Absence of Neurodegeneration and Neural Injury in the Cerebral Cortex in a Sample of Elderly Patients With Schizophrenia

Steven E. Arnold, MD; John Q. Trojanowski, MD, PhD; Raquel E. Gur, MD, PhD; Peter Blackwell; Li-Ying Han, MS; Catherine Choi

Background: The cognitive and functional deterioration that is observed in many “poor-outcome” patients with schizophrenia suggests a neurodegenerative process extending into late life. Previous diagnostic studies have excluded known neurodegenerative diseases as explanations for this dementia. However, we hypothesized that relatively small accumulations of age- or disease-related neurodegenerative lesions occurring in an otherwise abnormal brain could result in deterioration in schizophrenia.

Methods: Postmortem studies were conducted using 23 prospectively accrued elderly persons with chronic schizophrenia for whom clinical ratings had been determined before death, 14 elderly control patients with no neuropsychiatric disease, and 10 control patients with Alzheimer disease. Immunohistochemistry and unbiased stereological counting methods were used to quantify common neurodegenerative lesions (i.e., neurofibrillary tangles, amyloid plaques, and Lewy bodies) and cellular reactions to a variety of noxious stimuli (ubiquitinated dystrophic neurites, astrocytosis, and microglial infiltrates) in the ventromedial temporal lobe and the frontal and the calcarine (primary visual) cortices.

Results: No statistically significant differences were found between the patients with schizophrenia and the control patients without neuropsychiatric disease for the densities of any of the markers, while both groups exhibited fewer lesions than did the control group with Alzheimer disease. Correlation analyses in the schizophrenia sample failed to identify significant correlations between cognitive and psychiatric ratings and densities of any of the neuropathologic markers.

Conclusions: No significant evidence of neurodegeneration or ongoing neural injury in the cerebral cortex was found in this sample of elderly persons with schizophrenia. Furthermore, the behavioral and cognitive deterioration observed in late life did not correlate with age-related degenerative phenomena.

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A historically important hypothesis about the pathogenesis of schizophrenia is that it is due to a process of neural injury or neurodegeneration. This was first suggested by Emil Kraepelin,1 who emphasized the chronic deteriorating course of dementia praecox. Subsequent longitudinal studies have shown heterogeneity of outcome in schizophrenia; the conditions of some patients deteriorate, while the conditions of others improve or stabilize.2-5 Recent life-span studies of schizophrenia in late life have revealed frequent severe cognitive and functional impairments among elderly patients who are chronically institutionalized.6-7 However, not all investigators find cognitive decline over time,6,10 so further clinical and neurobiological study of this possibility, as well as its presumed neurodegenerative substrate, is warranted.

Arnold et al,6 and Davidson et al11 have found that as many as two thirds of institutionalized elderly patients with schizophrenia meet the DSM-IV11 criteria for an additional diagnosis of dementia and that the neuropsychological profile of this dementia resembles that seen in Alzheimer disease (AD).12 However, to date, neuropathologic studies have identified no abnormalities to explain the dementia in the overwhelming majority of patients.6,13-15 This is remarkable because postmortem studies of community populations consistently show that approximately 50% to 60% of elderly patients with dementia have AD, 20% to 30% have vascular dementia or mixed AD-vascular dementia, and 10% to 20% have dementia due to various other neurodegenerative, structural, or metabolic causes.16 Thus, the neurobiological basis for the dementia in “poor-outcome” patients with schizophrenia remains unknown.

A number of common alterations in the cellular and molecular composition of the brain occur with neurodegenerative diseases or as nonspecific responses to neural injury.
PATIENTS AND METHODS

