Schizophrenia Research and Treatment

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Guest Editors: Haiyun Xu, Vahram Haroutunian, George Bartzokis, and Martha E. Shenton

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Editorial Board

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Editorial

Oligodendrocytes in Schizophrenia

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Despite the many neuroimaging studies that suggest gray matter volume reductions in schizophrenia, there is no compelling postmortem evidence to suggest neuronal loss, nor is there a distinctive or specific signature of gray matter abnormalities in schizophrenia. Instead, there appears to be no observed focal lesion that characterizes gray matter pathology in schizophrenia. This state of affairs has led to a movement away from conceptualizing schizophrenia as resulting from a single lesion, to conceptualizing schizophrenia as arising from abnormal communication between brain regions. Abnormal connectivity between brain regions is not a new concept, as Bleuler (1911) postulated such abnormalities. What is new, however, is an appreciation that brain regions that are not spatially proximal may be connected functionally into neural networks and that to understand altered neural connectivity we need to have a better understanding of the connections between brain regions which are made possible by white matter, the main infrastructure in the brain that makes possible long distance communication among neurons. Accordingly, a focus on white matter connections in the brain has become increasingly of interest in schizophrenia, particularly in the areas of imaging studies, postmortem studies, and new animal models of schizophrenia. This special issue focuses on schizophrenia and oligodendrocytes, the latter a class of neuroglia that give rise to myelin. The primary aim of this special issue is to understand and to clarify further white matter pathology in schizophrenia and how it may contribute to disconnectivity among brain regions, which results in the observed cognitive, behavioral, and clinical symptoms in this disorder.

The first paper begins with a description of the theory that schizophrenia reflects a disorder of connectivity. The proposition put forth is that schizophrenia is, at least in part, the result of abnormal communication between brain regions that may be spatially distant but nonetheless functionally connected. As white matter is the main infrastructure for brain connectivity, this paper focuses on the use of a magnetic resonance imaging (MRI) technique called diffusion tensor imaging (DTI) to gain insight into the role of white matter abnormalities in schizophrenia. This paper also focuses on the functional implications of white matter abnormalities, particularly with regard to the possible role of myelin in modulating the transmission velocity of neural discharges. The paper ends with a speculative hypothesis about the relationship between gray matter and white matter abnormalities in schizophrenia.

The second paper also focuses on altered neuronal connectivity. Here, however, the focus is on altered connectivity and impaired myelination in a postmortem study of schizophrenia and normal controls, where electron microscopy is used to study myelinated fibers and oligodendrocytes. This morphometric study examines myelinated fibers in the prefrontal cortex in both gray and white matter. Six types of abnormal fibers and ultrastructural alterations are described in the schizophrenia sample. The study reveals increased pathological fibers in gray matter in both young and elderly patients that are associated with positive symptoms, while in elderly patients, the frequency of pathological fibers in white matter is increased and these changes are associated with more negative symptoms. The key implication here is that

altered myelinated fibers in white matter in schizophrenia likely follow alterations of myelinated fibers in gray matter that occur earlier in the course of illness.

The third paper is a postmortem study on age-related changes in the number of oligodendrocytes in prefrontal cortex in schizophrenia, bipolar disorder and major depression. The study reveals an age-related increase in numerical density of oligodendrocytes in layer VI and adjacent white matter of BA9 and 10 that is seen only in normal controls and not in schizophrenia or in mood disorders. The absence of the normal age-related increase in oligodendrocytes in patients suggests that this aspect of normal brain development is dysregulated in schizophrenia and in mood disorders, and confirms postmortem and imaging data, further highlighting the fact that the absence of a normal age-related increase in oligodendrocytes is a key shared feature in these psychiatric populations.

