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Searching for Neuropathology: Gliosis in Schizophrenia

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Abstract

The neuropathology of schizophrenia remains elusive. One indication of this elusiveness is that the literature, in contrast to that on the neuropathology of almost any other disease, deals predominantly with measures of normal structures rather than with the demonstration and characterization of pathological structures. An important exception to this trend has been the continued search, over four decades, for reactive glia. In this article, we review histological and radiological evidence for and against astrogliosis and microgliosis specifically associated with schizophrenia. The studies are generally limited by small samples, flawed designs, and potentially biased methods of counting cells. Interpretation of these studies is further complicated by the frequent presence of glial reactions in older individuals without psychiatric disease. Nonetheless, some of the positive findings in the literature cannot easily be dismissed. A sufficiently large autopsy study, weighted towards younger subjects, could provide a definitive answer, which if positive could be a major step towards finding an underlying pathological process.

Keywords

human; positron emission tomography; microglia; astrocytes; peripheral benzodiazepine receptor; glial fibrillary acidic protein

The “neuropathology” of schizophrenia

The neuropathological signature of schizophrenia is elusive. There are numerous reports of structural differences between the brains of people with and without schizophrenia, but failures of replication are common (recent reviews include (1–3)), and the reported abnormalities do not translate into neuropathological criteria that can be applied to individual brains for diagnosis. Unlike the recognizable histological hallmarks of many neurological diseases, the abnormalities reported in schizophrenia require measurement or counting. Recognition of differences is sensitive to technique, and there is almost always

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overlap between subjects with schizophrenia and those without psychiatric illness, and even more between schizophrenia and mood disorders (e.g., (4)). Quantitative imaging and autopsy studies may have provided insight by revealing, *on average*, larger cerebral ventricles, thinner cerebral cortices, and less labeling of synaptic components and interneurons, it would be unsatisfying (although perhaps ultimately necessary) to conclude that these differences are the “neuropathology” of schizophrenia, much as it would be unsatisfying to conclude that synaptic loss is the neuropathology of Alzheimer's disease. Synaptic loss is important in Alzheimer's disease (5–6), but unlike senile plaques, neurofibrillary tangles, and neuropil threads, it is neither necessary nor sufficient to make a diagnosis.

Functional deficits without recognizable neuropathology are not unique to schizophrenia. For example, in lupus erythematosus, focal neurological deficits without corresponding histologically demonstrable lesions are common and may reflect transient vascular impairment (7). A condition may be neuropathologically unrecognizable if its anatomical basis (e.g., altered distribution of water) is obscured by post mortem events. This may be the case, for example, with delirium induced by drugs or by imbalance of electrolytes, but it seems unlikely for a lifelong disease that often persists or progresses (especially in autopsy subjects, who tend to be inpatients or suicides), despite vigorous and partially effective treatment.

Alternatively, pathology may be missed if the histological methods are inappropriate. The loss of normal components, like myelin and Nissl substance, may be too mild to be recognized qualitatively, while pathological structures, like senile plaques, are readily appreciated with appropriate stains. While the classical neuropathological developments from the late 19th to mid-20th century continue to be relevant, histological diagnosis continues to progress. For instance, in the 1980's it became apparent that the Gallyas silver stain (8) was helpful for diagnosing frontotemporal dementias (reviewed in (9)), and the nosology and diagnosis of these conditions were further advanced in 2006 by the identification, of TDP-43 immunoreactive inclusions (10). However, aside from several studies showing neither an excess nor paucity of Alzheimer-type pathology (11–14), there are few reports of systematic application of methods that highlight neuropathological changes to search for pathology in schizophrenia. Studies of Alzheimer-type pathology in schizophrenia included immunohistochemistry for ubiquitin and other components of pathological inclusions seen in AD or other conditions, but no schizophrenia-associated pathology was observed (details in Supplement 1). None of these reports specifically mentions inclusions other than those of Alzheimer's and Lewy body diseases, but their silence on this point suggests the absence of obvious abnormalities. However, there is precedence for overlooking subtly stained inclusions in other conditions (9), and in Huntington's disease, the inclusions, as well as the publication first describing them (15), were overlooked for years.

There is a large variety of conventional and immunohistochemical techniques that could be used to screen for positively stained pathological abnormalities in autopsy brains from individuals with schizophrenia, but for the most part, such studies have not been reported. Presumably, either they were not performed, or negative results went unpublished.

