Magnetic Resonance Imaging of Mediodorsal, Pulvinar, and Centromedian Nuclei of the Thalamus in Patients With Schizophrenia

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**Background:** Postmortem and magnetic resonance imaging (MRI) data have suggested volume reductions in the mediodorsal (MDN) and pulvinar nuclei (PUL) of the thalamus. The centromedian nucleus (CMN), important in attention and arousal, has not been previously studied with MRI.

**Methods:** A sample of 41 patients with schizophrenia (32 men and 9 women) and 60 healthy volunteers (45 men and 15 women) underwent assessment with high-resolution 1.2-mm thick anatomical MRI. Images were differentiated to enhance the edges and outline of the whole thalamus, and the MDN, PUL, and CMN were outlined on all slices by a tracer masked to diagnostic status.

**Results:** Significantly smaller volumes of the MDN and PUL were found in patients with schizophrenia compared with controls. Volume relative to brain size was reduced in all 3 nuclei; differences in relative reduction did not differ among the nuclei. The remainder of the thalamic volume (whole thalamus minus the volume of the 3 delineated nuclei) was not different between schizophrenic patients and controls, indicating that the volume reduction was specific to these nuclei. Volume relative to brain size was reduced in all 3 nuclei and remained significant when only patients who had never been exposed to neuroleptic medication (n=15) were considered. For the MDN, women had larger relative volumes than men among controls, but men had larger volumes than women among schizophrenic patients.

**Conclusions:** Three association regions of the thalamus that have reciprocal connectivity to schizophrenia-associated regions of the cortex have significantly smaller volumes on MRI in patients with schizophrenia.

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POSTMORTEM STUDIES of schizophrenia have implicated abnormalities in the thalamus and in a number of structures that have efferent and afferent thalamic connections, including the amygdala and hippocampal formation, cingulate and prefrontal cortices, temporal lobe, and superior temporal gyrus. Since each thalamic subdivision has a unique reciprocal circuitry to and from affected cortical areas, separate assessment of these subdivisions is important. Two of the major association nuclei, the mediodorsal (MDN) and pulvinar nuclei (PUL), are of particular interest in schizophrenia. The connections of the MDN have been used to define the prefrontal cortex, a key area of functional and structural alteration in schizophrenia. Until the mid-1970s, it was thought that the prefrontal cortex received its thalamic input solely from the MDN; however, it is now apparent that the PUL also contributes to its innervation. The PUL is important in visual and possibly auditory attention, and it also has prominent interconnections with the temporal lobe, a second area of morphometric and functional change in schizophrenia. Schizophrenia-associated abnormalities of the MDN and PUL have been demonstrated in postmortem studies and in the anterior nucleus. Changes in the ventrolateral posterior nucleus have also been reported.

Until recently, the study of the anatomy of the thalamus in living subjects has been limited to visualization of the whole thalamus on magnetic resonance imaging (MRI) scans, and findings have been conflicting. Our group reported a technique that allows in vivo neuroimaging visualization of the MDN and PUL on MRI scans and demonstrated MDN volume loss in schizophrenia and PUL volume loss in schizophrenia spectrum disorders. We have also reported metabolic decreases in the region of the MDN in a separate population and in a subsample of the current patient group. The present study is an extension of this work with a greatly enlarged sample, and with the addition of delineation of the cen-
tromedian nucleus (CMN), one of the thalamic intralaminar nuclei that are believed to play an important role in attention related to arousal and activation of the cortex.26 Like the MDN and PUL, it has connections with the prefrontal cortex. Lesions of the intralaminar nuclei produce signs of executive dysfunction and attentional impairment like those observed with frontal cortical damage.27

The present study corroborates findings of reduced MDN and PUL volumes on MRI in this larger cohort of patients with schizophrenia and provides evidence that the volume of the CMN may also be reduced.

