Neuropathology of Schizophrenia: Cortex, Thalamus, Basal Ganglia, and Neurotransmitter-Specific Projection Systems

by Stephan Heckers

Abstract

This article reviews neuropathological studies in the search for an anatomical correlate of schizophrenia. Replication of many results has proven to be difficult. A consistent finding is the lack of significant gliosis in the neocortex. Intriguing findings that need further corroboration include decreased volume and cell number of the mediodorsal thalamic nucleus, cytoarchitectural alterations of the prefrontal cortex and upper layers of the anterior cingulate gyrus, and superior temporal gyrus abnormalities. Most neuropathological studies investigate regional brain volume and cell density. Highly variable shrinkage of brain tissue postmortem makes these estimates prone to bias and often not comparable across studies. So far, no strong clinicopathological correlations and no pathological criteria to diagnose schizophrenia have been established.

Schizophrenia Bulletin, 23(3):403–421, 1997.

Neuropathologists have made substantial progress in the search for causes of neuropsychiatric disorders. Initial findings such as ventricular enlargement or gross brain atrophy were often neither specific nor sensitive, but they allowed for the differentiation of abnormal from normal brains. Some pathological findings, such as plaques and tangles in Alzheimer's disease (Khachaturian 1985) or loss of striatal neurons in Huntington's disease (VonSattel et al. 1985) are now used to make and stage a diagnosis. Ventricular enlargement, reported for many but not all schizophrenia patients, has long been regarded as indication of an underlying pathology of cortex, white matter, or subcortical structures in schizophrenia (Southard 1915). Is ventricular enlargement a clue that points to a neurodegenerative or neurodevelopmental abnormality in schizophrenia (Benes 1993b)?

This review assesses progress in the neuropathological understanding of schizophrenia—with an emphasis on more recent studies of the prefrontal cortex, the anterior cingulate cortex, the auditory cortex, the thalamus, the basal ganglia, and the brainstem. Limbic structures of the medial temporal lobe are reviewed by Dwork (1997, this issue). Studies of the ventricular system, now performed more accurately by in vivo imaging techniques, are reviewed elsewhere (Shelton and Weinberger 1986; Kotrla and Weinberger 1995) and are not included here. Structural neuroimaging studies that are directly relevant to interpreting postmortem studies will be included.

Requirements for Neuropathological Studies of Schizophrenia

The scientific rigor of neuropathological studies of patients with schizophrenia has improved in recent years. I will briefly address requirements now considered essential for a sound neuropathological study (table 1; for further review, see Benes 1988; Casanova and Kleinman 1990; Kleinman et al. 1995) and will focus on a less well-known source of error: postmortem artifacts.

Reliable Diagnosis of Schizophrenia. Only recently have investigators begun to study patients who were diagnosed using standardized criteria. This makes it difficult to compare older studies with more recent ones: patients with dementia praecox and schizophrenia diagnosed before 1980 might be quite different from the schizophrenia patients diagnosed according to *DSM–III* or *DSM–III–R* criteria (American Psychiatric Association 1980, 1987). Even if only those patients who fulfill the current diagnostic criteria are included, they still may represent different subgroups of schizophrenia (catatonic, disorganized, paranoid, undifferentiated, and residual type). Conflicting

results of methodologically comparable studies might therefore be due to a true difference in the patient population (Andreasen et al. 1994b).

Comparison of Schizophrenia and Control Cases. The majority of earlier studies compared brains of schizophrenia patients with those the individual investigator considered to be "normal." Many important contributions—including those of Alzheimer (1897, 1913) and Southard (1914, 1915)—still await confirmation in controlled studies.

Matching of Cases for Gender and Age. Samples of normal individuals as well as schizophrenia patients show significant gender differences and age-related changes of parameters, such as regional brain volume (e.g., Schröder et al. 1975; DeLisi et al. 1989; de Lacoste et al. 1990; Heckers et al. 1990, 1991b). Differences between schizophrenia patients and normal samples are difficult to attribute to diagnosis if the samples have incompatible gender or age distributions.

Controlling for Presence of Neurological Disorders. The search for pathological changes in schizophrenia patients should not preclude a thorough screening for other pathological entities that could explain the psychotic features observed during a lifetime (Jellinger 1985). For example, patients with tumors and vascular lesions, even in areas not under study, should be excluded. Age-related changes (e.g., neurofibrillary tangles, neuritic plaques) should be documented.

Quantifying Abnormalities Without Knowledge of the Diagnosis. When schizophrenia cases are compared with control cases, they should be studied without knowledge of the diagnosis. Furthermore, the parameter under study should be quantified to allow for the comparison of different studies.

Table 1. Requirements for neuropathological studies of schizophrenia

1. Reliable diagnosis of schizophrenia
2. Comparison of schizophrenia and control cases
3. Matching of cases for gender and age
4. Controlling for presence of neurological disorders
5. Quantification of abnormalities without knowledge of the diagnosis

Postmortem Artifacts

When an investigator has taken all the precautions outlined above, the major challenge will be to assess and control for tissue changes after autopsy. The most significant effect to control for is the individual shrinkage of brain tissue. Previous studies have demonstrated that brain tissue shrinks in a highly variable fashion (between 40% and 60%) during fixation and staining (Schröder et al. 1975; Mouritzen Dam 1979; Heckers et al. 1990).

Tissue shrinkage affects the two most-studied parameters, volume and cell density. If the entire brain is available, brain volume can be determined after autopsy and fixation using the Archimedes principle (Weibel 1979) and after staining using the Cavalieri estimator (Gundersen et al. 1988a, 1988b). An individual shrinkage factor can then be calculated and the volume estimate can be corrected. Most investigators, however, do not have the entire brain at hand, and they estimate volume in a series of brain sections by multiplying the area of the slice by its thickness (Rosen and Harry 1990). If this volume estimate is not corrected by an individual shrinkage factor, it is highly biased and may reflect more the individual postmortem shrinkage of brain tissue than the proposed volume in vivo (Schröder et al. 1975; Gundersen 1992).

Cell-density estimates (cell number per unit volume) are equally biased if they are based on uncorrected volume estimates. Two additional sources of bias can affect the accuracy of cell-density estimates. First, counting *all* cells within one defined volume leads to overcounting cells that are only partially located within the scanned volume. The larger the cell and the thinner the section, the greater the overestimate. There are now simple and unbiased methods to avoid this counting error (Williams and Rakic 1988; Gundersen 1992). Second, estimates of cell density are often established in only a few microscopic fields that are not sampled systematically throughout the entire anatomical area studied. While such studies may demonstrate high reliability among raters, they do not necessarily reflect the true cell number in the anatomical area studied.

Total cell number (cell density $\times$ volume) is a much more powerful parameter. It is independent of any tissue shrinkage and can therefore be compared across studies (Coggeshall 1992; Gundersen 1992; Pakkenberg 1992). Total cell-number estimates require two important steps: First, volume is determined in a systematic sample of slices (typically about five sections in simple structures such as the amygdala or the thalamus). Second, cell density is determined in systematically sampled microscopic fields, which ensures that the estimates are a true representation of the sample. Each investigator can calculate the coefficient of error for the total cell-number estimate, which predicts the accuracy and reproducibility of the estimate. For example, two studies of the total neuron number in the subfields of the human hippocampus arrived at very similar estimates (both with coefficients of error below 10%), although volumes and cell densities were quite dif-

ferent due to different fixation and staining procedures (West and Gundersen 1990; Heckers et al. 1991a).

