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(Micro)Glia as Effectors of Cortical Volume Loss in Schizophrenia

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Contrary to the notion that neurology but not psychiatry is the domain of disorders evincing structural brain alterations, it is now clear that there are subtle but consistent neuropathological changes in schizophrenia. These range from increases in ventricular size to dystrophic changes in dendritic spines. A decrease in dendritic spine density in the prefrontal cortex (PFC) is among the most replicated of postmortem structural findings in schizophrenia. Examination of the mechanisms that account for the loss of dendritic spines has in large part focused on genes and molecules that regulate neuronal structure. But the simple question of what is the effector of spine loss, ie, where do the lost spines go, is unanswered. Recent data on glial cells suggest that microglia (MG), and perhaps astrocytes, play an important physiological role in synaptic remodeling of neurons during development. Synapses are added to the dendrites of pyramidal cells during the maturation of these neurons; excess synapses are subsequently phagocytosed by MG. In the PFC, this occurs during adolescence, when certain symptoms of schizophrenia emerge. This brief review discusses recent advances in our understanding of MG function and how these non-neuronal cells lead to structural changes in neurons in schizophrenia.

Key words: dendritic spine/inflammation/microglia/neuropathology/prefrontal cortex/pyramidal cell

Attempts to define structural brain alterations in schizophrenia during much of the 20th century failed to reveal consistent neuropathological changes. The state of affairs was so bad that the neurologist Plum[1] famously referred to the field as "the graveyard of neuropathologists," with Harrison[2] subsequently commenting that the field was noteworthy for "generating more heat than light and … memorable quotes rather than durable data." Fortunately, the last quarter of the 20th century saw the application of quantitative neuroanatomical methods to neuropathological studies and the advent of contemporary in vivo imaging methods. These advances allowed researchers to detect subtle, but consistent, anatomical changes in the brain in schizophrenia, and led to the claim that "no longer can there be doubt that there is underlying brain pathology,"[3] fulfilling the view of Kraepelin that schizophrenia is a brain disorder. Although some suggest that this view may be a bit optimistic,[5] meta-analyses of volumetric as well as longitudinal studies point to structural changes in schizophrenia (however, see also Heilbronner et al,[6] Vita et al,[7] Kambeitz et al,[8] and Olabi et al.[9]).

Neuropathology of Schizophrenia

Neuron Pathology

A key finding by Eve Johnstone et al,[10] using computed tomography, was ventricular enlargement in schizophrenia. Although intially thought to reflect disease progression,[11] subsequent studies noted ventricular enlargement in first-episode patients.[12,13]

If the ventricles are enlarging, yet the brain is encased in an unyielding skull, what "gives"? Imaging studies have consistently revealed a decrease in gray matter volume in schizophrenia.[12,14] These findings are corroborated by postmortem studies noting reduced cortical thickness.[15] Although these changes are not seen in each subject, group differences in ventricular enlargement, gray matter volume, and cortical thickness, particularly in the prefrontal and medial temporal cortices, are consistently observed in schizophrenia, including in studies of first-episode and antipsychotic drug (APD)-naïve patients.[16–19] Such changes have even been reported in subjects deemed at high risk for developing the illness, although only a minority of high-risk patients subsequently develop schizophrenia,[20] leaving open the possibility that this may not be specific to schizophrenia.

The loss of cortical volume and thickness suggests that there may be a loss of cortical neurons in schizophrenia. However, unbiased counts of total neocortical neuron number[21] and the number of neurons in the prefrontal cortex (PFC)[22] have uncovered no such difference. Instead, neuronal density is increased,[23–25] leading Selemon and Goldman-Rakic[26] to propose the reduced neuropil hypothesis of schizophrenia. Their formulation posits that a decrease in cortical volume in the face of a normal complement of neurons occurs secondary to a decrease in neuropil, including dendrites and axons.

Relatively early studies of cortical gene expression were consistent with this hypothesis, reporting a loss of dendrite- and axon-associated genes.[27] Although anatomical and immunoblot studies of axonal markers in schizophrenia led to conflicting results,[27–37] studies of dendrites consistently revealed dystrophic changes.[38–42] In particular, there is a decrease in the density of dendritic spines on PFC pyramidal cells (PCs) in schizophrenia,[38,42–45] but not in samples from a psychiatric control group[44] (primarily mood disorders subjects treated with APDs). Some studies of changes in spine density revealed selective effects on deep layer 3 (L3) PFC PCs, consistent with a decrease in soma size of L3 PCs.[30,46,47] Prefrontal cortical PCs appear to be most vulnerable to spine loss; a less pronounced decrease in spine density has been reported in the primary auditory[48,49] with no significant change in the visual cortex.[44]

