Postmortem Studies of the Hippocampal Formation in Schizophrenia

by Andrew J. Dwork

Abstract

Many postmortem studies report differences between the hippocampal formations of patients with schizophrenia and those of controls. These differences include volume changes, cell density changes, periventricular gliosis, senile degenerative changes, and abnormalities of neuronal size, position, or orientation. However, the findings are almost never common to all schizophrenia patients within a series. Furthermore, some well-designed studies are negative, and different positive reports are mutually contradictory. Some of the inconsistencies are methodological. The normal variation, over small distances, in the cytoarchitecture of the temporal allocortex creates particular difficulties when this region is studied with a limited number of sections, especially if the sample size is small. Other inconsistencies are probably the result of case selection. We review the methods and findings of some of these studies, stressing the dangers of eliminating (rather than evaluating) cases with definite neuropathologic changes. We conclude that the existing postmortem studies of temporal lobe morphology provide little conclusive evidence for the neural substrate of schizophrenia.


Over the past decade or so, a number of studies have reported abnormalities in the hippocampal formations (hippocampus, prosubiculum, subiculum, presubiculum, parasubiculum, and entorhinal cortex) of brains obtained at the autopsy of patients with schizophrenia. These abnormalities consist primarily of volume changes, cell density changes, periventricular gliosis, senile degenerative changes, and abnormalities of neuronal size, position, or orientation. Abnormalities in position and orientation of neurons have been interpreted as evidence for an early fetal lesion, while gliosis has been interpreted as evidence of a late fetal or postnatal insult, possibly of an infectious nature (figure 1).

These interpretations are arguable, but before considering the interpretations, it is worthwhile to scrutinize the evidence upon which they are based. The postmortem studies have been widely accepted, in aggregate, as demonstrating conclusively that in schizophrenia there is some abnormality in the hippocampal formation. They are often cited in other articles, beyond the scope of this review, reporting clinical, radiologic, and experimental evidence of hippocampal abnormality. Unquestioning acceptance of postmortem abnormalities, however, ignores several well-designed negative studies, as well as the mutual contradictions to be found among the various positive reports. The purpose of this review is to examine the methodology and conclusions of a number of recent postmortem studies of this hippocampal formation in schizophrenia and to consider the implications of the existing data for various etiological hypotheses.

Methodological Issues

Certain diseases, such as multiple sclerosis, meningitis, or tuberous sclerosis, are easily recognized on postmortem examination of the brain; a neuropathologist can make a definitive diagnosis and be reasonably certain that other neuropathologists reviewing the same material would agree. Other neuropathological phenomena, such as acutely ischemic neurons, senile plaques, and Lewy bodies, have characteristic appearances. However, while different neuropathologists looking at the same slides would agree fairly closely about the presence of such changes, they might well disagree about their significance, especially when the changes are not severe. Still other phenomena (such as neuronal loss, gliosis, or cytoarchitecture-
Most reported neuropathological abnormalities in schizophrenia are of this last type; hence, quantitative measurements help eliminate subjective differences between observers. Furthermore, neuropathological changes reported in the brains of schizophrenia patients are neither sensitive nor specific; they are simply associated statistically with schizophrenia. Often, they cannot be evaluated as present or absent by subjective evaluation of a brain or slide; thus, they must be evaluated quantitatively.

Such quantitative measurements are generally of three types: volume, cell density, and total cell number. They are related to a specific anatomical structure, such as the cerebral cortex or the anterior nucleus of the thalamus. Cell density is the number of cells of a given type (usually neurons) per unit volume. Total cell number, equal to cell density multiplied by volume, is the number of such cells in an entire anatomical structure.

Usually, these three-dimensional quantities are estimated from two-dimensional measurements. Volume of a neuroanatomical structure is estimated by measuring its cross-sectional area in several parallel planes. The cross-sectional areas are multiplied by the distance between cross sections, and the results are summed. The estimate can be made as accurate as desired by decreasing the distance between cross sections.

For two reasons, it is essential that the cross sections comprise the entire length of the structure of interest. Obviously, even if a structure is of a constant cross section, one cannot estimate its volume without estimating its length. Second, a cross-sectional area depends on the orientation of the plane in which it is measured, but as long as measurements are made through the entire structure, this orientation will not affect the volume measurement.

Since it is difficult to be certain that a plane of a section is oriented identically in two different brains, measurements of a fixed number of cross sections are not necessarily comparable from one brain to another. This difficulty is eliminated when volumes are estimated from a set of parallel cross sections that spans the entire structure.

Estimates of neuronal density depend upon (1) accurate distinction of neurons from glia and (2) a method of counting all neurons with equal probability, regardless of size or shape. Sophisticated yet simple methods are now available to achieve the second condition; these involve examining two adjacent sections and counting a neuron only when it first appears, that is, when it is present in the second section but not in the first (e.g., see West and Gundersen 1990). Earlier work achieved this condition reasonably well by counting neurons only if the nucleolus was present in the section, since nucleoli vary in size and shape much less than neuronal cell bodies do.

The distinction of neurons (especially small neurons) from glia is more problematic. There is no stain that labels all neurons or all glia. The distinction is always somewhat subjective and depends upon cell shape, nuclear morphology, and the presence of Nissl substance. Since large neurons are more easily recognized than small ones, there is always a danger that neuronal shrinkage will be interpreted as neuronal loss.

Artifactual shrinkage or swelling of tissue during fixation or processing will affect measurements of volume and cell density. However, since these effects are inversely proportional, total cell number is not affected.

Altered Cytoarchitecture of Entorhinal Cortex (table 1)

Disorganization of the entorhinal cortex in the brains of schizophrenia subjects was described by Jakob and Beckmann (1986), who studied the brains of 64 schizophrenia patients with an average age of 63 years. Twenty-two of these brains were found to be grossly normal.

![Figure 1. Nissl-stained section of human hippocampal formation, slightly anterior to level of lateral geniculate body](image-url)
which are adjacent to the transentorhinal cortex. Thus, unless one goes to exhaustive lengths to identify all subre-
cytoarchitectonic regions; superficial clusters of pre-a
(Braak 1980).

3. The widths of the pre-β and pri-α layers vary enor-
mously over small changes in medial or lateral position
(Braak 1980).

Braak (1980) divides the entorhinal cortex into nine
cytoarchitectonic regions; superficial clusters of pre-α
neurons are seen only in the three most lateral regions,
which are adjacent to the transentorhinal cortex. Thus,
unless one goes to exhaustive lengths to identify all subre-
gions of the entorhinal cortex and to define its borders, it
is impossible to know whether the features described by
Jakob and Beckmann (1986) represent departures from
the normal or merely different anatomical subregions.
Furthermore, the subjectivity inherent in this determina-
tion requires that the investigators be blind to clinical
diagnosis, and the article makes no statement that this was
the case.

A possible problem in this study is that all cases with
neuropathological findings of organic brain disease,
inflammation, degenerative processes, senile atrophy, or
presenile atrophy were excluded. The number of brains so
excluded was not stated, nor was there any indication of
the relative frequency of such cases among schizophrenia
subjects and controls. The existence of such exclusionary
neuropathology may not be independent of schizophrenia
(see below). Theoretically, if a neuropathological change
were more common in schizophrenia than in controls, but
occurred only in cytoarchitecturally normal entorhinal
cortices, excluding cases with that change would bias the
results toward finding cytoarchitectural abnormalities in
the brains of schizophrenia patients.