One strategy for the affirmative identification of neuropathology in schizophrenia has been to search for microglial and astrocytic reaction. Microglia are potential antigen-presenting cells. They are derived from monocytes, and like monocytes, they can transform into macrophages. Resting microglia have long, motile processes. The cells respond rapidly to injury or foreign material. Cell bodies expand, processes retract and thicken, and there is increased expression of HLA-DR, a class II major histocompatibility complex (MHC II)

molecule, and of CD68, a lysosomal glycoprotein. Reactive microglia eventually disappear, except perhaps for some that remain as macrophages.

Astrocytic reaction is slower and more persistent, characterized by hyperplasia, hypertrophy, and increased immunoreactivity for glial fibrillary acidic protein (GFAP) and others. Increased GFAP immunoreactivity can persist indefinitely, either as a “glial scar” in the vicinity of a destructive lesion, or farther away, as isomorphic gliosis, in which reactive astrocytes conform to local anatomy (16).

The studies of gliosis in schizophrenia have yielded mixed results. In this review, we evaluate the evidence for and against glial reactions in schizophrenia. Our assumption is that gliosis is a *normal* response to a pathological process, and that if present without other explanation, gliosis can be a sensitive indicator of an obscure or remote pathological process. The possibility of inherent pathology of glial cells themselves, particularly oligodendrocytes, in schizophrenia has been reviewed elsewhere (17–19)) and is outside the scope of this review.

Demographic details of the studies reviewed are in Table S1 (see Supplement).

Methodological considerations

Most quantitative reports on microglia and astrocytes in schizophrenia have determined numbers per unit area on one or more microscope slides of the region of interest (ROI). It is now well-recognized that such studies are susceptible to biases, and that unbiased counts require systematic, uniform random sampling of the entire ROI. Additionally, the probability of counting an object must be independent of its size or shape. With these conditions satisfied, the total number of objects in the ROI equals the number of objects counted divided by the fraction of its volume used for counting. If artifact or disease alters the volume of the ROI but not the number of target objects, the density of the target objects will change reciprocally, so the estimate of total number remains unchanged. However, there are several limitations in applying the principles of stereology to the evaluation of gliosis. Foremost is that the total number of astrocytes or microglia is probably less indicative of glial reaction than is glial density, which cannot be measured without bias unless one knows the volume of the ROI prior to fixation or other processing, which is rarely possible. One solution is to consider the biological relevance of the ratio of densities of two cell types (e.g., resting and activated microglia), since both densities will be affected equally by swelling or shrinkage of the tissue. Aside from this, one should eliminate the bias inherent in simple counting of cell profiles by using a physical or optical disector. This involves counting only objects that are seen in one level of the tissue, but not in an immediately adjacent level, as determined by examining two serial sections or adjacent depths in a single thick section, respectively. In this way, one can obtain an unbiased estimate of the cell density *after* histological processing.

The histological classification of glial cells is crucial. Immunoreactivity can be easy to classify, but there are few genes, if any, expressed uniquely and consistently by one type of brain cell (e.g. (20)). The alternative is to classify cells morphologically, usually with Nissl stains. Neurons are readily identified by their prominent cytoplasmic Nissl substance (rough endoplasmic reticulum) and nucleoli, and the chromatin of oligodendroglial nuclei is generally more dense and homogeneous than that of astrocytes. However, these distinctions are sometimes ambiguous, and we are unaware of any study of Nissl stains that attempts to exclude or to classify microglial, NG2 glia, and endothelial cells.

Positron emission tomography (PET) and autopsy studies of the peripheral benzodiazepine receptor (PBR)

During reactive processes, cerebral expression of the PBR correlates with that of microglial and macrophage antigens (21–26); reactive astrocytes probably contribute also (27–28). Two PET studies found increased binding of PBR ligands in schizophrenia. One (29) found a 17% greater binding potential, diffusely distributed in grey matter of young patients within 5 years of onset of schizophrenia, compared with healthy subjects. There was considerable overlap between subjects with and without schizophrenia, and some or all of the difference might be attributable to atypical antipsychotic drugs (30). In a small study of subjects recovering from acute psychosis, all treated with antipsychotic drugs, the only statistically significant finding was a ~50% greater binding potential in hippocampus (31). The authors suggested that focal reaction could be a feature of psychosis that becomes widespread as the disease progresses and becomes chronic. However, the study was limited by small samples, idiosyncratic statistical treatment, and inclusion of psychoses that could not be diagnosed as schizophrenia.

