Volumetric Evaluation of the Thalamus in Schizophrenic Male Patients Using Magnetic Resonance Imaging

Chiara M. Portas, Jill M. Goldstein, Martha E. Shenton, Hiroto H. Hokama, Cynthia G. Wible, Iris Fischer, Ron Kikinis, Robert Donnino, Ferenc A. Jolesz, and Robert W. McCarley

Background: *The thalamus, an important subcortical brain region connecting limbic and prefrontal cortices, has a significant role in sensory and cortical processing. Although inconsistently, previous studies have demonstrated neuroanatomical abnormalities in the thalamus of schizophrenic patients.*

Methods: *This structural magnetic resonance imaging study, based on segmentation of contiguous coronal 1.5-mm images, compared thalamic brain volumes of 15 chronic, male schizophrenic patients with 15 normal controls matched on age, sex, handedness, and parental socioeconomic status.*

Results: *There were no significant differences between patients and controls in thalamic volumes, right or left, adjusted for total brain volume; however, there were significantly different correlations of thalamic volumes with prefrontal white matter and lateral ventricles among patients, but not among controls. Thalamic volumes among patients were also significantly correlated with bizarre behavior, hallucinations, and thought disorder.*

Conclusions: *Findings suggest that connectivity between thalamic nuclei and prefrontal cortical areas are abnormal in chronic male schizophrenic patients. In addition, ventricular enlargement may be, in part, due to subtle reduction in thalamic volume and/or in volume of thalamocortical and corticothalamic fibers secondary to thalamic abnormalities. Finally, correlations with positive symptomatology underscore the role of the thalamus in gating or filtering of sensory information and coordination of cortical processing.* Biol Psychiatry 1998;43: 649–659 © *1998 Society of Biological Psychiatry*

Key Words: Schizophrenia, thalamus, magnetic resonance imaging

From the Clinical Neuroscience Division, Neuroscience Laboratory, Department of Psychiatry, Harvard Medical School, (CMP, JMG, MES, HHH, CGW, IF, RD, RWM); Harvard Medical School, Department of Psychiatry at Massachusetts Mental Health Center, Harvard Institute of Psychiatric Epidemiology and Genetics, (JMG); and Surgical Planning Laboratory, MRI Division, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (RK, FAJ).

Address reprint requests to Jill M. Goldstein, PhD, Harvard Institute of Psychiatric Epidemiology and Genetics, Massachusetts Mental Health Center, 74 Fenwood Road, Boston, MA 02115; or Robert W. McCarley, M.D., Brockton-West Roxbury VAMC, 940 Belmont St., Brockton, MA 02401.

Received July 18, 1996; revised April 15, 1997; accepted June 23, 1997.

Introduction

The primary brain areas implicated in schizophrenia are prefrontal cortex (e.g., Weinberger et al 1986; Andreasen et al 1990; Seidman et al 1996), and limbic and medial temporal lobe structures (e.g., Bogerts et al 1985, 1990; Shenton et al 1992; Falkai et al 1988). A few recent in vivo imaging studies have also implicated the thalamus in schizophrenia (Andreasen et al 1990, 1994; Buschbaum et al 1996; Flaum et al 1995; Goldstein et al 1996; Jernigan et al 1991; Seidman et al 1996). The idea that thalamic abnormalities may contribute to understanding the pathology in schizophrenia is not new, in particular in its role in attention and language processing (e.g., Mirsky 1991; Seidman 1983; Crosson and Hughes 1987; Kolb 1977). Moreover, the thalamus is an important part of the subcortical network, connecting, among other regions, limbic, basal ganglia, and prefrontal cortical regions (Kolb 1977; Groenewegen et al 1990; Pandya and Yeterian 1990). Since cortical activity is controlled and integrated, in part, by the thalamic nuclei, abnormalities in these areas may play a role in the pathogenesis of schizophrenia (Crosson and Hughes 1987; Gold and Weinberger 1991; Dolan et al 1993; Silverweig et al 1995).

Early postmortem studies did not show any significant difference in the total thalamic volume of schizophrenic patients compared to the thalamic volume of control subjects (Rosenthal and Bigelow 1972; Lesch and Bogerts 1984; Kelsoe et al 1988). However, three postmortem studies did find a significant reduction in the total number of neurons in the brains of schizophrenic patients compared to normal control brains, specifically in the mediodorsal thalamic nucleus (Hempel and Treff 1959; Baumer 1954; Pakkenberg 1990, 1992). In contrast, one postmortem study reported no significant difference in nerve cell density in the mediodorsal thalamus (Dom et al 1981).

Finally, comparing schizophrenic patients with normal controls, a number of recent in vivo magnetic resonance imaging (MRI) studies have reported significant reductions in thalamic volume (Flaum et al 1995; Goldstein et al 1996), thalamic area (Andreasen et al 1990; Buchsbaum et

0006-3223/98/$19.00
PII S0006-3223(97)00339-9

al 1996), or in differences between averaged pixel signal intensities reflecting abnormal increases or decreases in thalamic parenchyma or in adjacent white matter fiber tracts (Andreasen et al 1994). Further, a recent study indicated significant thalamic volume reductions in first-degree relatives of schizophrenics compared to normal controls (Seidman et al 1996). Although there have been seven previous structural MRI studies of the thalamus in schizophrenia, only a few have produced *volumetric* data, and have used slice thicknesses of 3 mm with 1.5-mm gaps between slices (Flaum et al 1995), 3 mm with no gaps (Goldstein et al 1996; Seidman et al 1996), and 5 mm with 2.5-mm gaps for diencephalon gray-matter structures (Jernigan et al 1991). In the present study, we used contiguous thin slice (1.5 mm) MR high-resolution images, on which automated and manual segmentation and three-dimensional (3D) surface rendering techniques were used to evaluate thalamic volumes in schizophrenic patients and controls.

Methods and Materials

The Sample

The sample for this study has been reported in previous publications (Shenton et al 1992). Briefly, 15 DSM-III-R schizophrenic patients (13 hospitalized) were selected from among patients at the Brockton Veterans Administration Medical Center, according to the following criteria: patients were male, right-handed, 20–55 years old, had never undergone electroconvulsive shock treatment, had no history of neurological illness, no major alcohol or drug abuse in the previous 5 years, no history of alcohol dependence and no secondary diagnosis of DSM-III-R alcohol abuse, and had not been receiving medications known to affect the results of MRI of the brain, such as steroids. The patients had a mean age of 37.6 years and standard deviation ($\pm$) 9.3, mean years of education of 11.7, and parental socioeconomic status (PSES) of lower middle class (Hollingshead classification of 3.4 $\pm$ 0.1). Their mean age of onset was 22.3 $\pm$ 2.8 years, mean duration of illness was 15.7 $\pm$ 8.8 years, and mean time hospitalized was 7.1 $\pm$ 4.6 years. Patient diagnoses were made in accord with DSM-III-R (American Psychiatric Association 1987) on the basis of chart review, and from information obtained from administration of the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott 1978). All schizophrenic patients were receiving neuroleptic medication (mean = 881 $\pm$ 683 mg/day chlorpromazine equivalent).