An expansion of this study, apparently including the
original cases plus additional ones, was published later by
the same authors (Jakob and Beckmann 1989). The
methodology and findings were similar to those in the
original report, but it is unclear why the numbers of
grossly normal cases and histologically equivocal cases in
the schizophrenia group are lower than before. These
investigators later described similar alterations in the
brains of four patients with manic-depressive illness
(Beckmann and Jakob 1991).

Arnold et al. (1991a) described similar findings in the
brains of six leukotomized schizophrenia subjects (mean
age 47) from the Yakovlev collection, while these abnor-
malities were not seen in five neurosurgical control brains,
including two with frontal leukotomy or lobotomy, nor in
11 other control brains. This study, too, was performed
effectively unblinded. Although photomicrographs were
examined by two investigators blind to clinical diagnosis,
the photographs were taken by an investigator who was
aware of the diagnosis and hence potentially subject to bias
in choosing the areas for photography. A recent study by
this researcher (Arnold et al. 1995a), described further below,
found normal neuronal densities in the entorhinal cortex
and made no mention of cytoarchitectural abnormality.

Bruton et al. (1990) examined the brains of 48 schiz-
ophrenia patients (mean age 68) and 56 controls collected
from a prospective study (further described below). Eight
brains of schizophrenia subjects had been eliminated
because of leukotomy, epilepsy, multiple sclerosis, and
acute infarction. The neuropathologists were blind to the
clinical diagnosis and found no evidence of histological

Table 1. Altered cytoarchitecture of entorhinal
cortex

<table>
<thead>
<tr>
<th>Reference</th>
<th>Abnormalities in gross configuration</th>
<th>Abnormal cytoarchitecture in entorhinal cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakob and Beckmann 1986</td>
<td>Present in 66%</td>
<td>34% equivocal; 31% definite; similar but less-pronounced findings in controls</td>
</tr>
<tr>
<td>Jakob and Beckmann 1989</td>
<td>Present in 74%</td>
<td>45% definite; 8% equivocal</td>
</tr>
<tr>
<td>Arnold et al. 1991a</td>
<td>100% of schizophrenia cases, 0% of controls</td>
<td></td>
</tr>
<tr>
<td>Bruton et al. 1990</td>
<td>Not found</td>
<td>Not found</td>
</tr>
</tbody>
</table>

Note.—Comparisons of conclusions from various studies. Data in Italic represent negative findings. Apparent discrepancies may be explained by methodological and other considerations (see text).

Presumably, these were normal microscopically as well,
whether this is not specifically stated. The remaining 42
brains showed an abnormal temporal sulcogyral pattern or
a “tendency toward microcephaly.” Among these, 22 con-
tained equivocal histological changes in the limbic allo-
cortex, not further described. The remaining 20 contained
“well-defined” changes, which consisted of pre-α neurons
in the pre-β layer, pre-α neurons in bands rather than
clusters, and “poorly developed” pre-β and pri-α layers.

The significance of these findings is difficult to evalu-
ate. Ten brains from nonschizophrenia subjects were
examined. The findings in these control brains are not
clearly stated, although it is noted that these, too, con-
tained pre-α neurons in the pre-β and pre-Γ layers. The
criteria for histological abnormality were not decided
before examination of the brains, nor were they clearly
defined post hoc. The findings described are subtle and
are in fact similar or identical to normal variations in
entorhino-cortical architecture:

1. In the medial portion of the entorhinal cortex, the
pre-α neurons are arranged in a band, rather than in clusters.

2. In the transentorhinal cortex, immediately lateral to
the entorhinal cortex, pre-α neurons are found at the same
depth as the pre-β and pre-Γ layers.

3. The widths of the pre-β and pri-α layers vary enor-
mously over small changes in medial or lateral position
(Braak 1980).
abnormality in the entorhinal cortex and no differences between groups with regard to abnormalities of gyration.

Compared with the studies cited above, this study had the advantages of prospective design, a larger and more appropriate control group, fewer conditions requiring elimination of brains from the original sample, and blindness to clinical diagnosis. While these advantages lend considerable credibility to the negative result, one cannot rule out the possibility that these investigators failed to recognize certain subtle abnormalities appreciated by Arnold et al. (1991a) and by Jakob and Beckmann (1986, 1989). However, if this is the case, the burden is on the latter investigators to define more precisely the criteria for cytoarchitectural abnormality.

Altered cortical cytoarchitecture, in the absence of gliosis, would most likely reflect abnormal migration of cortical neurons during development. Dramatic cortical dysplasias are sometimes associated with temporal lobe epilepsy. The abnormalities suggested by Jakob and Beckmann (1986, 1989) and by Arnold et al. (1991a) are much more subtle and were not found by Bruton et al. (1990). Their presence was not noted in any of the numerous other studies of the temporal lobe in schizophrenia discussed below. If they are indeed present, proof will require examination of multiple rostrocaudal levels by observers who are blind to clinical diagnosis.

Disorganization of Hippocampal Neurons (table 2)

Kovelman and Scheibel (1984) studied the left hippocampi of 10 chronic paranoid schizophrenia patients (average age 50) and 8 controls. Blind to clinical diagnosis, they measured the angles between the axes of hippocampal pyramidal cells and a reference line perpendicular to the wall of the lateral ventricle. At a middle rostrocaudal level of the interface of hippocampal field CA1 and prosubiculum, the schizophrenia subjects showed a (1) greater mean angle of deviation and (2) more cells with an angle of deviation greater than 35 degrees. Smaller but statistically significant differences were also seen at the CA1/2 and CA2/3 interfaces.

In contrast, no differences were seen in the posterior hippocampus. However, blocks from both hippocampal levels were not available on all subjects. It appears that midhippocampal blocks were available from only four schizophrenia subjects and five controls (see Kovelman and Scheibel 1984, figure 3), and the authors do not mention how these subgroups compared with regard to age, cause of death, or concurrent neurological disease. A larger number of posterior blocks were present and presumably represented a greater number of subjects.

A similar study was later performed on the right hippocampus, using a series of 11 schizophrenia cases and seven controls, including some of the original subjects (Conrad et al. 1991). There were important technical differences from the previous study:

1. All hippocampi were sampled at three rostrocaudal levels, and the data from the three levels were pooled for each interface.

2. The CA1/2 and CA2/3 borders were determined by cytoarchitectural properties, rather than by a geometric method employed in the previous study, which was reproducible but somewhat arbitrary.

3. An attempt was made to combine the degree of deviation and number of highly deviated cells into a single measure, termed "disorganization number."

At all three interfaces, there was greater disorganization in the samples from schizophrenia subjects, but this reached statistical significance only at CA1/2 and CA2/3, where the schizophrenia disorganization numbers were nearly double those at the prosubiculum/CA1 interface.

A similar determination of disorganization number in left hippocampi from the Yakovlev collection revealed no difference between schizophrenia patients treated with lobotomy or leukotomy and neurosurgical controls (Altschuler et al. 1987). This negative finding may be explained by missing sections of the anterior hippocampus.

