Thalamic and Prefrontal FDG Uptake in Never Medicated Patients With Schizophrenia

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Objective: Because neuroleptic treatment may cause long-lasting changes in brain structure and function, a group of patients with schizophrenia who had never been medicated was recruited to examine regional glucose metabolic rates in the frontal-striato-thalamic circuit.

Method: Twelve never medicated patients with schizophrenia (seven men, five women; mean age=29 years) and 13 normal volunteers (eight men and five women; mean age=28.5 years) underwent 18F-fluorodeoxyglucose (FDG) positron emission tomography, and coregistered anatomical magnetic resonance imaging scans were also obtained. During FDG uptake, subjects performed a spatial attention task previously shown to activate the pulvinar region of the thalamus.

Results: Diminished regional glucose metabolism was found in the medial dorsal nucleus, posterior thalamus, and prefrontal cortex of patients with schizophrenia relative to normal volunteers, extending earlier results from studies of medicated and previously medicated patients.

Conclusions: The finding of lower relative metabolic rates in the frontothalamic circuits of patients with schizophrenia is consistent with extended circuit deficits involving interactions of frontal executive areas with thalamic sensory and association processes.

The prefrontal cortex, striatum, and thalamus form a neural circuit important in regulating sensory input, attention, and action. Deficits in these three areas in schizophrenia have been widely reported in both structural (1) and functional (2) brain imaging studies. The thalamus comprises multiple nuclei that relay and filter sensory and higher-order inputs to and from the cerebral cortex and limbic structures. Thus, it is a candidate structure for abnormality in schizophrenia, a disease that includes disturbed sensory and attentional function (3). Especially important within the thalamus may be the medial dorsal nucleus (with its interconnections with the prefrontal cortex) and the pulvinar (also interconnected with frontal and temporal regions). Both nuclei interact with the cortex in high-level cognitive activity and have been found to have reduced volumes in schizophrenia in postmortem as well as magnetic resonance imaging (MRI) studies (4–6).

In our earliest positron emission tomography (PET) studies, which used 18F-fluorodeoxyglucose (FDG) and employed older-generation PET scanners with lesser in-plane resolutions of 15 mm (7) or 7.5 mm (8), we did not find decreased metabolic rates in the thalamus of unmedicated (previously medicated) schizophrenia patients compared with healthy subjects. In a study of never medicated schizophrenia subjects, we found less prominent regional glucose metabolic rate (rGMR) in the mediodorsal nucleus region (6). In another study of never medicated patients (9), blood flow decreases in the thalamus, frontal lobe, and temporal lobe were identified. With increased spatial PET resolution and coregistered structural MRI (1.2-mm thick slices) scans obtained for the entire thalamic volume, lower rGMR in the medial dorsal nucleus of unmedicated schizophrenia patients relative to healthy subjects was statistically confirmed, although whole thalamus metabolism did not differ between groups (10). However, when the nuclei were traced on coregistered MRI templates, decreased metabolic rates in the medial dorsal and centromedian nuclei (11), but not the pulvinar, were confirmed. Decreased rGMR in the remainder of the thalamus was again not found, indicating specificity of the effect to the medial association regions. That study, while large (61 normal subjects and 40 patients), was limited in having patients who, although unmedicated, had previously been treated with neuroleptics, which might have affected thalamic volume and rGMR. In addition, the uptake condition was the serial verbal learning task, which activates the frontal lobe but is not known to activate the pulvinar.