If total cell number cannot be calculated, it is still possible to compare different cell populations within the same specimen (e.g., neuronal versus glial cells, pyramidal versus nonpyramidal neurons, or cytochemically different cells visualized by immunohistochemistry or in situ hybridization), since they are theoretically affected equally by postmortem tissue shrinkage.

Investigators using immunohistochemical or in situ hybridization techniques must consider the possibility that the amount of protein or the messenger ribonucleic acid (mRNA) levels change postmortem before they are visualized. Rigorous matching for autolysis time and incubation parameters, as well as quantitative analysis, is necessary (Zoli et al. 1990). One additional way to reduce potential artifacts is to compare different cell populations labeled with the same or even different probes within the same specimen. A differential change—when one class of cells is altered between samples but another is unchanged—makes it less likely that the observed difference across samples is due to postmortem alterations.

The most likely contributors to the divergence of results of the studies reviewed here include true biological differences in subgroups of schizophrenia subjects; methodological errors, such as insufficient matching for gender and age; and the use of biased estimates, such as volume and cell density.

Neuropathological Findings

Cortex. Neuropathological studies of the cortex in schizophrenia have focused on the six-layered homotypical isocortex (association cortex) and on one type of idiotypical primary sensory cortex, the auditory cortex (table 2). Allocortical (hippocampus) and periallocortical areas (parahippocampal gyrus and cingulate gyrus), serving mainly limbic and memory functions, have been studied extensively in the past 20 years. Studies of the cingulate gyrus will be reviewed here; Dwork (1997, this issue) reviews studies of the hippocampal formation.

Two researchers—Alzheimer (1897, 1913) and Southard (1914, 1915)—offered the original description of several pathological findings in the cortex in dementia praecox/schizophrenia that remain the focus of research even today: volume loss of the cortical gray matter, differ-

Table 2. Cortex total cell number (N), cell density (N/V), and volume (V) in schizophrenia

Cortex	Increase	No change	Decrease
Total			
N	–	Pakkenberg 1993	–
N/V	Pakkenberg 1993	–	–
V	–	Rosenthal and Bigelow 1972 Heckers et al. 1991b	Pakkenberg 1987 Pakkenberg 1993
Prefrontal			
N/V	Benes et al. 1991 (L5) Selemon et al. 1995 (L3–6) Daviss and Lewis 1993 (L1–3,5)[1]	Dunlap 1924 Ferrero 1947 Akbarian et al. 1995 G: Benes et al. 1986, 1991 G: Selemon et al. 1995	*Alzheimer 1913* (L2,3) *Winkelman and Book 1949* Colon 1972 (L4,5) Benes et al. 1986 (L6) Benes et al. 1991 (L1,2) Akbarian et al. 1993a[2]
Anterior cingulate gyrus			
N/V	–	–	*Braitenberg 1952* (L2–4) Benes et al. 1986 (L5) Benes et al. 1991 (L2–6)
Superior temporal gyrus			
N/V	–	–	*Beheim-Schwarzbach 1952*
V	–	Hobson et al. 1995	*Southard 1915*[3] Falkai et al. 1995

Note.—Densities and total cell number of neurons except when indicated. G = glia; Qualitative studies in italics; [L1–6] indicates cortical layers 1–6.
[1]Calbindin- and calretinin-positive neurons.
[2]Nicotinamide adenine dinucleotide phosphate-diaphorase neurons.
[3]Schizophrenia patients with auditory hallucinations.

ential vulnerability of cortical neurons toward injury, low glial/neuronal cell ratio, and abnormalities in the position of neurons within the cortical layers. Alzheimer's first study (1897) described three cases with overall decreased neuronal density and unchanged glial cells and two cases with normal neuronal density with "Schiefstellung" (skewed position) of neurons and increased glial density. His second report (1913) of 18 cases stressed neuronal loss primarily in layers 2 and 3, skewed position of pyramidal cells, and decreased neuropil.

Southard (1910), initially skeptical about morphological changes in schizophrenia, studied 25 cases of dementia praecox and found internal hydrocephalus, more left-sided than right-sided lesions, temporal lesions (especially left superior temporal gyrus hypoplasia) in association with auditory hallucinations, parietal atrophy and sclerosis in catatonia, and frontal-lobe aplasia or atrophy in patients with delusions (Southard 1914, 1915). These lesions primarily affected the upper cortical layers and were not associated with pronounced gliosis (Southard 1919).

Neither investigator classified his patients according to current criteria, used quantitative techniques, or was blind to the diagnosis during the study. It is therefore remarkable that recent quantitative studies described neuronal loss in layers 2 and 3 of the prefrontal cortex and cingulate gyrus (see below), lack of gliosis (see below and Dwork 1997, this issue), abnormal orientation of pyramidal cells (see Dwork 1997, this issue), and superior temporal gyrus abnormalities (see below). However, many of these findings are still subject to debate.

Entire cortex. Pakkenberg (1987) reported a 12 percent reduction of total cortical volume in schizophrenia patients, whereas others found no significant difference between schizophrenia subjects and controls (Rosenthal and Bigelow 1972; Heckers et al. 1991*b*). Pakkenberg's finding (1987) of decreased cortex volume was derived from a sample of 29 institutionalized, chronic schizophrenia patients, with a mean age of 74 years, compared with a sample of 30 controls with a mean age of 71 years. A subsequent study of a subset of eight schizophrenia cases showed increased cell density and, therefore, a normal total neuron number in all four lobes of the cerebral cortex (Pakkenberg 1993). This stereological study demonstrated that decreased volume or increased cell density alone cannot be used to predict the total cell number.

Prefrontal cortex. The dorsolateral-prefrontal cortex—here broadly defined as an associational isocortical region, including Brodmann areas 8 to 10 and 44 to 47 (Broca's area) (Zilles 1990)—has been studied repeatedly, with conflicting results. Many early studies, with methods similar to those of Alzheimer's, described qualitative changes, but often with different results (for reviews, see

Winkelman and Book 1949; Peters 1956; David 1957). There is even one report of neuronal density in frontal-cortex specimens removed during surgery from 22 schizophrenia patients and 1 manic-depressive patient (Rowland and Mettler 1949). Here I will review the quantitative studies of neuronal density, specific neuronal markers, and glial density. Quantitative studies of neuronal density are conflicting (i.e., reporting normal, increased, and decreased cell density) and inconclusive.

Normal neuronal density: Dunlap (1924) studied eight cases of dementia praecox (ages 20 to 44 years) and five controls (ages 17 to 45 years), finding normal neuronal density in the superior frontal gyrus. Ferrero (1947) studied area 9 in five different groups of neuropsychiatric patients, including 12 schizophrenia subjects (9 females and 3 males, with a mean age of 67). He found somewhat thicker layers 3b, 5b, and 6a in the schizophrenia sample and highly variable cell densities, which was not different from the normal variation. Akbarian et al. (1995, see below) found no difference in the cell density of all or small neurons of area 9.