In contrast to the PET studies, binding of PBR ligand to autopsy tissue was 23–42% lower in schizophrenia in 3 of 26 sampled areas of grey matter (superior parietal lobule, visual cortex, and putamen) (32) despite reportedly higher affinity in the schizophrenia samples. (Further details in Supplement 1) The discordance between the PET and autopsy studies could be methodological (it is unclear how the PET studies measured nonspecific binding), random effects in small samples, medication effects (half of the autopsy subjects had not received neuroleptic drugs for at least 40 days; all the live subjects were medicated), or differences in statistical treatment of the data.

Autopsy studies of microglia

The earliest report of microglial alterations in schizophrenia was by Fisman (33), who examined brain stems from 24 mental hospital patients and 10 general hospital patients without history of mental illness. Neuropathological findings were given for each subject, so we have tested statistical significance, which the author did not. The surprising finding was the presence of “glial knots” and perivascular inflammation in or near the trigeminal nucleus. The “glial knots” were not described or illustrated but were said to resemble a viral infection, so we presume these were microglial nodules. These were present in 5 schizophrenia cases (including a case of “epilepsy with schizophreniform psychosis”), 3 psychiatric cases without schizophrenia, and none of the nonpsychiatric cases (chi-square = 9.5, df = 2, $p < 0.01$). However, ischemic or other neuropathological lesions in the brain stem (aside from glial knots or inflammation), were present in 7 schizophrenia cases, 9 of the other psychiatric cases, and 3 of the nonpsychiatric cases ($p = 0.001$). This study is intriguing, particularly in light of claims of astrocytic gliosis in diencephalon and rostral brain stem, and of excessive frequency of “incidental” neuropathological lesions in schizophrenia (see below), but there is no statement that the evaluations were done without knowledge of the clinical information, and the sample is so small that statistical tests are strongly influenced by the classification of the case with epilepsy.

Arnold et al. (34), in addition to looking for degenerative pathology (see above) determined densities of microglia and astrocytes immunoreactive for CD68* and glial fibrillary acidic protein (GFAP), respectively, in elderly subjects. There were no differences between chronic schizophrenia and nonpsychiatric subjects in hippocampal formation or neocortex. In this study and Radewicz et al. (35), there were significant positive correlations of microglial density with age in the nonpsychiatric group, but not in the schizophrenia group. This would be consistent with a model in which normal aging involves the loss of attributes

(in this case, perhaps certain synapses or dendritic spines) that had never developed in schizophrenia (19). Alternatively, age-related increases may simply occur earlier in schizophrenia.

Arnold et al. also (36) investigated the caudate nucleus and mediodorsal thalamic nucleus of elderly people without psychiatric disease and with schizophrenia or Alzheimer's disease. These areas are important components of frontal – limbic pathways involved in both disorders (37), and some stereological studies (38–41), but not all (42–44), report smaller volume and fewer neurons in the mediodorsal nucleus of the thalamus in schizophrenia (45). In this study, densities (measured at a single level by unbiased methods) of Nissl-stained neurons, neurofibrillary tangles, GFAP-immunoreactive astrocytes, and CD68-immunoreactive microglia did not differ between nonpsychiatric and schizophrenic subjects. There were likewise no differences when the densities were expressed as a ratio to neuronal densities.

Bayer et al. (46) used qualitative evaluations to compare HLA-DR immunoreactive microglia in postmortem frontal cortex and hippocampus of older subjects with schizophrenia, Alzheimer's disease, affective disorders, and without neurological or psychiatric disease. Out of 14 schizophrenia patients, 3 with late onset of the disease (40, 46, and 50 years) exhibited abundant HLA-DR immunoreactive microglia, with an activated appearance, in gray and white matter. Similar staining was found in 1 out of 6 subjects with an affective disorder, the onset of which was at age 75, in 4 of 8 subjects with Alzheimer's disease, and in none of 13 nonpsychiatric subjects. The presence of microgliosis in late-onset mental disorders suggests an association with early stages of disease (presuming that the late-onset subjects died sooner after onset); alternatively, schizophrenia and mood disorders with later onset may differ etiologically from cases with earlier onset.

