Magnetic Resonance Imaging of the Thalamic Mediodorsal Nucleus and Pulvinar in Schizophrenia and Schizotypal Personality Disorder

William Byne, MD, PhD; Monte S. Buchsbaum, MD; Eileen Kemether, MD; Erin A. Hazlett, PhD; Akbar Shinwari, MD; Vivian Mitropoulou, MA; Larry J. Siever, MD

Background: The importance of neuronal interactions in development, the cortical dependence of many thalamic nuclei, and the phenomenon of transsynaptic degeneration suggest possible abnormalities in thalamic nuclei with connections to other brain regions implicated in schizophrenia. Because frontal and temporal lobe volumes are diminished in schizophrenia, volume loss could characterize their primary thalamic relay nuclei (mediodorsal nucleus [MDN] and pulvinar).

Methods: Tracers delineated the thalamus, MDN, and pulvinar on contiguous 1.2-mm magnetic resonance images in 12 schizophrenic patients, 12 with schizotypal personality disorder (SPD), and 12 normal control subjects. The MDN and pulvinar were rendered visible by means of a Sobel intensity-gradient filter.

Results: Pixel overlap for delineation of all structures by independent tracers was at least 80%; intraclass correlations were $r=0.78$ for MDN and $r=0.83$ for pulvinar. Pulvinar volume was smaller in schizophrenic (1.22±0.24 cm$^3$) and SPD (1.20±0.23 cm$^3$) patients than controls (1.37±0.25 cm$^3$). Differences for MDN were not statistically significant; however, when expressed as percentage of total brain volume, pulvinar and MDN together were reduced in SPD (0.14%) and schizophrenic (0.15%) patients vs controls (0.16%). Reductions were more prominent in the left hemisphere, with MDN reduced only in the schizophrenic group, and pulvinar in both patient groups. Total thalamic volume did not differ among the 3 groups.

Conclusions: Measurement of MDN and pulvinar in magnetic resonance images is feasible and reproducible. Schizophrenic and SPD patients have volume reduction in the pulvinar, but only schizophrenic patients show reduction relative to brain volume in MDN.

Arch Gen Psychiatry. 2001;58:133-140

Schizophrenia involves impairments in multiple brain circuits that synaptically gate or relay information through the thalamus. Consequently, the thalamus is being scrutinized as a site of schizophrenia-related abnormalities. Postmortem studies of schizophrenia have revealed synaptic degeneration and volumetric loss in thalamic subdivisions.1-4 Neuroimaging studies have also detected schizophrenia-associated thalamic abnormalities5-9 but have not localized changes to anatomically defined thalamic subdivisions. Instead, they have described changes in size, shape, or function of broadly delimited thalamic regions or within the entire thalamus.

Because each thalamic subdivision has a unique set of efferent and afferent projections, localization of schizophrenia-associated changes could advance understanding of neuronal-circuitry impairments. The importance of neuronal interactions in brain development,10 the phenomenon of transsynaptic degeneration,11 and activity-related neuronal plasticity12,13 suggest mechanisms by which an abnormality in one brain region could induce abnormalities in others. Volume loss or other abnormalities in thalamic subdivisions may relate to abnormalities in their efferent and afferent fields. The fact that some thalamic nuclei remain cortically dependent (ie, exhibit degenerative changes when their cortical fields are damaged) into adulthood14 suggests that this expectation would hold whether the primary lesion occurred in early development or much later. Two macroscopically visible thalamic nuclei, the mediodorsal nucleus (MDN) and the pulvinar, are seen on magnetic resonance imaging (MRI) and appear salient to schizophrenia because of their connections with 2 regions implicated by neuroanatomical theories, ie, prefrontal and temporal cortex.