PATIENTS

Autopsies were performed on 23 patients with schizophrenia (group 1), 14 age-compatible control patients with no neuropsychiatric disease (group 2), and 10 patients with AD who served as “positive” controls (group 3). Table 1 and Table 2. All patients with schizophrenia were prospectively accrued from 8 state hospitals in Pennsylvania and were clinically assessed and diagnosed according to the DSM-IV criteria by research psychiatrists of the University of Pennsylvania Schizophrenia Mental Health Clinical Research Center, Philadelphia (under the direction of R.E.G.), as previously described. Of the 23 patients in group 1, 16 met the criteria for an additional diagnosis of dementia. Clinical features were characterized with standard research psychiatric rating instruments before death for correlation with the postmortem findings. These included the Mini-Mental State Examination,22 the Brief Psychiatric Rating Scale,23 the Scale for the Assessment of Positive Symptoms,24 the Scale for the Assessment of Negative Symptoms,25 the Abnormal Involuntary Movement Scale,26 and the activities of daily living subscale of the Physical Self-Maintenance Scale (Functional Assessment Scale).27 The mean (±SD) interval between testing and death was 10±6.7 months (range, 1-24 months). While there was a broad range, the mean values for the patients in group 1 characterized them as having moderate to severe dementia, moderate to severe global psychopathologic disease, marked negative symptomatology, questionable to mild positive symptomatology, rare tardive dyskinesia, and a need for assistance with basic activities of daily living.

Brain tissues from patients in groups 2 and 3 were obtained through the University of Pennsylvania Alzheimer Disease Center Core, Philadelphia. While none of these patients had undergone antemortem assessments, a review of their clinical histories found no evidence of major psychiatric illness. Most patients in group 3 had end-stage dementia. There were no differences among patients in the 3 groups for age (F2,44=1.67; P=0.2), sex (χ2=0.72; df=2; P=0.70), or postmortem interval (PMI; F2,44=0.50; P=0.61).

Gross and microscopic diagnostic neuropathologic examinations, which included examination of multiple cortical and subcortical regions, were performed for all patients. No neuropathologic abnormalities relevant to mental status were found in groups 1 and 2. Minor abnormalities were noted in 3 patients in group 1 (lucunar infarcts in 2 and posterior fossa meningioma in 1) and 2 patients in group 2 (lucunar infarcts in 1 and small bitemporal contusions in 1). Aside from abundant NFTs and APs, no other abnormalities were found in group 3. The diagnosis of AD was based on established consensus criteria.28

Tissue Processing and Immunohistochemistry

Blocks from the ventromedial temporal lobe, the middle frontal gyrus, the straight gyrus, and the calcarine sulcus were dissected at autopsy, fixed in ethanol (ethyl alcohol, 70%; sodium chloride concentration, 150 mmol/L) for 24 hours, paraffin embedded, and cut into 20-µm-thick sections. Pathologic markers were immunohistochemically identified with the following antibodies: PHF-129 for NFTs, 233230 for APs, RMO3231 for Lewy bodies, Ubi-1 (Zymed Labs Inc, South San Francisco, Calif) for ubiquitinated dystrophic neurites, 2.2B1032 for glial fibrillary acidic protein (GFAP) in astrocytes, and CD68 (DAKO Corp, Carpintere, Calif) for resting and active microglia. For the monoclonal antibodies (PHF-1, Ubi-1, 2.2B10, and RMO32), immunocytochemistry was performed using a previously described peroxidase-antiperoxidase procedure,33 and for the polyclonal antibodies (2332 and CD68), the avidin-biotin-complex method (Vector Laboratories Inc, Burlingham, Calif) was used. For each antibody and region, all cases were included in single, precisely timed runs.

Selection of Regions and Neuropathologic Marker Density Estimation

Six regions were delineated: entorhinal cortex (Brodmann area [BA] 28), subiculum and CA1 of the hippocampus, midfrontal cortex (BAs 9 and 46), orbitofrontal cortex (BA 11), and calcarine cortex (BA 17). The entorhinal and hippocampal sections were obtained from the anterior portion of the main body of the hippocampus. Regional boundaries were cytoarchitecturally determined in comparison with adjacent Nisslstained sections.34,35 Neurons in these subfields are especially vulnerable to the accumulation of pathologic lesions in AD36 and other neurodegenerative diseases (eg, Pick disease, amyotrophic lateral sclerosis—dementia complex).37 Midfrontal and orbitofrontal cortices were identified topographically and cytoarchitecturally.37 They are also vulnerable in various neurodegenerative diseases.36,38 The calcarine cortex (primary visual cortex) was chosen as an internal control region that is relatively resistant to the accumulation of neurodegenerative lesions.39,40

After codification of slides for blind measurements, the densities of NFTs, Lewy bodies, ubiquitinated dystrophic