The fourth paper reviews white matter abnormalities in schizophrenia, including imaging and postmortem findings on the disconnectivity theory of schizophrenia, a major theme that underlies the three previous papers in this special issue. This paper then reviews some of the white matter diseases that commonly lead to psychotic symptoms and then reviews transgenic and mutant mouse models of schizophrenia. More specifically, genetic mouse models such as Plp1 transgenic mice and mutant mice heterogeneous for either NRG1 or its receptor erbB4, as well as Nogo-A-deficient mice are reviewed. This is followed by a focus on the myelin toxicity model of mice fed cuprizone. In the early stage (the second and third week) of the cuprizone feeding, mice show higher dopamine levels and lower norepinephrine levels in their prefrontal cortex, along with behavioral changes indicative of increased CNS activity. In the late stage (weeks 4–6), when demyelination and oligodendrocyte loss are obvious, mice display cognitive deficits as well as deficits in social interactions that are reminiscent of social withdrawal seen in patients with schizophrenia. Importantly, this cuprizone-feeding mouse may be used as an in vivo platform for psychopharmacological studies testing the effects of antipsychotic drugs on white matter alterations and associated behavioral changes, in addition to providing a new animal model of schizophrenia.

The fifth and final paper of this special issue focuses on abnormal behavior and microstructural changes in juvenile mice that are repeatedly exposed to nonneurotoxic levels of amphetamine. These mice are compared with nonamphetamine treated mice. Oligodendrocyte numbers and three proteins expressed in mature oligodendrocytes are investigated in these young male mice at sacrifice. Treated mice showed higher locomotion and impaired spatial working memory, along with lowered Noga-A and GST-pi proteins, and lower MBP proteins, in frontal cortex and hippocampus and fewer mature oligodendrocytes in frontal cortex and corpus callosum, as well as lower MBP staining in frontal cortex, corpus callosum, and hippocampus, than untreated mice. These differences suggest that in wild-type mice late developing white matter is vulnerable to amphetamine and may lead to compromised white matter with increased dopamine in specific brain regions. Not only do these findings explain well the increased locomotion and impaired spatial working memory observed in amphetamine-treated mice, but also may serve as a principle for the amphetamine-treated mouse being used as a novel animal model of schizophrenia.

To summarize, compared to the focus on gray matter and neurons, research on white matter and myelin/glial has been sparse in schizophrenia. In this special issue, neuroimaging findings are presented that suggest that myelin abnormalities in schizophrenia may underlie the white matter abnormalities observed using diffusion tensor imaging techniques. Data from postmortem studies also confirm the presence of oligodendrocyte and myelin abnormalities in schizophrenia as well as mood disorders. Oligodendrocytes provide protection and improve communication between brain regions and the oligodendroglia-producing myelin is approaching maturity in the same time frame as the onset of symptoms. Further, normal age-related white matter increases and related gray matter changes that likely predate the white matter changes are dysregulated in schizophrenia and may contribute to the clinical symptomatology of the disease. Finally, the recently developed animal models are not only of help in understanding connectivity abnormalities in schizophrenia but also provide novel platforms to test novel therapeutic approaches for schizophrenic patients. Treatments specifically targeting white matter, for example, may improve on the efficacy of those treatments currently in use.

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Research Article

Diffusion Tensor Imaging, Structural Connectivity, and Schizophrenia

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A fundamental tenet of the "disconnectivity" theories of schizophrenia is that the disorder is ultimately caused by abnormal communication between spatially disparate brain structures. Given that the white matter fasciculi represent the primary infrastructure for long distance communication in the brain, abnormalities in these fiber bundles have been implicated in the etiology of schizophrenia. Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that enables the visualization of white matter macrostructure *in vivo*, and which has provided unprecedented insight into the existence and nature of white matter abnormalities in schizophrenia. The paper begins with an overview of DTI and more commonly used diffusion metrics and moves on to a brief review of the schizophrenia literature. The functional implications of white matter abnormalities are considered, particularly with respect to myelin's role in modulating the transmission velocity of neural discharges. The paper concludes with a speculative hypothesis about the relationship between gray and white matter abnormalities associated with schizophrenia.

1. Introduction

A notable feature of the neuroimaging literature in schizophrenia is the sheer number of brain structures that have been implicated as abnormal in patients with this disorder. The temporal cortices, medial temporal structures, and frontal lobes have consistently been shown to be morphologically and cytoarchitecturally abnormal in patients with schizophrenia, and abnormalities in the parietal and cingulate cortices, basal ganglia, and cerebellum are also common [1]. However, despite the multitude of gray matter (GM) structures that have been reported to be structurally compromised in patients with schizophrenia, it is notable that there are still no reliable biomarkers for the disease—in contrast, for example, to the amyloid plaques and neurofibrillary tangles that are prognostic for Alzheimer's disease. Furthermore, it is also notable that while GM abnormalities are ubiquitous in schizophrenia, there is no GM structure that is universally atypical in patients with the disease, or to which damage has consistently been shown to trigger psychotic symptoms [2].