Prefrontal cortex (PFC), regionally defined by some researchers on the basis...
SUBJECTS AND METHODS

SUBJECTS

Schizotypal Personality Disorder

Twelve SPD patients (11 men; 1 woman; mean age, 42.7 years; SD, 14.1 years; 11 right-handed) met DSM-IV39 diagnostic criteria based on interviews using the Schedule for Schizophrenia and Affective Disorders40 and the Structured Interview for DSM-III Personality Disorders.3 Their mean Brief Psychiatric Rating Scale41 score was 37.5 (SD, 6.20; range, 28-46). Ten patients were recruited from clinics at Mt Sinai Hospital, New York, NY, and Bronx Veterans Affairs Hospital, Bronx, NY, and from community psychiatrists; 2, from newspaper advertisements for people with loneliness and trouble with relationships. Seven of the 12 patients had never received medication, and all were free of medication for at least 2 weeks. Interrater reliability for SPD diagnosis was assessed on 56 individuals with 4 raters (2 for each subject); k values for each criterion ranged from 0.86 for magical thinking to 0.60 for suspiciousness (average, k = 0.73). For SPD vs other personality disorders, k = 0.90. Median educational level was 14 years. Illness onset was gradual and not precisely determined.

Schizophrenia

Twelve schizophrenic patients (11 men; 1 woman; mean age, 43.7 years; SD, 13.2 years; 11 right-handed), all recruited from the clinics at Mt Sinai Hospital and Bronx Veterans Affairs Hospital, underwent evaluation using the Comprehensive Assessment of Symptoms and History42 and diagnosis according to DSM-IV.39 Patients were neuroleptic naive (n=9) or neuroleptic free (median, 3 weeks; longest, 3 years); none had taken depot neuroleptics. Medians for educational level, age at onset of illness, and illness duration were 14 years, 23 years, and 20 years, respectively. Total Brief Psychiatric Rating Scale scores were obtained at the time of PET and MRI studies (mean, 55.2; SD, 14.2; minimum possible rating, 18).

Subjects with SPD underwent assessment using the Schedule for Affective Disorders and Schizophrenia because it extensively covers depressive symptoms, the most common comorbidity in SPD, whereas the Comprehensive Assessment of Symptoms and History was administered to schizophrenic patients because it is oriented toward a detailed evaluation of psychotic symptoms.

Controls

Twelve normal controls (11 men; 1 woman; mean age, 42.2 years; SD, 12.4 years) received the Comprehensive Assessment of Symptoms and History to exclude psychiatric illness in themselves or first-degree relatives and the Structured Interview for DSM-III Personality Disorders, modified for administration to normal controls, to screen out personality disorders. The controls, recruited from community newspaper advertisements and bulletin-board postings, underwent screening as described elsewhere, and were age- and sex-matched to the experimental subjects.44 Median educational level was 16 years. Median socioeconomic status level in controls was 3, the same as in the patient groups.

Subjects described herein are a subsample of those described in an earlier, less anatomically detailed PET and MRI report.8 After complete description of the study, subjects provided written informed consent.

MRI ACQUISITION

The same 1.5-T MRI scanner (LX Horizon; GE, Milwaukee, Wis) was used throughout (repetition time, 24 milliseconds; echo time, 5 milliseconds; flip angle, 40°; contiguous 1.2-mm thick axial slices; pixel matrix, 256 × 256; field of view, 23 cm). Images were coded, intermixed, and screened by neuroradiologists for white matter hyperintensities or other evidence of vascular or neoplastic abnormality. Inhomogeneities of the field main magnetic field were monitored monthly and compensated for with shims in the hardware. Radiofrequency field inhomogeneities were monitored using a cylindrical water-filled phantom; after a 1-pass gaussian filter was applied, the histogram was less than 10 U wide, and differences in signal-intensity values on the x- and y-axis 5 cm from the center would not be expected to exceed 1 U in 256. Image geometric linearity was monitored with a 100-mm square-cross phantom; current data showed a 1.6% difference between the vertical and horizontal scales, well within measurement error. Details of image acquisition were kept uniform throughout the study, and regularly obtained phantoms ensured consistency. Brain volume was determined by visual placement of points on the cortical rim and fitting a spline curve through the points on 16 to 20 planes spaced 6.5 mm apart from the highest plane with gray matter to the lowest plane in which frontal and temporal lobes were contiguous to match previously reported PET data.8 The intraclass correlation coefficient (ICC) for 2 raters, 10 brains, was 0.98.