For instance, neurofibrillar tangles (NFTs) and amyloid plaques (APs) are relatively specific features of AD,17 and Lewy bodies are typical of Parkinson disease and related conditions. More general indicators of neural injury include reactive astrocytosis, microglial proliferation, and accumulations of ubiquitin (an 8.6-kd heat shock protein induced by a variety of noxious stimuli) in neurons, neuronal processes, and glia.19,21

The present study was designed to test the hypotheses that abnormal neurodegeneration or neurol injury occurs in the brains of elderly poor-outcome patients with schizophrenia and that the quantities of neurodegenerative lesions correlate with deterioration of their clinical conditions. While not representative of schizophrenia at large, our sample is particularly well suited for these studies because of its severity, chronicity, and advanced age. Thus, if accumulated degenerative pathology is an aspect of schizophrenia, it should be more evident in this sample than in a younger or better-functioning groups.
neurites, astrocytes, and microglia were determined by using computer-assisted microscopy, systematic sampling, and nonbiased stereological object counting software40 (StereoInvestigator, MicroBrightField Inc, Colchester, Vt). Slides from the 47 patients underwent analyses in random order by either of 2 trained operators (C.C. or L.-Y.H.). Preliminary studies indicated high interrater and intrarater reliability for the stereological counting method with an intraclass correlation coefficient greater than 0.80 for the markers. Briefly, after the region was delimited at low power, a grid of predetermined size was randomly placed over the entire region by the software program. The objective was raised to ×40, and the program was engaged to direct the motorized stage on the microscope to stop at each intersection point of the grid for sampling. The fields were visualized on the video monitor with a superimposed counting frame, and objects were counted by using the optical fractionator and optical dissector.40,41 The counting frame remained superimposed on the image as the operator focused through a fixed depth of 10 μm in the section. All new objects coming into focus were counted if they were within the frame or touching either of the 2 inclusion lines and as long as they did not touch the exclusion lines of the box.

The NFTs were counted after identification by their immunoreactivity for PHF-1 and their characteristic appearance. Ubiquitinated dystrophic neurites were identified by their appearance as “dots” of various sizes. The GFAP astrocytes were identified by the presence of a visible nucleus and characteristic processes. Finally, the criteria for CD68 resting and activated microglia included small size, round or elongated nuclei, and scant cytoplasm (Figure 5).

For APs, we measured the total area occupied by amyloid deposits within 3 systematically selected ×20 fields in each of the regions of interest in each case using image analysis software (NIH Image, version 1.59, W. Rasband, National Institutes of Health, Bethesda, Md). This method obviated the inherent difficulty in counting individual plaques that may be contiguous or overlapping. The amyloid-laden area was determined in layers II and III of the entorhinal cortex, the pyramidal cell layer of subiculum and CA1, and layer V of midfrontal and orbitofrontal cortices. These layers were chosen because they are especially vulnerable to the accumulation of APs and other neurodegenerative lesions.49 In the calcarine cortex, layer IVb was chosen because of its particular resistance to neurodegenerative lesions. After standardizing the threshold, the total area of amyloid deposition within each captured field was determined automatically and expressed as a percentage of the area for the field.

DATA ANALYSIS AND STATISTICS

Normal aging and PMI effects were assessed for correlations with each neuropathologic measure within the nonneuropsychiatric control group (group 2). Correlations for these variables also were conducted for the schizophrenia group (group 1) with the consideration that an interaction between the disease state and the aging process could affect the accumulation of neurodegenerative lesions. In addition, the possible effect of antipsychotic medication was assessed with correlations between the medication dosage 1 month before death (expressed as chlorpromazine milligram equivalents) and each neuropathologic measure in each region of the brain that was studied. Because all of the markers we studied are considered to be age-related phenomena, we included age as a regressor in the analyses. Significant correlations for the other potentially confounding variables prompted their inclusion as regressors in subsequent analyses as well.

