Reduced Number of Mediodorsal and Anterior Thalamic Neurons in Schizophrenia

Keith A. Young, Kebreten F. Manaye, Chang-Lin Liang, Paul B. Hicks, and Dwight C. German

Background: The thalamus is a brain region of interest in the study of schizophrenia because it provides critical input to brain regions such as the prefrontal, cingulate, and temporal cortices, where abnormalities have been repeatedly observed in patients with schizophrenia. Post-mortem anatomic studies have rarely investigated the thalamus in this population.

Methods: Postmortem tissue was obtained from the left hemisphere of eight male schizophrenic patients and eight male age-matched control subjects. The optical dissector stereologic procedure was used to count neurons in the mediodorsal (MD) and anteroventral/anteromedial (AV/AM) nuclei of the thalamus.

Results: The number of neurons and volume of the MD were significantly reduced by 35% and 24%, respectively. The MD cell number reduction was a consistent finding; every control subject had more and every schizophrenic subject had fewer than 3.5 million neurons. Neuron number was also significantly reduced (16%) in the AV/AM nuclei.

Conclusions: The present data indicate that schizophrenia is associated with robust reductions in nerve cell numbers in nuclei that communicate with the prefrontal cortex and limbic system. These thalamic anatomic deficits may be responsible, in part, for previous reports of such prefrontal cortical abnormalities as reduced synaptic density, reduced volume, and metabolic hypofunction. Biol Psychiatry 2000;47:944–953 © 2000 Society of Biological Psychiatry

Key Words: Schizophrenia, postmortem brain, thalamus, mediodorsal nucleus, anterior nucleus, stereology

Introduction

Schizophrenia is a major mental illness that affects approximately one in every 100 people (Andreasen and Carpenter 1993). Individuals with schizophrenia exhibit a lack of motivation, abnormal thought content and process (e.g., delusions, paranoia, hallucinations and discontinuity of associations), and disturbance of emotion (i.e., inappropriate affect; Andreasen 1997a). Many schizophrenic patients also perform poorly on neuropsychologic tasks involving the frontal lobes and exhibit abnormal metabolic activity patterns in the prefrontal cortex (Berman et al 1986; Fletcher et al 1998; Weinberger and Gallhofer 1997) and anterior cingulate cortex (Haznadar et al 1997). Schizophrenic individuals who exhibit large numbers of errors of perseveration on the Wisconsin Card Sorting Test or who perform poorly on verbal working memory or sustained attention tests lack the normal pattern of metabolic activation in the dorsolateral prefrontal cortex (Goldberg et al 1994; Stevens et al 1998). Morphologic abnormalities in the dorsolateral prefrontal and anterior cingulate cortex have been identified as a possible anatomic basis for the behavioral and metabolic abnormalities of schizophrenia (Arnold and Trojanowski 1996; Buchanan et al 1998; Goldstein et al 1999; Rajkowska et al 1998; Selemon et al 1998).

The thalamus, which is an important source of subcortical input to the cortex, has become a recent focus of research in schizophrenia (Andreasen 1997b; Jones 1997a; Scheibel 1997). The majority of thalamic studies have utilized magnetic resonance imaging (MRI) (Andreasen et al 1994; Buchsbaum et al 1996; Gur et al 1998; Staal et al 1998). The data indicate that the thalamus of schizophrenic subjects is smaller than that of control subjects, although the magnitude of the volume reductions (10%) is relatively small. Quantitative postmortem morphologic studies, on the other hand, have found more substantial thalamic abnormalities in schizophrenic subjects. Using stereologic cell counting procedures, Pakkenberg (1990) reported a 40% reduction in the number of mediodorsal (MD) thalamic neurons in schizophrenic subjects, a finding apparently not related to neuroleptic treatment (Pak-
Considering the prominent frontal cortical deficits of schizophrenic individuals, an MD neuron number reduction is particularly intriguing because the MD is a major source of subcortical input to the frontal cortex (Giguere and Goldman-Rakic 1988; Ray and Price 1993). There have been few morphologic studies of the thalamus in subjects with schizophrenia. We expected our study to replicate the finding of Pakkenberg (1990), which described a reduction in the number of MD neurons, and also extend the examination of the thalamus by studying another thalamic region that projects to the limbic cortex, the anterior thalamic nuclei. The optical disector stereologic cell counting procedure was used to estimate the total number of neurons in control and schizophrenic postmortem brains. Neurons were counted in the MD nucleus, which projects to the dorsolateral prefrontal and orbitofrontal cortex, and the anteroventral-anteromedial (AV/AM) nuclei, which project to the cingulate and entorhinal cortex. We found robust reductions in the number of neurons in both the MD and AV/AM thalamus in schizophrenic subjects.