The normal control group, recruited from newspaper advertisements, consisted of 15 adult males (20–55 years old) previously screened for neurological or psychiatric histories, and matched to patients on age, sex, handedness, and PSES. Controls had no history of electroconvulsive shock treatment, neurologic illness, or steroid use, no lifetime history of drug/alcohol addiction or DSM-III-R abuse within the last 5 years, nor psychiatric illness in themselves or their first-degree relatives. There were no statistically significant differences between patients and controls in age, height, weight, head circumference, PSES, or in scores on the WAIS-R information subscale (Wechsler 1981).

Clinical evaluations were reported previously (Shenton et al 1992). Briefly, three instruments were used to assess type and severity of symptoms: the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1981), and the Thought Disorder Index (TDI; Johnston and Holzman 1979). The average score on the TDI was 60 $\pm$ 62, and median = 44. Normal subjects score $<$ 5. Using the Andreasen classification, 11 out of the 15 patients had mainly positive symptoms, and 4 were mixed. None of the patients had mainly negative symptoms, although some negative symptoms were present (mean global SANS score = 9.1).

Image Acquisition and Processing

The MRI scans were obtained through the entire brain on a 1.5-T General Electric SIGNA System (GE Medical System, Milwaukee, WI), using a 3D Fourier transform spoiled gradient-recalled (3DFT SPGR) acquisition in steady state. The SPGR images were obtained with the following parameters: echo time (TE) = 5 msec, repetition time (TR) = 35 msec, one repetition, nutation angle = 45 degrees, field of view = 24 cm, acquisition matrix = 256 $\times$ 256 $\times$ 124, voxel dimensions = 0.9375 $\times$ 0.9375 $\times$ 1.5 mm. These data were stored as 124 contiguous 1.5-mm coronal slices. Intracranial contents were measured by 108 contiguous double echo spin-echo 3-mm axial slices throughout the brain. Imaging parameters were: TE = 30 & 80 msec, TR = 3000 msec, field of view = 24 cm, acquisition matrix = 256 $\times$ 256, and voxel dimensions = 0.9375 $\times$ 0.9375 $\times$ 3 mm (see Shenton et al 1992 for details). Automated and manual segmentation methods, 3D slice editing techniques that allowed reformatting of slices in three different planes, and 3D surface rendering techniques were applied to the data collected to create 3D representations of the thalamus (Kikinis et al 1990; Cline et al 1990). Thalamic segmentation was performed using coronal slices. Sagittal and axial reslicing software was utilized to view the segmentation results in different planes.

Thalamic Boundary Definition

The automated segmentation procedures produced the separation of gray and white matter based on differences in signal intensity values (Kikinis et al 1990; Cline et al 1990). Manual segmentation of the thalamus occurred in 20–21 consecutive slices (out of an average of 120 slices over the entire brain). To overcome the problem of partial volume (PV) effects, we decided to include 50% of the PV area. The definitions of the landmarks used for the thalamus are described as follows. The most anterior boundary was difficult to resolve. We used the mammillary bodies of the hypothalamus. The ventralis anterior nucleus is just dorsal to the hypothalamus, bounded laterally by the internal capsule, dorsally by the lateral ventricle, and medially by the third ventricle. The posterior boundary was defined when the thalamus merged under the crus fornix. The thalamus was medially defined using the third ventricle. The inferior border was defined when the thalamus merged with the brain stem and the superior border, by

the main body of the lateral ventricle. (Duvernoy 1991; De Armond et al 1989; Roberts and Hanaway 1971; Haines 1991 were used as primary anatomical references.) Figure 1 presents an example of the thalamic segmentation of one coronal slice. Figure 2 is a 3D representation of the thalamus in relation to the ventricles. A more detailed description of the thalamic boundaries using a case example is presented in the Appendix.

Intrarater and interrater reliability were conducted by three raters (CMP, IF, RD). Since CMP measured all cases, intrarater reliability on the thalamic segmentation was assessed 6 months apart on 3 randomly selected cases. The volume difference between the first and the second measurement was negligible in all 3 cases (>1%). Interrater reliability, estimated by intraclass correlation coefficients, for 3 randomly selected cases across three raters was: .93 for total thalamic volume, .93 for right thalamic volume, and .91 for left thalamic volume.

Data Analyses

Volumes of the thalamus in the right and left hemispheres were segmented and analyzed separately and as total thalamic volume. All volumes were adjusted for intracranial brain volume to adjust for head size. Volumetric assessments presented below were thus divided by intracranial volume and multiplied by 100. Analysis of covariance (ANCOVA) was used to test for the effect of group (i.e., schizophrenics versus normal controls), controlled for age and PSES. We controlled for PSES because, even though this variable was not significantly different between groups, there were more parents of schizophrenics in the lowest social class than in the control parental group. The use of general linear models, such as ANCOVA, was appropriate, since tests of normality for the total, right, and left thalami in patients and in controls showed that these data were normally distributed in both groups.

We then tested whether there were differences between schizophrenics and normal controls in the relationships, i.e., covariance structure, or correlations, between the thalamus and some of the other key brain regions that are known to have specific neural connections to the thalamus and have been found to be abnormal in schizophrenia, i.e., prefrontal cortex, cingulate gyrus, striatum, hippocampus, amygdala, and the superior temporal gyrus. Temporal lobe structures and basal ganglia were of particular interest, since in previous work we found that they were significantly different in these patients than in the normal controls (Shenton et al 1992; Hokama et al 1995). We were specifically interested in a test of the *differences* in the covariance structure, or correlations, partialled for PSES and age, among patients versus controls, which consisted of normalizing the correlations using Fisher's *z* transformation (Fisher 1958). Tests of the differences in the correlational structure between patients and controls will not be influenced by any potential bias in correlating adjusted brain regions.