Radewicz et al. (35) compared densities of HLA-DR immunoreactive microglia in dorsolateral prefrontal, superior temporal, and anterior cingulate cortices of from elderly autopsy subjects with and without schizophrenia. Densities were significantly greater in schizophrenia across all layers in dorsolateral prefrontal cortex (28% greater, $p < 0.05$) and superior temporal cortex (57% greater, $p < 0.01$), without detectable destruction of tissue or infiltration by inflammatory cells. The microglia were mostly of resting morphology in both groups, but had a typical activated appearance in two cases of Alzheimer's disease included for comparison. Bernstein et al. (47), in reviewing this study, noted that microgliosis can increase with age (48). It is also confounding that, although histological Alzheimer's disease was exclusionary, both ROIs contained more senile plaques and neurofibrillary tangles in the schizophrenia cases than in the nonpsychiatric cases. Neither Bayer et al. (46) nor Radewicz et al. (35) reported microglial nodules.

Wierzb-Bobrowicz et al. (49) stained microglia in sections of frontal and temporal cortex from females with schizophrenia or without psychiatric illness. They describe “degenerative” loss of branching in class II major histocompatibility complex (MHC II)-immunoreactive microglia, but this is actually a feature of activation, as is clear in the illustrations of a subsequent paper on a large subset of these cases. In the first paper (49), nothing was counted, we are not told how many cases nor how many microglia showed the alleged degeneration, and there is no statement that the cases were evaluated without knowledge of diagnosis. Ultrastructural examination of several of the schizophrenia cases

*The term, “[antigen]-immunoreactive microglia,” usually refers to cells that are recognizable as microglia when stained for the relevant antigen alone. Double labeling for Iba-1 (which demonstrates both resting and activated microglia) and putative markers of activation reveals that many microglia that are apparently in the resting state contain punctate foci of immunoreactivity for CD68 or HLA-DR that are too small, on their own, to allow a cell to be recognized (unpublished results). In this review, we employ the usual terminology. The reader should not take this to mean that the balance of microglia completely lack the antigen of interest.

reportedly showed degenerative changes, but post mortem artifact is likely, and *the nonpsychiatric cases were not evaluated*, so degeneration cannot be substantiated. In their subsequent paper on the same cases (50), they determined anterior cingulate and inferior temporal densities of “ramified microglia” (presumably resting) and microglia with “damaged” processes (presumably activated) in 5 or 6 cases from each diagnostic group, measured separately at 10 successive cortical depths. They did not report statistical analyses but included data from each subject at each cortical depth. Nominally, densities of both types of microglia were substantially (3–13 times) higher in the schizophrenia subjects in most locations, and somewhat higher in the remaining locations. Many differences were statistically significant by t and Mann-Whitney U tests. This suggests that cortical densities of resting and activated microglia are elevated in middle-aged females with schizophrenia. The study is limited by small samples, absence of explanation of how the cases were chosen, and absence of a statement that counts were made without knowledge of diagnoses.

Steiner et al. (51) examined densities of resting, activated, and “amoeboid” microglia by morphological criteria in HLA-DR-immunostained sections from dorsolateral prefrontal anterior cingulate cortex, hippocampus, and mediodorsal thalamus. There was no statistically significant effect of diagnosis, but 2 schizophrenia subjects dying by suicide during acute psychosis had highly elevated numbers of microglial cells in anterior cingulate cortex and mediodorsal nucleus of the thalamus. A subsequent study of the same anatomical regions (52), found no significant effects of diagnosis, sex, age or hemisphere, but suicide was associated with several-fold higher densities than nonsuicides in the same diagnostic group, statistically significant in all regions except hippocampus. A limitation that, among the subjects with affective disorders, all suicides had a diagnosis of major depression, while 5 of 7 nonsuicides were diagnosed with bipolar disorder, although all were depressed at the time of death. Nonetheless, the effect of suicide appears to be robust, so *in vivo* imaging of TSPO might help to assess suicide risk in individual patients.

In summary, the data on microglia in schizophrenia are contradictory and inconclusive. Except for one study of subcortical structures, none of the studies employed currently acceptable counting procedures. That does not mean that they lack validity, but it does mean that the results were subject to biases, such as differences between diagnostic groups in cell size or tissue shrinkage. The samples are small; and most include mainly elderly subjects, in whom incidental lesions are common. The significance of the PBR, especially when measured by PET, is questionable. However, the elevation of PBR in live but not deceased subjects and the elevation of microglial density in suicides and in several cases of late-onset schizophrenia and depression suggest the possibility of microglial activation, perhaps resolving only slowly, in acute psychosis.