**Table 1. Specimen Characteristics**

<table>
<thead>
<tr>
<th>ID</th>
<th>Age&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TIF</th>
<th>PMI</th>
<th>Brain weight&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>76</td>
<td>12</td>
<td>6</td>
<td>1,440</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>B</td>
<td>75</td>
<td>84</td>
<td>9</td>
<td>1,300</td>
<td>Cancer</td>
</tr>
<tr>
<td>C</td>
<td>65</td>
<td>72</td>
<td>14</td>
<td>1,635</td>
<td>Aortic aneurysm</td>
</tr>
<tr>
<td>D</td>
<td>63</td>
<td>48</td>
<td>11</td>
<td>1,230</td>
<td>Congestive heart failure secondary to pneumonia</td>
</tr>
<tr>
<td>E</td>
<td>68</td>
<td>168</td>
<td>19</td>
<td>1,260</td>
<td>Congestive heart failure secondary to pneumonia</td>
</tr>
<tr>
<td>F</td>
<td>71</td>
<td>4</td>
<td>4</td>
<td>1,135</td>
<td>Pneumonia secondary to emphysema</td>
</tr>
<tr>
<td>G</td>
<td>65</td>
<td>84</td>
<td>30</td>
<td>1,270</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>H</td>
<td>40</td>
<td>22</td>
<td>36</td>
<td>1,600</td>
<td>Accident</td>
</tr>
<tr>
<td>I</td>
<td>94</td>
<td>7</td>
<td>8</td>
<td>1,100</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>J</td>
<td>45</td>
<td>48</td>
<td>11</td>
<td>1,400</td>
<td>Heart failure</td>
</tr>
<tr>
<td>K</td>
<td>59</td>
<td>12</td>
<td>14</td>
<td>1,490</td>
<td>Myocardial infarction secondary to lymphoma</td>
</tr>
<tr>
<td>L</td>
<td>60</td>
<td>168</td>
<td>6</td>
<td>1,500</td>
<td>Heart failure</td>
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<tr>
<td>M</td>
<td>60</td>
<td>168</td>
<td>8</td>
<td>1,430</td>
<td>Myocardial infarction</td>
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<tr>
<td>N</td>
<td>81</td>
<td>8</td>
<td>28</td>
<td>1,210</td>
<td>Congestive heart failure secondary to emphysema</td>
</tr>
<tr>
<td>O</td>
<td>72</td>
<td>8</td>
<td>30</td>
<td>1,620</td>
<td>Heart failure</td>
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<tr>
<td>P</td>
<td>48</td>
<td>24</td>
<td>18</td>
<td>1,660</td>
<td>Heart failure</td>
</tr>
</tbody>
</table>

TIF, time in formalin (months); PMI, postmortem interval (hours).
<sup>a</sup>Age in years.
<sup>b</sup>Brain weight in grams.

There have been few morphologic studies of the thalamus in subjects with schizophrenia. We expected our study to replicate the finding of Pakkenberg (1990), which described a reduction in the number of MD neurons, and also extend the examination of the thalamus by studying another thalamic region that projects to the limbic cortex, the anterior thalamic nuclei. The optical disector stereologic cell counting procedure was used to estimate the total number of neurons in control and schizophrenic postmortem brains. Neurons were counted in the MD nucleus, which projects to the dorsolateral prefrontal and orbitofrontal cortex, and the anteroventral-anteromedial (AV/AM) nuclei, which project to the cingulate and entorhinal cortex. We found robust reductions in the number of neurons in both the MD and AV/AM thalamus in schizophrenic subjects.