Christison et al. (1989), using a more extensive sample from the Yakovlev material and statistics specifically developed to analyze spatial orientation, also failed to
detect any difference between leukotomized schizophrenia cases, leukotomized controls, and nonleukotomized controls. Benes et al. (1991) found no difference between schizophrenia cases and controls in the orientation of pyramidal cells at the CA1/prosubiculum interface, but since this examination was limited to a posterior level of hippocampus, the result does not contradict that of Kovelman and Scheibel (1984).

Arnold et al. (1995a, 1995b) compared the brains of 14 prospectively examined patients with schizophrenia (mean age at death 71) to those of 10 subjects without neuropsychiatric disorder (mean age 76). Exclusion criteria for the subjects with schizophrenia included an ambiguous psychiatric diagnosis, substance abuse, neurological disorder preceding schizophrenia, subsequent neurological disorders that would significantly compromise brain function, and prolonged agonal state (Arnold et al. 1995b). The criteria for the comparison subjects were not specified (Arnold et al. 1995a).

Neuropathologic examination was normal in seven of the controls and in one revealed small, recent subdural hematomas without brain abnormality. Among the 14 schizophrenia subjects, neuropathologic examination was normal in 9. The four hippocampal subfields (CA1–4), subiculum, and three layers of entorhinal cortex were each examined at a single level by cresyl violet stain. Computerized-image analysis was used to determine the orientation of a set of neurons in the center of each region. Variance was determined for each set of neurons. The variance did not differ between schizophrenia cases and controls in any region.

These results thus fail to confirm those of Kovelman and Scheibel (1984) and Conrad et al. (1991). However, measurements were made in the centers of cytoarchitectural fields, while the earlier studies found the greatest degrees of disorganization at the interfaces between those fields.

Neuronal disorganization is difficult to evaluate statistically. The results are apparently sensitive to the method of measurement. In the first study of the left hippocampi, the greatest degree of disorganization was at the prosubiculum/CA1 interface. By contrast, when the new method of measuring disorganization number was applied to the left hippocampi (it is not clear whether these were the same as those used in the first study), this interface had the lowest disorganization numbers (Conrad et al. 1991).

The statistical methods employed by Christison et al. (1989) appear to be the most sophisticated. It would be of great interest to apply these methods to appropriately sampled brains.

A further caveat in interpreting these studies is that hippocampal anatomy, especially at the rostral end of the hippocampus, is exquisitely sensitive to rostrocaudal position. When the number of cases in each group is small, the possibility exists that a few brains from one group, but not the other, were randomly sampled at a level that normally produces high dissociation numbers. Such a result would be consistent with the observation that most of the measured dissociation numbers from the brains of schizophrenia patients were similar to those from controls, but a small portion were considerably higher (Conrad et al. 1991).

A possibly related finding by Arnold et al. (1991b), in a series of six schizophrenia cases (mean age 78), was a pronounced loss of neuronal immunoreactivity for the microtubule-associated protein 2 (MAP2) and MAP5 in the subiculum of five subjects and the entorhinal cortex of four. Alterations in these proteins could influence neuronal polarity or dendritic morphology, theoretically with pronounced functional effects.

My colleagues and I have in part replicated this finding (Rosoklija et al. 1996). Our sample consisted of 36 individuals hospitalized for schizophrenia, 9 for mood disorder, and 13 for dementia and 17 subjects without any history of psychiatric illness. Psychiatric diagnoses were determined by a review of clinical records (Keilp et al. 1995). The mean age was 77–78 for each of the psychiatric groups, and 60 for the nonpsychiatric group.

Immunoperoxidase staining for MAP2 was performed on paraffin sections, and immunoreactivity in the subiculum and CA4 was compared subjectively on coded slides. Pronounced loss of subicular immunoreactivity (compared with CA4) was present in 10 (28%) of the schizophrenia cases, 1 (11%) of the mood-disorder subjects, and 5 (38%) of the dementia subjects, but in none of the nonpsychiatric cases. Similar results were obtained if optical density of the subiculum was compared with that of CA4 by densitometry. Thus, in our study, loss of subicular MAP2 immunoreactivity in paraffin sections is strongly associated with schizophrenia but is not a specific or sensitive marker. Both antemortem (reviewed in Johnson and Jope 1992) and postmortem (Schwab et al. 1994) factors have been reported to affect MAP2 immunoreactivity, but we have so far detected no effect of these factors on our results.

The conflicting results, and the difficulties inherent in measuring spatial orientation of neurons and treating the data statistically, make it impossible to draw conclusions about the presence or absence of neuronal disarray in the hippocampal formation of individuals who suffered from schizophrenia. If present, abnormal orientation of neurons could be due to a migrational disorder. However, mature neurons are capable of morphologic changes, and their orientation could also be altered by growth or loss of adjacent glial processes. Thus, alteration of neuronal orientation could occur at any time, from a variety of causes, and

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could be a result (rather than a cause) of schizophrenia. Alterations in structural proteins such as MAP2 and MAP5 could affect neuronal orientation and—probably of greater functional significance—dendritic morphology. If altered orientation is accompanied by loss of MAP2, this might argue against a migrational abnormality, since an abnormally migrating neuron would still be expected to express MAP2.

Altered Hippocampal Volumes and Cell Densities (table 3a, b, and c)

There have been a number of quantitative studies of volumes and cell densities of various areas of the hippocampus. Brown et al. (1986) compared 41 brains of schizophrenia patients (mean age 67) with 35 from patients with affective disorders (mean age 68). The brains of the schizophrenia cases were derived from an original, unselected sample of 148; from these, 71 were eliminated because of failure to meet clinical diagnostic criteria, 7 because of leukotomy, 23 because of senile or vascular disease, and 6 because the appropriate section could not be assessed.

The brains from patients with affective disorder were similarly derived from an unselected group of 84. Structures were measured, blind to clinical diagnosis, on a single coronal slice just anterior to the mammillary bodies, at the level of the foramina of Monro.

Major anatomical findings were that in the brains from schizophrenia patients, the left parahippocampal gyrus was approximately 18 percent thinner, and the area of the temporal horn of the lateral ventricles was approximately twice that in the brains from patients with affective psychosis.

A particular strength of this study is that the schizophrenia cases were compared with other psychotics who died at the same hospital. However, ventricular volume cannot be determined from a single cross-sectional measurement of area. There could be real differences in ventricular length—or apparent ones, if the ventricle is angled differently. Moreover, another study (Bruton et al. 1990) found that the brains of schizophrenia subjects showed anteroposterior shortening. Cortical thickness is even less likely than cortical area to represent cortical volume, since two dimensions are missing.