Increased neuronal density: Benes et al. (1991) described increased pyramidal cell density selectively in layer 5 of area 10 in a sample of 18 schizophrenia and schizoaffective patients, compared with 12 controls. Selemon et al. (1995) studied neuronal and glial density in prefrontal area 9 and occipital area 17 in 16 schizophrenia subjects, 19 control cases, 6 schizoaffective patients, and 9 with Huntington's disease. Schizophrenia patients had significantly increased neuronal density in areas 9 (17%) and 17 (10%). In area 9, pyramidal and nonpyramidal neuronal density was increased in layers 3 to 6, with the largest increase (24%) in layers 5 to 6. Cortical thickness was reduced by 8 percent in the schizophrenia sample, reaching significance for layer 5 (7% decrease) only. Mean glial density was not significantly changed. Since glial density correlated negatively with the time of fixation in formaldehyde, all cases (14 controls, 6 people with schizophrenia) fixated for less than 5 years were analyzed separately. This revealed a 22 percent higher glial density in those with schizophrenia, which did not reach significance. Cell density was estimated using an unbiased method (Williams and Rakic 1988), but was not corrected for the significant shrinkage of the tissue blocks during fixation in formaldehyde and embedding in celloidin.

The fact that the schizophrenia cases were fixated significantly longer than the control cases—and the extreme individual variation of tissue shrinkage during fixation and staining (40% to 60%, see above)—make the finding of increased cell density in an unknown reference volume difficult to interpret. Furthermore, increased neuronal density in schizophrenia was not specific for the prefrontal cortex, since it was also found in the occipital cortex.

Daviss and Lewis (1993) studied a subpopulation of cortical interneurons with antibodies against calbindin and calretinin. They found an increased density of these local circuit neurons in layers 1 to 3 and 5 in area 46 of five schizophrenia patients compared with five controls.

Decreased neuronal density: Winkelman and Book (1949) studied 10 schizophrenia subjects and found decreased neuronal density primarily in the frontal cortex. They did not provide a quantitative analysis but described general as well as focal loss of neurons, increased number of astroglia, and mild subcortical demyelinization. Colon (1972) reported marked neuronal loss (57%) primarily in deeper layers 4 and 5 of area 10 (and also for areas 4 and 24). Benes et al. (1986) reported significantly decreased neuronal density in layer 6 of area 10 in a sample of seven schizophrenia cases compared with nine control cases. In a subsequent study of a different sample of 18 schizophrenia and schizoaffective patients and 12 controls, Benes et al. (1991) found decreased density of small neurons in layers 1 and 2 of area 10.

Akbarian et al. (1993a) studied a small subset of cortical neurons that express the enzyme nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) in five schizophrenia patients matched for age, sex, and autolysis time with five controls. Some gray- as well as white-matter neurons of the adult human brain express NADPH-d, which is coexpressed with, or even identical to, nitric oxide synthase. These neurons have been shown to be particularly resistant to cytotoxic injury. In all schizophrenia subjects, NADPH-d neurons were significantly fewer in the cortex and directly adjacent white matter, and four persons with schizophrenia showed a significantly increased number in the deep white matter. This bimodal pattern of altered NADPH-d cell density was interpreted as dislocation of neurons or impaired programmed cell death rather than as cell loss; neurons that are destined to reach the subplate and then the cortex either arrest during development in the white matter or are spared from programmed cell death.

Studies of neuronal markers: Glantz and Lewis (1993) found a significant decrease of synaptophysin immunoreactivity (a marker of synapse density) in a sample of six schizophrenia patients compared with six sex- and age-matched controls in areas 9 and 46. Horton et al. (1993) used the immunoreactivity for ubiquitin (a heatshock related protein) as a probe for neurodegeneration in a sample of 17 schizophrenia subjects (mean age 69) and 26 controls (mean age 72). They found no difference in the degree of ubiquination in the prefrontal cortex. Akbarian et al. (1995) studied the left superior frontal gyrus (Brodmann area 9) in 10 chronic schizophrenia patients and 10 controls matched for age, gender, and autolysis time. As mentioned above, they found no difference in the density of all neurons or in the density of small, round, or ovoid neurons in any of the six cortical layers. However, they found significantly fewer neurons expressing mRNA for glutamic acid decarboxylase$_{67}$ (GAD$_{67}$) in layers 1 to 5 in the schizophrenia sample. GAD$_{67}$ is one of the two isoforms of GAD and is present in both the cell bodies and the axon terminals of gammaaminobutyric acid (GABA)ergic neurons throughout the central nervous system. The difference in GAD$_{67}$ mRNA was most pronounced in layers 2 (48% decrease) and 1 (40% decrease) and was still significant in layers 3 to 5 (30% decrease). In contrast, the density of neurons expressing calcium-calmodulin-dependent protein kinase (CamKII) mRNA was not different between samples.

This differential mRNA change in two neuronal populations makes methodological errors of the in situ protocol less likely, although not impossible (see Lee and Tobin 1995); it also makes postmortem shrinkage less of a problem. Decreased GAD mRNA in the absence of significant cell loss could be a sign of functional down-regulation of inhibitory interneurons in a cortex that has developed normally and has not undergone significant degeneration during life.

Glial density: In contrast to the conflicting results of neuronal density studies, glial density was consistently found to be normal. The two studies by Benes et al. (1986, 1991) determined glial density in the prefrontal cortex and found no significant differences between schizophrenia patients and controls. Selemon et al. (1995) reported an increased neuronal density in the schizophrenia sample without a significant change in glial density.

Conclusion: The most robust finding of neuropathological studies of the prefrontal cortex in schizophrenia is the lack of significant gliosis. However, qualitative studies have not consistently shown changes of neurons, as has been suggested by the large body of qualitative studies. Even studies of the same anatomical areas (e.g., for area 9) have revealed conflicting results (Dunlap 1924; Ferrero 1947; Akbarian et al. 1995; Selemon et al. 1995). Different fixation techniques, staining methods, and counting algorithms make it virtually impossible to compare results of the different studies. It is fair to say that changes in neuron number in the frontal cortex of schizophrenia patients are not as dramatic and widespread as in neurodegenerative diseases such as Huntington's disease or Alzheimer's disease. However, only unbiased estimates of total cell number, which can be compared across studies, will reliably assess glial and neuronal number in schizophrenia. The studies by Pakkenberg (1987, 1993), showing increased neuronal density in a significantly smaller cortex in schizophrenia, exemplify that volume or cell density alone cannot predict total cell number.

If there is cell loss, are subsets of cortical neurons—such as GABAergic interneurons, glutamatergic pyramidal cells, and NADPH-d–positive neurons—selectively vulnerable to injury? If so, at which point in the life cycle of the cortical neuron does the injury occur? Studies using immunocytochemical, in situ hybridization, and receptor-binding techniques are needed to answer these questions. The increased neuron/glia ratio, as reported by some investigators, is often interpreted as evidence for developmental abnormalities in the prefrontal cortex in schizophrenia. The finding of displaced NADPH-d positive neurons in the prefrontal cortex by Akbarian et al. (1993a) adds new evidence to this line of thinking. It will be important to confirm this finding in a larger sample and to study whether other types of cortical cells are affected in a similar fashion (i.e., displaced to the white matter).