**Methods and Materials**

**Brains**

The left thalamus was obtained from eight male control subjects with no history of psychiatric disturbance and eight male schizophrenic subjects diagnosed according to DSM-IV criteria (Table 1). The Diagnostic Evaluation after Death was used to obtain postmortem diagnosis of schizophrenic subjects. The brains were obtained from Terrell State Hospital, the Waco VA Medical Center, and the Stanley Foundation Neuropathology Consortium. All brains were grossly normal at autopsy and there was no evidence of ischemic brain damage in the thalamus of any of the subjects. Neuropathologic examinations were available on 13 of the brains. There was no histopathologic evidence of neurodegenerative changes in the cortex or hippocampus of any of these brains. The schizophrenic patients were chronically treated with neuroleptic drugs until near the time of death. Schizophrenic and control groups did not differ significantly in age (schizophrenic group mean ± SD, 65.4 ± 11.3 years; control group, 64.9 ± 16.7 years), postmortem interval (schizophrenic group, 16.1 ± 11.5 hours; control group, 15.3 ± 9.2 hours), or time in formalin fixative (schizophrenic group, 16.1 ± 11.5 months; control group, 15.3 ± 9.2 months). One potential diagnostic confound in the present study was lack of information about the alcohol or drug abuse history in many of the subjects, particularly during adolescence and early adulthood.

**Histology**

Before sectioning the thalamus, the tissue block was immersed in a solution of 20% sucrose and 10% formalin for 2–3 weeks. A single block containing the entire left thalamus was serially sectioned in the coronal plane on a freezing microtome. Although the microtome thickness was set at 60 μm, the actual average distance advanced for each cut was measured to be 56 μm. After Nissl staining every 20th section with cresyl violet, the regional boundaries of the two thalamic nuclei (Jones 1997b) were delineated at low magnification with a 2.5× objective (Figure 1). The MD begins just caudal and ventral to the AV and ends at the level of the rostral pulvinar. Its medial border is near the lateral wall of the third ventricle except where it merges into the massa intermedia. It is bounded laterally by the fasciculus mammillo-thalamicus anteriorly and by the internal medullary lamina and centromedian nucleus posteriorly. The large
cells of the centrolateral nucleus clearly delineate the lateral boundary of the MD for most of its rostral-caudal extent. The densocellular portion of the MD was included. The lateral ventricle, fornix, anterior nuclei, and laterodorsal nucleus lie on its superior surface and are clearly recognizable. Most posteriorly, the inferior limit merges with the nucleus parafascicularis and centromedian nuclei. The external borders of the AV/AM nuclei are clearly demarcated. The nuclei are encapsulated by the white matter track of the internal medullary lamina; however, the border between the two nuclei often is difficult to identify in Nissl stained coronal sections. We therefore combined the AV nucleus with the AM nucleus to form a single region of interest (AV/AM) for cell counting purposes.

The tissue processing and staining procedures produced approximately 50% tissue shrinkage. The final Z-axis thickness in all specimens measured between 22 and 25 μm. Thus, we used a 5-μm upper guard zone, a 7–10-μm lower guard zone and a 10-μm-thick counting frame. The sampling coefficient of error (CE; Scheaffer et al 1996) was estimated with the StereoInvestigator software (version 1.3; MicroBrightField, Colchester, VT) providing a measure of the variance of the sampling procedure. The biological CE provides an estimate of the variability in neuron counts between specimens (Table 2). The CE estimates in the present study indicate that sampling variances for the MD and AV/AM regions were lower in magnitude than the inherent biological variance, indicating that the stereologic sampling parameters used in the study were sufficient to detect relatively small group differences between schizophrenic and control subjects.