Autopsy studies of astrocytes

Falkai and Bogerts (53) examined Nissl stains of hippocampus from subjects with schizophrenia or without psychiatric disease. Hippocampi were smaller in the schizophrenia subjects and total numbers of glia (not subclassified) generally lower, with statistically significance in CA3, CA4, presubiculum, and parasubiculum. Glial densities were not reported, but as computed from average volumes and total counts for each region, densities of glia in schizophrenia were ~25% lower than in nonpsychiatric subjects among females and 6% – 27% higher among males. The findings constitute a weak argument against hippocampal gliosis among females with schizophrenia. In contrast, these investigators conducted a stereological study of the posterior hippocampus (54), counting neurons, astrocytes, and oligodendrocytes on Nissl stains, found no difference in volume nor total number of astrocytes overall or in any hippocampal subfield. Benes et al. (55), on Nissl stains of prefrontal, anterior cingulate, and primary motor cortices, found nominally lower glial

densities in schizophrenia than in nonpsychiatric subjects in all layers of each region except cingulate layer 3. Although the differences were generally in the range of 20–30%, none reached statistical significance except in layer 3 of motor cortex. A nearest-neighbor analysis of these cases showed virtually identical distributions of glia in the schizophrenia and nonpsychiatric cases (56). Identifying neurons, astrocytes, and oligodendrocytes on Nissl stains, Pakkenberg (57) obtained unbiased estimates neurons, astrocytes, and oligodendrocytes (actually, all cells not in the first two categories) in brains of elderly individuals. In mediodorsal nucleus of the thalamus and medial and ventrolateral portions of nucleus accumbens, counts of neurons, astrocytes, and oligodendrocytes were significantly lower, by about half, in schizophrenia. Volume differences were somewhat smaller, so densities, nominally lower, did not differ significantly. No such differences were found in ventral pallidum or basolateral amygdaloid nucleus. Immunohistochemistry for S100 β . (58) revealed elevated macroglial densities in dorsolateral prefrontal cortex and in white matter (where the cells appeared to be mostly oligodendrocytes) from individuals with paranoid schizophrenia, but not with residual schizophrenia.

In hematoxylin and eosin stains of corpus callosum (59), numerical densities of glial nuclei, counted by a technician, were unaffected by diagnosis, while semiquantitative ratings of gliosis, based on identification of astrocytes and glial processes by a neuropathologist, showed significantly greater gliosis at the rostral and caudal ends in late onset schizophrenia than in early onset schizophrenia. Caudally, gliosis was more extensive in late onset schizophrenia than in nonpsychiatric cases. Numerical counts included all glial subtypes, while semiquantitative ratings were specific to astrocytes and presumably influenced by morphological signs of reactivity.

The first use of glial cytoplasmic stains to study schizophrenia is probably Nieto and Escobar (60), studying 10 subjects with chronic schizophrenia and 3 without psychiatric disease. Using a variant of Hortega's lithium-silver carbonate stain, they found pronounced gliosis through much of the gray matter in diencephalon and midbrain of "all the cases of schizophrenia that can be considered as uncomplicated by other diseases." The illustrated gliosis appears quite intense and predominantly astrocytic, but the number of affected cases is unstated, *the nonpsychiatric results are not reported*, and there is no assurance that the examinations were performed without knowledge of clinical information. The authors conclude (p. 2658), "The gliosis observed in these diencephalic structures either may or may not have a pathologic significance." Janice Stevens (61), reviewed Holzer stains of brains of 28 chronic schizophrenia patients (mean age 44, all <50), excluding subjects with vascular or infectious diseases. (Holzer gives a purple color whose distribution is close to that of GFAP, which may be the substrate of the stain (62)). In 18 cases, gliosis was found in one or more periventricular structure, including hypothalamus in 16. In 16 adult nonpsychiatric cases (mean age 40, all <56), similar gliosis was found in only one. This study reinforces the finding of Nieto and Escobar (60), although ambiguous results from a group of psychiatric subjects without schizophrenia leave some doubt about specificity (discussed in (63)). Using Holzer stains, Casanova et al. (64) found no gliosis in entorhinal cortex of subjects with schizophrenia.