Anterior cingulate cortex. The anterior part of the cingulate gyrus (Brodmann area 24) is a periallocortical, agranular area that is generally considered to be part of the limbic system. Braitenberg (1952) studied this area in 30 cases, including 7 with schizophrenia, from the Vogt collection (table 2). In a purified sample of nine cases without any additional neuropathological alterations, he found decreased neuronal density and decreased staining of nerve cells with Nissl-stain, interpreted as a sign of degeneration, in layers 2 to 4 in the schizophrenia patients, but not in the controls. One of the very few electronmicroscopical studies of schizophrenia patients (Aganova and Uranova 1992) reported swelling of synapses in layers 1 and 2 of area 24.

Benes and coworkers studied area 24 extensively using Nissl-stain, immunohistochemistry, and autoradiography (Benes 1993a). Their initial finding (in a sample of 10 schizophrenia subjects with a mean age of 60, and 10 controls with a mean age of 66) was decreased neuronal density in layer 5 in the schizophrenia cases (Benes et al. 1986). A second study of the same sample described abnormal aggregates of layer 2 neurons, which were smaller and separated by wider distances in the schizophrenia cases (Benes and Bird 1987). The hypothesis that these wider spaces were filled with vertical axons was studied using antibodies against the 200-kilodalton neurofilament subunit (a component of the axonal cytoskeleton) and against glutamate (Benes et al. 1987, 1992a). Schizophrenia patients showed 25 percent more vertical axons, which might indicate an increased associative input into the anterior cingulate gyrus in schizophrenia.

A third cell density study in a sample of 18 schizophrenia and schizoaffective patients (mean ages 53 and 49, respectively) and 12 controls (with a mean age of 59) revealed a significant deficit in small interneurons in layers 2 to 6 without changes in glial density (Benes et al. 1991).

To test whether the loss of small cortical neurons, presumably GABAergic interneurons, is related to changes in GABA receptor density, autoradiography was used to localize the binding of bicuculline-sensitive titrated muscimol in a sample of six schizophrenia patients and eight controls (Benes et al. 1992b). This study showed a significant and preferential increase in $GABA_A$ receptor binding in layers 2 and 3, but not in layers 5 and 6 in persons who had schizophrenia, with and without exposure to neuroleptics, which could suggest a compensatory up-regulation of $GABA_A$ receptors secondary to the loss of GABAergic interneurons of layers 2 and 3.

Conclusion: The quantitative findings of Benes et al. are in accordance with Braitenberg's (1952) previous qualitative description and have been integrated into a comprehensive neuroanatomical model of anterior cingulate dysfunction in schizophrenia (Benes 1993a). Briefly, increased excitatory input via associate fibers, decreased inhibitory input due to loss of inhibitory interneurons, and increased dopaminergic tone cause excess firing of the pyramidal cell of the anterior cingulate gyrus. The methodology of the Benes studies is sound (blind quantitation, matched samples, correction for confounding variables). However, several features will make it difficult to compare her results with those of others to come. First, cell-density estimates are highly sensitive to differential tissue shrinkage postmortem. Second, the distinction of small neurons from pyramidal neurons and from glial cells is not trivial. Further, her small neuron/pyramidal neuron ratio, as well as neuron/glia ratio, are very different from those of other investigators (for review, see Braak and Braak 1986). Finally, the second-highest density of small neurons in area 24 was found in layer 4, although area 24 is defined as agranular cortex, which lacks layer 4 (Brodmann 1909; Zilles 1990).

Auditory cortex. The primary auditory and unimodal auditory association areas (Brodmann areas 41, 42, 22), located on the superior temporal gyrus, make up the only sensory cortical region reported to be altered in schizophrenia (table 2). Southard (1914, 1915) was the first to document decreased volume in the left superior temporal gyrus in dementia praecox patients with auditory hallucinations. He studied 25 patients with dementia praecox, diagnosed as either paranoid or catatonic. Of the 12 cases with auditory hallucinations, 9 showed "striking evidence of temporal-lobe involvement" (especially a smaller left superior temporal gyrus), whereas only 4 of the 13 cases without evidence of hallucinations showed some kind of temporal-lobe pathology. This pathology was not significantly correlated with "internal hydrocephalus," which Southard found in nine cases (five without hallucinations, two of which showed temporal-lobe abnormalities, and four with hallucinations, three of which showed such abnormalities).

Southard's study did not include controls or other psychiatric cases and was not quantitative. His study design was more directed toward detecting clinicopathological correlations in individual cases, which he studied exhaustively with the available techniques of his time. It is therefore important to refer to two recent in vivo imaging studies (Barta et al. 1990; Shenton et al. 1992), which reported a significant association between auditory hallucinations or thought-disorder index and superior temporal gyrus volume in schizophrenia patients. However, preliminary data from a recent postmortem study of 19 such patients and 21 control subjects do not indicate a significant difference in the volume of the left or right superior temporal gyrus in schizophrenia subjects (Hobson et al. 1995). Considering Southard's findings, it will be important to subdivide this sample into schizophrenia patients with and without auditory hallucinations.

Beheim-Schwarzbach (1952) reported a qualitative, cytological study of the superior temporal gyrus in a sample of 21 schizophrenia cases from the Vogt collection. All cases showed normal cell densities in the internal Heschl gyrus but "gaps of cells" in the more lateral aspects of the superior temporal gyrus, primarily in layers 3 and 5. Abnormalities of NADPH-d–positive neurons in medial and lateral parts of the temporal lobe (Akbarian et al. 1993b), similar to those described by the same authors for the frontal lobe (see above), are reviewed in detail by Dwork (1997, this issue).

The planum temporale, of which the posterior superior temporal gyrus is an external landmark, is intimately involved in the production and comprehension of language. In right-handed individuals, the surface area of the left planum temporale is usually much larger than that of the right. Falkai et al. (1995) reported disturbed planum temporale asymmetry in a sample of 24 schizophrenia patients and 24 control subjects matched by sex and age. The asymmetry coefficients for the planum temporale cortex volume and anterior-posterior diameter were significantly different between schizophrenia patients and controls. Five magnetic resonance imaging (MRI) studies of planum temporale asymmetry found either a significant reduction in the normal left > right asymmetry (DeLisi et al. 1994; Rossi et al. 1994; Petty et al. 1995) or no difference in the planum temporale asymmetry coefficient (Kleinschmidt et al. 1994; Kulynych et al. 1995).

One pathological study investigated sylvian fissure asymmetry, which is closely related to planum temporale and superior temporal gyrus asymmetry in the human cortex. Falkai et al. (1992) reported a 16 percent shorter left sylvian fissure in schizophrenia subjects who lacked the usual left > right asymmetry. Unfortunately, they com-

pared photographs of lateral views from postmortem specimens on which parts of the sylvian fissure cannot be assessed if hidden by overlapping cortex. One in vivo study (Bartley et al. 1993) used the superior technique of measuring sylvian fissure length in three-dimensional cortical renderings from MRI images of 10 normal monozygotic twins and 10 monozygotic twins discordant for schizophrenia. Both sets showed the normal sylvian fissure asymmetry, and there was no difference within the 10 discordant twin pairs.