**Stereology**

One of us (KFM), who was blinded to the identification of the brains, performed all stereologic procedures. Before the start of the experiment, a pilot study was performed to determine the

![Figure 1. Photomicrographs of Nissl-stained coronal sections of the thalamus in control case C. Frozen sections were cut at 60-μm thickness on a freezing microtome. After staining and coverslipping, the section thickness measured 22–25 μm. A dashed line delineates the boundaries of the anteroventral/anteromedial nuclei of the thalamus (AV/AM) at several different rostro-caudal levels. The AV/AM begins in section 141 and ends at the level of section 281. The mediodorsal nucleus of the thalamus (MD) begins at the level of section 241 and ends at the level of section 444. Also illustrated are the laterodorsal nucleus (LD) and the habenula (H). Four levels of the thalamus are illustrated spanning a distance of 18.18 mm, from rostral (section 141) to caudal (section 444). Marker bars, 1.0 mm.](image)
optimal counting procedures. Using a “counting frame” that measured 140 × 80 × 10 μm, we varied the number of counting frames (Figure 2) to identify from 100 to 600 neurons in several replicate counts of a set of nine sections through the MD in one case. The results indicated that counting 200–600 neurons produced similar estimates of total neuron number. We adjusted the number of counting frame placements used to count cells in the two nuclei based on this result. Outlines of each region of interest were digitized using StereoInvestigator software.

Nine to 11 sections were analyzed in each thalamic region. Using more than 100 counting frames systematically placed throughout the entire rostral-caudal extent of the nucleus, the average density of neurons in the counting frames was determined using a 25× oil immersion objective (N.A. 0.75). Neurons were identified as Nissl positive cell bodies containing a nucleolus that was clearly in focus within the counting frame (Figure 3). Thalamic nuclear volumes were calculated with Cavalieri’s estimate from areas calculated by the StereoInvestigator software using the outlined borders in each tissue section. The total number of neurons in each region was estimated by multiplying the average counting frame neuronal density and the calculated volume of the thalamic region of interest (cell number/μm³ × total nucleus volume [μm³] = estimated total cell number).

Statistics
A Student’s t test was used to compare cell number, nuclear volume, and neuron density between the schizophrenic group and control group. The p values reflect Bonferroni correction for two multiple comparisons. Analysis of covariance for age, postmortem interval, and time-in-formalin was performed with neuron number as the dependent variable.

Results
Total Cell Number
Anatomic changes were readily apparent in the MD and AV/AM of the schizophrenic group, the most prominent change being a marked reduction in the total number of neurons (Table 3). There was a mean of 4.15 million neurons in the MD from control subjects and a mean of 2.70 million neurons in the MD of schizophrenic subjects (t = 5.14, p < .001), a 35% reduction. In every control subject, the MD nucleus contained more than 3.5 million neurons; in every schizophrenic subject, it contained less (Figure 4). Values obtained in the current study for control MD neuron numbers are in agreement with two previously published values (Harding et al 1994; Xuereb et al 1991). Analysis of covariance was used to test for effects of several covariates on MD neuron number estimates. These included age [F(1,11) = 0.75, p > .4], time in formalin fixative [F(1,11) = 0.13, p > .7], and postmortem interval [F(1,11) = 0.4, p > .5]. The main effect of diagnosis remained significant after accounting for these covariates [F(1,11) = 24.7, p < .0004]. Neuron numbers were also reduced by an average of 16% in the AV/AM of schizophrenic subjects, from 807,000 to 674,000 (t = 2.91, p < .012). Unlike the MD, in the AV/AM there was overlap in the range of neurons for schizophrenic subjects and control subjects.