Finally, we were interested in whether, and if so, how, thalamic volumes among the patients related to their clinical presentation and severity, particularly positive symptoms. A recent study argued that thalamic abnormalities are key to understanding the expression of positive symptoms (Andreasen et al 1994). Adjusted thalamic volumes (left, right, and total) among the schizophrenic patients were correlated with global scores of positive symptoms (i.e., SAPS; Andreasen 1984), which included auditory hallucinations, delusions, and bizarre behavior, and total score on the Thought Disorder Index (Johnston and Holzman 1979). Negative symptoms (i.e., SANS; Andreasen 1981), which included affective flattening, alogia, avolition–apathy, asociality, and attentional behavior ratings, were also examined in relation to thalamic volumes. These analyses were exploratory, given that the sample in this study was characterized as "mainly positive." The nonparametric Spearman's correlation coefficient, rho, was applied using two-tailed significance tests. Spearman's rho was selected because it takes into account outliers that can skew findings, particularly in small sample sizes.

Results

Differences in Thalamic Volumes between Patients and Controls

Results of the ANCOVAs, controlling for age and PSES, showed that there were no significant differences in the adjusted volumes for the right, left, nor total thalamus between controls and patients, respectively (right: $\bar{x} = 0.44 \pm 0.01$ vs. $\bar{x} = 0.45 \pm 0.01$; left: $\bar{x} = 0.44 \pm 0.04$ vs. $\bar{x} = 0.44 \pm 0.01$; total: $\bar{x} = 0.88 \pm 0.02$ vs. 0.89 ± 0.02). Thalamic volumes unadjusted for intracranial brain volume also showed no significant differences between controls and patients, respectively (right: $\bar{x} = 7.01 \pm 0.64$ vs. $\bar{x} = 7.20 \pm 0.75$; left: $\bar{x} = 6.91 \pm 0.81$ vs. 7.06 ± 0.63; total: $\bar{x} = 13.9 \pm 1.4$ vs. $\bar{x} = 14.26 \pm 1.3$).

We then tested for differences between patients and controls in relationships between thalamic volume and other brain regions of interest (ROIs) found to be important in schizophrenia and with which thalamic nuclei are known to have significant connections. Table 1 presents the significant correlations between the left and right adjusted thalamic volumes and the other brain ROIs. Correlations between left and right thalamic volumes and ROIs not listed in Table 1, i.e., middle, inferior, and orbital prefrontal cortex, cingulate gyrus, amygdala, superior temporal gyrus, and putamen, were not significantly different between patients and controls. In general, as shown in Table 1, there was a greater likelihood of significant differences in the correlations between thalamic volume and ROIs between patients and controls in the left hemisphere than in the right.

The main finding in Table 1 is the significant negative correlations between the left and right thalamus with left and right ventricles among the patients, but not among controls, indicating that the smaller the thalamus, the larger the ventricles. There was little variability in the size of the ventricles among controls (SD = 0.16; $\bar{x} = 0.44$),

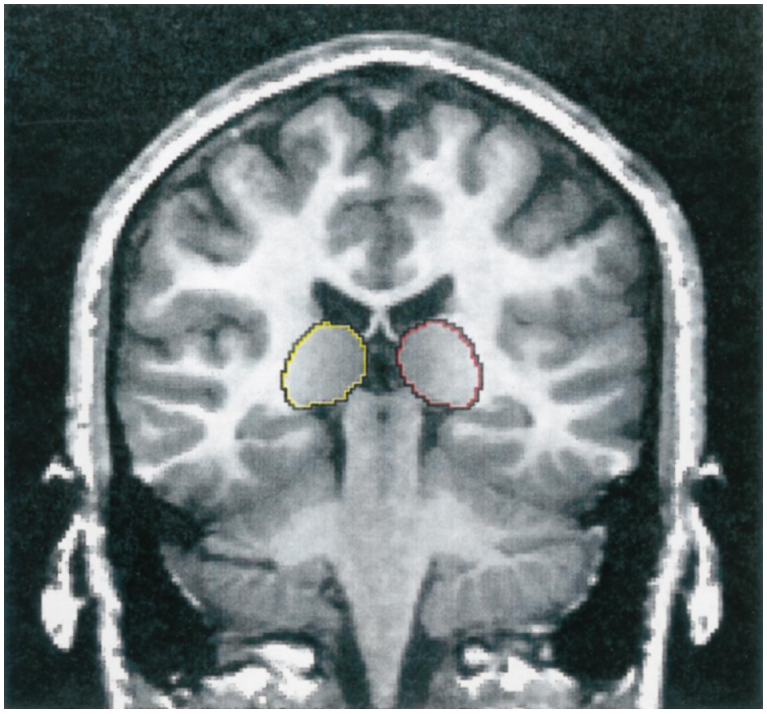

Figure 1. Example of the segmentation of the thalamus on one coronal slice.

Figure 2. Three-dimensional representation of the thalamus in relation to the ventricles.

Table 1. Significant Correlations of Right and Left Volumes of Brain Regions of Interest with Right and Left Thalamic Volumes between Schizophrenics and Controls

Level	Schizophrenics (n = 14)	Controls (n = 15)	p-value[a]
Left thalamus			
Left ventricle	−.65	.30	.01
Left hippocampus	.30	.13	ns
Left posterior temporal	.58[b]	.47	ns
Left superior frontal	.16	−.58[b]	.05
Left caudate	.24	.58[b]	ns
Left frontal white matter (total)	.39	−.31	.086
Left frontal gray matter (total)	−.02	−.36	ns
Right thalamus			
Right ventricle	−.61[b]	.13	.05
Right hippocampus	.28	.61[b]	ns
Right posterior temporal	.30	−.19	ns
Right superior frontal	.17	.03	ns
Right caudate	.44	.72[c]	ns
Right frontal white matter (total)	.45	.08	ns
Right frontal gray matter (total)	.13	−.02	ns

[a]Correlations were standardized using Fisher's Z transformation to test for whether the correlations between left and right thalamic volumes with ROIs were different between groups, i.e., for patients versus controls.

[b]$p < .05$, [c]$p < .01$. These are tests of whether the correlations of right and left thalamic volumes with ROIs are significant *within* group.

whereas in patients, the variability was more than twice the variability among the controls (SD = 0.37; $\bar{x}$ = 0.52). This is compatible with pathological processes operating on ventricular volume with variable severity in the patients.

In addition, the right hippocampus was significantly correlated with the right thalamus among the controls, but not among the patients. That is, among the controls, the larger the right thalamic volume, the larger the right hippocampus. This relationship did not hold for the left side among controls or patients. However, a test of the *differences* between patients and controls in the correlation between the right thalamus and hippocampus was not significant. The left and right caudate were more positively correlated with the left and right thalamus among controls than among patients, although the differences between controls and patients were not significant. Further, the left superior frontal cortex was significantly negatively correlated with left thalamus among the controls but not among the patients. Thus, among the controls, the larger the left thalamus, the smaller the left superior frontal cortex. This did not hold for the right hemisphere.