REGIONAL ASSESSMENT AND MORPHOMETRY

The MDN and pulvinar were delineated in serial slices proceeding dorsally and then ventrally (typically 8-11 slices), beginning with the level at which the structure was most clearly demarcated (see Figure 1 for approximate level). For MDN and pulvinar, spline points were placed on lines of demarcation established by a Sobel intensity-gradient filter. A 3 × 3 maximizing function (ie, local search in the

of MDN projections,15 may have volumetric and functional loss in schizophrenia.16-20 Volume loss in PFC could cause MDN shrinkage; alternatively, volume loss in MDN could cause volume loss in PFC.

Attentional disturbances in schizophrenia have been linked to sensory-perceptual dysfunction by theories postulating disturbed stimulus selection or filtering. Some researchers, emphasizing strategic planning, future orientation, and executive function deficits, have posited PFC dysfunction21-24 or failure of thalamofrontal connectivity.25 Others, influenced by sensory hyperactivity in schizophrenia, have invoked the temporal lobe as a site of cerebro failure. Studies have found frontal and temporal size reductions on MRI,16,26 gray matter heterotopias in frontal and temporal white matter,26 and frontal and temporal deficits on functional imaging.17,18 Complex deficits in sensory and perceptual processing in schizophrenia could suggest disturbances in frontal and temporal

©2001 American Medical Association. All rights reserved.
The medial border is defined by the interface of brain matter with cerebrospinal fluid; lateral and posterior borders, by the internal medullary lamina. anteriorly, the lamina is heavily myelinated, in sharp contrast with surrounding gray matter. More posteriorly, the lamina appears less heavily myelinated, and contrast to surrounding thalamus is partly based on the extremely rich vascular supply running within the lamina. Multiple Sobel filter lines were sometimes seen in this region. Fortunately, a conspicuous anatomical feature allows a reliable caudomedial border to be established. The pulvinar (derived from pulvisus, Latin for “cushion”) forms a cushionlike eminence that protrudes into the ventricle. The point at which the ventricular wall abruptly deviates medially to form that eminence establishes the pulvinar’s rostromedial extent (Figure 1). This point (usually lying on the line established by the Sobel filter) defined the border between the MDN and the pulvinar on the medial aspect of the thalamus. The dorsal extent of the nucleus was taken as the most dorsal level at which the Sobel filter circumscribed an ovoid structure situated medially within the thalamus and lying primarily posterior to the level of the mamillotalthalamic tract. The MDN’s ventral extent was taken as the most ventral level at which the Sobel filter circumscribed an ovoid structure that appeared to be continuous with the MDN as delineated in the more dorsal sections. This generally corresponded to 1 MRI slice above the plane in which the superior colliculus appeared, in agreement with our observations of the ventral extent of the nucleus in histological sections.

**Pulvinar**

Medial and posterior borders were unambiguously defined by their interface with cerebrospinal fluid. The lateral border was established by the internal capsule. Medially, the anterior border was defined by the posterior border of the MDN. More laterally, the anterior border was defined by the corticofugal tract, a myelinated band of fibers extending from the lateral extent of the thalamus to join the internal medullary lamina at the MDN’s postero medial edge. The ventral extent of the pulvinar merges imperceptibly with the pretectum and was taken as the most ventral level at which the Sobel filter circumscribed a structure that appeared continuous with that identified as the pulvinar in more dorsal sections. This usually occurred at or slightly above the level of the superior colliculus. The dorsal extent of the pulvinar coincides approximately with the dorsal extreme of the MDN. It was defined as the most dorsal level at which the Sobel filter circumscribed a structure extending to the posterior extent of the thalamus and continuous with profiles identified as pulvinar in more ventral sections. **(Figure 2).** **Figure 3** shows the entire thalamus reconstructed in 1 subject.

**RELIABILITY**

Two tracers independently outlined the whole thalamus (W.B. and E.K.), the MDN (W.B. and E.K.), and the pulvinar (W.B. and A.S.) on 8 subjects. The ICCs and the proportion of overlapping pixels between the tracers (pixels common to traced outlines divided by number of pixels included by either tracer) were computed. The ICC for whole thalamus volume between 2 tracers was 0.90; percentage of pixel overlap between tracers 1 and 2 was 95.2%, and that between tracers 2 and 1 was 93.8%. Tracing of individual nuclei had acceptable reliability (79.6% and 90.4% pixel overlap for the MDN; 90.6% and 90.1% for the pulvinar). The ICCs for the MDN and the pulvinar were r = 0.78 and r = 0.83, respectively.