Nucleus Volume and Cell Density
We also tested for differences in nuclear volume and neuron density between schizophrenic and control subjects. In addition to a reduction in neuron number, there was a significant 24% reduction in the volume of the MD in schizophrenics (t = 3.73, p = .002; Table 3 and Figure 5). Although there was a 17% reduction in the volume of the AV/AM in the schizophrenic brains, the

Table 2. Stereologic Sampling Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MD</th>
<th>AV/AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling grid size (μm × 10³)</td>
<td>2.0 × 1.5</td>
<td>1.2 × 1.0</td>
</tr>
<tr>
<td>Mean # sections counted (± SD)</td>
<td>11.1 (1.0)</td>
<td>9.5 (1.4)</td>
</tr>
<tr>
<td>Mean # of neurons counted (± SD)</td>
<td>345 (101)</td>
<td>204 (33)</td>
</tr>
<tr>
<td>Sampling CE (Scheaffer et al 1996), neuron number</td>
<td>0.049</td>
<td>0.064</td>
</tr>
<tr>
<td>Sampling CE (Gunderson and Jensen 1987), neuron number</td>
<td>0.05</td>
<td>0.07</td>
</tr>
<tr>
<td>Biological CE, neuron number</td>
<td>0.064</td>
<td>0.054</td>
</tr>
</tbody>
</table>

MD, mediodorsal nucleus of the thalamus; AV/AM, anteroventral/anteromedial nuclei of the thalamus.

* For schizophrenic and control groups combined (n = 16).

* Estimated coefficient of error for the variance in sampling, given for a representative brain (Scheaffer et al 1996).

* Estimated coefficient of error for the variance in sampling, nugget corrected estimator, given for a representative brain (Gunderson and Jensen 1987).

* Coefficient of error for the between-subject variance of the control group = SEM/mean (n = 8).
difference between the schizophrenic group and the control group was not statistically significant ($t = 1.92, p = .077$). The MD was found in the same number of sections along the rostro-caudal length in schizophrenic group (11.25 ± 1.2 sections) and the control group (10.88 ± 0.9 sections; $t = 0.693, p = .49$). Similarly, the AV/AM was found in the same number of sections along the rostro-caudal length in schizophrenic brains (9.37 ± 1.8 sections) and control brains (9.62 ± 1.3 sections; $t = 0.283, p = .78$). Neuronal densities in both the MD and AV/AM nuclei were not significantly different in the two groups (Table 3); however, six of the eight schizophrenic subjects had lower MD neuron densities than each of the control subjects. There was no evidence for a neuron density reduction in the AV/AM because both subject groups had the same range of density values and virtually identical mean densities.

Table 3. Thalamic Neuron Number, Nuclear Volume, and Neuronal Density

<table>
<thead>
<tr>
<th></th>
<th>Neuron number</th>
<th>Volume</th>
<th>Neuronal density</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MD</td>
<td>AV/AM</td>
<td>MD</td>
</tr>
<tr>
<td></td>
<td>Number $10^6$ ± SD (n)</td>
<td>mm$^3$ ± SD (n)</td>
<td>Neurons/mm$^3$ ± SD (n)</td>
</tr>
<tr>
<td>Control group</td>
<td>4.15 ± 0.53 (8)</td>
<td>0.807 ± 0.101 (8)</td>
<td>248 ± 35 (8)</td>
</tr>
<tr>
<td>Schizophrenic group</td>
<td>2.70 ± 0.59 (8)</td>
<td>0.674 ± 0.071 (7)</td>
<td>188 ± 29 (8)</td>
</tr>
<tr>
<td>$t$ test</td>
<td>$p &lt; .001$</td>
<td>$p = .012$</td>
<td>$p = .002$</td>
</tr>
</tbody>
</table>

MD, mediodorsal nucleus of the thalamus; AV/AM, anteroventral/anteromedial nuclei of the thalamus.
Discussion

**Thalamic Neuron Number Reductions in Schizophrenia**

Our study clearly indicates that there is a marked reduction in the number of MD neurons in the postmortem schizophrenic brain. It represents the first replication of an initial report of a reduction in the number of MD neurons in schizophrenic subjects (Pakkenberg 1990). A striking observation of both our study and the earlier report (Pakkenberg 1990) is that there is virtually no overlap in the ranges of the MD neuron numbers between normal control subjects and schizophrenic subjects. In our experiment, each of the eight control subjects had more neurons than each of the 8 schizophrenic subjects, whereas in the Pakkenberg study, 11 of the 12 control subjects had more neurons than each of the 12 schizophrenic brains. These findings are also remarkable because of the magnitude of the MD neuron number reductions: on average more than one third of the normal complement of MD neurons is missing from the schizophrenic brain. The large magnitude of the deficit and the consistency of the reduction from patient to patient are uncommon in schizophrenia research, in which anatomic deficits are not found consistently in every patient (Arnold and Trojanowski 1996). The marked reduction in neuron number in the MD is arguably the most robust neuroanatomic deficit in schizophrenia research reported to date.