Finally, the left and right frontal white matter correlated differently with the left and right thalamus among patients and controls. Frontal white matter was positively correlated with the size of the thalamus, bilaterally, among patients. However, frontal white matter was negatively correlated with the size of the left thalamus among controls, and uncorrelated with the size of the right thalamus among controls. Total frontal gray matter did not significantly correlate with the size of the thalamus among patients or controls. Although the correlations with total white matter on the left did not reach significance, the difference in the correlations on the left between patients and controls was close to significant ($p < .086$).

Correlations of Thalamic Volumes with Clinical Symptoms among Patients

Correlations between right, left, and total adjusted thalamic volumes with four of the global negative symptom ratings (affective blunting, alogia, apathy, asociality) and total negative symptom score were not significant among patients. However, there was some suggestion that attention was related to thalamic volume (total thalamic volume: rho = −.51, p = .06). As one would predict, the

Table 2. Effect Sizes[a] in Previous MR Imaging Studies Comparing Schizophrenic Male Patients with Normal Male Controls on Total Thalamic Size

Authors	Male sample size	Slice size	Male effect sizes	
			Unadjusted volumes	Adjusted volumes
Jernigan et al (1991)	28sz	5 mm w/2.5-mm gaps		
	19nc		.11	.08
Andreasen et al (1994)	39sz			
	47nc	Signal intensity differences	.75–1.0[b]	NA
Flaum et al (1995)	66sz			
	43nc	3 mm w/1.5-mm gaps	.55[b]	Values not reported
Buchsbaum et al (1996)	19sz	7.5 mm; area assessed		
	12nc		.10	.10
Goldstein et al (1996)	17sz			
	12nc	3 mm, no gaps	.35	.80[b]

sz, schizophrenic subjects; nc, normal controls.

[a]Effect size was calculated according to Cohen (1977): mean volume of the controls minus the mean volume of the patients divided by the pooled standard deviation.

[b]Significant difference in thalamic size at $p < .05$.

direction of the effects suggests that the more severe the attentional problems, the smaller the thalamic volume.

In contrast, there was a stronger relationship between positive symptoms and thalamic volume. That is, the correlation of adjusted total thalamic volume with total positive symptom rating was statistically significant (rho = −.69, $p < .04$), reflecting mainly a correlation with the left (rho = −.64, $p = .06$) and to a lesser extent, the right (rho = −.44, $p = .23$). Results suggest that the smaller the thalamic volume, the higher the positive symptom severity. This correlation was primarily due to two global scales, i.e., hallucinations and bizarre behavior. The global hallucinations score significantly correlated with left and right thalamic volumes (respectively, rho = −.52, $p = .057$; and rho = −.60, $p = .02$), and with total thalamic volume (rho = −.59, $p = .02$). We specifically looked at the relationship of auditory hallucinations to thalamic volumes, since they have been related to superior temporal gyrus abnormalities (Barta et al 1990), and our sample of patients showed significant structural abnormalities in the superior temporal gyrus (Shenton et al 1992). However, auditory hallucinations were not significantly correlated to left or right thalamic volumes (respectively, rho = −.38, $p = 22$; and rho = −.46, $p = .13$). The SAPS bizarre behavior scale also significantly correlated with total thalamic volume (rho = −.54, $p = .05$), with a rho = −.50, $p = .07$ for left and a rho = −.51, $p = .06$ for the right. In addition, left and right thalamic volumes were not significantly correlated with the global delusions score nor formal thought disorder, as measured by the SAPS or the TDI in the total sample.

Discussion

Male schizophrenic patients in this study did not have a significant difference in thalamic volume (total, right, nor left) compared to matched normal controls. Most of the previous work on the thalamus in schizophrenia was conducted in postmortem studies, some of which demonstrated significant differences (Hempel and Treff 1959; Baumer 1954; Dom et al 1981; Pakkenberg 1990), whereas others did not (Rosenthal and Bigelow 1972; Lesch and Bogerts 1984; Kelsoe et al 1988). It is difficult to compare findings in this study with postmortem work, given differences in diagnostic criteria, areas assessed, the nature of the variables measured, and small sample sizes in postmortem work. However, we were initially surprised that there were no significant differences in thalamic volumes in our sample of chronic male patients, given recent MRI studies showing significant thalamic area and volumetric reductions and image intensity abnormalities (Andreasen et al 1990, 1994; Flaum et al 1995; Goldstein et al 1996), especially in male schizophrenic patients (Andreasen et al 1990; Goldstein et al 1996).

Although this study included a small sample size, thus necessitating replication, we would argue that limitations of sample size do not wholly account for the lack of significance in this study. We calculated the approximate effect sizes for males (ES = mean volume of the controls − mean volume of the patients/pooled standard deviation; Cohen 1977) in a number of the previous imaging studies listed in Table 2: Andreasen et al 1994 (ES already provided); Flaum et al 1995; Buchsbaum et al 1996; Jernigan et al 1991; and Goldstein et al 1996. The approximate ESs for each of these studies were, respectively, .75, .55 (among male subjects), .10 (for adjusted and unadjusted volumes), .11, and .35 (for unadjusted volumes)/.80 (for adjusted volumes among male subjects). The ES for our study, which was .27 for unadjusted volumes and .50 for adjusted volumes, is in line with the previous work. Thus, although the Andreasen and Flaum studies, which were significant, had the highest ESs and largest samples, sample size alone did not wholly account for the range of effect sizes found across studies.

We understand that a larger sample size is important to replicate findings. However, we would argue that the differences in boundary definitions most likely contributes to explaining the inconsistencies of findings reported in the literature. For example, in our study, the lateral and medial geniculates were included in the measurement of the thalamus. However, in Andreasen et al 1990 and Goldstein et al 1996, studies in which significant thalamic volumetric differences among male subjects emerged, the geniculates were not included in the thalamic definition, given less ability to reliably measure the geniculates using 10-mm (Andreasen et al 1990) or 3-mm (Goldstein et al 1996) slices rather than the 1.5-mm slices used in this study. We would argue that significant differences between schizophrenics and controls will emerge when *only specific nuclei* are considered. This was true for previous imaging studies, some of which had sample sizes similar to ours. For example, Buchsbaum et al (1996) reported no significant differences in total thalamic area ($n = 19$ male subjects; 1 female subject), but did report a significant reduction in patients in the right posterior and left anterior thalamic regions. Jernigan et al (1991) found a statistically nonsignificant volumetric reduction among schizophrenic patients compared to normals in a measure of total diencephalon, including the thalamus. However, there was a significant reduction in the anterior thalamus in patients when considered apart from the total thalamus. Andreasen et al (1994) also identified thalamic abnormalities in particular thalamic regions, i.e., lateral and medial and the right posterior and left anterior regions.