**STATISTICAL ANALYSIS**

Data were expressed in cubic centimeters for each region of interest (ROI). Variance of the diagnostic groups for both nuclei did not differ significantly (Levene F test for variability). Volumes of the nuclei were normally distributed, and the Kolmogorov-Smirnov test for both nuclei did not reject a nonnormal distribution (P = .29). Multivariate analysis of variance for volume used a 3-group (controls and schizophrenic and SPD patients) × 2-nuclei (MDN and pulvinar) × 2-hemispheres (right and left) mixed-factorial design. A 3 × 2 mixed-factorial design was used for the whole-thalamus volume analysis. The first variable consisted of the 3 groups; the second, the 2 hemispheres. Separate analyses of variance (ANOVAs) were performed for each ROI (including total thalamus), ROI (thalamic volume−ROI), and ROI/brain volume. Our statistical approach allowed (1) specific a priori hypothesis testing with a single F (main effect of group indicating bilateral nuclear effects) to moderate type I error within the MRI-based outline of the thalamus and (2) assessment of the specificity of findings for an individual ROI (group × structure × hemisphere). Follow-up 2-tailed t tests (α level, P < .05) examined specific contrasts suggested by the literature. Strictly speaking, it could be argued that we should use 1-tailed tests for smaller schizophrenic MDN, since that was our hypothesis based on findings in postmortem studies in several studies. However, specification of the number of tails and exact P value permits the reader to interpret the findings.

The schizophrenia-associated abnormalities of MDN and pulvinar found in postmortem studies have yet to be demonstrated in vivo. They have not been examined in schizotypal personality disorder (SPD), which has genetic-phenomenological links to schizophrenia (2 MRI studies reported thalamic volume reductions in relatives of schizophrenic patients). Shared brain abnormalities might account for the common deficits that characterize schizophrenia-spectrum disorders, whereas differences
might explain the diminished severity of psychosis that distinguishes SPD from schizophrenia. Our objective was to compare the size of the MDN and pulvinar in patients with schizophrenia and SPD with findings in normal control subjects. Our hypothesis was as follows: (1) schizophrenic patients would have a smaller volume of the MDN than controls, and (2) both major association nuclei of the thalamus (MDN and pulvinar) would show smaller volumes in schizophrenic than SPD patients, who in turn would show smaller volumes than controls.

RESULTS

BRAIN AND THALAMIC VOLUME

Mean total brain volume was not significantly different in the schizophrenic (1272 cm³; SD, 134 cm³) or SPD (1392 cm³; SD, 210 cm³) group compared with controls (1341 cm³; SD, 68 cm³). Average thalamic volume across right and left hemispheres did not significantly differ in the schizophrenic (4.43 cm³; SD, 0.35 cm³) and SPD (4.58 cm³; SD, 0.42 cm³) groups vs controls (4.68 cm³; SD, 0.40 cm³; F1,33=1.39; P=.26), and follow-up group differences were not statistically significant when tested 2-tailed (control vs schizophrenic groups, t22=0.67; P=.50). At the observed effect size of 0.67 for thalamic volume, 45 subjects per group would be required to detect a significant control vs schizophrenic group difference with power of 0.90.

THALAMIC NUCLEI

When pulvinar and MDN were analyzed together in a 3-way ANOVA, there was a significant main effect of patient group for nuclear size relative to brain volume (F2,33=3.35; P=.047), but the effect of patient group for nuclear size (F2,33=3.09; P=.06) and a group × nuclear size interaction did not reach statistical significance (F2,33=2.94; P=.07).