We should also note that the two groups differed with

<table>
<thead>
<tr>
<th>Reference</th>
<th>Brain weight</th>
<th>Brain length</th>
<th>Hemispheric volume</th>
<th>Cerebral cortical volume</th>
<th>Central gray matter volume</th>
<th>Strialt size</th>
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<tbody>
<tr>
<td>Brown et al. 1986;</td>
<td>Reduced 6% (fixed)</td>
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<td>–</td>
<td>NS</td>
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<td>Colter et al. 1987</td>
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<tr>
<td>Crow et al. 1989;</td>
<td>Reduced 4.5% (fixed), NS</td>
<td>4.5% shorter</td>
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<td>Bruton et al. 1990</td>
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<tr>
<td>Falkai and Bogerts 1986</td>
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<tr>
<td>Bogerts et al. 1990</td>
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<tr>
<td>Jeste and Lohr 1989</td>
<td>NS</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Kovelman and Scheibel 1984</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>NS</td>
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<td>Heckers et al. 1991</td>
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<td>–</td>
<td>NS</td>
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<tr>
<td>Pakkenberg 1987</td>
<td>Reduced 8%</td>
<td>–</td>
<td>Reduced 8%</td>
<td>Reduced 12%</td>
<td>Reduced 7%</td>
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<td>Benes et al. 1991</td>
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<td>Christion et al. 1989</td>
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<tr>
<td>Arnold et al. 1995a,</td>
<td>NS</td>
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<tr>
<td>1995b</td>
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</table>

Note.—Comparisons of conclusions from various studies. Data in italics represent negative findings. Apparent discrepancies may be explained by methodological and other considerations (see text). NS = not significant.
Table 3b. Altered hippocampal volumes and cell densities

<table>
<thead>
<tr>
<th>Reference</th>
<th>Lateral ventricle size</th>
<th>Temporal horn size</th>
<th>Amygdala volume</th>
<th>Total hippocampal volume</th>
<th>Volume, CA1-4</th>
<th>Neuronal cell density, CA1-4</th>
<th>Neuronal cell number, CA1-4</th>
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</thead>
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<tr>
<td>Brown et al. 1986; Colter et al. 1987</td>
<td>NS</td>
<td>97% larger cross-section</td>
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<tr>
<td>Crow et al. 1989; Bruton et al. 1990</td>
<td>-</td>
<td>100% larger (lateral projection)</td>
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<td>Falkai and Bogerts 1986</td>
<td>-</td>
<td>-</td>
<td>Decreased ~15%</td>
<td>Decreased ~20% all sectors</td>
<td>NS</td>
<td>Decreased ~20% all sectors</td>
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<td>Falkai et al. 1988</td>
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<td>-</td>
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<tr>
<td>Bogerts et al. 1990</td>
<td>-</td>
<td>-</td>
<td>Decreased 13-18%</td>
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<tr>
<td>Jeste and Lohr 1989</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Decreased 46%, CA4 only</td>
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<td>Decreased ~30% in CA3 and CA4; NS in CA1 or CA2</td>
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<td>Kovelman and Scheibel 1984</td>
<td>-</td>
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<td></td>
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<td>Pakkenberg 1987</td>
<td>Increased 33%</td>
<td>-</td>
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<td></td>
</tr>
<tr>
<td>Christison et al. 1989</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akbarian et al. 1993b</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td>~50% decrease NADPH-d neurons</td>
<td></td>
</tr>
<tr>
<td>Arnold et al. 1995a, 1995b</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note.—Comparisons of conclusions from various studies. Data in italics represent negative findings. Apparent discrepancies may be explained by methodological and other considerations (see text). CA = cornu ammonis; NS = not significant; NADPH-d = nicotinamide adenine dinucleotide phosphate-diaphorase.
Table 3c. Altered hippocampal volumes and cell densities

<table>
<thead>
<tr>
<th>Reference</th>
<th>Parahippocampal volume</th>
<th>Entorhinal neuronal density</th>
<th>Entorhinal neuronal number</th>
<th>Entorhinal neuronal size</th>
<th>Hippocampal white-matter volume</th>
<th>Parahippocampal white matter</th>
<th>Hippocampal pyramidal cell size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. 1986; Colter et al. 1987</td>
<td>~18% thinner (left)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduced</td>
</tr>
<tr>
<td>Crow et al. 1989; Bruton et al. 1990</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Falkai and Bogerts 1986</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Falkai et al. 1988</td>
<td>Decreased 12–34%</td>
<td>Decreased 23–53%</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Bogerts et al. 1990</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jeste and Lohr 1989</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kovelman and Scheibel 1984</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heckers et al. 1990a</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heckers et al. 1990b</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heckers et al. 1991</td>
<td>-</td>
<td>-</td>
<td>9% reduction left; NS right</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pakkenberg 1987</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Benes et al. 1991</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Reduced ~15%</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Christison et al. 1989</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Akbarian et al. 1993b</td>
<td>-</td>
<td>No change in NADPH-d neurons</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arnold et al. 1995a, 1995b</td>
<td>NS</td>
<td>16% smaller in layer II</td>
<td>-</td>
<td>-</td>
<td>Reduced 14% in CA1, 21% in subiculum</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note.—Comparisons of conclusions from various studies. Data in italics represent negative findings. Apparent discrepancies may be explained by methodological and other considerations (see text). NS = not significant; CA = cornu ammonis; NADPH-d = nicotinamide adenine dinucleotide phosphate-diaphorase.
This is a large study with careful neuropathological examinations of an apparently unselected series of schizophrenia cases, and the findings are thus of great interest. Unfortunately, a somewhat confusing presentation of the data makes further analysis difficult. For example, the number of schizophrenia cases in the "purified group" appears variously as 22 (text, Crow et al. 1989); 19 (figure 2, Crow et al. 1989); 18 (text, Bruton et al. 1990); and 16 (appendix, Bruton et al. 1990). In addition, the detailed planimetry data (Crow et al. 1989) are presented for only 42 schizophrenia cases and 53 controls, with no explanation for the excluded cases.

Morphometric studies were performed on a sample of brains (mostly left hemispheres) from the Vogt collection (Falkai and Bogerts 1986; Falkai et al. 1988; see also Bogerts et al. 1985), consisting of 13 schizophrenia cases (mean age 43), and 11 controls matched for age. Volumes were derived from measurements of the areas of various hippocampal regions on myelin-stained sections at 0.5 to 1 mm intervals through the length of the hippocampal formation; numerical densities of neuronal and glial cell nuclei were determined on adjacent, Nissl-stained sections. No changes in cell density were found in any region, but volume and total neuronal number were decreased in the entorhinal cortex and most areas of the hippocampus by 6 to 39 percent.

The measurements in these studies used appropriate methodology. In particular, determination of total neuronal numbers is not influenced by shrinkage of tissue. The only apparent possibility for technical bias would require the unlikely event that the neurons of schizophrenia subjects had nuclei with a smaller rostrocaudal dimension than those of controls (artificially lowering determined cell density), and that the tissue underwent a greater degree of shrinkage (artificially lowering volume while raising cell density back to normal).

More problematic, however, are the small sample size and the uneven sex distribution: 7 of 11 controls but only 2 of 13 schizophrenia cases were male. Since most of the measurements were influenced by sex, correction for sex distribution is necessary, and this cannot be done reliably with such small samples (e.g., for male schizophrenia patients, results are based on a sample size of two).

The article describing the hippocampal measurements (Falkai and Bogerts 1986) also contains an inconsistency that impairs comparisons with the results of other investigators: Average values of the total neuronal cell count for each region, which should roughly equal average cell density times average volume, are approximately 10 times greater than the products obtained from the values presented. Evidently, there is a typographical error here, but it is not obvious where it occurs. As stated, the control value for total pyramidal cell number in CA1–4 is approx-
imately five times greater than values obtained independently by West and Gundersen (1990) and Heckers et al. (1991) (see below), which are fairly close. Likewise, the relative sizes of the different hippocampal compartments differ considerably from those reported in the latter two studies. However, whatever the reasons for these differences among studies, they do not seem likely to explain the observed differences between schizophrenia cases and controls.