Conclusion: Left superior temporal gyrus abnormalities have been described in schizophrenia patients (Falkai et al. 1995), especially in those with auditory hallucinations (Southard 1914, 1915). The lack of such changes in schizophrenia cases *without* auditory hallucinations would establish a stronger clinicopathological correlation. Furthermore, other brain areas that are potentially involved in abnormal auditory perception should be investigated. The intriguing finding by Southard, the recent pathological studies of Falkai et al., and the recent MRI studies (Barta et al. 1990; Shenton et al. 1992) raise further questions: How does decreased volume of the superior temporal gyrus correlate to functional abnormalities of the temporal lobe (McCarley et al. 1993; Waddington 1993)? What is the underlying cellular abnormality? Further analysis of this brain region in schizophrenia seems warranted.

Thalamus. Few investigators have studied the thalamus, and most have singled out the mediodorsal nucleus (the second largest and phylogenetically most progressed thalamic nucleus) for study (table 3). This nucleus is characterized by two different neuronal types (magno- and parvocellular) and topographical organization of afferent and efferent connections to the prefrontal cortex and limbic structures.

The volume of individual thalamic nuclei, as well as the entire group of thalamic nuclei, was found to be unchanged in at least two studies. Rosenthal and Bigelow (1972) found similar volumes of the thalamus in 10 schizophrenia cases compared with 10 controls, matched for gender and age. Lesch and Bogerts (1984) studied 15 schizophrenia and 12 control cases from the Vogt collection, which were not matched for gender, and found the volume of all large thalamic subnuclei and of the thalamus as a whole unchanged in schizophrenia. However, they found a reduced thickness of the periventricular gray matter surrounding the third ventricle. Stein and Ziegler (1939) reported a morphometric analysis of the entire thalamus in 28 patients with dementia praecox and 6 with manic-depressive illness. This well-performed quantitative study found no significant differences in total thala-

Table 3. Thalamus total cell number (*N*), cell density (*N/V*), and volume (*V*) in schizophrenia

Thalamus	Increase	No change	Decrease
Total			
N/V .	–	–	*Fünfgeld 1954*
			Bäumer 1954
V	–	Stein and Ziegler 1939[1]	–
		Rosenthal and Bigelow 1972	
		Lesch and Bogerts 1984	
Mediodorsal nucleus			
N	–	–	Pakkenberg 1990 (N+G)
N/V	Hempel and Treff 1959 (G)	Dom et al. 1981	Treff and Hempel 1958
		Pakkenberg 1990 (N+G)	
V	–	–	Pakkenberg 1990

Note.—Densities and total cell number of neurons except when indicated: G = glia, N+G = neurons and glia; Qualitative studies in italics.
[1]Schizophrenia patients compared with other psychiatric patients.

mic volume or cell density between these two samples of neuropsychiatric patients.

Pakkenberg (1990) found a significantly decreased volume of the left mediodorsal nucleus in a sample of 12 schizophrenia patients (mean age 63), compared with 12 controls (mean age 62). Of interest, a recent MRI study of 39 male schizophrenia patients with a mean age of 30 and 47 male controls, matched for age, height, and educational level, found thalamic abnormalities (Andreasen et al. 1994a). Effect-size mapping (i.e., subtracting the averaged MRIs of all patients from those of all controls and searching for signal-intensity difference of each voxel) revealed significant differences primarily on the right side and in lateral regions, as well as the adjacent white matter. This was interpreted as evidence of decreased thalamic size, mainly due to changes in lateral parts of the thalamus. However, Andreasen et al. did not perform area measurements to arrive at volume estimates, which makes it difficult to compare this study with previous volumetric studies.

Fünfgeld (1954) and Bäumer (1954) studied cellular changes of the thalamus in brains of the Vogt collection. Fünfgeld reported cell loss and "Schwundzellen" (dwarf or wasting cells, as defined by changes of Nissl-stained cytoplasmic material) in seven out of eight cases of catatonic schizophrenia. Bäumer studied 51 brains, including 17 from schizophrenia cases, and also found cell loss and Schwundzellen—primarily in the mediodorsal, anterior, and ventral thalamic nuclei. In a series of quantitative studies of the mediodorsal nucleus in primarily catatonic schizophrenia patients, Hempel and Treff reported a reduction of neuronal density (maximally 44%), increased glial density, increased volume of glial cells, and increased volume of neuronal nuclei (Treff and Hempel 1958, 1959; Hempel and Treff 1959). While they used quantitative techniques, they were aware of the diagnosis at the time of the analysis, and the sample size in each of

the studies was smaller than 10. Dom et al. (1981) compared five catatonic schizophrenia cases with five normal ones and found no differences in medial thalamus neuronal density.

The study by Pakkenberg (1990), which examined only left hemispheres, provides an unbiased estimate of total cell number in the mediodorsal nucleus of the thalamus. In the sample of 12 schizophrenia subjects, cell density was not significantly reduced, but the total number of neurons (–40%), astrocytes (–44%), and oligodendroglia cells (–45%) was significantly decreased. All schizophrenia subjects were chronically institutionalized, all had been treated with neuroleptics, seven had developed dyskinesias, and some had received electroconvulsive therapy and insulin coma treatment; however, these confounding variables were not correlated with cell number. This elegant stereological study provides absolute cell numbers that can be compared across studies.

Conclusion: The most compelling finding is that by Pakkenberg (1990) of decreased total neuronal and glial number in the mediodorsal thalamic nucleus of schizophrenia cases. The study design is optimal, and the finding is much more solid than the previous studies of cell density in the brains of the Vogt collection. However, Pakkenberg's patient sample might not be representative for schizophrenia, and the various treatments of the schizophrenia subjects might have affected the finding. Furthermore, we do not know whether the neuronal loss affects the different cell types or the medial and lateral parts of the mediodorsal nucleus differentially. Confirmation by an independent stereological study in a different sample would establish neuronal loss in the mediodorsal nucleus as a very robust neuropathological finding in schizophrenia research.

The finding of thalamic abnormalities, as reported by Andreasen et al. (1994a), is in contrast to at least two volumetric postmortem studies (Rosenthal and Bigelow

1972; Lesch and Bogerts 1984). However, it is conceivable that the right thalamic abnormalities, attributed to lateral aspects of the thalamus in the Andreasen study, are due to a primary shrinkage of the mediodorsal nucleus. This would be similar to the finding of a smaller left mediodorsal thalamic nucleus in schizophrenia (Pakkenberg 1990). Several important questions deserve further study: Is the mediodorsal thalamic nucleus smaller in schizophrenia? If so, is there hemispheric asymmetry? Are sensory relay nuclei in more lateral parts of the thalamus equally affected?

