh W, Ehrhardt J. Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. *Biol Psychiatry*. 1992;31:221-240.
27. Keshavan MS, Bagwell WW, Haas GL, Sweeney JA, Schooler NR, Pettegrew JW. Changes in caudate volume with neuroleptic treatment [letter]. *Lancet*. 1994;344:1434.
28. DeLisi LE, Tew W, Xie S, Hoff AL, Sakuma M, Kushner M, Lee G, Shedlack K, Smith AM, Grimson R. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. *Biol Psychiatry*. 1995;38:349-360.
29. Jernigan TL, Press GA, Hesselink JR. Methods for measuring brain morphologic features on magnetic resonance images: validation and normal aging. *Arch Neurol*. 1990;47:27-32.
30. Jernigan TL, Archibald SL, Berhow MJ, Sowell ER, Foster DS, Hesselink JR. Cerebral structure on MRI, I: localization of age-related changes. *Biol Psychiatry*. 1991;29:55-67.
31. Andreasen NC, Swayze VW 2nd, Flaum M, Yates WR, Arndt S, McChesney C. Ventricular enlargement in schizophrenia evaluated with computed tomographic scanning: effects of gender, age, and stage of illness. *Arch Gen Psychiatry*. 1990;47:1008-1015.
32. Steen VM, Løvlie R, MacEwan T, McCreadie RG. Dopamine D3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenic patients. *Mol Psychiatry*. 1997;2:139-145.
33. Løvlie R, Thara R, Padmavathi R, Steen VM, McCreadie RG. Ser9Gly dopamine D3 receptor polymorphism and spontaneous dyskinesia in never-medicated schizophrenic patients. *Mol Psychiatry*. 2001;6:6-7.

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