These investigators also determined bilateral hippocampal volumes from paraffin sections of a second group of 18 schizophrenia patients (mean age 52) and 21 controls who died from 1985 to 1988 (Bogerts et al. 1990). Measurements of each case were corrected individually for tissue shrinkage. Total hippocampal volumes were significantly decreased bilaterally among schizophrenia cases as compared with controls—18 percent for men and 13 percent for women. These values were equal on both sides and were very similar to those obtained previously (Bogerts et al. 1985; Falkai and Bogerts 1986).

Jeste and Lohr (1989) studied hippocampal volumes and cell densities in the brains of the Yakovlev collection by methods similar to those employed on the Vogt collection (Bogerts et al. 1985; Falkai and Bogerts 1986). Their sample consisted of 13 leukotomized schizophrenia patients (mean age 44), 9 leukotomized controls, and 16 normal controls. Both sides were examined, and sectors CA1 through CA4 were evaluated independently.

Statistically significant results were a lower pyramidal cell density in the left CA3 compared with normal controls and in the left CA4 compared with leukotomized controls, along with bilaterally smaller CA4 volumes compared with leukotomized controls (46% smaller on left, value for right side not given). CA1, CA2, and CA3 showed trends bilaterally toward smaller volumes than leukotomized controls.

Volumetric results are thus consistent with those from the Vogt collection, but in terms of neuronal density, the results are contradictory. Kovelman and Scheibel (1984, see above) found no differences between schizophrenia patients and controls in neuronal density in any portion of the hippocampus.

Heckers et al. (1990a) applied modern stereological techniques, with individualized adjustments for shrinkage, to the brains of 20 schizophrenia patients (average age 64) and 20 controls matched for age and sex. Eight brains of schizophrenia subjects and seven of controls were eliminated because of histopathological changes; two brains with "incipient senile changes" were not excluded.

No substantial or statistically significant changes were found in the volumes of hemispheres, amygdala, or hippocampi. There was a nonsignificant trend toward larger lateral ventricles in the brains of schizophrenia cases (24% larger on left, 17% on right), with similar results for the anterior and posterior horns bilaterally and the left temporal horn, but not the right.

When the sample was restricted to paranoid schizophrenia cases (11 patients) and their age- and sex-matched controls, the lateral ventricles of the brains of schizophrenia subjects were significantly larger on the left side, but not on the right. Based on a subsample consisting of 18 schizophrenia cases and 18 controls, there were no differences in the volume of parahippocampal gyrus (Heckers et al. 1990b).

The authors point out that in the volumetric studies performed so far, the borders of the entorhinal cortex had been determined by gross landmarks, rather than by cytoarchitectonics. They note that the normal sulcal variations at the lateral edge of the entorhinal cortex make its delineation by gross inspection unreliable, especially in studies (e.g., Brown et al. 1986) that rely on measurement of the area at a single level. Furthermore, they note that the deficit in entorhinal cortical neuronal number in the brains of schizophrenia cases, as reported by Falkai et al. (1988), was based purely upon a volumetric loss with neuronal density unchanged. They suggest, therefore, that future morphometric studies of the entorhinal cortex in schizophrenia should use cytoarchitectonic criteria for delineating its borders. This suggestion is reasonable, but I would add the warning that if the entorhinal cortices examined contained the cytoarchitectural aberrations described by Jakob and Beckmann (1986, 1989) and by Arnold et al. (1991a), even borders determined by cytoarchitecture could be ambiguous.

In a separate, younger sample of 13 schizophrenia cases (average age 54) and 13 controls, Heckers et al. (1991) found no differences between groups in the volumes of total hippocampus, hippocampal pyramidal cell layers, or the pyramidal cell layer in individual subfields of the hippocampus. However, the derived volume of left hippocampal white matter (total minus pyramidal cell layer) was 9 percent lower in schizophrenia patients than in controls (contradicting a 1986 finding of Falkai and Bogerts, who measured this directly). Neuronal densities and total numbers of neurons in hippocampal subfields showed no differences between groups.

Pakkenberg (1987) found a 33 percent increase in ventricular volume for 29 schizophrenia cases (mean age 74) compared with 30 age-matched controls without neurological or psychiatric illness. Individual ventricular horns were not analyzed. Since the medical exclusion criteria for controls were considerably more rigorous than for schizophrenia patients, differences between the two groups could be an artifact of selection. However, at least
two findings related to ventricular size cannot be attributed to selection artifacts:

1. Among controls, ventricles were significantly larger in the subgroup above age 65, while this was not the case for the schizophrenia sample;

2. The ventricles of Type II schizophrenia subjects were significantly larger than those of Type I schizophrenia subjects.

Benes et al. (1991), using material from the McLean Hospital brain bank, examined the brains of 14 schizophrenia cases (mean age 51) and 9 controls (mean age 59). Vibratome-cut sections were stained directly to eliminate tissue shrinkage. The investigation was limited to a single posterior level. No differences were found between groups in the cross-sectional areas of the sectors CA1 through CA4, nor in the total number of pyramidal cells in each sector. As in the study of Brown et al. (1986), measurements of area or cell number at a single level cannot necessarily be generalized to an entire structure.

These authors also measured the pyramidal cell cross-sectional area, which was approximately 15 percent smaller in the brains of schizophrenia cases (p < 0.01). No alteration in pyramidal cell size, shape, or orientation was found by Christison et al. (1989), who studied 17 schizophrenia cases, (mean age 45 years), 14 leukotomized controls, and 18 nonleukotomized controls from the Yakovlev collection.

In the study described above, Arnold et al. (1995a) found no differences between schizophrenia and control subjects in neuronal density of any portion of the hippocampus, subiculum, or entorhinal cortex. They did, however, find neuronal cross-sectional areas to be smaller in the brains of the first group. In the three regions where these results achieved statistical significance—CA1, subiculum, and the pre-α layer of the entorhinal cortex—the cross-sectional areas were 14 to 21 percent lower in the brains of schizophrenia patients.

Akbarian et al. (1993a, 1993b) found, in a small series of schizophrenia patients, a decrease of 50 percent in the numerical densities of nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) positive neurons in neocortical and hippocampal gray matter and increased numbers in deep white matter underlying the neocortex. This finding was interpreted as evidence for altered neuronal migration. The argument for this explanation is that these neurons, which are relatively resistant to hypoxic or degenerative death, remain as markers of an arrested migration of neurons from a germinal matrix to cortex. In this case, one would expect to find decreased numerical densities of neurons in neocortical gray matter and the hippocampus.

Although the question of loss of gray matter volume and absolute neuronal number in various brain regions is quite controversial, there is only one report of decreased numerical density of hippocampal neurons in schizophrenia, and the loss is considerably less than 50 percent (Jeste and Lohr 1989). A loss of 50 percent of neuronal density would be readily apparent on routine histological examination, which has not been reported. If the migration of neurons were arrested in white matter, as proposed, one might also expect an increased incidence of gray matter heterotopias in the white matter, and this too has not been described in schizophrenia. Furthermore, if impaired migration of neurons into a region were consistently represented in later life by a loss of NADPH-d positive neurons, the absence of such a loss in the entorhinal cortex would tend to contradict the theories of Jakob and Beckmann (1986, 1989) and Arnold et al. (1991a)—that the observed alterations in entorhinal cortical architecture represent impaired neuronal migration during development.