In the current study we selected a specific task known to activate the pulvinar (12) for the uptake condition and recruited patients who had never been medicated. We have undertaken two separate, independent coregistration methods to replicate thalamic effects and used internal brain fiducial landmarks to assess coregistration accuracy and alignment in the 12-point affine transformation to standard space.
**Table 1. Clinical Characteristics of a Group of Never Medicated Patients With Schizophrenia Recruited for a PET Study of Regional Glucose Metabolism in the Fronto-Striato-Thalamic Circuit**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Schizophrenia Patients (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary DSM-IV diagnosis</strong></td>
<td>N</td>
</tr>
<tr>
<td>Schizophrenia, paranoid type</td>
<td>4</td>
</tr>
<tr>
<td>Schizophrenia, undifferentiated type&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>2</td>
</tr>
<tr>
<td>Schizophreniform disorder&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Psychotic disorder not otherwise specified</td>
<td>1</td>
</tr>
<tr>
<td><strong>Secondary DSM-IV diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Schizotypal personality disorder</td>
<td>1</td>
</tr>
<tr>
<td><strong>Mean SD</strong></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (weeks [median=26])</td>
<td>183.284</td>
</tr>
<tr>
<td>BPRS total score</td>
<td>51.5</td>
</tr>
<tr>
<td>GAF score (past month)</td>
<td>29.5</td>
</tr>
<tr>
<td><strong>Comprehensive Assessment of Symptoms and History&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td></td>
</tr>
<tr>
<td>Delusions</td>
<td>3.8</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2.1</td>
</tr>
<tr>
<td>Bizarre behavior</td>
<td>2.2</td>
</tr>
<tr>
<td>Formal thought disorder</td>
<td>1.3</td>
</tr>
<tr>
<td>Catatonia</td>
<td>0.4</td>
</tr>
<tr>
<td>Alogia</td>
<td>1.4</td>
</tr>
<tr>
<td>Affective flattening</td>
<td>1.2</td>
</tr>
<tr>
<td>Inappropriate affect</td>
<td>1.1</td>
</tr>
<tr>
<td>Avolition/apathy</td>
<td>2.3</td>
</tr>
<tr>
<td>Anhedonia/asociability</td>
<td>2.6</td>
</tr>
<tr>
<td>Attentional impairment</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Abnormal Involuntary Movement Scale score&lt;sup&gt;e&lt;/sup&gt;</strong></td>
<td>1.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Two subjects initially diagnosed as schizophreniform were determined at follow-up to have schizophrenia.

<sup>b</sup>Symptoms had fully remitted within 6 months but patient continued to receive antipsychotic medication.

<sup>c</sup>Subject had consumed no alcohol in the week preceding the study evaluations; no evidence of alcohol withdrawal syndrome or clinical instability was noted as a result of alcohol abstinence; criteria for alcohol dependence were not met.

<sup>d</sup>Dimensions rated on a 0–5 scale, with 0=mild, 1=moderate, 2=moderate, 4=marked, and 5=severe.

<sup>e</sup>For the two patients with scores >0.

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**Method**

**Subjects**

A group of 12 psychotic patients (seven men and five women; mean age=29.0 years [SD=9.8, range=20–46]) was recruited from the greater Dayton, Ohio, area and was evenly divided between inpatients and outpatients. After complete description of the study, all subjects completed a verbal “informed consent post test.” All participants went through this test and gave written informed consent. Subjects were evaluated with the Comprehensive Assessment of Symptoms and History (13), 18-item version of the Brief Psychiatric Rating Scale (BPRS) (14), and the Abnormal Involuntary Movement Scale (AIMS) (15) and were given their diagnosis by a psychiatrist (D.S.L.) who used DSM-IV criteria. Patients had either never been medicated (N=11) or almost never medicated (one subject had a lifetime neuroleptic exposure of no more than five doses several years before this study evaluation). Subject characteristics are summarized in Table 1. Following study evaluation, all subjects were immediately referred for psychiatric treatment.

Thirteen healthy comparison subjects (eight men and five women; mean age=28.5 years [SD=8.0, range=19–41]) were age- and sex-matched to the experimental subjects. Informed consent was obtained as described earlier. Comparison subjects were assessed by a psychiatrist (D.S.L.). Participating subjects had no history of psychiatric illness, substance use disorder, clinically significant head trauma, or active neurological disease. Comparison subjects did not significantly differ from ill subjects with respect to race (all but three healthy subjects and one schizophrenia patient were white), handedness (all but one healthy subject were right-handed), years of education (mean=14.5 [SD=2.2] and 13.7 [SD=2.4], respectively), or family-of-origin socioeconomic status (mean Hollingshead Two-Factor Index of Social Position [16] score=34.6 [SD=7.0] and 31.3 [SD=19.9]).