The number of MD neurons in normal subjects has been estimated to be approximately 4 million in two previous studies (Harding et al 1994; Xuereb et al 1991) and in our study; however, Pakkenberg (1990) reported that control brains have approximately 2 million MD neurons. This disparity is most likely due to differences in defining the borders of the MD (B. Pakkenberg, personal communication, August 1999). Thus, although both Pakkenberg (1990) and Xuereb et al (1991) used similar paraffin embedding tissue processing procedures, MD volumes in the Pakkenberg study were 50% smaller than in the Xuereb et al study.

Our study is the first to quantify the number of neurons in the anterior nucleus of the thalamus in the schizophrenic brain. Neuron numbers in the AV/AM were reduced by 16% on average. Unlike the MD, however, there was overlap between normal and control neuron numbers. These data suggest that AV/AM neuron number reductions may be present in only a subset of schizophrenic individuals, whereas MD reductions are more consistently found in the great majority of patients. It also has been reported that there is a reduction in parvalbumin-positive neurons in the AV nucleus of schizophrenic subjects (Danos et al 1998). It is interesting that the AV/AM is interconnected with medial temporal lobe (hippocampal) circuits of the limbic system, where many morphologic and functional abnormalities have been observed in schizophrenia (see Arnold and Trojanowski 1996 for review).

The thalamic neuron reductions so far revealed are present in nuclei providing input to prefrontal and temporolimbic cortex, in which anatomic deficits have been observed in postmortem and MRI studies. In a recent report, for example, Goldstein et al (1999) used MRI to
measure the volume of 48 separate regions of the cerebral cortex. The greatest volumetric reductions were observed in the middle frontal gyrus, frontoorbital cortex, the insula and the anterior cingulate cortex. The first three of these brain regions have strong connectivity with the MD nucleus (Giguere and Goldman-Rakic 1988; Ray and Price 1993), whereas the anterior cingulate is a primary cortical target of the AV/AM nuclei (Vogt et al 1987). Our data suggest that thalamic neuron number reductions may contribute to cortical volume deficits. Further quantitative study of all thalamic nuclei is underway to determine the full extent of thalamic abnormalities in schizophrenia.

Thalamic Volume and Density Measurements

In the MD of schizophrenic subjects, a significant reduction in tissue volume was observed. These data support previous MRI studies that have identified modest thalamic volume reductions in schizophrenic individuals (Andreassen et al 1990; Flaum et al 1995; Gur et al 1998; Staal et al 1998). In one study (Buchsbaum et al 1996), for example, the volume of the left anterior thalamus was selectively reduced by 15%. Because there is a reduction in the volume of the thalamus in never-medicated schizophrenic individuals (Buchsbaum et al 1996; Gur et al 1998; Pakkenberg 1992), it appears unlikely that neuroleptic effects are responsible for such volume reductions. Increased volumes of the lateral ventricles accompany smaller thalamic volumes in schizophrenic subjects (Portas et al 1998). These MRI findings raise the possibility that thalamic volume reductions may be associated with the enlargement of the lateral ventricles observed in schizophrenia (Cannon et al 1998; see review by McCarley et al 1999). The modest reduction in whole thalamic volume (<10%) reported in some MRI studies of schizophrenic individuals (Andreassen et al 1990; Flaum et al 1995) and reports of normal thalamic size in other studies (Wolkin et al 1998; for review, see McCarley et al 1999) suggest that thalamic volume changes in schizophrenia may be limited to select regions of the thalamus such as the AV/AM and MD.