There also appears to be a methodological problem with these two articles. Repeated measures of each variable for individual patients were combined across the cohort and tested as independent measurements. In other words, when 10 measurements were obtained for a single anatomical compartment in each of 7 subjects, the sample size was apparently treated as 70, rather than 7—which would drastically affect calculations of standard error and statistical significance. This error may have been partially offset, however, if between-subject variance was smaller than within-subject variance, as was the case for the prefrontal measurements.

The plethora of morphometric studies of the brain in schizophrenia points to the lack of obvious neuropathological findings, which, if present, would obviate the need for morphometry. The morphometric studies yield no consistent results, except possibly for ventricular enlargement. Some of the most sophisticated studies show no difference between schizophrenia cases and controls. Even if a loss of gray matter or neurons were present, this would at best indicate where to look for more specific changes.

In the absence of specific changes, certain explanations for neuronal loss (such as infarction) can be ruled out, but a definitive explanation cannot be invoked. Large cerebral ventricles reflect a loss of brain substance or an increase in intraventricular pressure. As we have noted, there is considerable disagreement on the question of where a loss of brain substance may take place in schizophrenia. Accompanied by periaqueductal gliosis, ventricular enlargement may suggest an early infection with aqne ductal stenosis, but the evidence for periaqueductal gliosis is equivocal (see below).
Gliosis (table 4)

Nieto and Escobar (1972) employed Hortega’s lithium-silver carbonate impregnation for the demonstration of glia in 10 brains of chronically hospitalized schizophrenia patients (aged 29 to 52) and 3 nonpsychiatric controls (aged 31 to 43). In “all the cases of schizophrenia that can be considered as uncomplicated by other diseases” (p. 2658), there was a diffuse gliosis that involved the mesencephalic reticular formation, hypothalamus, medial and anterior nuclei of the thalamus, and periaqueductal gray matter. In four cases, there was a marked gliosis of the hippocampal formation. Nissl and myelin stains revealed no abnormalities.

This report fails to include many details that would be crucial to its interpretation. There is no discussion of the method for selecting cases, except for a statement that they were of long-standing evolution, without signs of malnutrition. It is not clear whether cases with “other diseases” were excluded before or subsequent to the selection of the 10 brains studied. The method of comparison with controls is not stated, nor is there mention of whether this was done blind to diagnosis. The significance of these intriguing results is thus ambiguous. The authors conclude, “The gliosis observed in these diencephalic structures either may or may not have a pathologic significance” (Nieto and Escobar 1972, p. 2658).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gliosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nieto and Escobar</td>
<td>Gliosis of mesencephalic reticular formation, hypothalamus, medial and anterior nuclei of the thalamus, and periaqueductal gray matter; hippocampal formation involved in some cases</td>
</tr>
<tr>
<td>Stevens 1982</td>
<td>Fibrillary gliosis around third ventricle and cerebral aqueduct and in basal forebrain</td>
</tr>
<tr>
<td>Bruton et al. 1990</td>
<td>No difference from controls (in cerebral cortex, white matter, or periventricular structures) if cases with focal pathology are excluded; greater than controls if all cases are included</td>
</tr>
<tr>
<td>Roberts et al. 1986</td>
<td>No difference from controls in any region of brain</td>
</tr>
<tr>
<td>Falkai and Bogerts</td>
<td>Fewer glial cells in several sectors of hippocampal formation</td>
</tr>
</tbody>
</table>

Table 4. Gliosis

Stevens (1982) reviewed the brains of schizophrenia patients who were under age 50, fulfilled standardized criteria for schizophrenia, were free of vascular or infectious diseases that might produce diffuse cerebral gliosis, and on whom adequate pathological material was available. This group consisted of 28 patients (mean age 44) from a collection of approximately 60 patients with a clinical diagnosis of schizophrenia who died and were autopsied at St. Elizabeth’s Hospital in Washington, DC, between 1956 and 1963. Controls consisted of a group of 28 patients from the same hospital with nonschizophrenic neuropsychiatric disorders (mostly neurologic diseases with well-established neuropathologic findings). A third group of cases free of neurologic or psychiatric disease comprised 3 from the Yakovlev collection and 18 from another hospital. The mean ages of these control groups were 46 and 37, respectively; the nonpsychiatric controls included two children, aged 10 and 12 years.

Except for the three cases from the Yakovlev collection, a Holzer stain was performed on all sections. This stain demonstrates very clearly the cytoplasm and processes of reactive and fibrillary astrocytes. Slides were examined blind to clinical diagnosis.

Gliosis was observed in 18 cases. The subependymal region, bed nucleus of stria terminalis, hypothalamus, amygdala, substantia innominata, and hippocampus were each involved in at least nine cases. In the neuropsychiatric controls, gliosis was felt to be more specifically related to the expected lesions; except for one case, the nonpsychiatric controls “did not show the degree or distribution of gliosis observed in the schizophrenic or psychiatric control material” (Stevens 1982, p. 1137).

One difficulty in interpreting this study is that the results for the two control groups are given only in descriptive terms. For example, we are not specifically told how many of the neuropsychiatric controls showed periaqueductal gliosis, or what the differences in degree of gliosis were between the nonpsychiatric controls and the schizophrenia cases. It is also not clear how many of the brains of schizophrenia subjects had focal lesions in the basal ganglia; there are a total of 14 instances of neuronal loss or infarction, but these could have occurred in as few brains as 4 or as many as 14. As pointed out by Bruton et al. (1990), some of the gliosis observed in the brains of schizophrenia subjects could have been secondary to these lesions.

Furthermore, although cases were examined blind to clinical diagnosis, it is not clear whether all sections from a single case were given the same code number, in which case evaluation of one section could be subjectively influenced by focal pathology in another from the same brain. Finally, although the presence of gliosis in the brains of schizophrenia patients did not appear to correlate with age,
the lack of gliosis in the nonpsychiatric control group could nonetheless be related to the younger age of its subjects.

Bruton et al. (1990) found increased gliosis in the cerebral cortex, white matter, and periventricular structures of unselected (see above) schizophrenia cases compared with controls. However, focal lesions were present in 44 percent of the brains of schizophrenia patients and 21 percent of the controls; when these cases were eliminated, there was no evidence of increased gliosis in the brains of schizophrenia subjects. Jellinger (1985) found brainstem gliosis as the major neuropathological finding in the brains of 6 of 100 psychotic patients; 47 were normal, but the remainder had other neuropathological diagnoses, and some of these may have had brainstem gliosis as well.