All subjects fasted for at least 4 hours before reporting to the PET department. Blood glucose determination was performed before FDG administration, and all subjects had a normal blood glucose level (healthy subjects: mean=83.9 mg/dl [SD=8.8, range=66–98]; schizophrenia patients: mean=86.5 mg/dl [SD=8.2, range=74–100]).

**PET Scans**

FDG was administered intravenously (mean=7.8 mCi, SD=0.6). Emission scanning commenced 40 minutes following the injection of FDG. The data were acquired with an ECAT EXACT HR+ PET scanner in three-dimensional mode (17). Subjects were positioned in the PET camera with the canthomeatal line parallel to the in-plane field of view. Before acquisition of the FDG data, a 68Ge/68Ga transmission scan was acquired for 5 minutes to correct for the attenuation of radiation. A single emission scan of 20 minutes’ duration was acquired. The data were reconstructed by using ECAT version 7.2 software implementation of filtered back-projection (4-mm Hann filter) with a pixel size of 1.84×1.84×2.4 mm. The average interval between FDG injection and commencement of PET scanning was 45.04 minutes (SD=1.51), with no difference between healthy subjects (mean=44.64 minutes [SD=1.39, range=40–46]) and schizophrenia patients (mean=45.55 minutes [SD=1.57, range=44–50]).

**MRI Scans**

1<sup>T</sup>-weighted axial MRI scans were acquired with the GE Signa 5x system (General Electric, Milwaukee) (TR=24 msec, TE=5 msec, flip angle=40°, slice thickness=1.2 mm, pixel matrix=256×256, field of view=23 cm, total slices=128). The interval between FDG PET and MRI scans averaged approximately 1 day for schizophrenia patients (mean=90.2 days, range=0–3) and 2 weeks for comparison subjects (mean=13.6 days, range=3–70).

**Uptake Condition**

During the 40-minute FDG uptake period, all subjects carried out a visual attention task that required separation of target stimuli from competing surroundings as in our earlier PET study (12). Subjects visually fixated upon a dot corresponding to the center of the screen then looked at stimuli positioned horizontally at 2° to the right or to the left of the central fixation point. The target stimulus (the letter O) either appeared alone as an upper-case character or as a lower-case character surrounded by eight other letters (Figure 1). In half of the trials, the letter C or the digit zero (0) were presented as distracters. The subject’s task was to click on the mouse each time he detected the letter O either alone or surrounded by small letters, ignoring the C and the 0, and to press on the right button for a right-sided target and the left button for a left-sided target. The overall size of the stimuli was controlled so that the big letters were of the same dimensions as the pattern of small letters surrounded by flankers (i.e., each stimulus display was 19×22 mm). Each display was flashed for 150 msec. There were four experimental runs, each 264 seconds in duration, with a brief rest interval of 24 seconds between each session. Each run began with a 24-second period of blank screen followed by a block of 12 display stimuli, eight of one type and four drawn at

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**References**

1. Hollingshead Two-Factor Index of Social Position
2. BPRS total score
3. GAF score (past month)
4. Comprehensive Assessment of Symptoms and History
5. Abnormal Involuntary Movement Scale score
6. T1-weighted axial MRI scans
7. FDG uptake period
8. Visual attention task
9. Target stimulus
10. Distracters
11. Uptake condition
12. Previous PET study
were adjacent to the medial dorsal nucleus. The medial dorsal nucleus for MRI (from low values in gray to high values in white) and 2) they rapidly change in values along a unidimensional column of pixels between the two halves of the posterior thalamus along the y=–24 level (z=12 because it was close to the center of the medial dorsal nucleus bounding box in the Talairach atlas at this location at y=–44. The midline was found on the MRI at x=0 in 62% and an error of one pixel on either side (~2 or 2) in 92%. The midpoint was found on PET at x=0 in 38% and within an error of one pixel on either side in 100%. The differences in distance between the location of maximum first derivative points on MRI and PET were 0 pixels for 53% of subjects and within one pixel error for 71%. The anterior cingulate landmark was somewhat more variable anatomically with a mean of 26.7, 71% of subjects within the one pixel error, and the Talairach atlas position y=30. The differences between the location of maximum first derivative points between MRI and FDG were 0 for 53% and within one pixel for 85%. Thus, the combined error of brain standardization and coregistration (PET locations) was within one pixel (2 mm) in 80–90% of landmark examinations and adequate for regional examination of the thalamus. This compares favorably with the typical width of the medial dorsal nucleus, 6–8 mm. For comparison, the thalamus is 21 mm wide (x) and 30 mm long (y) at this level, a median dorsal nucleus bounding box in the Talairach atlas at this level (z=12) would be 9 mm in the x dimension and 13 mm in the y dimension.