Because dendritic spines are the primary site of excitatory inputs to the PC, the loss of spines on PCs may lead to significant disruptions in excitatory signaling to corticofugal pathways. Unfortunately, there have been very few studies probing the correlation of dendritic spine density changes and cognitive performance (see Kim et al,[50] Cahill et al,[51] and Hains et al[52]), with none focusing on different times during development. Moreover, although it has been suggested that cognitive deficits are already present in first-episode schizophrenia,[53] this is an oversimplification, with deficits in performance of certain cognitive tasks (such as working memory) differing from those in processing speed. In addition, most studies of cognition in schizophrenia do not determine the degree to which such changes may be secondary to negative symptoms or other domains.[54] At this time, the functional impact of dendritic spine changes on specific symptom domains is unknown.

However, by comparing the shape of lost (vulnerable) and remaining dendritic spines, one may glean limited insight into function. Morphological parameters have long been used to categorize spines into different classes, including spines that hyperacute anatomists have fancifully described as thin-, stubby-, and mushroom-shaped.[55,56] These adjectives are of limited utility: various parameters of spine shape (such as spine head diameter, which should be larger in mushroom than thin spines) show considerable overlap across different types of spines.[57] Nonetheless, thin spines, which are relatively long and lack a wide head, have been advanced as being immature and more likely to lack α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid AMPA receptors, ie, have functionally silent synapses[58,59] (however, see also Busetto et al[60]), whereas larger, mushroom-shaped spines are thought to be mature.[61] Only very recently has there been an assessment of the types of spines present in schizophrenia.[62] This study reported that thin spines were preferentially lost in the auditory cortex, which was interpreted to suggest that there is a deficit in newly formed spines in the cortex. We await confirmation of these recent data, including in the PFC.

If dendritic spines are decreased in number, there may be corresponding decreases in the presynaptic partners of lost spines. However, postmortem studies of changes in presynaptic elements in schizophrenia, including proteins involved in vesicular trafficking and release, have yielded conflicting results.[27–37] Several factors may contribute to the inconsistent results, including different dependent variables (mRNA vs protein levels), APD treatment, and differences in the areas and layers of the cortex being sampled. Still another reason for the conflicting data may be that most studies examining presynaptic changes have analyzed markers of synaptic release common to all neurons, thereby capturing both inhibitory and excitatory presynaptic elements. Because presynaptic axons forming synapses with spines are excitatory, more consistent results emerge when excitatory inputs are analyzed separately: there is a decrease in cortical levels of the glutamatergic marker vesicular glutamate transporter (VGluT) 1 (but not VGluT2, another glutamate transporter).[63–65] Because VGluT1 and VGluT2 are mainly expressed by cortical and subcortical glutamatergic neurons, respectively,[66–68] synapses formed by different afferent sources defining different circuits with distinct PCs may be compromised in schizophrenia.

Glial Pathology

One index of a shift in the targets of scientific inquiry in brain disorders over the past decade has been the introduction of neologisms such as gliotransmission. The scientific blinders that limited attention to neurons have been removed, leading to a broad interest in non-neuronal as well as neuronal elements of the nervous system. In particular, there is today a much greater appreciation of the diverse roles played by glia.

In 1982, Stevens[69] reported that reactive astrocytosis (an increase in astrocytes that occurs in response to cellular damage) was present in the thalamus, limbic areas, and periventricular sites in about ~70% of patients with schizophrenia; these observations were consistent with some earlier reports of gliosis in diencephalic and mesencephalic regions.[70,71] However, these early studies of reactive astrocytosis did not use unbiased methods,

now *de rigueur*,[72,73] to determine cell number or density, and lacked many methodological details and some control procedures, clouding interpretation of the results. Coupled with a lack of assessment of potential confounding variables,[74] substantial differences in the conclusions of early and more contemporary studies of glial changes in schizophrenia are not surprising.

Astrocytes. Roberts et al[75] examined 20 different brain areas for evidence of astrogliosis in the brains of schizophrenic subjects. They found no difference in the numbers of cells expressing the astrocytic marker glial fibrillary acidic protein (GFAP).[76,77] Roberts et al[78] subsequently replicated their initial finding in a larger cohort, and most subsequent studies of schizophrenia also failed to detect an increase in the number or density of astrocytes.[75,78–96] Studies of GFAP mRNA and protein levels largely corroborated the anatomical data.[36,95,97–102]

Thus, available postmortem data suggest that there are probably no substantial changes in the number or density of astrocytes in the cortex in schizophrenia.[103] Future studies utilizing a different marker of astrocytes, aldehyde dehydrogenase 1 family, member L1 (Aldh1L1), which in contrast to GFAP appears to be an invariant marker of astrocytes[104] may reveal subtle, region-specific changes in astrocytes.