PULVINAR

Volume of the pulvinar was significantly smaller in the SPD and schizophrenic groups than in controls (Table 1). With correction for brain size, the relative volume of the pulvinar was also significantly reduced (Table 1). For volume and relative volume, there was no significant group × hemisphere interaction. However, because the size difference across groups was so marked (14.9% across all groups; main effect of hemisphere, F1,33=29.7, P<.001), right and left hemispheres were examined separately (Table 2), revealing that the major size reductions were in the left thalamus. The t tests examining right minus left difference scores for volume data revealed significant asymmetry (right>left) in schizophrenic and SPD patients (t12=3.09 and t12=3.65, respectively; P<.01) but not controls (t12=2.01; P<.10). There were no significant differences in asymmetry when difference scores for schizophrenic and SPD groups were compared separately with control scores (t12=−0.45 vs t12=−0.77; P=.65; the effect size of 0.18 for control vs schizophrenic group is small, and the effect size of 0.32 for control vs SPD group would require n=150 for 80% power).

MEDIODORSAL NUCLEUS

Volume of the MDN was smaller in the SPD and schizophrenic groups than in controls (Table 1). With correction for brain size, the relative volume of the MDN was also significantly reduced (Table 1). For volume and relative volume, there was no significant group × hemisphere interaction. However, because the size difference across groups was so marked (11.9% across all groups; main effect of hemisphere, F1,33=22.1, P<.001), right and left hemispheres were examined separately (Table 2), revealing that the major size reductions were in the left thalamus. The t tests examining right minus left difference scores for volume data revealed significant asymmetry (right>left) in schizophrenic and SPD patients (t12=2.89; P<.01) but not controls (t12=0.24; P=.58) groups, whereas
the greater asymmetry in patient groups than in controls was not significant ($t_{22}=1.75; P=.10$; effect size, 0.71; $n=30$ in each group for 80% power).

**COMMENT**

Previous studies of anatomically delineated thalamic divisions in schizophrenia have relied on postmortem material and have been mainly restricted to the MDN. Our study examined the MDN and the pulvinar in living subjects. Evidence was obtained of a reduction in the volume and relative size of the pulvinar in both schizophrenia and SPD. The MDN was also reduced in volume, but this reduction was statistically significant only for the left hemisphere and only in schizophrenia. Since the volume of the whole thalamus or whole brain was not significantly reduced in schizophrenia or SPD, the reductions observed in the nuclei cannot be attributed to generalized brain-size reduction. Failure to detect significant volume loss in the whole thalamus is consistent with most but not all studies.

An interesting implication of the present study is that of a common neurologic substrate (pulvinar volume loss) in 2 schizophrenia-spectrum disorders (schizophrenia and SPD). In contrast, MDN volume loss appears specific to schizophrenia. The widespread connections of the pulvinar with temporal association and sensory cortices suggest that associational and perceptual disturbances may be linked to abnormalities in the pulvinar. On the other hand, although patients with SPD manifest some peculiarities of thinking and associations, they do not show the severe formal thought disorder (eg, frequent derailment or incoherence) of schizophrenia. The MDN, via its projection from the dentate of the cerebellum, has been...
proposed as a potential substrate for schizophrenic thought disorder. That proposal is based on analogy to the motor system in which complex movements are conceptualized as being built up from simple movements (ie, modules) that are assembled into meaningful sequences by the cerebellum. Complex thoughts may be similarly constructed from modules (ie, partial thoughts) that are sequenced by the cerebellum. Because these neurons may have widespread projections, including connections to temporal association and visual and auditory cortices—suggest the pulvinar as another site for interregional communication failure. The pulvinar, which is absent in rodents, increases in size and complexity from monkeys to apes to humans, in which it is the largest thalamic nucleus. Lateral regions of the pulvinar have widespread projections, including connections to temporal association and visual and auditory cortices. These connections suggest a potential role for the pulvinar in the unusual associations and sensory disturbances of schizophrenia. Moreover, the role of the left pulvinar in language and the association of dominant left-lateral pulvinar lesions with "semantic paraphasias sometimes deteriorating into jargon" suggest the pulvinar's potential importance in schizophrenic speech disturbance. The pulvinar (especially medial regions) also has reciprocal connections with the PFC, suggesting a possible link between the pulvinar and prefrontal abnormalities of schizophrenia.