Possibly in response to the ongoing failure to identify a distinctive neuropathological signature for the disorder, there has been a movement away from the idea that schizophrenia is caused by a focal neural insult in favor of the idea that schizophrenia arises from abnormal neural communication. The fundamental tenet of the "disconnectivity" theories of schizophrenia is that rather than being caused by normal interactions between pathologic GM structures, the symptoms of schizophrenia instead arise from pathologic interactions between pathologic GM structures [3].

For example, Frith [4] has suggested that delusions of control could arise because of disrupted communication between frontal areas initiating movement and parietal areas processing the sensory consequences of that movement. Crow [5], on the other hand, has suggested that auditory hallucinations could arise from aberrant communication between language-related regions in the temporal cortices, bilaterally. Furthermore, while some "disconnectivity" theories have emphasized the role of aberrant synaptic plasticity in the etiology of schizophrenia [6, 7], others have focused on the role of structural abnormalities in the fibers connecting spatially disparate populations of neurons—that is, the white matter (WM).

WM is primarily constituted of the phospholipid processes of oligodendrocytes, which are a class of neuroglia. These processes, which are known as myelin, wrap around axons in the central nervous system, insulating the membrane and increasing the conduction velocity of action potentials. Myelinated axons with similar destinations bundle together into fiber tracts, and it is these fiber tracts that constitute the infrastructure for long-distance communication between spatially disparate GM regions. In light of the fact that fiber tract damage can disrupt or even disable communication between connected brain regions [8], and given that psychotic symptoms are unusually common in patients with WM diseases (such as metachromatic leukodystrophy [9] and multiple sclerosis [10]), a number of researchers have speculated as to the existence and implications of WM abnormalities in patients with schizophrenia, [2, 11–14]. The results of genetic analyses that have revealed the abnormal expression of several myelination-related genes in patients with schizophrenia [15] have also contributed to an increased interest into the role of WM abnormalities in the disorder.

While the basic idea that WM abnormalities could underlie the symptoms of schizophrenia is not new (Bleuler discussed the possibility in 1911), it has only recently become the topic of focused empirical investigation. A major reason for this is technical: WM is notoriously difficult to measure *in vivo* via conventional structural brain imaging techniques such as magnetic resonance imaging (MRI) because of its apparent homogeneity. Furthermore, imaging WM with functional imaging techniques such as positron emission tomography (PET) and functional MRI (fMRI) is also problematic, due to the fact that the metabolic profiles of oligodendrocytes are at least partially independent of task-induced changes in neuron metabolism. And while several *in vitro* stereologic studies have been undertaken in schizophrenia patients postmortem, an acknowledged disadvantage of the technique is the generally suboptimal quality of the tissue, unless a postmortem can be arranged quickly [16]. Given these methodological limitations, it is fair to say that the development of diffusion tensor imaging (DTI) in the 1980s [17] opened the door to the direct empirical investigation of WM abnormalities in patients with schizophrenia, by enabling an accurate quantification of WM integrity *in vivo*. An example of how DTI can be used to identify specific WM fiber bundles (in this case, the corpus callosum), based on their diffusion properties, is displayed in Figure 1.

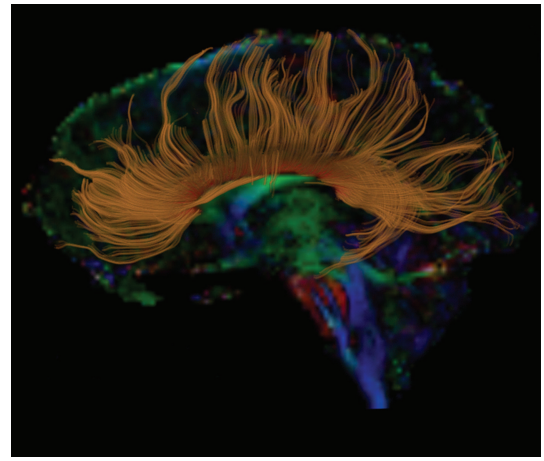

Figure 1: Fiber tractography of the corpus callosum (in gold) overlaid onto a color-by-orientation image extracted from a Diffusion-Tensor Image.