Microglia. There has long been considerable interest in the role of inflammation in promoting neuropathological changes in schizophrenia.[103,105,106] Interest has piqued over the past decade with genetic studies revealing associations of schizophrenia with the major histocompatibility locus,[107] and more recently with specific variations in complement component 4 being strongly linked to the risk for developing schizophrenia.[108]

Because microglia (MG) are the immune cells of the brain, potential changes in the number, density, and function of MG have been scrutinized. It should not be surprising to learn that this area of research is also littered with inconsistent results. Studies using various markers to label MG have resulted in reports of increased density of MG,[85,109–111] increased MG activation,[109,112] and degenerating MG cells.[109,113] In contrast, other studies have found no change in these parameters.[82,84,93,114–116] A recent meta-analysis of studies examining MG density in postmortem tissue concluded that the preponderance of evidence is consistent with a significant increase in MG density and a corresponding upregulation of MG-related proinflammatory genes in schizophrenia.[117]

Studies of MG in schizophrenia have in part been confounded by issues common to all postmortem studies, ranging from the use of APDs or other drugs to agonal state. However, there is another concern specific to MG: although MG occupy a restricted central nervous system (CNS) niche, virtually all MG markers are also present in (peripheral) monocytes and macrophages. The recent identification of transmembrane protein 119 (Tmem119)[118,119] and potentially sialic acid–binding immunoglobulin-like lectin H (Siglec-H)[120] as selective markers of central MG but not peripherally derived cells should open the door for more accurate studies of MG number and density in schizophrenia.

An indirect approach to identifying changes in MG and inflammatory processes in schizophrenia has been through the development of radioligands for positron emission tomography studies of MG. Radioligands for the 18 kDa translocator protein (TSPO), a protein thought to be involved in steroidogenesis,[121,122] have been proposed to be useful in monitoring inflammatory processes and MG activation in various disorders,[123,124] including schizophrenia. Expression of TSPO is upregulated in inflammatory states and diseases[125–128] and during MG activation.[124,129] Early imaging studies with TSPO tracers generated conflicting results because the contribution of allelic variants in TSPO binding was not appreciated.[130] However, subsequent studies, conducted at various stages of the illness, were also inconsistent.[131–140] It has become clear that TSPO is not a specific marker of MG: the protein is also expressed in peripheral (and CNS-infiltrating) macrophages and monocytes, and has been reported to bind to astrocytes, endothelial cells, and perhaps even neurons.[141–144] Moreover, TSPO expression is increased substantially in response to a proinflammatory challenge in rodent, but not in human, MG.[145] These considerations and others have cast doubt on the utility of TSPO as a marker of MG activation and inflammation.[130,143,146–150]

Where Do the Lost Dendritic Spines Go in Schizophrenia?

During brain development, the number of synapses is not constant. In early postnatal development, synapses on neurons are formed in excess.[151] Some of these supernumerary synapses are subsequently removed (pruned), while others are strengthened,[152] optimizing the signal-to-noise ratio. The age at which mature neuron structure is achieved varies across brain regions. The PFC is the last area to mature, finally stabilizing in the third decade of life.[153]

Peak density of PFC synapses[153,154] occurs during adolescence, the period during which certain symptoms of schizophrenia typically emerge, leading Feinberg[155] to propose that schizophrenia may result from a defect in synaptic elimination programmed to occur during adolescence. This neurodevelopmental hypothesis was followed by several others,[156] which posit that the consequences of an insult during the second or third trimester of pregnancy lie dormant until manifest in adolescence.

Efforts to understand the process of synapse removal during development have revealed a critical role for MG, the innate immune cells of the CNS. Microglia are CNS macrophages derived from yolk-sac progenitors that

migrate to the neural tube early in embryonic development,[157] and which locally renew by self-proliferation.[158] They are highly dynamic cells, extending and retracting their processes to surveil brain parenchyma for signs of insult or injury.[159,160] Microglia also play key roles in the healthy brain (see Tremblay et al,[161] Hong et al,[162] and Kierdorf and Prinz[163]), including in the modification of synaptic architecture in an experience-dependent manner, elimination of apoptotic neurons, and the formation of dendritic spines.[164–166] Under physiological conditions, MG engulf excess synapses early in development in subcortical areas[167,168] through complement-mediated pathways.[168,169]

In the rat, MG transiently engulf dendritic spines on PFC PCs at postnatal day 39,[170] an age corresponding to late adolescence in humans (see Mallya et al[170]). Presynaptic glutamatergic terminals synapsing with spines are also pruned by MG, but slightly later than spines, consistent with spine outgrowth preceding synapse formation.[171–173] These data agree with Feinberg's[155] hypothesis, suggesting a deranged enhancement of physiological synapse pruning by MG during adolescence culminates in a reduced number of PFC PC dendritic spines.