In our study, the density of neurons in the MD and AV/AM nuclei of schizophrenic subjects was normal even though total neuron numbers were significantly reduced in these nuclei. The 15% lower mean density of neurons in the MD was not significantly different from control subjects, although it is possible that a larger sample size would have identified this change as significant. Our data suggest that there is a large effect of nuclear volume reduction on neuron number in the MD of schizophrenics. Nonetheless, the findings do not exclude the possibility that neuron number reductions in this region are the product of both a density and a volume reduction. The findings in the MD contrast with the pattern observed in the AV/AM, in which neuronal density was virtually identical in both groups. This latter observation replicates a recent study (Danos et al 1998) that identified differences in the density of a select population of thalamocortical neurons in the AV but did not find a significant change in the density of AV neurons.

Historically, anatomic studies have relied on measurement of neuronal density and regional volume, measurements that in our study provided a less robust indication of thalamic neuropathology than total neuron counts. Because postmortem tissue preservation and tissue shrinkage influence volume and density measurements, there is often greater variance associated with these measures compared with neuron number estimates. Variable tissue shrinkage from subject to subject has no net effect on total neuron counts when stereologic procedures are used (West 1994). The observation that neuronal density and nuclear volumes are reduced only modestly or are unaffected in the thalamus of schizophrenic individuals provides one explanation for why the thalamus has not been previously recognized as a locus of robust anatomic change in schizophrenia.

Relationship between Thalamic Deficits in Schizophrenia and Cortical Anatomy and Function

Because of the intimate connections between the thalamus and cortex, thalamic neuron number reductions in schizophrenia may have profound influences on cortical anatomy and function. There are reciprocal connections between the MD and dorsolateral prefrontal, orbitofrontal, frontal eye fields, and insular cortices (Giguere and Goldman-Rakic 1988; Mufson and Mesulam 1984), and the AV/AM region with the anterior cingulate cortex (Vogt et al 1987). Thalamic neuron number reductions in MD and AV/AM may contribute to the reported anatomic changes in the frontal and cingulate cortex of schizophrenic subjects. In particular, the findings are relevant to the “reduced neuropil” hypothesis (Selemon and Goldman-Rakic 1999). This hypothesis is based on the observation that there are increased densities of neurons in the middle lamina of the dorsolateral prefrontal cortex of schizophrenic individuals, but no reductions in neuron number, suggesting that there is a decreased amount of cortical neuropil in certain lamina (Akbarian et al 1995; Davies and Lewis 1995; Selemon et al 1998; Selemon and Goldman-Rakic 1999). Other prefrontal anatomic deficits include decreased dendritic spine density for middle lamina pyramidal neurons (Garey et al 1998), reductions in synaptic protein levels (Glantz and Lewis 1997), and abnormalities in the distribution of serotonin-1A/2A receptors (Burnet et al 1996). In the anterior cingulate...
The important role played by the thalamus in support of disorder (Erkwoh et al 1997; Sabri et al 1997). Because of metabolic activity is associated with delusions and thought Szelies et al 1991). Finally, the thalamus is metabolically particularly prone to create disturbances in verbal memory (Casselli et al 1991; Squire and Moore 1979; and language (Casselli et al 1991; Szelies et al 1991). In schizophrenia, a reduction in the number of thalamocortical axons innervating the frontal lobes could contribute to the observed reductions in neuropil and spine density. Our findings of neuron number reductions in the thalamus of schizophrenic subjects suggests that perturbation of thalamocortical connections may contribute to reduced neuropil and other cortical deficits in schizophrenia.

Thalamic cell number reductions in schizophrenia may also contribute to metabolic activation deficits observed in the frontal cortex. Thalamic projections provide excitatory input to the frontal cortex, which influences the level of cortical metabolism and blood flow. For instance, animal studies have shown that inhibition of MD neuron activity selectively depresses metabolic activity in the frontal cortex (Young et al 1994); in humans, thalamic vascular accidents often induce frontal lobe metabolic hypoactivity (Casselli et al 1991; Szelies et al 1991). In schizophrenic individuals, a reduction in the number of thalamic neurons available to activate or sustain frontal cortex neural activity may impair metabolic activation during performance of verbal working memory and sustained attention tests, resulting in frontal cortical metabolic hypoactivity (Berman et al 1986; Fletcher et al 1998; Goldberg et al 1994; Stevens et al 1998; Weinberger and Gallhofer 1997).