For analyses of between-group differences, we collapsed the 6 individual regions into 3: hippocampal, frontal, and calcarine. This was done to generate a meaningful neural system–density value and to avoid over weighting the 3 ventromedial temporal regions in comparison with the 2 frontal regions and the 1 visual region. The mean hippocampal score was the average of the density values for the entorhinal cortex, subiculum, and CA1. Similarly, midfrontal and orbitofrontal cortices were combined into a “frontal” mean. Group differences for each neuropathologic measure were analyzed in analyses of covariance (ANCOVA), with the diagnostic group as the independent variable, marker densities in the 3 regions as the repeated-measures dependent variable, and age as the regressor. These were followed by post hoc Scheffe 5 tests to assess between-group differences in each region. To further assess possible region–specific differences, individual ANCOVAs were similarly performed. Analyses were conducted using statistical software (Statview 4.1 and SuperANOVA, Abacus Concepts Inc, Berkeley, Calif). An α level of .05 was used to determine significance.

Whether or not patients in group 1 had excessive amounts of neurodegenerative lesions compared with patients in group 2, we also considered the possibility that a person with an otherwise abnormal brain may be more vulnerable to the neuropsychological impact of any “normal” age-related neurodegenerative changes. We explored this by determining correlations between the summary scores for each of our clinical measures and the density values for each of the neuropathologic markers.
and astrocyte density in the frontal region ($r = -0.49$, $P < .04$) and microglia in the hippocampal region ($r = -0.56$, $P < .02$).

**MARKERS OF NEURODEGENERATION AND NEURAL INJURY**

We found significant between-group differences for the densities of NFTs, APs, ubiquitinated dystrophic neurites, GFAP astrocytes, and microglia, with group 3 having much higher density values than the other 2 groups, as expected (Table 3 and Figures 1-5). Analyses of individual regions revealed no differences between groups 1 and 2 for any marker. No RMO32 immunoreactive Lewy bodies were observed in any cortical region in any of the cases.

Ubiquitin-immunoreactive dots of varying sizes, which represent degenerating axons, dendrites, and, perhaps, other cellular debris, were found freestanding in the cortices and in association with APs but not NFTs. Because of this association, we also performed an ANCOVA using the percentage area of AP as an additional regressor. This failed to diminish the between-group differences in the repeated-measures ANCOVA ($F_{2,1,42} = 25.20$, $P < .001$) or for individual regions in post hoc analyses.

**Table 1. Demographic Data**

<table>
<thead>
<tr>
<th>Group</th>
<th>1 (n=23)</th>
<th>2 (n=14)</th>
<th>3 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>79.8 (8.2)</td>
<td>75.3 (12.1)</td>
<td>81.8 (6.6)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>8/15</td>
<td>6/8</td>
<td>5/5</td>
</tr>
<tr>
<td>Postmortem interval, h</td>
<td>11.0 (3.1)</td>
<td>11.4 (5.3)</td>
<td>9.9 (3.8)</td>
</tr>
<tr>
<td>Brain weight, g</td>
<td>1192 (158)</td>
<td>1223 (193)</td>
<td>1141 (173)</td>
</tr>
</tbody>
</table>

*Group 1, patients with schizophrenia; group 2, control patients with no neuropsychiatric disease; and group 3, “positive” control patients with Alzheimer disease. Data, except for sex, are given as mean (SD).

**Table 2. Clinical Data for Subjects With Schizophrenia (n=23)**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, y</td>
<td>24.7</td>
<td>5.6</td>
<td>16-39</td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>55.1</td>
<td>9.2</td>
<td>38-76</td>
</tr>
<tr>
<td>Antipsychotic dosage, CPZ mg</td>
<td>225</td>
<td>291</td>
<td>0-900 (7 drug free)</td>
</tr>
<tr>
<td>MMSE</td>
<td>12.3</td>
<td>8.6</td>
<td>0-28</td>
</tr>
<tr>
<td>BPRS</td>
<td>59.0</td>
<td>21.1</td>
<td>20-87</td>
</tr>
<tr>
<td>SANS</td>
<td>2.69</td>
<td>1.34</td>
<td>0.33-4.65</td>
</tr>
<tr>
<td>SAPS</td>
<td>0.91</td>
<td>0.58</td>
<td>0.0-2.19</td>
</tr>
<tr>
<td>FAS</td>
<td>2.04</td>
<td>0.75</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>AIMS</td>
<td>1.70</td>
<td>1.15</td>
<td>1-5</td>
</tr>
</tbody>
</table>

*CPZ mg indicates chlorpromazine milligram equivalents; MMSE, Mini-Mental State Examination; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; FAS, the Functional Assessment Scale of the Physical Self-Maintenance Scale; and AIMS, Abnormal Involuntary Movement Scale.