The role of developmental synaptic pruning is not limited to MG. Astrocytes have been shown to participate in synapse elimination,[174] both directly (via recognition of an unidentified "eat-me" signal on a synapse destined for elimination through phagocytic pathways[175]) and indirectly (in which release of transforming growth factor β regulates the expression of complement component C1q at synapses, recruiting MG to the site[176]). Although the overall number of reactive astrocytes may not be increased in schizophrenia, there may be changes in one type of reactive astrocyte[177,178] (the "A1" astrocyte, which are induced by activated MG and thought to be neurotoxic [see Liddelow et al[177] and Liddelow and Barres[178]]).

Future Studies of Microglial Involvement in Schizophrenia

Microglia have historically been thought to adopt different morphologies based on their functional state. Surveilling MG are extensively branched and have a smaller somata than activated MG, which assume a large ball-like shape with few or no processes (see Hanisch and Kettenmann[179] and Ransohoff and Perry[180]). In contrast to this traditional view, recent data indicate that during pruning of synapses MG do not assume a classic "activated" morphology, instead displaying many branched processes.[168,170,181] These findings suggest that there are at least two different types of activated MG: those triggered in response to a pathological challenge, and those activated to engage in physiological neuronal sculpting. Furthermore, MG phenotype is governed by unidentified local cues, adding to the complex heterogeneity of MG.[182] Disentangling the processes and signals that dictate the functional state of MG during developmental phagocytosis as opposed to those mediating inflammation- and pathology-based phagocytosis will be critical for future understanding of MG function in health and disease.

An issue not often addressed but critical to our understanding of MG is how to assess the relative contribution of MG that are intrinsic to the CNS from infiltrating macrophages generated in the periphery. Studies of developmental pruning have used markers common to both peripheral or central cells, such as ionized calcium-binding adapter molecule 1 (Iba1) and the fractalkine receptor CX_3CR1. However, in the healthy CNS, MG are the resident macrophages, while peripheral macrophages are mainly restricted to perivascular spaces, meninges, and the choroid plexus.[183,184] The extent to which the blood–brain or cerebrospinal fluid–brain barriers may be porous under conditions such as inflammation or in illnesses such as schizophrenia is not known. Similarly, it is not clear to what degree peripherally derived monocytes enter the CNS at circumventricular sites,[185] and from there migrate to other areas.

Translating Microglial Dysfunction to Therapeutic Strategies

The elucidation of the mechanisms whereby developmentally specific synaptic pruning occurs may lead to new therapeutic targets for mitigating structural and functional changes in schizophrenia. Neuronal elements destined for elimination have undefined (but in part possibly complement-related) "find-me" signals that target MG to the neuron and "eat-me" signals that then cue the MG to phagocytose a particular spine or axonal element. There are also "don't-find-me" and "don't-eat-me" signals that help a spine evade detection and pruning, similar to those seen in apoptotic cells.[186] Pharmacological or molecular suppression of the former or amplification of the latter, particularly during adolescence, when spine pruning is active, might diminish excess pruning of spines on PFC PCs, thereby averting some of the behavioral pathology of schizophrenia. However, it is likely that too much suppression will result in too many spines, as seen in autism spectrum disorder (ASD) and Fragile X syndrome.[187] Notably, in both ASD and schizophrenia, social cognition is impaired, suggesting that there may be an optimal spine number above or below which negative consequences occur.

Concluding Remarks

Psychiatry has moved from questioning whether schizophrenia is a brain disease to determining how structural changes in certain brain areas and circuits lead to symptoms. Attempts to understand the pathophysiology of schizophrenia have become more challenging with the realization that schizophrenia is not a disease of neurons, but also critically involves non-neuronal cells. However,

this added complexity may reveal important new drug targets for the treatment—or even prevention—of schizophrenia. Our appreciation of the many physiological roles played by MG is rapidly growing and points to the need for new methods to allow one to demonstrate conclusively if MG are effectors of the "excess synaptic elimination programmed to occur during adolescence" first posited by Feinberg[155] 35 years ago.

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