### METHODS

#### PATIENTS

Forty-one patients (32 men and 9 women; mean age, 36.9 years; SD, 15.2 years; range, 18-73 years) were recruited from the Mount Sinai, Elmhurst, and Bronx Veterans Affairs hospital centers, New York, NY, where they serve as neighborhood care centers and referral centers. We included every referred patient who was not receiving neuroleptic drugs at the point of contact, for whom the physician and patient would agree to participate in brain-imaging studies, and who met our competency-to-participate criteria. Patients came from emergency department admission, outpatient clinics, and volunteer sources. Most cases entered through new emergency department admissions and patients in outpatient clinics known by physicians not to be taking medications currently or appearing for clinic visits in an unmedicated state. None of the patients were currently undergoing long-term hospitalization. Thirty-six patients were right-handed, 1 was left-handed, and 4 were mixed in handedness based on the Edinburgh Inventory.28 The patients underwent evaluation with the Comprehensive Assessment of Symptoms and History29 and received a diagnosis of schizophrenia (n = 37) or schizoaffective disorder (n = 4) according to DSM-IV criteria. Patients had never previously received medication (n = 15) or had been neuroleptic free for a minimum of 2 weeks (n = 26). Total psychopathology scores on the 18-item Brief Psychiatric Rating Scale30 ranged from 25 to 89 (mean, 52.4; SD, 12.7; median, 51). Median educational level was 13 years.

#### CONTROLS

Sixty healthy volunteers (45 men and 15 women; mean age, 40.1 years; SD, 15.9 years; range, 20-81 years) were recruited by means of advertisement in local newspapers and notices on hospital bulletin boards in support staff areas to minimize differences in educational levels. Fifty-eight volunteers were right-handed, 2 were left-handed, and none were mixed in handedness. All received a Comprehensive Assessment of Symptoms and History interview to exclude those with a history of psychiatric illness in themselves or in their first-degree relatives. Median educational level was 16 years. Mean±SD parental socioeconomic status (SES) in controls (2.89±0.79) was somewhat lower than patients (3.55±1.22; effect size, 0.75).

All participants underwent screening by means of medical history, physical examination, and laboratory testing. Individuals with a history of substance abuse/dependence, positive findings for drugs of abuse in a urine sample tested on the day of the positron emission tomography scan, neurological disorders, or head trauma were excluded. After a complete description of the study, all participants gave written informed consent and were paid for their participation in this study. Of the 41 participants with schizophrenia, 12 were included from our previous cohort,31 as improvement in anatomical boundary definition of the MDN and tracing of an additional thalamic nucleus (CMN) permitted retraction in each of these participants.

### MRI ACQUISITION AND ASSESSMENT

The MRI scans were acquired using the same 1.5-T scanner (LX Horizon; GE Medical Systems, Milwaukee, Wis) Signa 5 system with a spoiled-gradient sequence (repetition time, 24 milliseconds; echo time, 3 milliseconds; flip angle, 40°; pixel matrix, 256×256; field of view, 23 cm) yielding 124 contiguous 1.2-mm thick axial slices. Details of image acquisition, coding, and scaling are described elsewhere.1 Data were expressed in cubic centimeters for each region of interest (ROI) (Table 1 and Table 2) and as relative to brain volume as previously performed.

### OUTLINING THALAMIC NUCLEI

Delineation of the whole thalamus, MDN, and PUL began at the level at which the structure was most clearly demarcated as described in detail and illustrated previously.1 A refinement to the delineation of the MDN and PUL was possible, as further study of the internal medullary lamina using the Sobel intensity-gradient filter indicated that 2 distinct limits (an inner [more medial] and outer [more lateral] boundary) could be demonstrated (Figure 1). At the level of the habenula, between the split lines of the internal medullary lamina, the CMN is found through its extent until the level of the superior colliculus (Figure 1 and Figure 2).

### STATISTICAL ANALYSIS

With absolute and relative volumes of 3 nuclei and 2 hemispheres, the strategy of using 12 t tests for basic analysis and

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**Table 1. Volumes of the Whole Thalamus and Nuclei**

<table>
<thead>
<tr>
<th>Group</th>
<th>Whole Thalamus</th>
<th>MDN</th>
<th>PUL</th>
<th>CMN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Patients with schizophrenia</td>
<td>6.13 (0.73)</td>
<td>5.94 (0.75)</td>
<td>0.66 (0.12)</td>
<td>0.60 (0.12)</td>
</tr>
<tr>
<td>(n = 41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>6.37 (0.69)</td>
<td>6.10 (0.68)</td>
<td>0.89 (0.12)</td>
<td>0.66 (0.10)</td>
</tr>
<tr>
<td>(n = 60)</td>
<td></td>
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</tbody>
</table>

*Abbreviations: ANCOVA, analysis of covariance; CMN, centromedian nucleus; MDN, mediodorsal nucleus; PUL, pulvinar nucleus.