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Although there were no differences between groups 1 and 2 for any of the neuropathologic markers studied, we determined the extent to which the clinical features correlated with neuropathologic findings. This was prompted by our hypothesis that the accumulation of any neurodegenerative lesions might affect cognition or psychiatric status in persons with schizophrenia if their illness caused them to be less resilient to the toxic effects of such lesions. No significant correlations were observed between clinical variables and any neuropathologic markers for any region.

**COMMENT**

In this series, we used a panel of highly sensitive and molecularly specific antibodies to identify diverse pathologic features of the most common neurodegenerative diseases, as well as general responses to neural injury, in a sample of elderly poor-outcome patients with schizophrenia. The temporal and frontal regions that we evaluated are known to be preferentially vulnerable to aging, neurodegenerative disease, and other types of neural injury. Furthermore, these regions have been invoked as abnormal in schizophrenia. We found no differences between patients with schizophrenia and control patients with no neuropsychiatric disease for any marker in any region. Therefore, the hypothesis that neurodegenerative disease processes or postmaturational neu-
and specificity of classic histological stains; and the lack in the selection of regions of interest; limited sensitivity to review of the medical record; inconsistencies in tissue fixation and processing protocols optimized to preserve the antigens of interest. Regions of interest were defined using cytoarchitectural criteria, and we identified the neuropathologic markers using immunohistochemistry with well-characterized molecule-specific antibodies. Finally, we used computer-assisted random systematic sampling and stereological counting methods for reliable and unbiased counts.

Some potential limitations in our design should be recognized. One concerns the regions we chose to study. We selected the cortical regions because of their known vulnerability to neurodegenerative processes. A broader array of cortical and subcortical regions were surveyed in diagnostic neuropathologic examinations that preceded our quantitative analyses, and no pertinent abnormalities were identified. Nevertheless, subtle but important neurodegenerative abnormalities could still occur in subcortical or other cortical regions. Another limitation is our choice of neuropathologic markers. We studied the most important and common disease-specific and non–disease-specific markers that reflect diverse mechanisms of cell death. Programmed cell death is another mode of cell death that is not necessarily accompanied by an elevation of the neurodegenerative markers we studied, and, thus, it warrants future study. A third limitation is the relatively small sample available for correlation analyses; caution is warranted in drawing firm conclusions from the negative findings. Finally, we cannot rule out extremely remote, occult, or indolent neurodegenerative processes. All of the markers we studied are dynamic and persist only to varying degrees after neurodegenerative processes. All of the markers we studied are dynamic and persist only to varying degrees after neurodegenerative processes. All of the markers we studied are dynamic and persist only to varying degrees after neurodegenerative processes. All of the markers we studied are dynamic and persist only to varying degrees after neuronal injury. Thus, we can say for certain only that we found no evidence for ongoing or recent neurodegeneration or neuronal injury in schizophrenia in late life.

**METHODOLOGICAL CONSIDERATIONS**

Our study was designed to overcome many of the methodological limitations that have beset postmortem research in schizophrenia. Among these have been the uncertainties inherent in using diagnoses from the medical record or retrospective application of diagnostic criteria to review of the medical record; inconsistencies in tissue handling, preparation, and fixation; inconsistencies in the selection of regions of interest; limited sensitivity and specificity of classic histological stains; and the lack or inadequacy of quantitative methods of analysis to detect subtle brain abnormalities. All of our patients were accrued prospectively and underwent antemortem assessments that included clinical rating scales that could be used for clinicopathologic correlation. The postmortem intervals between death and autopsy were short, and autopsies were performed uniformly with tissue fixation and processing protocols optimized to preserve the antigens of interest. Regions of interest were defined using cytoarchitectural criteria, and we identified the neuropathologic markers using immunohistochemistry with well-characterized molecule-specific antibodies. Finally, we used computer-assisted random systematic sampling and stereological counting methods for reliable and unbiased counts.

**COMPARISON WITH PREVIOUS STUDIES**

Previous studies of AD-related pathology in schizophrenia have been controversial. For example, some studies of archival specimens reported an increased prevalence of AD among patients with schizophrenia. However, other studies that used better-characterized specimens and quantitative methods found no increase in AD-related lesions, and we confirm this finding in the present study.