The importance of incidental lesions is underscored by Bruton et al. (65), who, with Holzer staining, found gliosis in cerebral cortex, white matter, and periventricular structures with significantly increased frequency in 48 elderly schizophrenia subjects (periventricular gliosis in 60%) compared with nonpsychiatric subjects matched for age and sex (periventricular gliosis in 40%). However, after eliminating cases with other neuropathological features (~60% of each group), they found no difference in the frequency of gliosis in any region, although the schizophrenia subjects in this subgroup still had larger cerebral ventricles than the nonpsychiatric cases. The negative result was confirmed (66) by radioimmunoassay for

diazepam binding inhibitor, a putative marker for glial cells and presumed endogenous ligand for TSPO (67). The negative result raises questions about the significance of the gliosis found in the two earlier studies, but since those used younger subjects, incidental lesions (e.g., small infarcts) were probably rare. The issue is unresolved, and crucial to our understanding of schizophrenia. Unexplained periventricular and periaqueductal gliosis could be the result of a remote inflammatory process (e.g., infection) that might account for larger lateral ventricles in schizophrenia. However, if the gliosis is explained by incidental lesions associated with aging, it tells us nothing about schizophrenia.

Densitometric measurements of GFAP immunoreactivity in many regions, including detailed examination of subfields of the hippocampal formation, yielded no significant differences in staining intensity (68–69). The basal forebrain and diencephalon (68) were sampled extensively, but in cases poorly matched for age and sex. Both studies argue against chronic astrocytosis in schizophrenia. One limitation, however, is the reliance on uncalibrated densitometry. A value of 0 is “black” and 63 is “white.” Unlike a spectrophotometer, a video camera does not use a reference beam to define 100% transmittance. The scale is arbitrary and potentially variable, unless calibrated with a gray scale standard. Furthermore, the relationship between concentration of antigen and amount of immunoperoxidase product is not necessarily linear nor the same for all specimens. The authors partially compensated for variability by subtracting the measured density of a fixed region assigned to “background;” it would be wise to set an upper limit as well. Nonetheless, Carl Stevens et al. (70), confirmed the negative result by counting the GFAP-immunoreactive glia in the same sections. A more important limitation is that the sample is too small to clarify the issues surrounding diencephalic gliosis in schizophrenia.

Several studies of numerical densities of GFAP-immunoreactive cells found no difference between elderly or middle-aged subjects with schizophrenia or without psychiatric illness, in a variety of hippocampal and neocortical regions (34–35, 71–73). Rajowska et al. (74) measured the area fraction and cell packing density of GFAP-immunoreactive astrocytes in dorsolateral prefrontal cortex (BA 9). GFAP-immunoreactive glial cell bodies and processes occupied 32% less area in layer 5 in the schizophrenia sample ($p = 0.006$), the packing density of GFAP-immunoreactive cell bodies (but not glial nuclei identified by Nissl stain) was 81% greater, and layer 5 was 14% thinner, while there were no differences in layers 3 and 4 combined. Area fraction measurements are exquisitely sensitive to thresholding, but if correct suggest a layer-specific astrocytic atrophy, or a decreased expression of GFAP in astrocytic processes, possibly with increased expression in cell bodies. The results are more suggestive of an astrocytic abnormality than an astrocytic reaction.

In summary, reactive astrocytosis in neocortex or hippocampus seems unlikely, but the possibility of gliosis in periventricular structures requires further study, preferably in younger subjects who are less likely to harbor incidental lesions.

Conclusions

Astrocytosis and microgliosis are common findings in brains at autopsy, especially from middle age onwards, when most people die. The autopsy studies of gliosis in schizophrenia have generally been too small, too primitive in design, and too poorly controlled to give definitive answers.

A large study of microgliosis and astrocytosis, including sizeable numbers of young subjects, is needed. To estimate roughly the required sample size, we listed, when available, the coefficients of variation (standard deviation/mean) of the measures of gliosis in the studies included in this review. Mean (unweighted) and median were 0.6, with a 95%

confidence interval of ~0.5 to ~0.7, both for nonpsychiatric and schizophrenia samples. To estimate the magnitude of a biologically significant difference, we referred to the pathological grading of Huntington's disease (75), where caudate astrocytosis is characteristic. Astrocytic density in caudate was ~50% greater in stage 1 disease than in the absence of disease. Also, microscopic fields that neuropathologists interpreted as mildly gliotic contained ~50% more astrocytes than fields without gliosis. Thus, a mild gliosis corresponds to an effect size that could be as low as 0.7 (50% difference/70% coefficient of variation). At $\alpha = 0.05$, 34 subjects per group give a power of 0.8, and 55 give 0.95. This estimate assumes that the ROI contains only the gliotic area. If gliosis affects only part of the ROI, the effect size will be smaller.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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