2. Diffusion Tensor Imaging—A Brief Introduction

DTI enables inferences to be made in terms of the integrity and orientation of fiber tracts on the basis of patterns of water diffusion. DTI is noteworthy in that it can provide information in terms of WM anatomy that is simply not accessible with any other method—either *in vivo* or *in vitro*. Diffusion—otherwise known as Brownian motion—refers to the random movement of particles, such as water molecules, as a result of unpredictable, thermally driven molecular collisions. In an unrestricted medium, a water molecule is equally likely to move in one direction as another. However, in brain tissue the diffusion of water molecules is restricted by obstacles in the local environment such as cell membranes, myelin sheaths, and macromolecules. The extent to which diffusion is restricted differs between the different tissues of the brain. In the cerebrospinal fluid (CSF), for example, there are relatively few obstacles to diffusion, and hence the average shape of the resultant diffusion is approximately spherical: this is known as isotropic diffusion. In contrast, in a WM fiber bundle the densely packed and homogeneously oriented bundles of myelinated axons provide a considerable barrier to water diffusion. In this case, water is more likely to diffuse parallel to the WM bundle rather than perpendicular to it, which will make the shape of the resultant diffusion less spherical and more ellipsoidal: this is known as anisotropic diffusion—see Figure 2. By calculating the distance in which water diffuses in a given voxel in a given amount of time (i.e., in the order of milliseconds) for at least six noncollinear directions, it is possible to reconstruct a three-dimensional shape that best describes the pattern of water diffusion occurring in a given voxel. The shape best describing this pattern of diffusion is conventionally modeled as an ellipsoid, and the important point is that the volume and shape of this ellipsoid provide information about the diffusion properties and hence the microstructural features of the brain tissue.

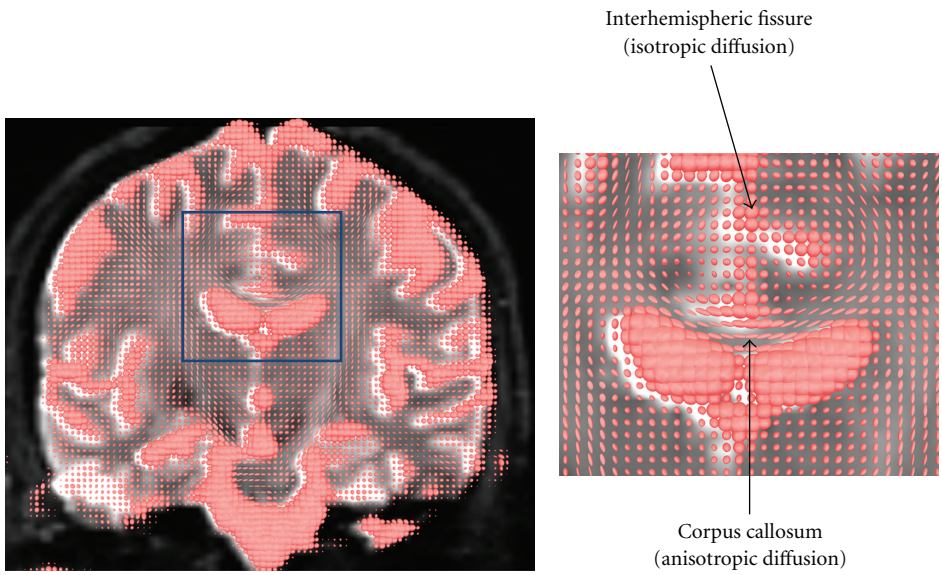

Figure 2: The shape of water diffusion in the different tissues of the brain. (a) depicts the variations in the shape of water diffusion across a coronal slice of brain tissue, while (b) is a zoomed-in section of (a). As illustrated in (b), the shape of diffusion in the inter-hemispheric fissure is approximately spherical, as there are few obstacles to diffusion in the CSF. In contrast, the tightly aligned, myelinated fibers of the corpus callosum form a significant obstacle to diffusion. Diffusion is more likely to occur parallel to the white matter fibers as opposed to perpendicular to them, and thus the shape of diffusion is ellipsoidal in these voxels.