Investigations of astrocytosis in schizophrenia have figured prominently in discussions of neurodevelopmental vs postmaturational neural injury hypotheses for schizophrenia, but the results also have been controversial. Studies using the traditional Holzer stain have reported subcortical fibrillary gliosis, particularly in periventricular, periaqueductal, and basal forebrain regions. In contrast, numerous other studies using Nissl stains or GFAP immunohistochemistry have failed to find astrocytosis in patients with schizophrenia com-
pared with persons with no neuropsychiatric disease. Methodological issues have been raised with a number of these studies, chiefly the sensitivities and specificities of staining methods and the type and duration of fixation before staining. We found no difference in GFAP-immunoreactive astrocytosis between groups with and without schizophrenia, similar to results in another cohort from our registry.

To our knowledge, there has been only 1 previous study of ubiquitin in schizophrenia. Horton et al found no increase in ubiquitin in the prefrontal cortex of patients with schizophrenia, although the mean postmortem interval before tissue fixation in that study was 105 hours. We focused on ubiquitinated dystrophic neurites as a general index of neuronal degeneration that is present in a host of neurodegenerative diseases, as well as in normal aging and age-associated cognitive impairment.

Our negative results in the group with schizophrenia with this sensitive marker provide further strong evidence against there being neural injury in the disease.

Finally, microglia have been found to be increased in a number of pathologic conditions but have not been studied previously in schizophrenia. Of special relevance to the consideration that microglia might be increased in schizophrenia are several reports of the abnormal lymphocyte production of immunoregulatory cytokines, including interleukin 2 and interleukin 6, that have been related to clinical and medication status.

We were particularly interested in whether these immunologic abnormalities might be reflected in abnormal microglial density in the brain. Again, no abnormality was found.

OTHER CONSIDERATIONS TO EXPLAIN THE DEMENTIA OF SCHIZOPHRENIA IN LATE LIFE

Without evidence of conventional neurodegenerative pathologic changes in schizophrenia, other factors must be considered to explain the dementia. It remains possible that the effects of normal age-related changes are amplified in the presence of presumably abnormal neural circuitry in schizophrenia. This is especially pertinent given the topographic similarities between the brain regions in which neuroanatomic abnormalities have been reported and those that are most vulnerable in aging and the common neurodegenerative diseases. For instance, abnormalities in cytoarchitecture, neuron density, and innervation have been described in the entorhinal cortex in schizophrenia. Most of these have been presumed to result from aberrant development of the fetal brain. From a neurodegenerative perspective, the entorhinal cortex is the first region in the brain to accumulate NFTs in aging and AD and is the most severely affected, and, along with the prefrontal cortices, it is severely affected in various other dementias, such as diffuse Lewy body disease, Pick disease, amyotrophic lateral sclerosis–dementia, and non-Alzheimer frontal lobe dementia. We postulate that the effects of any neurodegenerative lesions occurring in already dysfunctional neural systems might be great enough to cause dementia. We sought a correlation between dementia (and other clinical features) and neurodegenerative markers and did not find one. As an alternative, we speculate that there is a correlation between the “baseline” severity of developmentally based abnormalities and clinical features, including dementia, in late life. The task remains to better delineate the nature of such abnormalities.

Other possible mechanisms should be considered to explain the deterioration in the conditions of patients with schizophrenia in late life. Beyond a contribution from psychosocial factors, such as chronic institutionalization or the effects of long-term use of antipsychotic medication, other cellular and subcellular neurobiological mechanisms might include disease and age-related regressive changes in dendritic arborization or axonal plexi, neuronal atrophy, nucleolar shrinkage and changes in RNA content, changes in protein metabolism, increased vulnerability to oxidative or excitotoxic damage, slowed axoplasmic transport, alterations in the neuronal cytoskeleton, and altered synaptic integrity and synaptic transmission. The study of these aspects of neuron structure and function in the context of the clinical expression of schizophrenia over the life span may further elucidate the basis of this severe illness.

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Reprints: Steven E. Arnold, MD, Center for Neurobiology and Behavior, University of Pennsylvania, 142 Clinical Research Bldg, 415 Curie Blvd, Philadelphia, PA 19104 (e-mail: alveus@mail.med.upenn.edu).

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