These studies are consistent with postmortem work, in

which, specifically, the dorsomedial and anterior thalamic nuclei were found to be abnormal in schizophrenia. The dorsomedial and anterior nuclei are the primary thalamic nuclei that connect with prefrontal cortex, a key region found to be abnormal in schizophrenia (Weinberger et al 1986). In particular, the dorsomedial thalamic nucleus constitutes the most prominent subcortical afferent to the prefrontal cortex (Fuster 1989). Further, studies have identified the pulvinar (Posner and Peterson 1990; Mesulam 1990) and the reticular formation and intralaminar nuclei (Kinomura et al 1996) as related to attentional processing, a key deficit in schizophrenia (Mirsky et al 1991; Seidman 1983), which we found to be correlated with thalamic size in patients. We would therefore argue that when specific nuclei are considered, e.g., dorsomedial, anterior, pulvinar, reticular formation, and intralaminar nuclei, significant volumetric differences between schizophrenic patients and controls will emerge.

Given the extensive connections between thalamic nuclei and other brain regions found to be abnormal in schizophrenia, we tested for correlational differences among patients versus among controls between thalamic volume and specific prefrontal, temporal, cingulate, and basal ganglia brain areas. Although we chose a limited number of predicted ROIs, we had a small sample to test for numerous correlational differences, and thus, the results should be considered exploratory. However, we found that there was a greater number of "different" significant correlations among patients compared to among controls, in the left hemisphere, particularly regarding correlations of left thalamic volume with left prefrontal white matter, than in the right hemisphere. This suggests that, although there were no significant overall volumetric differences between groups, there may be subtle volumetric abnormalities and abnormal connectivity between specific cortical regions and thalamic nuclei, particularly in the left hemisphere. This is consistent with previous work showing abnormalities in the left hemisphere among primarily male schizophrenic patients (Bogerts et al 1990; Friston et al 1992). In fact, male patients in this study demonstrated significantly more abnormalities in left medial and superior temporal regions (Shenton et al 1992) and left basal ganglia (Hokama et al 1995) than on the right. Although our sample of patients exhibited increased left hemisphere abnormalities, thalamic abnormalities in schizophrenic patients in general may be bilateral, given recent work by Andreasen et al (1994), reporting increased thalamic abnormalities especially in the right hemisphere.

We also found significantly different correlations among patients than among controls between lateral ventricular volume and thalamic volumes in the right and left hemispheres. In patients only, the smaller the thalamic volumes bilaterally, the greater was the ventricular cerebrospinal fluid, bilaterally. This is consistent with an earlier study reporting lateral ventricular enlargement among primarily male schizophrenic patients, particularly at the level of the anterior thalamus (Kelsoe et al 1988). The relationship between ventricular and thalamic volumes is interesting and may reflect decreased volume of the interconnections of the thalamocortical fiber tracts, due to thalamic abnormalities reflected in subtle volume alterations. In fact, recent work by Andreasen et al (1994) reported abnormalities in schizophrenic patients compared to normal controls in the thalamus *and* its adjacent white matter tracts.

Thalamic volumes in these patients were also significantly related to the severity of positive symptomatology, i.e., bizarre behavior and hallucinations. Given the central role of the thalamus in filtering or gating sensory information to cortical brain regions (Jones 1985), and the integration of cortical processing and behavior (Crosson and Hughes 1987), it is not surprising that we found significant relationships of thalamic volumes with bizarre behavior, hallucinations, and thought disorder. The significant relationship of thalamic volume with bizarre behavior is consistent with findings in these patients regarding abnormalities in the basal ganglia, which were also related to severity of bizarre behavior (Hokama et al 1995). This fits nicely with animal studies that have demonstrated the connectivity between caudate, putamen, and dorsomedial thalamic nucleus (e.g., Kolb 1977). Further, one of the major efferent pathways of the globus pallidus, found to have the largest basal ganglia abnormality in these patients (Hokama et al 1995), is to the ventral anterior thalamic nucleus. In another previous analysis of these subjects, right middle frontal gyrus was significantly correlated with severity of delusions (Wible et al 1995). In conjunction with thalamic correlations with positive symptoms, this suggests that perhaps thalamic connections with prefrontal regions, i.e., dorsolateral prefrontal cortex (DLPFC), are affected in these schizophrenic patients. This is consistent with a recent positron emission tomography study suggesting a corticosubcortical imbalance in schizophrenic patients that included DLPFC and anterior thalamic regions (Friston et al 1992).

Variability in thalamic volumes among patients was also significantly related to hallucinations. Again, the thalamic role in gating sensory information seems to be important for the production of positive symptoms involved with sensory processing (i.e., hallucinations). Although in previous work we found significant abnormalities in the superior temporal gyrus (STG) that were related to formal thought disorder (Shenton et al 1992), STG volume was not significantly related to thalamic volumes in this study. Thalamic volume was also not significantly

correlated with negative symptomatology. However, since our sample of male patients was primarily characterized by positive symptoms, the small variability in negative symptom ratings may have resulted in decreased statistical power to find significant correlations between thalamic volume and negative symptom expression.

Findings on the relationships between symptomatology and thalamic volumes must be viewed as exploratory, given the small sample size in this study. Further, the relationships between current symptomatology, perhaps reflecting "state" characteristics, with structural brain volume, reflecting "trait" characteristics, should be interpreted with caution. However, our findings are consistent with previous work suggesting a primary role for the thalamus in the production of positive symptoms (e.g., Crosson and Hughes 1987; Andreasen et al 1994) and raise hypotheses for future studies.

Although the study presented here produced a number of nonsignificant results regarding overall thalamic volume differences in patients compared to normal controls, it raises some important issues for structural MRI studies that examine the role of the thalamus in schizophrenia. First of all, the thalamus, which is a composite of several functionally different nuclei, is a difficult structure to segment. One must make decisions about which nuclei have to be included in the definition of the thalamus, which may have implications for finding significant differences between patients and controls. Further, the decision regarding which specific nuclei may be included in the definition may be as dependent on practical concerns as on theory, such as the resolution of the MR images and the ability of one's software to segment in alternative MR planar views. Finally, the ability to segment specific areas of the thalamus, rather than the thalamus as a whole, may be more fruitful in identifying significant thalamic differences between schizophrenic patients and controls and may provide a better understanding of the role of the thalamus in schizophrenia.