Three of the more common diffusivity indices that have been examined in the DTI literature are fractional anisotropy (FA), mean diffusivity (MD), and, more recently, Mode. FA is a measure of the sphericity of the diffusion ellipsoid. FA can vary between values of zero and one, with completely spherical diffusion having a value of zero and perfectly aspherical (e.g., linear) diffusion having a value of one. In a WM bundle, reduced FA is generally assumed to reflect damage to the axon membrane, reduced axonal myelination, reduced axonal packing density, and/or reduced axonal coherence [18], while increased FA has been suggested to reflect supranormal levels of myelination or axonal sprouting [19]. On the other hand, MD is dependent on the volume of the diffusion ellipsoid, that is, the average displacement of water molecules as a result of diffusion in a given amount of time. MD is highest in tissues where there are few impediments to water diffusion (e.g., CSF), and lowest in tissues where diffusion is restricted at least one direction (e.g., WM). Although FA and MD are (almost) mathematically independent, they are generally found to be inversely related in the brain, such that tissue showing highly anisotropic diffusion (such as WM) generally shows low MD. Mode is a relatively recently developed index that provides additional information in terms of the 3D shape of the diffusion ellipsoid than that provided by FA. Roughly speaking, for a given FA value, Mode describes whether the diffusion ellipsoid is shaped like a cylinder (i.e., having highly "tubular" anisotropy) or like a disk (i.e., having highly "planar" anisotropy) [20]. When considered in combination with FA, the Mode of a diffusion ellipsoid provides unique information as to the microstructural features of the underlying WM. For example, the presence of fiber crossings has been associated with reductions in Mode [21, 22]. Hence, the finding that schizophrenia patients show supranormal levels of Mode in the corpus callosum has been argued to reflect a reduction in the density of fibers adjacent to this fasciculus [23].

3. White Matter Abnormalities in Schizophrenia—Do They Exist and What Do They Mean?

The first DTI study that investigated WM abnormalities in patients with schizophrenia was performed by Buchsbaum et al. [24] in 1998. Since that time, over 100 DTI studies have been performed on patients with schizophrenia. By far the most consistent finding has been of FA reductions in the patients, with significant reductions being reported in the corpus callosum, superior longitudinal fasciculus, inferior longitudinal fasciculus, arcuate fasciculus, uncinate fasciculus, cingulum bundle, and fornix [13, 18, 23, 25–47]. The observation of FA reductions in patients with schizophrenia raises the question as to what are the physiologic underpinnings of these FA abnormalities. Research by Beaulieu [48] indicates that axonal membranes are the primary determinant of anisotropic water diffusion in fiber bundles, with axonal myelination also modulating anisotropy to a significant, albeit lesser, extent. Hence one possibility is that the reduced FA observed in schizophrenia patients is due to a pathologic reduction in the number of neurons, and hence their associated axons. However, there is little evidence to suggest a significant reduction in neuron number in the brains of schizophrenia patients

relative to healthy people [49]. By contrast, there is evidence to suggest that the characteristic GM reductions observed in schizophrenia patients are likely the result of a reduction in the density of dendrites, spines, axon-terminals, and neuroglia [50]. In light of this, an alternative possibility is that the FA abnormalities in schizophrenia are caused by damage to the myelin-sheaths of oligodendrocytes.