*Data are expressed as mean (SD). Main effect of diagnosis, F1,99 = 5.25 ([P = .03]; with age as covariate, F1,98 = 7.94 ([P = .006]. This lesser volume effect was not significantly stronger for any one of the nuclei (no higher-order interactions with group). Follow-up ANCOVA for each nucleus separately confirmed this difference for the MDN (F1,98 = 6.18 ([P = .02]) and PUL (F = 6.45 ([P = .01]) but not for the CMN (F = 1.48 ([P = .22]).
another 24 for sex comparisons is vulnerable to type I statistical error. For this reason, as in our previous study, we analyzed data with multivariate analysis of covariance (ANCOVA)33 with independent groups (controls and schizophrenic patients), and repeated measures for thalamic nuclei (MDN, PUL, and CMN) and hemisphere (right and left) for absolute and relative volume with age as a covariate. Additional analyses with sex as a second independent group dimension were also performed. We report the univariate F where single nuclei are tested and multivariate F with the Rao $R$ when all 3 nuclei enter the ANCOVA. Where higher-order interactions with groups are not significant, they are not noted. The age ANCOVA does not affect higher-order interactions of group, since the age is identical for all nuclei and hemispheres. Results of the Levene test for inequality of variance between controls and schizophrenic participants for each ROI were not statistically significant.

Unless otherwise indicated, data are expressed as mean±SD.

### RESULTS

#### ABSOLUTE NUCLEAR VOLUMES

Patients with schizophrenia had a significantly smaller volume of the 3 delineated nuclei considered together than controls (Table 1). The effect sizes for the differences between controls and patients with schizophrenia for the mean of the right and left hemispheres for the MDN, PUL, and CMN were 0.40, 0.38, and 0.21, respectively. The percentage reductions were 6.7%, 6.1%, and 6.7%, respectively, for the mean of the right and left hemispheres for the 3 nuclei. Patients with schizophrenia had smaller mean brain volumes than normal volunteers (1246±116 vs 1297±121 cm$^3$; $t = 2.11$ [$P = .04$]), suggesting the need to examine the regional specificity of the effect using thalamic volumes corrected for brain volume. Correlations between whole brain volume and thalamic volumes were positive and significant for the left and right hemispheres for whole thalamus (0.34 and 0.39, respectively), MDN (0.24 and 0.34, respectively), and PUL (0.22 and 0.32, respectively), but not the CMN (0.07 and 0.12, respectively). We also corrected for thalamic volume with and without the constituent nuclei as a second examination of specificity.

![Figure 1. Centromedian nucleus (CMN).](image)
Figure 2. Outline of the centromedian nucleus (CMN) in 4 participants. A, Anatomical magnetic resonance image of the thalamus. B, Differentiated view with enhancement of edges. C, Outline of the CMN created with fitting of spline curve. Points are deposited on the differentiated image on white lines with a mouse, and the spline curve is fitted through these points. Three additional participants are shown in D-F, G-I, and J-L.
As with absolute data, patients with schizophrenia had significantly smaller relative volumes of the 3 association nuclei than controls (Table 2). The effect sizes for the MDN, PUL, and CMN were 0.78, 0.55, and 0.36, respectively. We also computed the volume relative to the thalamic volume (nucleus in each hemisphere divided by the whole thalamic volume in that hemisphere) and corrected thalamic volume (nucleus in each hemisphere divided by the difference of the whole thalamic volume in that hemisphere and the nuclear volume). These ANCOVA findings were similar, confirming smaller nuclei for MDN, PUL, and CMN in patients with schizophrenia (significant main effects of diagnostic group, F$_{1,98}^{*}$ = 4.23 and F$_{1,98}^{*}$ = 4.26, respectively [P = .04]).