Although loss of excitatory projection neurons to the PFC might account for schizophrenia-associated volume loss in MDN and pulvinar, a loss of interneurons must also be considered. Both nuclei are believed to contain some neurons of telencephalic origin. Because these neurons migrate into the diencephalon through the gangliothalamic body after most thalamocortical connections have been established, they are likely to be interneurons. Disruption of the telencephalic germinal zone or of the migration of

Figure 3. Volume rendering in 3 dimensions of thalamus viewed looking down from the top with mediodorsal nucleus in red and pulvinar in blue. Orientation is the same as in Figure 1.

Table 1. Volume and Relative Size of Thalamic Mediodorsal Nucleus and Pulvinar in Schizophrenia and Schizotypal Personality Disorder

<table>
<thead>
<tr>
<th>Group</th>
<th>MDN</th>
<th>Pulvinar</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (n = 12)</td>
<td>0.79 (0.12)</td>
<td>1.37 (0.25)</td>
<td>2.16 (0.71)</td>
</tr>
<tr>
<td>Schizophrenic (n = 12)</td>
<td>0.73 (0.12)</td>
<td>1.22 (0.24)</td>
<td>1.94 (0.62)</td>
</tr>
<tr>
<td>SPD (n = 12)</td>
<td>0.78 (0.15)</td>
<td>1.20 (0.23)</td>
<td>1.98 (0.57)</td>
</tr>
</tbody>
</table>

* MDN indicates mediodorsal nucleus; SPD, schizotypal personality disorder; and ANOVA, analysis of variance.
† For 2-way ANOVA on each structure, main effect of group for pulvinar, F2,33 = 3.82, P = .03; main effect of group for MDN, F2,33 = 1.55, P = .23. For 3-way ANOVA on both structures, main effect of group, F2,33 = 3.09, P = .06.
‡ For 2-way ANOVA on each structure, main effect of group for pulvinar, F2,33 = 4.21, P = .02; main effect for MDN, P = NS. For 3-way ANOVA on both structures, main effect of group, F2,33 = 3.35, P = .047.

Consistent with our hypothesis of abnormalities in efferent and afferent fields of abnormal thalamic divisions, schizophrenia-associated anatomical anomalies have been described for the following 2 projection fields of the MDN: the PFC and the cerebellar dentate. The abnormalities of the PFC have been hypothesized to be atrophic changes due to a loss of excitatory glutamatergic input, such as that supplied by the MDN. Loss of volume and cells within the MDN could reflect a loss of excitatory input to the PFC. If there is indeed an etiologic link between the schizophrenia-associated changes described for MDN and PFC, one might propose a corresponding link between PFC abnormalities and volume loss in the pulvinar, since the medial pulvinar and the MDN have similar connections with the PFC. We are examining postmortem histological sections to determine whether the MRI-detected volume loss is distributed throughout all divisions of the pulvinar or restricted to its medio-dorsal portion.

Changes in the MDN might instead be secondary to abnormalities that have been described in its cortical fields. Although auditory, visual, and somatosensory pathways primarily pass through the ventral posterior and geniculate nuclei, the complex associational thalamocorticothalamic loop of the lateral orbito-frontal and dorsolateral PFC independently involves anterior and medio-dorsal regions of the thalamus. The sensory information processed in the PFC is probably derived primarily from corticocortical connections. The proposal that schizophrenia involves faulty filtering of sensory signals from input to the cortex via the thalamus is consistent with our observation of a loss of the normal correlation between glucose metabolism in the thalamus and PFC in PET studies.

Temporothalamic interactions also merit consideration for their potential role in schizophrenia-related disturbances. The important interactions between the pulvinar and the occipital and temporal lobes—areas of visual and auditory processing—suggest the pulvinar as another site for interregional communication failure. The pulvinar, which is absent in rodents, increases in size and complexity from monkeys to apes to humans, in which it is the largest thalamic nucleus. Lateral regions of the pulvinar have widespread projections, including connections to temporal association and visual and auditory cortices. These connections suggest a potential role for the pulvinar in the unusual associations and sensory disturbances of schizophrenia. Moreover, the role of the left pulvinar in language and the association of dominant left-lateral pulvinar lesions with "semantic paraphasias sometimes deteriorating into jargon" suggest the pulvinar's potential importance in schizophrenic speech disturbance. The pulvinar (especially medial regions) also has reciprocal connections with the PFC, suggesting a possible link between the pulvinar and prefrontal abnormalities of schizophrenia.