The thalamus and medial dorsal nucleus were also assessed using a stereotaxic region of interest atlas approach for confirmation (21). This method has stored coordinates for MNI brain structures including the thalamus and the medial dorsal nucleus. Last, one of the authors (E.M.K.) traced the whole thalamus, medial dorsal nucleus, and pulvinar on raw unresliced MRI templates exactly as previously reported (4, 5). FDG images were coregistered to these anatomical images as before. Relative meta-

FIGURE 1. Stimulus Display Elements of the Visual Attention Task Given to Subjects During FDG Uptake

Data Analysis

Significance probability maps of the datasets were created using two complementary methods, statistical parametric mapping software (SPM) (18) and the FMRIB Software Library (FSL), version 5.00 (www.fmrib.ox.ac.uk/fsl). We chose SPM2 to survey the entire smoothed brain and FSL with our own R programs to evaluate the primary brain region, the thalamus with unsmoothed MRI template coregistered images. For SPM2, the FDG images were first spatially normalized to the FDG template defined with the SPM 99 software (and subsequently converted for SPM2) using the default parameters for spatial normalization, adjustment for whole brain metabolic rate by covariance, and 8-mm smoothing. Both SPM and FSL data are unitless. The normalized images were then closely inspected to ensure proper alignment. A schizophrenia and healthy group comparison was made by using the two-sample t test criterion. The t test results were then displayed on the FDG template. For closer examination of the thalamus, we used FSL processing. MRI anatomical images had the brain extracted from the skull with the Brain Extraction Tool (19) and were placed in standard position (anterior and posterior commissures in the same plane, midline x=0, vertical level z=0) using a 6-parameter transform. No images were smoothed by filtering using the FSL method. The FDG images were coregistered to each individual’s anatomical image again with the 6-parameter transform and the FMRIB Linear Image Registration Tool (20). Next, each person’s MRI anatomical images were transformed to Montreal Neurological Institute (MNI) coordinates with a 12-point transformation and the transformation matrix used to similarly transform the unsmoothed FDG images, which were then divided by the whole brain average metabolic rate. The FDG images then had pixel-by-pixel t tests computed using our own program in the R computer language (http://www.r-project.org). Since we had already reported medial dorsal nucleus FDG decreases in two earlier and entirely independent samples (11), both predicting the finding in advance of SPM application, images were thresholded at p<0.05. This provides an alternate coregistration method unbiased by systematic group differences in brain rGMR, since the FDG itself did not enter the coregistration transformations. The FDG data was unsmoothed (in the FSL analysis) for maximum spatial resolution in a priori hypothesis testing. While SPM maps are typically corrected for multiple comparisons because of their exploratory nature, this analysis was confirmatory of our earlier FDG studies and neuroanatomical studies of the medial dorsal nucleus.