**WHOLE THALAMUS VOLUME**

Whole thalamus absolute volumes of right and left hemispheres did not differ significantly between the schizophrenic (6.13 ± 0.73 cm$^3$ and 5.94 ± 0.75 cm$^3$, respectively) and control groups (6.37 ± 0.69 cm$^3$ and 6.10 ± 0.68 cm$^3$, respectively; F$_{1,98}^{*}$ = 3.63 [P = .059]), and follow-up group differences were also not statistically significant when tested (1 tailed) (right thalamus, t$_{90}^{*}$ = 1.65 [P = .10]; left thalamus, t$_{90}^{*}$ = 1.07 [P = .29]). When the relative volume was tested, patients with schizophrenia had smaller volumes than controls (main effect of group, F$_{1,98}^{*}$ = 6.69 [P = .01]). When we examined the whole thalamus volume minus the 3 association nuclei, then the absolute volume (ANCOVA, F$_{1,98}^{*}$ = 0.63 [P = .42]) and the relative volume (ANCOVA F = 0.008 [P = .92]) did not differ between groups, indicating that any whole thalamic size decrease, whether absolute or relative size, was attributable to the MDN, PUL, and CMN and not the remaining thalamic structures.

**EFFECT OF SEX**

Men had larger absolute thalamic nuclei than women (F$_{1,97}^{*}$ = 11.56 [P < .001]), but when relative size was examined, there were no significant sex effects or higher-order interactions with diagnosis in the 4-way analysis of variance (ANOVA) with diagnosis and sex as independent group dimensions. No significant differences between men and women were observed in relative thalamic size when all 3 nuclei were examined. However, follow-up ANCOVA revealed a significant diagnosis × sex interaction for the MDN (F$_{1,97}^{*}$ = 4.94 [P = .03]) that was larger in women (.0032) than men (.0030) among controls but larger in men (.0029) than women (.0026) among schizophrenic patients. No significant interactions with sex were observed for the PUL or the CMN for absolute or relative data. There were no significant differences between men and women with schizophrenia for performance on a serial verbal learning test (mean number of words correct, 7.94 ± 3.80 vs 8.07 ± 4.51; t$_{35}^{*}$ = −0.07 [P = .94]) or for mean Brief Psychiatric Rating Scale total scores (49.6 ± 17.5 vs 52.0 ± 14.0; t$_{35}^{*}$ = −0.43 [P = .66]).

No differences between patients who previously and never received medication were found when all 3 nuclei were entered into multivariate ANOVA, and the follow-up univariate ANCOVA for the MDN and PUL also revealed no significant differences in size. However, the absolute size of the CMN was larger in the patients with schizophrenia who previously received medication (0.151 cm$^3$) compared with those who never did (0.119 cm$^3$) (ANCOVA with age as covariate, F$_{1,38} = 5.41$ [P = .035]), but this effect was not significant for the relative volume data (F$_{1,38} = 1.09$ [P = .30]), which showed the differences between controls and patients above. When we compared volume in controls with that in the 15 patients who never received medication, the findings remained significant for the absolute (F$_{1,72} = 4.81$ [P = .035]) and the relative MDN size (F$_{1,72} = 6.99$ [P = .01]). The findings also remained significant for the PUL (absolute F$_{1,72} = 8.32$ [P = .005]; relative F$_{1,72} = 8.80$ [P = .004]) and CMN (absolute F$_{1,72} = 8.69$ [P = .004]; relative F$_{1,72} = 8.79$ [P = .004]).

**EFFECT OF AGE**

There was no statistically significant difference in the mean age of controls (40.1 ± 15.9 years) vs schizophrenic patients (36.9 ± 15.2 years). With the Statistica Test of Parallelism, the slopes of the age regression lines did not differ between controls and schizophrenic patients for the absolute left (F$_{1,97} = 0.676$ [P = .41]) or right (F$_{1,97} = 1.86$ [P = .18]) or relative left hemispheric thalamus (F$_{1,97} = 0.257$ [P = .61]) or right (F$_{1,97} = 0.262$ [P = .61]); therefore, age was used as a covariate in all ANCOVAs on each ROI. Regression analysis for total thalamic volume in controls revealed a significant negative correlation between total thalamic size and age for the right (R$^2$$_{1,38} = 0.20$ [P < .001]) and left hemispheres (R$^2$$_{1,38} = 0.16$ [P < .001]). However, in schizophrenic patients, this correlation was not statistically significant for either hemisphere (right, R$^2$$_{1,38} = 0.225$ [P = .35]; left, R$^2$$_{1,38} = 0.0401$ [P = .21]). Similar analyses on absolute and relative measures demonstrated a tendency for all parts of the thalamus to be somewhat reduced in older participants. However, ANOVA comparison of participants older and younger than the mean age of 39 years failed to produce any significant diagnostic group × age interactions for any of the 3 nuclei.