Although loss of excitatory projection neurons to the PFC might account for schizophrenia-associated volume loss in MDN and pulvinar, a loss of interneurons must also be considered. Both nuclei are believed to contain some neurons of telencephalic origin. Because these neurons migrate into the diencephalon through the gangliothalamic body after most thalamocortical connections have been established, they are likely to be interneurons. Disruption of the telencephalic germinal zone or of the migration of
neurons into the diencephalon might produce cell and volume loss in both MDN and pulvinar. One study described a schizophrenia-associated loss in the pulvinar of small neurons that were hypothesized to be interneurons.31

Our study is limited by several considerations. First, the sample size of 36 (12 in each group) limited power to detect small total thalamic volume decreases. Indeed, a meta-analysis of 14 MRI studies that measured the thalamus in schizophrenia suggested “a statistically significant, small-to-moderate effect size for thalamic size reduction in schizophrenia suggested”.(66) Second, the extent to which structures identified as MDN and pulvinar on MRI overlap with those identified in histological sections is unknown; however, the lines established on MRI scans by the intensity-gradient filter are consistent from one brain to the next and allow subregions of the thalamus to be identified reliably. Nevertheless, current MRI resolution did not permit assessment of thalamic nuclei in addition to the MDN and pulvinar. Thus, it is not yet possible to determine whether thalamic volume changes in schizophrenia and SPD are restricted to those nuclei or involve additional nuclei. Finally, in the absence of significant clinical correlations, the functional significance of the observed volume changes remains speculative.

Postmortem histological work is necessary to determine the exact units of thalamic cytoarchitecture and the neuronal phenotypes affected in schizophrenia, but such studies are extremely laborious and can only be performed on relatively small samples of brains, typically from older individuals. Moreover, diagnostic information, postmortem intervals, and tissue fixation are often less than optimal for autopsy specimens. Partly for these reasons, the specificity of thalamic abnormalities to schizophrenia as opposed to other chronic psychiatric conditions has been explored inadequately. Although neuroimaging lacks the fine-grained resolution of histological work, and the exact correspondence between histologically defined nuclei and gradient-filter MRI borders remains to be established, in vivo studies allow many more subjects to be examined, provide greater diagnostic precision, allow both hemispheres of the brain to be assessed, and avoid uncertainties introduced by artifacts of tissue fixation and other histological procedures. In addition to providing information on brain function in living subjects, neuroimaging studies promise to increase the efficiency of labor-intensive postmortem studies by identifying thalamic regions that are most affected in schizophrenia and the schizophrenic subgroups that exhibit the greatest struc-tural abnormalities. Postmortem studies then may be able to target specific brain regions and patient populations to clarify the precise units of cytoarchitecture that are affected and to characterize the nature of the abnormalities at cellular and molecular levels.

Accepted for publication October 10, 2000.

This project was supported by grants MH40071, MH60023 (Dr Buchsbaum), MH59589 (Dr Byne), MH42827 (Dr Siever), and MH56460 (Dr Hazlett) from the National Institute of Mental Health. The VISN-3 Mental Illness Research Education and Clinical Center (Bronx, NY) also provided support, with young investigator awards from the National Alliance for Research on Schizophrenia and Depression (Great Neck, NY) (Dr Byne and Hazlett), a Veterans Affairs (Washington, DC) Merit Review grant (Dr Siever), the Charles A. Dana Foundation (New York, NY), and the private contribution of Mrs Grace De Wolff (Dr Kemether).

Craig Geneve, Bradley R. Buchsbaum, and Rayzel Kinderlehrer provided technical assistance.

Corresponding author and reprints: William Byne, MD, PhD, Veterans Affairs Medical Center, Department of Psychiatry (1F-29), 130 W Kingsbridge Rd, Bronx, NY 10468 (e-mail: byne@mindspring.com).
REFERENCES


INTERNEURONS IN PREFRONTAL AND CINGULATURE CORTEX OF SCHIZOPHRENIC AND SCHIZOFRACTIVE PATIENTS. Arch Gen Psychiatry. 1991;48:996-1001.