We examined the quality of the FMRIB Linear Image Registration Tool coregistration and standardization to MNI space on the final MNI FDG and anatomical images. We chose the horizontal slice at z=12 because it was close to the center of the median dorsal nucleus. Three regions were chosen as internal fiducial marks: 1) along the x=0 midline, the transition from the gray matter of the posterior cingulate (Brodman’s areas 29, 30) to the white matter of the corpus callosum; 2) along the x=–4 anteroposterior line, the transition from the gray matter of areas 24 and 32 to the white matter or the genu of the corpus callosum; and 3) the fluid space between the two halves of the posterior thalamus along the y=–24 line. These landmarks were chosen because 1) there would be a rapid change in values along a unidimensional column of pixels for both PET (from high values in gray to low values in white) and for MRI (from low values in gray to high values in white) and 2) they were adjacent to the medial dorsal nucleus. The medial dorsal nu-

random from the other three types to maintain expectancy. The four display types were large letter in 1) left or 2) right hemifield and small letter with flankers in 3) left or 4) right hemifield. The order of runs was counterbalanced across subjects. The subjects were signaled with a blue flash in case of a miss or an error. Subjects were trained before FDG administration.
Results

SPM Mapping

Patients with schizophrenia had lower relative metabolic rates in the thalamus and lateral prefrontal cortex, especially at the orbitofrontal levels (Figure 2). A significant reduction in metabolic rate was also noted in additional cortical areas, including the insula, temporal lobes, parietal lobe (Brodmann's area 39), and the anterior cingulate at its most dorsal level (Brodmann's area 24) (22). The posterior putamen was also less active in ill subjects. The centers of the thalamic regions were at −6, −16, 8 and at 6, −16, 8 (total volume=297 voxels, $Z_{\text{max}}=2.37$ and 2.32, respectively).

Pixel-by-Pixel Examination of the Thalamus

Coregistration is illustrated in Figure 3, and detailed examination of Talairach $z=12$ slice in Figure 4. The red area in Figure 4 indicates pixels where the healthy subjects have higher relative metabolic rates than patients with schizophrenia ($p<0.05$, two-tailed), which extends across the region of the medial dorsal nucleus and pulvinar.

Stereotaxic Region-of-Interest Examination of the Thalamus

The medial dorsal nucleus had a relative metabolic rate significantly higher in healthy volunteers (mean=11.8, SD=0.64) than patients with schizophrenia (mean=11.2, SD=0.64) ($t=2.88$, df=23, $p=0.008$). The whole thalamus did not differ between normal subjects and patients (mean=10.0 [SD=0.43] and 9.7 [SD=0.49], respectively). Repeated measures two-way analysis of variance (ANOVA) with whole thalamus and medial dorsal nucleus for the right and left hemisphere revealed a significant diagnostic group difference ($F=6.66$, df=1, 23, $p<0.02$) and a significant interaction between group and region of interest (whole thalamus, medial dorsal nucleus alone) ($F=6.45$, df=1, 23, $p<0.02$), indicating that the metabolic group difference effect for the medial dorsal nucleus was significantly greater than for the whole thalamus. There was no significant diagnostic group-by-hemisphere or diagnostic group-by-hemisphere-by-structure interaction.

MRI Template-Traced Nuclei

A lower metabolic rate in the medial dorsal nucleus for patients with schizophrenia (mean=2.59, SD=0.29) versus healthy subjects (mean=2.76, SD=0.28) was confirmed ($F=4.62$, df=1, 18, $p<0.05$), and this was specific to the medial dorsal region when compared with the remainder of the thalamus in a three-way ANOVA (diagnostic group [healthy, schizophrenia] by structure [medial dorsal, remainder of thalamus] by hemisphere [right, left]), with a significant group-by-structure interaction ($F=5.51$, df=1,
It is of interest that all subjects except one schizophrenia patient had higher relative values in the medial dorsal nucleus than in the remainder of the thalamus. While the relative metabolic rate was lower in the pulvinar in patients with schizophrenia, this difference did not reach statistical significance. The correlation between the stereotaxic medial dorsal nucleus and the traced medial dorsal nucleus was 0.51.

**Task Performance**

All healthy subjects and all but one patient performed the task above chance levels and completed responses in every trial block during the uptake period. Removal of the one schizophrenia subject who did not perform the task did not alter the significance of the group comparison t test on the medial dorsal nucleus (t=2.31, df=22, p=0.03) or the diagnostic group difference with ANOVA (F=4.32, df=1, 22, p<0.05).