Roberts et al. (1986) evaluated gliosis by densitometric measurements of immunoreactivity for glial fibrillary acidic protein, an intermediate filament protein of astrocytes. The brains (five from schizophrenia subjects and seven from controls) were a subset of those employed in the study of Bogerts et al. (1985) and, except for one control brain, were included in the study of Falkai and Bogerts (1986). Although the quantitative significance of densitometry of immunoperoxidase staining is not definitely established, values for the striatum of patients with Huntington’s chorea were significantly different from those of controls. No difference was found between controls and schizophrenia subjects. It is possible that the measurement employed in this study, while capable of detecting gliosis in the striatum of Huntington’s chorea (which can be striking) was not sufficiently sensitive to detect a lesser degree of gliosis that might occur in schizophrenia. Also, while both Holzer and glial fibrillary acidic protein stains are sensitive for active gliosis, the Holzer stain is probably better for evaluating long-standing, static gliosis. There was no comment regarding focal lesions in these brains.

These studies suggest that if there is increased gliosis in the brains of schizophrenia subjects, it is secondary to the more frequent presence of focal lesions. This points to the importance of studying the frequency of conventional neuropathological lesions in the brains of schizophrenia cases, rather than eliminating such cases from studies in order to find a “pure” neuropathological lesion of schizophrenia. Jellinger (1985) remarked on the frequent presence of a variety of neuropathological lesions in the brains of schizophrenia subjects, and several studies report increased senile degeneration (see below).

### Senile Degeneration (table 5)

Prohovnik et al. (1993) reviewed the reports from all 1,046 neuropathological examinations performed at the New York State Psychiatric Institute from 1978 through

<table>
<thead>
<tr>
<th>Reference</th>
<th>Senile degeneration (senile plaques and neurofibrillary tangles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prohovnik et al. 1993</td>
<td>Increased</td>
</tr>
<tr>
<td>Wisniewski et al. 1994</td>
<td>Increased in postneuroleptic era, not in preneuroleptic era</td>
</tr>
<tr>
<td>Buhl and Bojsen-Møller 1988</td>
<td>Increased</td>
</tr>
<tr>
<td>Jellinger 1985</td>
<td>High rates among psychotics, especially diagnostic groups with older median age; no controls</td>
</tr>
<tr>
<td>Bruton et al. 1990</td>
<td>NS</td>
</tr>
<tr>
<td>El-Mallakh et al. 1991</td>
<td>NS</td>
</tr>
<tr>
<td>Casanova et al. 1993</td>
<td>NS</td>
</tr>
<tr>
<td>Purohit et al. 1993</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note.—Comparisons of conclusions from various studies. Data in italics represent negative findings. Apparent discrepancies may be explained by methodological and other considerations (see text). NS = not significant.

1987. After they excluded 6 cases for missing data and 45 patients who died before age 50, there remained 544 with a clinical diagnosis of schizophrenia (mean age 78); 258 with a clinical diagnosis (as reported to the neuropathologist—usually the chart diagnosis) of dementia (mean age 77); and 47 with a diagnosis of affective disorder (mean age 75). The primary analysis was based upon the original neuropathological diagnoses, which were not blind to clinical diagnosis.

A pathological diagnosis of Alzheimer’s disease (AD) had been made in 51 percent of the brains of dementia cases, 28 percent of the brains of schizophrenia subjects, and 15 percent of the brains of patients with affective disorder. The rate in schizophrenia cases was nearly double that in affective disorder ($X^2 = 3.7; \text{df} = 1; p < 0.06$). When the data were stratified by age, the frequency of AD diagnoses was constant at 50 percent for dementia patients, but increased steadily among schizophrenia cases—from 3 percent in the sixth decade to 50 percent in the ninth decade ($p < 0.0001$).

Since the original pathological diagnoses of AD had been neither blind to clinical diagnosis nor made according to modern research criteria, a small sample of the original cases was reevaluated, blind to clinical diagnosis. In the reevaluation, cases were considered definite AD if—on examination of sections stained with Bielschowsky silver stain or thioflavine S stain and on immunohistochemistry with Alz 50—they fulfilled Khachaturian (1985) criteria for senile plaque densities and showed moderate or severe neuritic pathology in neocortical regions other than the inferior temporal gyrus. Using
these stringent histologic criteria, 82 percent of the original AD diagnoses were confirmed for dementia patients, but only 33 percent for schizophrenia patients. All cases originally thought free of AD were confirmed as such.

To estimate the true rate of AD in schizophrenia cases, one must multiply by 0.33 the number of original neuropathological AD diagnoses in schizophrenia patients. However, this correction factor may not be accurate, since it is based on only four confirmations of 12 original pathological diagnoses of AD. The rates thus obtained are greater than population estimates based on living people until the ninth decade, when the difference disappears.

A possibly more appropriate comparison, which gives similar results, is between the total number of original neuropathological diagnoses of AD and the rates of "many" neurofibrillary tangles and senile plaques in the temporal lobes of an unselected autopsy series (Miller et al. 1984), since many of the original pathological AD diagnoses that failed to be confirmed had significant neurofibrillary pathology in the hippocampal formation. Thus, it appears that chronically institutionalized schizophrenia patients dying in the sixth through eighth decades probably have a greater than normal frequency of significant neurofibrillary pathology in the hippocampal formation, and possibly also an elevated frequency of neocortical findings consistent with AD.

The strength of this study is in the unusually large number of schizophrenia subjects. Weaknesses include minimal and possibly unreliable clinical information; unblinded and loosely defined original pathological diagnoses, of which only a small subsample was tested more rigorously; and a possible bias in the selection of patients for autopsy.

The possibility has also been suggested that hospitalized schizophrenia patients may have AD because AD plus schizophrenia could prevent discharge. This explanation seems unlikely, however, since most of the patients had remained in the hospital continuously or nearly so since the fourth or fifth decade of their lives. If AD were causing them to remain hospitalized, the rate of AD should already be quite high in patients who die in the fifth decade, and the dramatic age-associated increase would probably not be seen. It is not unlikely, however, that these patients represent an unusually pernicious form of schizophrenia.

This theory is one possible explanation for the finding of Wisniewski et al. (1994) that neurofibrillary pathology is increased in the brains of elderly schizophrenia patients treated with neuroleptics, but not in those of elderly schizophrenia patients who died before the introduction of these drugs. While the pathological changes may be a result of the drugs, it is also possible that the discharge of patients who responded well to neuroleptics caused the inpatient population to become dominated by patients whose response to neuroleptics was poor, and that such individuals were more likely to develop neurofibrillary pathology.

In a detailed study (Dwork et al. 1996) of 66 elderly and chronically institutionalized individuals with schizophrenia (mean age 78), only 5 (8%) met the Khachaturian (1985) neuropathological criteria (age-dependent senile plaque counts) for AD. This result is close to the adjusted estimate from the study of Prohovnik et al. (1993). Clinical diagnosis and the presence of cognitive impairment were ascertained by standardized chart review (Keilp et al. 1995). All but one of the 17 schizophrenia cases above age 84 had definite cognitive impairment. Restricting analysis to individuals under age 85 revealed greater numbers of neuritic plaques and neurofibrillary tangles in the 29 schizophrenia patients with definite cognitive impairment (mean age 74) than in the 20 without such impairment (mean age 73). Levels of neuritic senile plaques and neurofibrillary tangles in the schizophrenia cases without definite cognitive impairment were substantially lower than in nonpsychiatric patients without such impairment—a finding also present in the study of El-Mallakh et al. (1991). The schizophrenia subjects below age 85 had levels of plaques and tangles similar to a group of 21 chronically institutionalized mood disorder patients (mean age 71), but definite cognitive impairment was over six times more prevalent in the schizophrenia group (29/49) than in the mood disorder group (2/21) ($X^2 = 14.7; df = 1; p = 0.0001$).