Basal Ganglia. The neostriatum (caudate nucleus, putamen), the limbic striatum (nucleus accumbens), and the globus pallidus have been studied neuropathologically in schizophrenia (table 4). Four studies found decreased or normal volumes of basal ganglia structures. From the Vogt collection, Bogerts et al. (1985) studied the left hemispheres of 13 schizophrenia cases (10 females, 3 males) with a mean age of 41, and 9 controls (3 females, 6 males) with a mean age of 53. They found normal volumes of the caudate nucleus, putamen, nucleus accumbens, and external globus pallidus, but a 20 percent volume reduction of the internal globus pallidus. A second study (Bogerts et al. 1990) of a new brain collection covered both hemispheres of 18 people with schizophrenia (9 females, 9 males, mean age 52) and 21 controls (7 females, 14 males, mean age 54). This second study had essentially the same results. Brown et al. (1986) compared 41 schizophrenia patients (mean age 67) to those with affective psychosis, Huntington's disease, and Alzheimer's disease and found

no significant differences in the area of the striatum and pallidum sampled on only one slice per brain. Pakkenberg (1990) studied the nucleus accumbens and the ventral pallidum in the same sample that showed the thalamic abnormalities (see above). The volume of the nucleus accumbens was decreased in the schizophrenia subjects, and the ventral pallidum was normal.

One stereological postmortem study (Heckers et al. 1991b) of 23 schizophrenia cases (13 females, 10 males, mean age 62) and 23 sex- and age-matched controls found increased volumes of the striatum and globus pallidus in the schizophrenia sample, which was significant for the striatum on the left and for the globus pallidus on the right. Of interest, this surprising postmortem finding was subsequently corroborated by MRI studies (Jernigan et al. 1991; Breier et al. 1992; Swayze et al. 1992; Buchanan et al. 1993; Elkashef et al. 1994). A recent MRI study (Chakos et al. 1994) of 29 first-episode schizophrenia patients and 10 healthy control subjects measured the volumes of cerebral cortex, lateral ventricles, and caudate nuclei at the beginning of the study and after 18 months. Patients were treated with neuroleptic medication during this time. On followup, the patients showed a 5.7 percent volume increase of the caudate nuclei, whereas the controls showed a 1.6 percent volume decrease. This indicates that volume increase in the caudate nucleus can be seen in young first-episode schizophrenia cases and that it may be related to exposure to neuroleptic medication. A similar change in caudate volume with neuroleptic treatment was reported by Keshavan et al. (1994). Of interest, Chakos et al. (1995) reported reversal of caudate volume

Table 4. Basal ganglia total cell number (N), cell density (N/V), and volume (V) in schizophrenia

Basal ganglia	Increase	No change	Decrease
Neostriatum			
N/V	–	–	*Hopf 1954*
V	Heckers et al. 1991b	Bogerts et al. 1985 Brown et al. 1986[1] Bogerts et al. 1990	–
Nucleus accumbens			
N	–	–	Pakkenberg 1990 (N+G)
N/V	*Stevens 1982* (G)	–	–
V	–	Bogerts et al. 1985 Bogerts et al. 1990	Pakkenberg 1990
Globus pallidus			
N	–	Pakkenberg 1990[2] (N+G)	–
V	Heckers et al. 1991b	Pakkenberg 1990[2]	Bogerts et al. 1985[3] Bogerts et al. 1990[3]

Note.—Densities and total cell number of neurons except when indicated: G = glia, N+G = neurons and glia; Qualitative studies in italics.

[1]Schizophrenia patients compared with other psychiatric patients; area measurement only.
[2]Ventral pallidum.
[3]Internal globus pallidus.

increase seen with typical neuroleptics after switching to clozapine.

Neuronal density was investigated in four studies. Hopf (1954) found Schwundzellen (dwarf cells) in 10 out of 10 catatonic schizophrenia patients and no changes in paranoid and hebephrenic schizophrenia cases from the Vogt collection. Stevens (1982) reported an extensive, qualitative neuropathological study of 25 schizophrenia subjects (mean age 44, diagnosed retrospectively according to the ninth revision of the International Classification of Diseases [World Health Organization 1978] criteria), 28 nonschizophrenia psychiatric patients, and 21 controls. For schizophrenia cases (with sarcoidosis, colloid cyst, astrocytoma, and Alzheimer's disease, respectively) were excluded, but two schizophrenia cases with bilateral globus pallidus infarcts remained in the study. The important findings in the striatum of the schizophrenia sample were patchy fibrillary gliosis in the nucleus accumbens and loss of primarily large neurons in the globus pallidus. Arendt et al. (1983) studied 14 controls and 58 cases of neuropsychiatric disorders, including 3 female schizophrenia cases (mean age 48) who showed normal neuronal density in the external globus pallidus. The stereological study by Pakkenberg (1990) found normal neuronal and glial densities in the globus pallidus and nucleus accumbens. The total number of neurons and glial cells in the nucleus accumbens was decreased due to significant volume loss (see above).

Two studies used immunohistochemical methods to study the striatum in schizophrenia. Heckers et al. (1993) found decreased expression of choline acetyltransferase in striatal cholinergic interneurons in a sample of six schizophrenia and schizoaffective patients compared with six controls. Mai et al. (1993) reported a morphometric analysis of structures containing the neuropeptides vasopressin and oxytocin, using neurophysin-immunoreactivity as a marker, in 11 schizophrenia and 10 control cases of the Vogt collection. Fiber density was decreased in the globus pallidus, most pronounced in the internal pallidum, and increased in the substantia nigra.

Conclusion: Despite the long interest in an abnormal dopaminergic innervation of the striatum in schizophrenia, there are only few and equivocal neuropathological studies. The striatum shows a complex organization of GABAergic projection neurons, cholinergic interneurons, and glutamatergic and dopaminergic afferents. There are no good quantitative, case-control studies of this complex cytochemical organization in schizophrenia. Do the nucleus accumbens and globus pallidus show degenerative changes? The quantitative study by Pakkenberg (1990) did not find decreased neuronal density and increased glial density, as suggested by the qualitative research of Hopf

(1954) and Stevens (1982). Recent MRI studies have shown that the finding of basal ganglia volume increase (Heckers et al. 1991b) seems to be closely related to the use of typical neuroleptics. Which component of the basal ganglia contributes to this plasticity? So far, we have conflicting results and need more advanced neuropathological studies of the striatum in schizophrenia.

Neurotransmitter-Specific Projection Systems. Four groups of neurons (dopaminergic neurons in the substantia nigra and ventral tegmental area, cholinergic neurons in the basal forebrain and upper brainstem, noradrenergic neurons in the locus ceruleus, and serotonergic neurons in the raphe nuclei) project diffusely to cortical and subcortical areas and modulate signal transmission. In contrast to the extensive search for neurochemical abnormalities in schizophrenia, few structural studies are reported for these systems (table 5).

Three qualitative studies described periventricular and periaqueductal gliosis potentially affecting diffusely projecting neurotransmitter systems. Fisman (1975) studied 10 controls and 24 psychiatric patients using qualitative neuropathological methods. Controls and psychiatric patients showed brainstem lesions, but six out of the seven schizophrenia cases without other cerebral disease showed "glial nodules and perivascular infiltration," interpreted as the result of a viral infection. The qualitative study by Stevens (1982), which reported striatal abnormalities (see above), revealed patchy fibrillary gliosis "that was maximal in the periventricular and periaqueductal regions." Bruton et al. (1990) reported a prospective, extensive pathological study of 56 schizophrenia patients and 56 age- and sex-matched controls. They found a "significant increase in fibrous glia" in the cerebral cortex, white matter, and periventricular structures. Cortical and white matter gliosis were significantly correlated with focal brain damage (e.g., degeneration of the substantia nigra, calcification of the hippocampus, tumors, and strokes) but periventricular gliosis was not. Thus, the etiology of periventricular gliosis might be different from cortical and white matter gliosis.