**Discussion**

Our results confirm earlier studies that reported relative metabolic rate reduction in the thalamus and lateral prefrontal cortex in patients with schizophrenia, extending those findings in several important ways. We have demonstrated these findings in a group of never medicated patients, indicating that these reductions could not be due to medication artifacts. Further, the use of an uptake condition demonstrated to have thalamic activation in earlier PET studies enhances the strength of the conclusions. Replicating the results with methodologically complementary pixel-by-pixel t test methods and traced templates allows both whole-brain exploration and the specific regions to be exhaustively tested. These specific methodological steps appear to have enhanced the power of the FDG PET images to confirm group differences in comparison with some earlier studies that used medicated patients, an eyes-closed resting condition, or lower-resolution image acquisition.

The limitations of our present study include the relatively modest number of never medicated subjects, image resolution and coregistration quality, and the use of relative metabolic rates. While somewhat smaller than two earlier studies of never medicated patients (6, 9), we had adequate power to detect differences in thalamic rGMR. Methods are currently being explored to overcome image resolution limitations by applying a partial volume correction to the image data. However, this correction has not been fully validated and has the potential to introduce a large bias into the analysis (23, 24). With a structure as small as the thalamus or medial dorsal nucleus (6–9 mm wide), image coregistration and the quality of structure position standardization are critical. We evaluated joint error in our examination of FDG image coordinates and found that about 75% of subjects’ FDG landmarks adjacent to the medial dorsal nucleus lay within one 2-mm pixel of a standard location and of the matching MRI template. Last, we thresholded the significance probability images at the p<0.05 level without correction. This lacks correction for multiple t testing, but since the study was focused specifically on the medial dorsal region (the relative metabolic rate of which was previously reported to be reduced [11]), and the dorsolateral prefrontal cortex was previously explored with significance probability mapping (25), it seemed appropriate to consider the maps as confirmatory rather than exploratory. The medial dorsal region selected a priori and assessed using stereotaxic position also yielded a p=0.0083 probability (0.0041 one-tailed in replication). While absolute metabolic rates for the medial dorsal nucleus could have been obtained with the FDG method, there is no evidence that total brain metabolic rate differs between normal subjects and patients with schizophrenia. Thus the small regions of thalamic and prefrontal metabolism reductions seen in Figure 2 seem unlikely to have artifactually arisen on the basis of other large areas of cortical metabolic rate shifts.

One might argue that patients with schizophrenia lacked motivation to perform the task and that differences in the

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**FIGURE 3. MNI Spatial Normalization and Coregistration With Fusion Image**

[Image of brain scans]
medial dorsal nucleus were an indirect artifact of diminished involvement in successful task performance, rather than an indication of primary regional pathology. Against this is the fact that all but one patient participated in the task and performed well above chance levels (results were unchanged after omission of the one nonperforming patient). Further, motivational areas (Brodmann’s areas 11, 12) and vigilance areas (Brodmann’s area 32) did not show significant decrease or increase, suggesting that failure in non-specific task engagement regions is not entirely responsible for the medial dorsal nucleus deficit. It is interesting that patients with obsessive-compulsive disorder may have higher blood flow in their thalamus (26). Thus, potential reciprocal interactions between attention (medial dorsal nucleus) and motivation (orbital and medial prefrontal cortex), the impairment of which is a central feature of the schizophrenia syndrome, cannot be ruled out.

Our use of unmedicated and previously untreated patients is important in relating the findings to schizophrenia rather than medication effects. Studies have reported decreases in relative metabolic rate in the frontal lobe with clozapine (27) and haloperidol (28) but not with risperidone (29), so the use of unmedicated patients is especially important for establishing this finding. It is interesting that patients with higher dorsolateral prefrontal metabolic rates were reported likely to respond to clozapine (30).