It has been demonstrated that myelin abnormalities alone can result in significant reductions in FA. For example, Nair and colleagues [51] compared wild-type mice and transgenic *shiverer* mice (who show abnormalities in myelin but not to the axon membrane) and found that the *shiverer* mice had significantly decreased FA in the corpus callosum. Furthermore, Song and colleagues [52] found evidence indicating that it is possible to distinguish between axonal damage and dysmyelination on the basis of the distinctive patterns of diffusivity abnormalities induced by these injuries. Specifically, Song et al. [52] demonstrated that while the amount of diffusion perpendicular to the principal orientation of the optic nerve (which they termed "radial diffusivity") was increased in *shiverer* mice with severe dysmyelination, the amount of diffusion parallel to the tract ("axial diffusivity") was unaffected. Conversely, Song et al. [53] demonstrated that axonal injury concurrent with myelin preservation resulted in a decrease in axial diffusivity but no change in radial diffusivity. The significance of these findings is clear in the context of a recent study by Ashtari et al. [54] who found that schizophrenia patients exhibited abnormally increased radial diffusivity in the inferior longitudinal fasciculus, but no difference in axial diffusivity, putatively indicating the presence of myelin abnormalities but the absence of axonal abnormalities. And finally, in an electron microscopy study (with a very short postmortem delay of four to six hours), Uranova et al. [55] reported evidence of oligodendrocyte degeneration and myelin damage in the prefrontal cortex and caudate nucleus of patients with schizophrenia. When taken in combination, these results suggest that myelin abnormalities are at least partially responsible for the FA reduction typically observed in patients with schizophrenia. If myelin abnormalities are at least partially responsible for the FA reductions in patients with schizophrenia, then what causes these abnormalities? Furthermore, what is the relationship (if any) between the myelin abnormalities inferred with DTI and the GM abnormalities that have been consistently observed in these patients both *in vivo* and *in vitro*?

It is well established that one of the principal functions of myelin is to increase the transmission velocity of action potentials traveling along axons by increasing membrane capacitance and reducing ion leakage through the axon membrane [8]. Furthermore, there is evidence to suggest that diffusivity indices are correlated with indices of conduction velocity measured via electroencephalography. For example, Whitford and colleagues [56] found a significant negative correlation between the FA of the visual fibers of the corpus callosum and interhemispheric transfer time as measured with visually evoked potentials in both schizophrenia patients and healthy controls. Given the evidence indicating that patients with schizophrenia exhibit myelin abnormalities in at least some WM bundles, particularly in those bundles that connect the frontal lobe with the rest of the brain, it seems reasonable to assume that this would result in significant transmission delays in neural communication between spatially disparate GM regions, such as between the frontal lobe and the temporal cortex (see [57]). And as has been pointed out by both Fields [11] and Aboitiz [58] even small transmission delays resulting from damaged myelin could severely disrupt the synchronicity of disparate GM regions.

In light of this, it is notable that several studies have reported evidence of abnormal synchrony in the electroencephalogram (EEG) in patients with schizophrenia [59, 60]. This finding is particularly salient given the role that neural synchrony has been proposed to play in perceptual (and possibly cognitive) integration—abilities that are ubiquitously aberrant in patients with schizophrenia. Recent work into the functional role of the N-methyl D-aspartate- (NMDA-) receptor has also led to increased interest in terms of the role of neural synchronization in the etiology of schizophrenia. The NMDA receptor is distinctive in that it is both ligand and voltage-gated [61]. That is, the receptor will only allow cation influx if glutamate is bound to the receptor at the same time as the postsynaptic membrane is depolarized. Given its distinct physiology, the NMDA-receptor has been implicated as a "synchrony detector" that may play a role in determining which synapses are eliminated during development [62]. More specifically, synchronous synaptic activity (which has been associated with NMDA-receptor activation [63]) has been suggested to result in synaptic preservation, while asynchronous activity has been suggested to facilitate or even promote synaptic pruning [64].

Taken together, these findings might be explained by a speculative hypothesis as to the relationship between the GM and WM abnormalities present in patients with schizophrenia. The hypothesis, which has been described in detail elsewhere [65], suggests that some cases of schizophrenia arise because of currently undetermined developmental/environmental triggers causing the abnormal expression of myelin-related genes during the normative peripubescent period of myelination of the association cortices. The resultant myelin is consequently structurally damaged and hence functionally damaged in its ability to insulate the axon membranes and increase conduction velocity. This results in small but significant transmission delays in communications between spatially disparate GM structures. These transmission delays result in a disruption in neural synchronization, such as between primary neural discharges and their corollaries [57]. This results in both the symptoms of psychosis and the exaggerated synaptic pruning (possibly mediated by the NMDA-receptor) in the GM regions connected by this functionally retarded WM. In a similar vein, Moises et al. [66] have suggested that there may be a causal relationship between abnormalities in glial growth factors and synaptic destabilization in patients with schizophrenia.