**COMPARISON WITH PREVIOUS SAMPLE**

When the 12 patients with schizophrenia and 12 controls (previously reported) were removed from this cohort and the 3-way ANCOVAs were repeated (n = 77), the results were quite similar (despite reduction in power) for the MDN (main effect of diagnosis, F$_{1,72} = 11.02$ [P = .001]; diagnosis × sex interaction in the smaller cohort, F$_{1,72} = 3.33$ [P = .07]) and PUL (main effect of diagnosis, F$_{1,72} = 10.75$ [P = .002]). For the CMN, there were no significant main effects or group interactions. In an examination of the left mediadorsal volume alone, which was not significantly smaller in the original sample (controls, n = 12; patients, n = 12; 313 vs 290 mm$^3$; t$_{22} = 1.70$
We had previously observed a similar effect size (0.575) to the effect size in the additional controls and patients (0.777) (controls, n = 48; patients, n = 29; 0.305 ± 0.035 ± 0.042 ± 0.040 vs 290; t_{58} = 3.12 [P = .02]; data × 100 to match relative table convention in the present report).

**CLINICAL CORRELATIONS**

Within the patient group, there were no significant correlations between relative nuclear size and total Brief Psychiatric Rating Scale scores, positive or negative symptom scale scores, or age of illness onset. We also examined the differences between patients with good and poor outcomes as defined elsewhere and found no significant differences. We examined the correlations between nuclear volume and performance on a serial verbal learning task on an exploratory basis and found positive correlations between the serial order score on the volume of the right CMN for absolute (r_{56,1} = 0.52; [P = .001]) and relative volume (r = 0.44 [P = .002]); these correlations were not found in the controls. In controls, the number correct was significantly correlated with the volume of the right MDN (r = 0.28 [P = .03]).

**CONTROLS**

We examined the demographic and structural characteristics of the thalamus in the control group alone in a 4-way ANOVA on absolute size with independent groups for age (above and below the average age of 39 years), sex (men and women), structure (MDN, PUL, and CMN), and hemisphere (right and left). Men had larger nuclei than women (F_{1,56} = 6.30 [P = .02]), and this effect was significantly more pronounced (sex × structure interaction, F_{1,112} = 5.79 [P = .004]; Rao R^2 = 3.13 [P = .051]; Greenhouse-Geisser P = .02) for the PUL (1.674 vs 1.490 cm^3; F_{1,56} = 6.98 [P = .01]) than for the MDN (0.685 vs 0.647 cm^3) or the CMN (0.152 vs 0.139 cm^3). The right hemisphere nuclei were larger than the left (F_{1,56} = 4.59 [P = .04]), and this right/left hemispheric asymmetry was significantly more pronounced for the PUL (1.616 vs 1.548 cm^3; F_{1,56} = 4.89 [P = .03]) than for the MDN (0.677 vs 0.655 cm^3) or the CMN (0.148 vs 0.143 cm^3) by ANOVA (hemisphere × structure interaction, F_{1,112} = 3.22 [P = .04]; but Rao R^2 = 2.12 [P = .13]). Younger participants had larger nuclei than older participants (F_{1,56} = 7.49 [P = .08]), and this difference was significantly more pronounced for the PUL (1.684 vs 1.480 cm^3; F_{1,56} = 8.53 [P = .002]) than for the MDN (0.686 vs 0.646 cm^3) or the CMN (0.151 vs 0.139 cm^3), as statistically confirmed by ANOVA (age × structure interaction, F_{1,112} = 7.21 [P = .001]; Rao R^2 = 3.90 [P = .03]).

For relative data, the same pattern was largely present, with younger individuals having relatively larger nuclei (main effect of age, F_{1,56} = 3.41 [P = .07]) and the effect being larger (age × structure interaction, F_{1,112} = 3.05 [P = .0515]; but Rao R^2 = 3.97 [P = .03]) in the PUL (0.00681 vs 0.00641; F_{1,56} = 5.34 [P = .02]) than in the MDN or the CMN. The age × structure × hemisphere interaction with means similar to those found for absolute volume was at a trend level (Rao R^2 = 2.97 [P = .059]). Thus, the demographic characteristics seem weakly associated with brain size and are less pronounced in ANOVA where brain size has been removed. This interpretation is supported by the appearance of significant interactions of age × structure (F_{1,112} = 7.21 [P = .001]), sex × structure (F_{1,112} = 5.79 [P = .004]), and hemisphere × structure (F_{1,112} = 3.22 [P = .04]) when the whole thalamus size is entered as a covariate in an analysis of the absolute volumes.