Reductions in MD and AV/AM neuron number, through interactions with frontal circuits, have the potential to influence behaviors relevant to schizophrenia. MD lesions in rats produce increased perseverative behaviors (Hunt and Aggleton 1998), and perseverative behaviors are observed in schizophrenic subjects performing the Wisconsin Card Sorting Task (Berman et al 1986; Goldberg et al 1994). Strokes that selectively affect the MD and AV/AM can induce a schizophrenialike thought disorder characterized by bizarre, disconnected, and incoherent speech patterns (Chatterjee et al 1997). Accidental thalamic lesions that affect the MD and anterior nuclei are particularly prone to create disturbances in verbal memory and language (Casselli et al 1991; Squire and Moore 1979; Szelies et al 1991). Finally, the thalamus is metabolically activated during episodic hallucinations (Silbersweig et al 1995), and elevated thalamic, frontal, and cingulate metabolic activity is associated with delusions and thought disorder (Erkwoh et al 1997; Sabri et al 1997). Because of the important role played by the thalamus in support of cortical processing, it is clear that the substantial reduction in the number of neurons in the MD and anterior nuclei of schizophrenics could have profound effects on cortical metabolic activation deficits and behavioral signs and symptoms of schizophrenia.

Mechanisms Involved in Thalamocortical Pathology in Schizophrenia

There are a variety of mechanisms that could potentially account for the observed pattern of MD and AV/AM neuron number reductions in schizophrenia. Broadly defined, the mechanisms fall into two categories: developmental and degenerative. First, fewer MD and anterior thalamic neurons may have been generated, or they may have died during the development and maturation of the brain. A developmental mechanism promoting thalamic neuron number reductions would include a failure to develop or maintain appropriate synaptic connections with cortical targets. Developmental processes have been widely implicated as factors in producing anatomic deficits in schizophrenia (Andreasen 1997b; Hyde and Weinberger 1990; Jones 1997a; Raedler et al 1998; Stefhen and Murray 1997). Alternatively, a degenerative process could be involved in MD and AV/AM nerve cell number reductions. Thalamic neurons may develop normally but subsequently die because of a necrotic degenerative process. This later process usually produces alterations of glial cells (gliosis) in the regions where neuronal degeneration has occurred. As an example, following dorsolateral prefrontal cortical lesions in rats, a secondary neuronal degeneration occurs in the MD. Thalamic gliosis is observable for at least 40 days after the lesion placement (van Eden et al 1998); however, in schizophrenic individuals there are no increases in the number of glial cells in the MD nucleus (Pakkenberg 1990). The lack of a gliotic reaction in the schizophrenic brain has been interpreted as evidence against a necrotic involvement in the disease. Further investigation is needed to determine why there are fewer neurons in the thalamus of patients with schizophrenia.

In conclusion, our study identifies the MD and AV/AM thalamus as regions of robust nerve cell number reduction in schizophrenia. The “double hit” on the MD and anterior thalamus in schizophrenia is consistent with other data that indicate that the frontal cortex and limbic system are anatomically handicapped in schizophrenia. The MD and anterior thalamic “lesions” appear to be well positioned to influence the signs and symptoms of schizophrenia (Andreasen 1997b) by decreasing motivation, causing failure of mental activities, and altering emotional responses through interactions with executive and emotional control centers in the frontal and cingulate cortex. Historically, it...
has been difficult to find marked abnormalities in the schizophrenic brain that parallel those found in diseases such as Huntington’s disease and Parkinson’s disease, making the study of schizophrenia difficult to approach from a mechanistic level; however, the finding of robust neuroanatomic deficits in the thalamus provides an opportunity to better focus anatomic research in schizophrenia. It is likely that further study of the thalamus in schizophrenia will reveal important clues about the etiology of this debilitating mental illness.

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