Other studies have also confirmed reduced thalamic FDG uptake in schizophrenia (31, 32) (reviewed elsewhere [11]). Last, using functional MRI (fMRI), reduced activation in the thalamus has been observed. The anterior thalamic region as well as the medial and anterior frontal lobe had reduced fMRI blood oxygenation level-dependent activation in medicated patients with schizophrenia during the continuous performance test of vigilance (33), both areas adjacent to but not exactly overlapping with our regions. Less thalamic activation in schizophrenia was also seen in other fMRI studies (34). However, significant thalamic activation was observed in medicated patients with schizophrenia but not in normal subjects during performance of the Sternberg memory task (35), although apparently no direct map of group differences in activation was presented.

Examination of the pixel-by-pixel maps indicates that medial and posterior portions of the thalamus appear to be the main regions of the thalamus with decreased metabolic rates. The thalamus comprises multiple nuclei that relay and filter sensory and higher-order inputs to and from the cerebral cortex and limbic structures (3). The biggest thalamic substructures, the medial dorsal nucleus and the pulvinar (both visible on MRI), are of particular interest in attention because of their reciprocal connections with the prefrontal and temporal regions and because their size and metabolic rate appear diminished in imaging studies of patients with schizophrenia. The medial dorsal nucleus has strong interconnections with the dorsolateral prefrontal cortex (36), and the connections of the medial dorsal nucleus have been used to define the prefrontal cortex (37), a key area of executive action and focusing of attention thought to be defective in schizophrenia (reviewed by Buchsbaum and Hazlett [2]). Crosson (38) suggests the medial dorsal nucleus as a critical element in an attentional “selective engagement” system that impacts semantic functions in schizophrenia.

It should be noted that the use of never medicated patients may be especially important in establishing regional metabolic differences in the thalamus and that even thalamic volume may be affected by neuroleptics (39). The recent report of decreased thalamic D2 receptor binding in the medial portion of the thalamus in drug-naïve patients with schizophrenia (40) indicates that both chronic and acute medication effects could influence thalamic metabolic rate. That important study not only supports a role for the medial thalamus in schizophrenia but also sug-
gests that the medial regions of the thalamus are potentially informative for understanding medication effects as well.

Until the mid-1970s it was thought that the prefrontal cortex received its thalamic input solely from the medial dorsal nucleus; however, it is now apparent that the pulvinar also contributes to its innervation (41, 42). The pulvinar, important in visual and possibly auditory attention (43–45), also has prominent interconnections with the parietal and temporal lobe. The current findings of decreased metabolic rate in the medial and posterior regions of the thalamus, prefrontal cortex, and posterior temporal and parietal regions tend to confirm a network of frontothalamic and parieto-temporal-thalamic rGMR concurrently diminished in patients carrying out a task demonstrated to activate the pulvinar (12).

Much work in the field of visual neurophysiology suggests that the pulvinar signals the importance or relevance of stimuli that fall inside classically defined visual receptive fields (43). Neurophysiological studies in animals have found that neurons of the pulvinar respond specifically to stimuli to be the target of a saccade (46). These findings suggest that the pulvinar may play a role in “visual salience,” that is, the attention-related selection of a target (44), and “directed attention” (12). The anatomy and projections of the pulvinar suggest functional cortical-thalamic-cortical loops involved in a variety of functions including salience, attention, and working memory (43). The fact that both the medial dorsal nucleus and the pulvinar express D2 type dopamine receptors (40), together with their demonstrated role in selective attention, fits well with recent formulations of schizophrenia as a hyperdopaminergic state that leads to an aberrant assignment of salience to elements of one's experience (47). According to that model, both typical and atypical antipsychotics “dampen the salience” of abnormal experiences via blockade of D2 receptors and by doing so, allow the resolution of symptoms.

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Major support was provided by Wallace-Kettering Neuroscience Institute. Use of imaging resources supported by the United States Air Force, Air Force Research Laboratory (AFRL/HEOP), Air Force Materiel Command, under cooperative agreement F33615-98-2-6002.

The authors thank Tonya Perkins, Marilyn Brackney, Kelly Dunigan, Kerry Kovacs, Yuliya Lelchuk, and Drs. Jogesh Mukherjee, Martin Satter, and Kingwai Chu for technical assistance. The authors also thank Drs. Bing Shi, T.K. Narayanann, and Steve Mattmuller for radiopharmaceutical production.

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