It thus appears that chronically institutionalized schizophrenia patients are abnormally sensitive to the cognitive effects of AD-type changes or some associated process, perhaps because they have diminished cognitive reserve. However, the anatomical substrate for this is unknown.

Buhl and Bojesen-Møller (1988) reviewed brains from 100 consecutive deaths in a psychiatric department. Neuropathological criteria for AD were appropriately stringent, requiring neurofibrillary tangles in the neocortex and hippocampus and large numbers of neuritic senile plaques in the frontal and temporal neocortex. The group included 23 schizophrenia cases (mean age 80); 8 of these (35%) fulfilled neuropathological criteria for AD. None of 10 age-matched controls without clinical evidence of neurological or psychiatric disease showed any senile plaques or significant numbers of hippocampal neurofibrillary tangles.

Jellinger (1985) reviewed two autopsy series of 101 and 100 psychotic patients. AD or senile dementia of the Alzheimer type (SDAT) was present in 38 from the former series and 19 from the latter. The three largest groups
in the latter series were paranoid schizophrenia cases (n = 22, median age 62, AD/SDAT frequency 14%); schizophrenia defect state (n = 38, median age 67, 21% AD/SDAT); and paranoid psychosis (n = 16, median age 76, 38% SDAT).

Bruton et al. (1990) found senile plaques in 40 percent of the brains of schizophrenia patients and neurofibrillary tangles in 33 percent; the results in the control group were virtually identical. Eight brains were excluded because of a clinical history of neurological surgery or disease, but none for conditions associated with plaques and tangles. Even if all eight brains contained plaques and tangles and were included in the schizophrenia sample, the proportion of brains with plaques and tangles would be 46 and 43 percent, respectively, which would not be significantly different from controls (X^2 = 1.3; df = 1; p < 0.2).

In a study of 10 intellectually impaired and 7 intellectually intact schizophrenia cases (mean ages 84 and 62, respectively) and 7 control subjects, El-Mallakh et al. (1991) found no difference between either schizophrenia group and the controls in terms of cell density in the nucleus basalis of Meynert, frontal plaque density, or hippocampal plaque density. There was a statistically significant increase in hippocampal plaques in the brains of intellectually impaired schizophrenia patients compared with those who were intellectually intact, but this could be explained by the 22-year age difference between the groups.

Casanova et al. (1993) found very few senile plaques or neurofibrillary tangles in the brains of 10 cognitively impaired schizophrenia cases, mean age 66. Purohit et al. (1993) examined the brains of 13 cognitively impaired schizophrenia patients, mean age 79. No brain had sufficient evidence of senile degeneration to warrant a diagnosis of AD. There were no neocortical neurofibrillary tangles, and neocortical senile plaque densities were similar to those in a group of 12 nondemented, nonschizophrenia controls. Moderate numbers of hippocampal neurofibrillary tangles were present in four schizophrenia subjects (30%); comparison with controls is not given. There was no correlation between senile degenerative changes and the degree of cognitive impairment.

Apparently, there are differences between studies that cannot be attributed to methodological factors and hence must depend on sample differences. In this regard, we note that preliminary analysis of thioflavine S stain on sections of the first 29 cases (mean age 71) from a European series of unselected schizophrenia cases shows moderate or severe hippocampal neuritic pathology in only 5 (17%) (Dwork et al., unpublished data).

It is also important to note that large samples would be needed to detect an increased prevalence of full-blown AD in schizophrenia subjects. For example, an observed rate of 5 percent among controls and 10 percent among schizophrenia patients would require more than 200 subjects in each group to be statistically significant (X^2 = 3.841; df = 1; p < 0.05).

Conclusions

The postmortem abnormality most consistently observed from one study to another in the brains of schizophrenia cases is enlargement of the lateral ventricles, or the temporal horns, possibly only on the left side. Even the negative study of Heckers et al. (1990a) found a trend in this direction and a statistically significant enlargement of the left lateral ventricle in the brains of paranoid schizophrenia patients. However, ventricular enlargement is neither sensitive nor specific as a neuropathological feature for the diagnosis of schizophrenia. Large ventricles per se can hardly account for the tremendous functional abnormalities of the brains of schizophrenia subjects, and there is little agreement about the structures at whose expense the ventricles might have enlarged.

There are several negative studies of the temporal lobe in schizophrenia, and the positive studies tend to be mutually contradictory. Thus, except possibly for ventricular enlargement, there is no abnormality of the temporal lobe that can be considered proven. One possibility is that there is no structural abnormality in the temporal lobe.

Another possibility is that we are only now beginning to look with the proper methods. Immunohistochemistry for MAP2 demonstrates dramatic abnormalities in many cases. MAP2 levels can change rapidly, so there is no reason to conclude that the observed subicular deficit represents a primary lesion of schizophrenia. However, this observation does tend to confirm at least a secondary abnormality in the hippocampi of many schizophrenia cases. If this reflects an important abnormality of subicular dendrites, one would then expect abnormal communication between the hippocampus and cerebral cortex, which could in theory contribute to cognitive impairment, misconception of reality, or distorted connections of affect to action or thought content.

The alternate explanation—normal dendritic connections and function in the absence of MAP2—might tell us less about schizophrenia but would in itself be very interesting. The finding provides at least a starting point for further neuropathological investigations, such as the use of Golgi impregnation or electron microscopy to examine the morphology of subicular dendrites. Additional starting points may be generated when abnormalities are demonstrated with other neurochemical markers.

A third possibility for the lack of consistent findings in the temporal lobe may be related to study design. Many
studies have eliminated specimens that contained neuropathological changes characteristic of other diseases. There are at least three reasons not to do this. First, it then becomes impossible to determine whether schizophrenia increases one’s risk for neuropathological features of another neurological disease. Second, there may be an underlying difference in the brains of schizophrenia patients who do or do not develop some apparently unrelated neuropathological change. To avoid this possible problem, it would be best to use population-based samples of schizophrenia subjects and controls and to include all, regardless of other conditions affecting the brain, which should be carefully documented and analyzed. Finally, there may be differences in the presentation of a classical neuropathological change in the brain of a schizophrenia case and in that of a nonschizophrenia subject, either because the underlying substrate is different, or because the etiology of the change is different. If cases containing the change are excluded, this will never be detected.

A frequent problem in these studies is small sample size. Much of what is published could be considered pilot data, to be replicated in large populations. Unfortunately, large samples are not always feasible. The brains may not be available, and some of the examinations are extremely time consuming.

The manifestations of this illness are varied, and schizophrenia may comprise more than one biological disease. It is notable that no study with a schizophrenia sample size greater than six found any single abnormality throughout the entire sample. A useful approach to this diversity might be to establish a standardized set of clinical and pathological examinations, to be performed in addition to the measures of interest to a particular study. This would improve the comparability of studies involving different cohorts, and it would facilitate the combining of data from different studies. Such a set might also allow the detection of particular clinical subsets of schizophrenia cases whose brains display a consistent anatomical variation. Combined clinical, pathological, and neuroanatomical studies of schizophrenia are needed to elucidate the nosology and the etiology of this condition.

References


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