This work was supported by grants from the National Institute of Mental Health (NIMH) [MH K02 MH 01110 (MES), MH 1R29 50747 (MES), MH R01 40,799 (RWM)], and by MERIT and Schizophrenia Center Awards from the Department of Veterans Affairs (RWM), and NARSAD Senior Investigator Award (RWM), and was initiated by JMG with support from an NIMH Clinical Research Training Fellowship in Biological Psychiatry, Department of Psychiatry, Harvard Medical School at Massachusetts Mental Health Center (1991) and a Scientist Development Award to JMG, K21 MH00976 (1992–1994).

References

Andreasen NC (1981): *Scale for the Assessment of Negative Symptoms (SANS).* Iowa City, IA: Dept. of Psychiatry, University of Iowa College of Medicine.

Andreasen NC (1984): *Scale for the Assessment of Positive Symptoms (SAPS).* Iowa City, IA: Dept. of Psychiatry, University of Iowa College of Medicine.

Andreasen NC, Ehrhardt JC, Swayze VW II et al (1990): Magnetic resonance imaging of the brain in schizophrenia. *Arch Gen Psychiatry* 47:35–44.

Andreasen NC, Arndt S, Swayze V II, et al (1994): Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. *Science* 266:294–298.

Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE (1990): Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *Am J Psychiatry* 147: 1457–1462.

Baumer H (1954): Veranderungen des Thalamus bei Schizophrenie. *J Hirnforsch* 1:157–172.

Bogerts B, Meetz E, Schonfeld-Bausch R (1985): Basal ganglia and limbic system pathology in schizophrenia: A morphometric study of brain volume and shrinkage. *Arch Gen Psychiatry* 42:784–791.

Bogerts B, Ashtari M, Degreef G, Alvir JM, Bilder RM, Lieberman JA (1990): Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. *Psychiatry Res* 35:1–13.

Buchsbaum MS, Someya T, Teng CY, et al (1996): PET and MRI of the thalamus in never-medicated patients with schizophrenia. *Am J Psychiatry* 153:191–199.

Cline HE, Lorensen WR, Kikinis R, Jolesz AF (1990): Three-dimensional segmentation of MR images of the head using probability and connectivity. *J Comput Assist Tomogr* 14: 1037–1045.

Cohen J (1977): *Statistical Power Analysis for the Behavioral Sciences,* rev. New York: Academic Press.

Crosson B, Hughes CW (1987): Role of the thalamus in language: Is it related to schizophrenic thought disorder. *Schizophr Bull* 13:605–621.

De Armond SJ, Fusco MM, Dewey MM (1989): *Structure of the Human Brain. A Photographic Atlas.* New York: Oxford University Press.

Dolan RJ, Bench CJ, Liddle PF, et al (1993): Dorsolateral prefrontal cortex dysfunction in the major psychoses: Symptom or disease specificity? *J Neurol Neurosurg Psychiatry* 56:1290–1294.

Dom R, De Saedelar J, Bogerts B, Hopf A (1981): Quantitative cytometric analysis of basal ganglia in catatonic schizophrenics. In: Perris C, Struwe G, Jansson B (eds). *Biological Psychiatry.* Amsterdam: Elsevier, pp 723–726.

Duvernoy HM (1991): *The Human Brain: Surface, Three-Dimensional Sectional Anatomy and MRI.* New York: Springer-Verlag.

Falkai P, Bogerts B, Rozumek M (1988): Limbic pathology in schizophrenia: The entorhinal region—A morphometric study. *Biol Psychiatry* 24:515–521.

Fisher RA (1958): Statistical methods for research workers. Edinburgh: Oliver & Boyd.

Flaum M, Swayze VW II, O'Leary DS, et al (1995): Effects on diagnosis, laterality, and gender on brain morphology in schizophrenia. *Am J Psychiatry* 152:704–714.

Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RSJ

(1992): The left medial temporal region and schizophrenia: A PET study. *Brain* 115:367–382.

Fuster JM (1989): *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe,* 2nd ed. New York: Raven Press.

Gold JM, Weinberger DR (1991): Frontal lobe structure function and connectivity in schizophrenia. In: Kerwin R, Dawbarn, McCulloch, Tamminga, CA, editors. *Neurobiology and Psychiatry.* Cambridge: Cambridge University Press.

Goldstein JM, Seidman LJ, Goodman JM, et al (1996): The impact of sex on cognition and structural brain abnormalities in schizophrenia. *Biol Psychiatry* 39:575.

Groenewegen HJ, Berendse HW, Wolters JG, Lohman AHM (1990): The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: Evidence for a parallel organization. In: Uylings HBM, Van Eden CG, De Bruin JPC, Corner MA, Feenstra MGP, editors. *Progress in Brain Research: Vol 85. The Prefrontal Cortex.* Amsterdam: Elsevier, pp 105–118.

Haines DE (1991): *Neuroanatomy: An Atlas of Structures Sections and Systems.* Baltimore: Urban & Schwarzenberg.

Hempel KJ, Treff WM (1959): Quantitative untersuchungen uber relative zell- und Zellkernvolumina bei klinisch gesunden and schizophrenia. *J Hirnforsch* 4:412–454.

Hokama H, Shenton ME, Nestor PG, et al (1995): Basal ganglia volume abnormalities in schizophrenia: An MRI study. *Psychiatry Res Neuroimaging* 61:209–229.

Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Braff DL (1991): Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenics. *Arch Gen Psychiatry* 48:881–890.

Johnston MH, Holzman PS (1979): *Assessing Schizophrenic Thinking.* San Francisco, CA: Jossey-Bass.

Jones ED (1985): *The Thalamus.* New York: Plenum Press.

Kelsoe JR, Cadet JL, Pickar D, Weinberger DR (1988): Quantitative neuroanatomy in schizophrenia. *Arch Gen Psychiatry* 45:533–541.

Kikinis R, Jolesz FA, Gerig G, et al (1990): 3D morphometric and morphometric information derived from clinical brain MR images. In: Hohne KH, Fuchs H, Pizer SM, et al, editors. *3D Imaging in Medicine.* Berlin: Springer-Verlag, pp 441–454, F60.

Kinomura S, Larsson J, Gulyas B, Roland PE (1996): Activation by attention of the human reticular formation and thalamic intralaminar nuclei. *Science* 271:512–515.

Kolb B (1977): Studies on the caudate-putamen and the dorsomedial thalamic nucleus of the rat: Implications for mammalian frontal-lobe functions. *Physiol Behav* 18:237–244.