Two studies showed no increased gliosis in the brainstem of schizophrenia cases. Hankoff and Peress (1981) studied 27 patients (8 schizophrenia and 19 nonschizophrenia control cases) and described clusters of microglial cells or perivascular infiltrates in 7 of their cases, but in only 1 schizophrenia patient. Stevens et al. (1988) counted astroglial cells that stained with an antibody against glial fibrillary acidic protein (a marker for one subtype of astrocytes). They found normal astrocyte density in the periventricular gray matter of the third ventricle in five schizophrenia subjects, compared with seven con-

Table 5. Brainstem/basal forebrain total cell number (*N*), cell density (*N/V*), and volume (*V*) in schizophrenia

Brainstem/basal forebrain	Increase	No change	Decrease
Brainstem			
N/V	*Fisman 1975* (G)	Stevens et al. 1988 (G)	—
	Stevens 1982 (G)	Hankoff and Peress 1981(G)	
	Bruton et al. 1990 (G)		
Substantia nigra			
N	—	Bogerts et al. 1983 (N+G)	—
V	—	—	Bogerts et al. 1983
Locus ceruleus			
N	—	Karson et al. 1991	—
		Garcia-Rill et al. 1995	
N/V	—	Lohr and Jeste 1988	—
PPN + LTD			
N	Karson et al. 1991	Manaye et al. 1995	—
	Garcia-Rill et al. 1995		
NbM			
N/V		Arendt et al. 1983	*Von Buttlar-Brentano 1952*
	—	El-Mallakh et al. 1991	*Averback 1981*

Note.—Densities and total cell number of neurons except when indicated: G = glia; N+G = neurons + glia; Qualitative studies in italics; PPN = pedunculopontine nucleus; LTD = lateral dorsal tegmental nucleus; NbM = nucleus basalis of Meynert.

trol cases. Furthermore, the caudate nucleus of four schizophrenia cases showed astrocyte density similar to the control cases and significantly less compared with four cases with Huntington's disease.

Four quantitative studies of dopaminergic and noradrenergic neurons revealed no significant changes in cell number. Bogerts et al. (1983) looked at the neuromelanin-containing neurons of the substantia nigra/ventral tegmental area of a sample of six schizophrenia patients not exposed to neuroleptic treatment, comparing them with those of six controls. The volume of the lateral substantia nigra area was decreased, and the size of neuromelanin-containing perikarya in the mesolimbic part of the dopaminergic cell group decreased. There were no changes in the total number of nerve cells and glial cells. Lohr and Jeste (1988) studied neuromelanin-containing cells of the locus ceruleus in 15 leukotomized schizophrenia patients (mean age 46), 11 leukotomized patients with diagnoses other than schizophrenia (mean age 52), and 13 controls (mean age 52). There was a nonsignificant trend for decreased locus ceruleus volume but normal cell density and total neuron number. Karson et al. (1991) and Garcia-Rill et al. (1995) used an antibody against tyrosine hydroxylase to stain the catecholaminergic neurons of the locus ceruleus. Both studies found no change of total neuron number, but Karson et al. (1991) reported a significantly reduced cell size of the locus ceruleus neurons in schizophrenia subjects.

Two qualitative studies described degeneration of cholinergic basal forebrain neurons. Von Buttlar-Brentano (1952) studied nine schizophrenia cases from the Vogt collection and described a decrease in cell size, but did not give a description of the normal cell. Averback (1981) studied 35 controls, 45 cases of Huntington's disease, 7 of Alzheimer's disease, and 13 of schizophrenia. For all three disease states (including 11 cases of schizophrenia), he reported vacuolar degeneration and glial cell clusters surrounding the large neurons of the ansa peduncularis, a subgroup of cholinergic neurons of the basal forebrain.

Two quantitative studies reported normal cell density of cholinergic basal forebrain neurons: Arendt et al. (1983) for a sample of 3 schizophrenia patients and El-Mallakh et al. (1991) for a sample of 10 intellectually impaired and 7 intellectually intact schizophrenia patients. The projections of the cholinergic basal forebrain, studied with acetyl cholinesterase histochemistry in different cortical areas, were found to be normal in a sample of six schizophrenia and schizoaffective patients compared with six controls (Heckers et al. 1993).

Karson et al. (1991) studied the pedunculopontine nucleus (PPN) and the lateral dorsal tegmental nucleus (LDT), using NADPH-d reactivity as a marker for cholinergic neurons. The total number of NADPH-d neurons was significantly higher in the four schizophrenia cases (mean age 63), compared with the five control cases (mean age 60), which was interpreted as evidence for an

increased number of cholinergic brainstem neurons in schizophrenia. In a subsequent study by the same group (Garcia-Rill et al. 1995), this finding was corroborated in at least some of nine schizophrenia patients compared with four nonschizophrenia psychiatric cases and five control cases (eight of the nine previously analyzed cases were included in the study). Total cell number, determined by counting all PPN and LDT neurons in every eighth section through the right brainstem, was increased in the schizophrenia sample by 64 and 56 percent for PPN and LDT, respectively, reaching significance only for the PPN due to large variance mainly in the schizophrenia sample. As in the previous study, the number of locus ceruleus neurons was unchanged in the schizophrenia sample. The NADPH-d neurons in all three groups showed a regional distribution and mean cell size similar to that known for neurons stained with choline acetyltransferase (ChAT) immunohistochemistry, which supported the assumption that NADPH-d can be used as a marker for cholinergic PPN and LDT neurons.

However, a recent study (Manaye et al. 1995) found no differences in the number of ChAT-positive neurons in the PPN and LDT of three schizophrenia cases and six controls. Also, in 8 schizophrenia and 11 control cases, there was no difference in the number of Nissl-stained PPN neurons.

A Western immunoblot study of the pontine tegmentum of younger individuals (25 schizophrenia cases with a mean age of 34 and 28 nonschizophrenia cases with a mean age of 35) revealed a significantly lower concentration of ChAT in the schizophrenia sample (Karson et al. 1993). A lower level of the acetylcholine-synthesizing enzyme ChAT seems at variance with an increased number of cholinergic neurons in the same area. One possible explanation is a decreased cholinergic input into the pontine tegmentum, since most of the ChAT enzyme is localized in cholinergic axons and terminals (Garcia-Rill et al. 1995).

Conclusion: Gliosis in the periventricular and periaqueductal white matter was demonstrated in three qualitative studies (but not in the quantitative study by Stevens et al. 1988). In contrast to cortical and white matter gliosis, found in some cases diagnosed with schizophrenia that revealed focal brain damage on pathological examination, periventricular and periaqueductal gliosis were not related to any focal damage. The cause remains obscure (remnant of an infectious or inflammatory process?), and further studies are needed. Four methodologically sound studies (providing total cell number) demonstrated normal neuronal and glial numbers in the sustantia nigra and the locus ceruleus. Quantitative studies of the cholinergic basal forebrain neurons have demonstrated no significant

changes. Studies of the cholinergic brainstem neurons are conflicting: NADPH-d–positive neurons in the PPN and LDT were found to be elevated in at least some schizophrenia subjects, whereas the number of ChAT-positive neurons was unchanged and the level of ChAT was found to be decreased.