In this large sample, we were able to replicate the MDN and PUL MRI findings in an independent sample, to demonstrate that the decrement in volume does not affect all thalamic regions, and to observe that the effect was greatest in patients who had never received medication, indicating that it was not a product of pharmacological treatment. With the connections of all 3 of the delineated nuclei and the frontal lobe, these findings tend to implicate the importance of prefrontal-thalamic circuits in schizophrenia. Recent data suggesting fewer projections from the MDN to the prefrontal cortex are consistent with this view. Similarly, temporal-thalamic circuits are implicated by volume reductions in the PUL and the temporal lobe. In the postmortem study from our group, the MDN and PUL were reduced in volume in patients with schizophrenia. Patients also showed reduced neuronal number in the MDN, parvo cellular subdivision, and PUL and reduced neuronal size in the MDN, caudodorsal subdivision, and PUL.

In the present MRI study, we were able to demonstrate the specificity of volume loss to the delineated nuclei, with the volumes of the remainder of the thalamus clearly not different in controls vs patients with schizophrenia. We also demonstrated that the nuclear volume effect size was larger when the data were expressed relative to whole brain size than when absolute data were analyzed, indicating that the phenomenon in patients was not merely smaller total brain with proportionately smaller thalamic nuclei, but a loss of thalamic nuclear volume beyond variation in whole brain size. Although the CMN was not significantly smaller in the much smaller postmortem sample, relative size data were significant in the large MRI sample. A review of other MRI studies of thalamic volume shows several reports indicating reduced relative volume but some failures to detect size differences. Automated deformation-based morphometry also detected reduced thalamic size. In our study, the effect sizes for the relative size were 0.78 for the MDN, 0.44 for the relative whole thalamus, and 0.10 for the remainder of the thalamus after subtraction of the MDN, PUL, and CMN. Our effect size of 0.44 for the whole thalamus is slightly larger than the estimate of 0.35 from the meta-analysis, which was based on 11 studies with 313 patients with schizophrenia and whole thalamic volume adjusted for brain size. Thus, the effect is not large but seems to affect all of the delineated nuclei. The effect size in our postmortem sample (full cohort), which included only the chronically and severely ill, was 1.02. This may reflect greater tracing precision in histological ma-
tal or greater effects associated with old age, greater severity, or longer-term illness.

Our thalamic and nuclear volumes for the postmortem and MRI tracings follow the same relative proportions; the MDN, PUL, and CMN are 14%, 22%, and 3%, respectively, of the total thalamus in postmortem controls and 11%, 24%, and 2%, respectively, in the MRI scans. The postmortem volumes tend to be smaller by about 25%, consistent with estimates of shrinkage artifact in formalin-fixed frozen postmortem sections. If tissue is embedded in a hydrophobic polymer for slicing, the volume loss may be up to 75%. This variation in shrinkage depending on histological method accounts for some of the apparent discrepancies in the postmortem literature and indicates advantages for in vivo imaging.