Lesch A, Bogerts B (1984): The diencephalon in schizophrenia: Evidence for reduced thickness of the periventricular grey matter. *Eur Arch Psychiatry Neurol Sci* 234:212–219.

Mesulam MM (1990): Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol* 28:597–613.

Mirsky AF, Anthony BJ, Duncan CC, Ahern MB, Kellam SG (1991): Analysis of the elements of attention: A neuropsychological approach. *Neuropsychol Rev* 2:109–145.

Pakkenberg B (1990): Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. *Arch Gen Psychiatry* 47:1023–1028.

Pakkenberg B (1992): The volume of the mediodorsal thalamic nucleus in treated and untreated schizophrenics. *Schizophr Res* 7:95–100.

Pandya DN, Yeterian EH (1990): Prefrontal cortex in relation to other cortical areas in the rhesus monkey: Architecture and connections. In: Uylings HBM, Van Eden CG, De Bruin JPC, Corner MA, Feenstra MGP, editors. *Progress in Brain Research: Vol 85. The Prefrontal Cortex.* Amsterdam: Elsevier, pp 63–94.

Posner MI, Peterson SE (1990): The attention system of the human brain. *Ann Rev Neurosci* 13:25–42.

Roberts MP, Hanaway J (1971): *Atlas of the Human Brain in Section.* Philadelphia: Lea & Fibiger.

Rosenthal R, Bigelow LB (1972): Quantitative brain measurements in chronic schizophrenia. *Br J Psychiatry* 121:259–264.

Seidman LJ (1983): Schizophrenia and brain dysfunctions: An integration of recent neurodiagnostic findings. *Psychol Bull* 9:195–238.

Seidman LJ, Faraone SV, Goldstein JM, et al (1996): Reduced subcortical brain volumes in nonpsychotic siblings of schizophrenic patients. *Biol Psychiatry* 39:602.

Shenton ME, Kikinis R, Ferenc JA, et al (1992): Abnormalities of the left temporal lobe and thought disorder in schizophrenia. *N Engl J Med* 327:604–612.

Silverweig DA, Stern E, Frith C, et al (1995): A functional neuroanatomy of hallucinations in schizophrenia. *Nature* 378:176–179.

Spitzer RL, Endicott J (1978): *Schedule for Affective Disorders and Schizophrenia,* 3rd ed. New York: New York State Psychiatric Institute, Biometrics Research.

Wechsler D (1981): *WAIS-R Manual: Wechsler Adult Intelligence Scale, Revised.* New York: Harcourt Brace Jovanovich.

Weinberger DR, Berman KF, Zec RF (1986): Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Arch Gen Psychiatry* 43:114–124.

Wible CG, Shenton ME, Hokama H, et al (1995): Prefrontal cortex: A quantitative magnetic resonance imaging study. *Arch Gen Psychiatry* 52:279–288.

Appendix

ROI Definition

The thalamus (left and right thalami) was defined on 20–21 consecutive slices rostrally to caudally. Since it is crucial to obtain a reliable segmentation of the ROI, we produced, in each case, a "slice by slice" illustration of ROI definition, along with the anatomical landmarks. Figure 3 is a sample case (1 control subject, coronal plane only) in which the anatomical landmarks are displayed. Note that some structures are described only as they appear in the first of the sequentially presented images and may not be reported in the following section (to avoid constant repetition of anatomical landmarks).

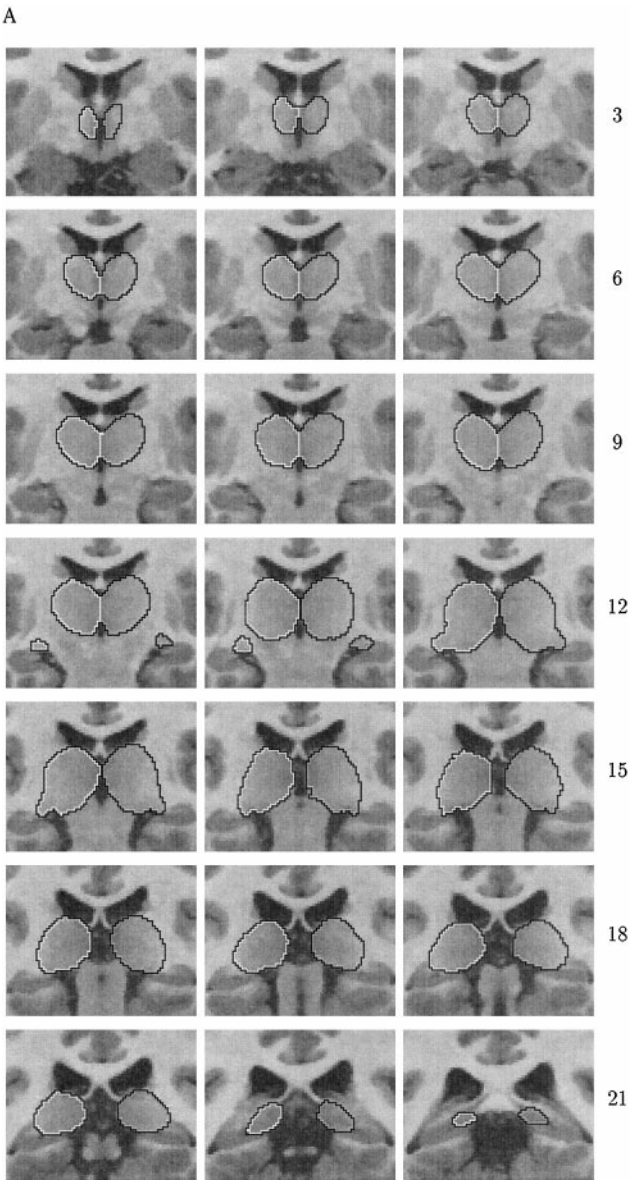

Figure 3. A case example of the segmentation of thalamic boundaries on 21 coronal slices.

Description of ROI on Coronal Slices, with Caudal–Rostral Progression

Most anterior slice #1: The most anterior part of the thalamus is shown here. Note the onset of the ventralis anterior nucleus just dorsal to the hypothalamus. Boundaries are: laterally, the internal capsule; dorsally, the main body of the lateral ventricle; and medially, the third ventricle.

Slice #2: Note the anterior nuclei (reference atlas: Duvernoy 1991 pages 116, 118; Roberts and Hanaway 1971 Table 17).

Slice #3: The mammillary bodies are clearly visible (reference atlas: Roberts and Hanaway 1971 Table 17). Note also the size of the caudate nucleus. The thalamus is well resolved.

Slice #4: Note the merger of the mammillary bodies of the hypothalamus (reference atlas: Roberts and Hanaway 1971 Table 19), the globus pallidus, and the putamen. The lateral profile of the thalamus presents a small partial volume effect.