Discussion

Neuropathological studies of schizophrenia have established neither a single lesion nor strong clinicopathological correlations. Moreover, there are no neuropathological criteria to diagnose or stage schizophrenia. Although the studies reviewed here have progressed from qualitative descriptions to blind, quantitative, case-control studies, they still produce conflicting results. Neuronal and glial density, regional brain volume, and architecture of cortical neurons and gyri are the focus of most current studies. What are the promising leads in these studies? What is necessary to resolve the dispute over divergent results?

Cell Density Studies. Altered neuronal density in postmortem specimens can be due to abnormal development of neurons, changes of neuron numbers in the developed brain, decreased or increased neuropil, or tissue changes during fixation and staining. Decreased neuronal density accompanied by increased glial density is typically seen after degenerative changes of the brain, whereas decreased neuronal density accompanied by unchanged glial density is often interpreted as an indicator of brain injury during development (because this is a time when the glial response to injury is decreased or absent). So far, studies of neuronal density have reported decreased, increased, or unchanged density in the cortex; decreased or unchanged density in the thalamus and the basal ganglia; and increased or unchanged density in the brainstem (tables 2 to 5). As pointed out above, it will be important either to eliminate the bias introduced by postmortem tissue changes by using total cell-number estimates or to reduce this bias by comparing different subpopulations of cells within the same specimen. This will allow us to answer the question: Is the neuron number changed in schizophrenia? If there is neuronal loss, are subsets of neurons differentially vulnerable to injury, and when does the injury occur?

Studies so far point to a vulnerability of supragranular cortical neurons (layers 2 and 3) and NADPH-d and GABAergic cortical neurons (Alzheimer 1913; Jakob and Beckmann 1986; Benes 1993a; Akbarian et al. 1993a, 1995). The attractive theory of cortical maldevelopment in schizophrenia proposes an impaired migration of *some* cortical neurons from the ventricular wall to their final

cortical destination (for review, see Weinberger 1995). This could explain the decreased neuronal density in supragranular layers unaccompanied by a significant increase in glial density, the increased density of supragranular neurons in deeper layers, the increased density of cortical neurons in the underlying white matter, and (although less stringent) an abnormal gyration of the cortex. However, decreased neuronal density in supragranular layers is still controversial, and evidence of misplaced cortical neurons is either qualitative or awaits corroboration by further quantitative studies. The most robust finding so far is the lack of cortical gliosis. The neurodevelopmental theory of schizophrenia will be greatly advanced if a reduction or displacement of (supragranular) neurons can be established by unbiased and independent studies.

Decreased neuronal density in the striatum, thalamus, and brainstem was reported in earlier studies, whereas more recent studies have reported a reduced total cell number in the nucleus accumbens and mediodorsal thalamic nucleus, an unchanged cell number in the globus pallidus, and even an increased cell number in the brainstem (tables 3 to 5). Increased gliosis in the basal ganglia, thalamus, and brainstem, as reported in earlier studies, could not be corroborated in more recent studies (tables 3 to 5). While there has been a renewed interest in cortical abnormalities, there are very few studies investigating the complex organization of subcortical structures in schizophrenia. There are essentially no studies of the different neuronal subpopulations in the thalamus and basal ganglia and very few of the neurotransmitter-specific projection neurons of the brainstem. Considering the importance of cortical-subcortical interaction and the variety of subcortical targets for neuroleptic medication, it will be a major challenge to explore a subcortical pathology in schizophrenia.

Volumetric Studies. Three significant volumetric changes in schizophrenia, originally observed postmortem and now increasingly by in vivo imaging, are a smaller thalamus, larger basal ganglia components, and a smaller superior temporal gyrus. However, the results are not consistent. First, one study reported reduced volume of the left mediodorsal thalamic nucleus in postmortem specimens (Pakkenberg 1990), but in vivo imaging of the thalamus revealed lateral thalamic abnormalities on the right (Andreasen et al. 1994*b*). Second, postmortem and in vivo imaging studies reported basal ganglia volume increase (Heckers et al. 1991*b*; Jernigan et al. 1991; Breier et al. 1992; Swayze et al. 1992; Buchanan et al. 1993), but recent MRI studies reported a significant effect of neuroleptic medication on the size of the caudate nucleus in schizophrenia patients (Chakos et al. 1994; Keshavan et al. 1994).

Postmortem volumetric studies, with their intrinsic problem of tissue shrinkage, will become less important as in vivo imaging techniques become more accurate in delineating the boundaries of anatomical structures. Volumetric in vivo studies can follow patients over time, compare patients on and off medication, and use the powerful twin- and family-study design. Such studies have already added significantly to our understanding of schizophrenia (Kotrla and Weinberger 1995). However, the major question of volumetric studies remains: What does volume change indicate? This has been the riddle of ventricular enlargement found in many but not all schizophrenia patients (Shelton and Weinberger 1986). Therefore, neuropathological studies will remain crucial in elucidating the microscopic equivalent of volumetric abnormalities.

Architectural Studies. The architecture of cells within the cortical mantle and the configuration of gyri and fissures on the cortical surface have attracted the interest of schizophrenia researchers since Alzheimer's study in 1897. The current interest in cytoarchitectural abnormalities is mainly driven by the neurodevelopmental theory: If schizophrenia is not characterized by massive cell loss and significant gliosis in the adult brain (as suggested by most of the studies), the "schizophrenia lesion" might be acquired early in development, could be more subtle, and could involve qualitative alterations of cell shape, cell position, connectivity, and the normally asymmetric development of gyri and fissures in both hemispheres. Most of the cytoarchitectural findings are reported for the limbic and paralimbic structures of the temporal lobe (see Dwork 1997, this issue), but abnormalities of the superior temporal gyrus (Southard 1915; Barta et al. 1990; Shenton et al. 1992; Falkai et al. 1995) and displacement of NADPH-d–positive cortical neurons to the underlying white matter (Akbarian et al. 1993*a*, 1993*b*) are two important findings in the isocortex of schizophrenia patients that need to be replicated. The challenge of this approach is the question "What is normal?"—which requires quantitation that goes beyond the rather simple schema of "more or less."

Clinicopathological Correlations. It will be important for neuropathologists to establish strong clinicopathological correlations in schizophrenia. Studying patients with more circumscribed symptoms (such as auditory hallucinations), rather than studying syndromal constructs such as schizophrenia, might yield stronger correlations of neuropathological changes and clinical symptoms. For example, do only schizophrenia subjects with auditory hallucinations show abnormalities of the superior temporal gyrus? How do those with auditory hallucinations com-

pare with other patients with such hallucinations? It will also be important to study the anatomical pattern of the lesions described in schizophrenia. For example, do patients with abnormalities of the mediodorsal thalamic nucleus also show changes in closely connected areas such as the prefrontal cortex, anterior cingulate gyrus, or limbic structures of the temporal lobe?

Neuropathological studies of schizophrenia have demonstrated that changes are more subtle than those in established neurodegenerative diseases and more widespread than those in system diseases. The study of well-defined subgroups and the use of techniques that allow comparison of results across studies will advance the neuropathology of schizophrenia. Then we can close the "graveyard of neuropathologists" (Plum 1972).

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