The CMN showed significantly smaller relative size in the present study, and the direction of the difference in CMN volume between controls (0.163±0.027 cm$^3$) and schizophrenic patients (0.141±0.042 cm$^3$) is in the same direction in the postmortem data ($P=.16$ for the analysis as performed in the postmortem study with age, postmortem interval, fixation time, and brain weight as covariates; $F_{1,10}=4.35$ [P=.051] for CMN volume divided by brain weight with only age as a covariate as in the MRI data). It might be argued that because the CMN is widely regarded as having primarily motor functions, regulating the output of the caudate nucleus and putamen in concert with the dopaminergic input from the substantia nigra, it might be less directly involved in schizophrenia than the MDN with its extensive frontal cortical connections. However, the CMN also projects to cortical regions involved in schizophrenia and is believed to participate in functions that are impaired in schizophrenia. The present data suggest that the size of the CMN may vary as a function of neuroleptic exposure, consistent with the observation in rats that this nucleus is activated by exposure to typical and atypical neuroleptics, and consistent with its connections with other structures that also exhibit volume expansion with neuroleptic exposure. Volume increase in the caudate nucleus in schizophrenia has been hypothesized to reflect increased dopaminergic innervation, probably secondary to neuroleptic treatment or an interaction between neuroleptic treatment and the pathophysiology underlying schizophrenia, since 2 longitudinal MRI follow-up studies found progressive enlargement in striatal volume after neuroleptic treatment. In a recent study from our group, reduced caudate volume was found in schizophrenic patients who never received medication compared with controls, and increased (relative to control values) dorsal putamen volume was found in those who previously received medication. Similar findings were reported in other subsequent studies, including greater increases in the putamen than caudate nucleus in patients who previously received medication. However, abnormalities in glutamatergic synapses in the thalamus in schizophrenia must also be considered.

The significant diagnosis × sex interaction that we observed for the volume of the MDN is consistent with several previous observations in which normal sex differences are attenuated or reversed in schizophrenic patients. Based primarily on extrapolations from animal research, it is widely believed that sexual differentiation of the human brain is largely a midtrimester event. A midtrimester event has also been implicated in the pathogenesis of schizophrenia. A midtrimester perturbation of normal brain development might, therefore, alter the normal course of brain sexual differentiation in addition to setting the stage for the subsequent development of schizophrenia.

Our group has previously reported significant correlations between Brief Psychiatric Rating Scale scores and glucose metabolism in the thalamus, indicating that functional measures may be more sensitive to the clinical state in schizophrenia than measures only of volume reduction. Although efforts were made to recruit volunteers matched by educational level and parental SES, a small bias toward individuals with more years of college (4 vs 1) and higher parental SES (2.89 vs 3.55) was observed. Since parental SES and education might be anticipated to be correlated with liability for schizophrenia, removing these differences with ANCOVA could be misleading.

Decreased gray matter density in the thalamus was reported when MR images were compared using significance probability mapping. The reduced volume seen in our MRI studies combined with the reduced volume and neuronal number, and reduced metabolic rate is consistent with the concept that the MDN in patients with schizophrenia is compromised and that smaller numbers of smaller (and presumably less active) neurons carry out a reduced amount of information processing. The reduction in size is seen with absolute data and those expressed relative to whole brain volume. This may reflect the removal of irrelevant body-size associated variance, because effect sizes were larger when data corrected for total brain size were examined; if the thalamus merely shrank along with all other brain structures, we might have anticipated a smaller effect size for relative than absolute data. The percentage reduction in absolute MDN volume we observed is small (6.7%) compared with the larger volume reductions seen in the postmortem studies by the research groups of Pakkenberg, Byne et al., Popken et al., and Young et al. cited above (27%, 15%, 17%, and 24%, respectively). This may reflect a combination of factors, including statistically more variable measurement of volume in MRI than postmortem material, differential contributions to MRI density of different types of neurons, and characteristics of the parvocellular subregion that might shift the lateral edge of the entire MDN on MRI. Nevertheless, our findings match those of the 4 postmortem studies and provide data on a much larger and younger cohort without the confounding factor of old age, variation in postmortem interval, and fixation shrinkage. Since putatively atrophic changes have been described in 1 of the cortical targets of the MDN, these data are also consistent with our overarching hypothesis that schizophrenia-related pathology in a particular subdivision of the thalamus is etiologically related to pathology in its projection fields. The localization of schizophrenia-associated
changes to thalamic subregions is a step in the understanding of neuronal circuit impairments that may be involved in the symptomatology of the schizophrenias. The finding of reduced PUL volume in the large sample used in the present study adds weight to our previous observations based on much smaller in vivo and postmortem samples. The PUL is a large, heterogeneous structure that occupies nearly a quarter of the total thalamic volume and consists of several subdivisions with unique patterns of connectivity. If our overarching hypothesis is correct, subsequent postmortem studies may find that the volume changes in the PUL disproportionately affect its medial portion, which may be further subdivided into a centrolateral subdivision with a preponderance of prefrontal connections similar to those of the MDN, and a medial subdivision (ie, the medial subdivision of the median PUL) with a preponderance of temporal connections.

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