Slice #5: Note the mammillothalamic tract (reference atlas: Roberts and Hanaway 1971 Table 19; Duvernoy 1991 page 125).

Slice #6: Note the interpeduncular fossa and the appearance of the mammillothalamic tract (reference atlas: Roberts and Hanaway 1971 Table 19; Duvernoy 1991 page 125. See also Duvernoy 1991 page 126 and Roberts and Hanaway 1971 Table 21).

Slice #7: On slice #14, note the globus pallidus on left subject (reference atlas: Roberts and Hanaway 1971 Table 21).

Slice #8: On slice #13, note the extension of the interpeduncular fossa.

Slice #9: The medial lemniscus (ML) is clearly evident (reference atlas: Duvernoy 1991 pages 133, 131; Roberts and Hanaway 1971 Table 23), as are the zona incerta hypothalami (reference atlas: Duvernoy 1991 pages 123, 125, 127, 129), the subthalamic nucleus (Duvernoy 1991 pages 123, 128), the crus cerebri (Duvernoy 1991 page 127), and the putamen (reference atlas: Roberts and Hanaway 1971 Table 23; Duvernoy 1991 page 128). The contour of the thalamus appears well resolved; there is a modest partial volume effect. The lateral geniculate nuclei (LGN) is not visible anymore; the optic tract appears (reference atlas: Roberts and Hanaway 1971 Tables 23, 21; Duvernoy 1991 pages 121, 129). Note the volume of the massa intermedia.

Slice #10: The brain stem is clearly evident, as is the ML (reference atlas: Duvernoy 1991 pages 133, 131; Roberts and Hanaway 1971 Table 23). Note also the substantia nigra lateral to the red nucleus (reference atlas: Roberts and Hanaway 1971 Tables 23, 21), the interpeduncular fossa (Roberts and Hanaway 1971 Table 28), and the putamen (reference atlas: Roberts and Hanaway 1971 Table 23; Duvernoy 1991 page 128).

Slice #11: Note the massa intermedia of the thalamus (“interthalamic adhesion”) (reference atlas: Roberts and Hanaway 1971 Table 21). The interpeduncular fossa is just visible (reference atlas: Roberts and Hanaway 1971 Tables 23, 21). Within the thalamus, the dorsomedial nucleus (DMN) appears; the white matter can be seen that separates the main body of the thalamus from the LGN. Note also the red nucleus (reference atlas: Duvernoy 1991 pages 132, 130; Roberts and Hanaway 1971 Table 28), the

myelinated medial longitudinal bundle in the brain stem (MLB) (reference atlas: Roberts and Hanaway 1971 Tables 23, 25), the ML (reference atlas: Roberts and Hanaway 1971 Tables 23, 25; Duvernoy 1991 pages 133, 131), and the substantia nigra (Roberts and Hanaway 1971 Table 23). See also De Armond et al 1989 page 110.

Slice #12: Note the DMN, the stria medullaris of the thalamus, and the putamen (reference atlas: Duvernoy 1991 pages 130, 132; Haines 1991 page 129). The lateral and inferior limit of the thalamus can be seen. In this slice, MLB emerges bilaterally in the brain stem (reference atlas: Roberts and Hanaway 1971 Table 25). The profile of the medial geniculate nuclei (MGN) in the background of the cerebrospinal fluid (CSF) is not visible anymore (reference atlas: Duvernoy 1991 pages 132, 236). It is important to try to locate the subthalamic nucleus (reference atlas: Roberts and Hanaway 1971 Table 23).

Slice #13: Note the silhouette of the third ventricle, the stria medullaris of the thalamus, the cerebral peduncles, and the hippocampus (reference atlas: Duvernoy 1991 page 236). The DMN is now clearly evident; the putamen is evident on the left subject. To delineate the brain stem from the thalamus (when the habenula is not visible) it is necessary to draw a line from the hypothalamic sulci of the third ventricle to the deepest indentation of CSF, ventrally and medially to the MGN (reference atlas: Duvernoy 1991 page 187).

Slice #14: To delineate the thalamus from white matter, we decided to include arbitrarily, but systematically 50% of the partial volume visible on the lateral contour of the thalamus. Moreover, several anatomical atlases were comparatively used as a reference for the segmentation of this area (atlases: Duvernoy 1991 pages 141, 148, 240; Roberts and Hanaway 1971 Table 25). Note the DMN and the brain stem closing on the gap between the two thalami to form the third ventricle.

Slice #15: Note the LGN, the MGN, the DMN, the habenula, and the posterior commissure (reference atlas: Duvernoy 1991 pages 140, 142, 240). To resolve the brain stem from the thalamus at this level it is necessary to draw a line dorsally from the habenula to the deepest indentation of the CSF, ventrally and medially to MGN. The lateral limit is marked by the internal capsule.

Slice #16: Note the aqueduct and the periaqueductal gray matter, and the clear presence of LGN and MGB as ventral bumps on the pulvinar (reference atlas: Duvernoy 1991 page 243; Haines 1991 page 125; Roberts and Hanaway 1971 Table 27).

Slice #17: The brain stem is clearly delineated from the pulvinar. Note the fourth ventricle, the aqueduct, and the hippocampal sulcus. Boundaries were: laterally, temporal stem; ventrally, CSF.

Slice #18: Note the fourth ventricle and the pineal gland (slightly visible in the background of the CSF of the cistern of the great cerebral vein). The pulvinar appears ball-shaped (reference atlas: Roberts and Hanaway 1971 Table 29).

Slice #19: Note that the superior and inferior colliculi appear as bilateral globes. The pulvinar does not appear clearly along with the tail of the caudate nucleus (reference atlas: Duvernoy 1991 page 146; Roberts and Hanaway 1971 Table 29).

Slice #20: Boundaries are: dorsally, the lateral ventricles; ventrally, the cistern of the great cerebral vein; laterally, temporal stem; medially, CSF (reference atlas: Duvernoy 1991 page 146). Note also the superior colliculi. The pulvinar again, as in the previous slice, appears now as a rounded structure separated from the parahippocampal gyrus by the CSF of the cistern of the great cerebral vein.

Slice #21: A small portion of the pulvinar appears between the crus fornix and the CSF of the cistern of the great cerebral vein (also called superior cistern) (reference atlas: Duvernoy 1991 pages 146, 148, 244). The crus fornix and the splenium of the corpus callosum cross diagonally. Note also the lateral ventricles, the cistern of the great cerebral vein, the hippocampus, the parahippocampal gyrus, and the temporal stem.