This theory is clearly speculative and should be treated with caution in the absence of a great deal more empirical evidence. However, if nothing else, this theory acts as an example of how WM abnormalities could potentially

underpin both the symptoms of schizophrenia and the GM atrophy characteristic of the disease. Moreover, if the WM abnormalities exhibited by schizophrenia patients did indeed underlie their psychological and physiological pathologies, then this could provide an alternative target for pharmacologic interventions. For example, if myelin abnormalities were ultimately found to underlie the hyperdopaminergic state characteristic of schizophrenia, which the results of Roy [67] at least tentatively suggest, then targeting the root of the problem with medications used to preserve WM (such as those in development for the treatment of multiple sclerosis [68]) would potentially provide a useful adjunct or even a better alternative to the dopamine antagonists currently used in antipsychotic pharmacotherapy. It has also been suggested that the efficacy of current antipsychotic medications may, at least in part, be due to their effects on periadolescent myelination [69]. The idea that pharmacotherapy could be used to target the root cause of the abnormal neurochemical profile exhibited by patients with schizophrenia is a tantalizing prospect, and one that is worthy of pursuit in the years ahead.

4. Conclusions

DTI is unique in its ability to investigate *in vivo* the structural integrity of WM fiber bundles, which represent the neuroanatomical infrastructure for long-distance communication in the brain. The consistency of WM abnormalities observed in schizophrenia patients via DTI has been one of the factors underlying the emergent (or rather, re-emergent) conceptualization of schizophrenia as a disorder of abnormal connectivity between spatially disparate brain structures. This conceptualization provides a novel theoretical framework in terms of the etiology of the disease and opens the door for the development of novel diagnostic tools and novel treatment. When considered in combination with other biomedical tools tuned to different aspects of brain physiology (e.g., oxygenation with fMRI, neurochemistry with nuclear magnetic resonance spectroscopy, electrodynamics via EEG, genetic profile via microarray technology, etc.), the development of DTI as a WM-imaging tool provides us with an unprecedented opportunity to understand the root causes of schizophrenia—an understanding that is necessary for the targeted development of successful treatment programs. The promise of new, knowledge-based breakthroughs in the treatment of this devastating disorder makes this an exciting time to be involved in schizophrenia research.

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Research Article

Ultrastructural Alterations of Myelinated Fibers and Oligodendrocytes in the Prefrontal Cortex in Schizophrenia: A Postmortem Morphometric Study

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Schizophrenia is believed to result from altered neuronal connectivity and impaired myelination. However, there are few direct evidence for myelin abnormalities in schizophrenia. We performed electron microscopic study of myelinated fibers and oligodendrocytes and morphometric study of myelinated fibers in the prefrontal cortex in gray and white matters in schizophrenia and normal controls. Six types of abnormal fibers and ultrastructural alterations of oligodendrocytes were found in schizophrenia. No significant group differences in area density of myelinated fibers were found. Frequency of pathological fibers was increased significantly in gray matter in young and elderly schizophrenia patients and in patients with predominantly positive symptoms. In contrast, in white matter, frequency of altered fibers was increased significantly in elderly patients, in patients with predominantly negative symptoms, and correlated with illness duration. Progressive alterations of myelinated fibers in white matter might be followed by alterations of myelinated fibers in gray matter in schizophrenia.

1. Introduction

Growing evidence coming from neuroimaging and postmortem studies support the notion that altered neuronal connectivity in schizophrenia is associated with disturbed myelination in different fiber tracts [1–9]. Abnormalities of oligodendrocytes in gray and white matters in schizophrenia are among the most consistent findings. Myelin and oligodendrocyte abnormalities have been reported in schizophrenia in neuroimaging, neurocytochemical, microarray, and morphometric studies [1].

In vivo neuroimaging studies demonstrated reduced white matter volume in the prefrontal cortex [10]. Buchsbaum et al., [11] in PET study, found an increased relative metabolic rates in white matter in schizophrenia. Metabolic abnormalities in fronto-striatal-thalamic white matter tracts have been reported in schizophrenia [12]. MR diffusion tensor imaging (DTI) can measure and visualize organization of white matter fiber tracts *in vivo*. DTI studies of white matter in schizophrenia demonstrated a significant reduction in fractional anisotropy (FA) in frontal lobe and the relationships between white matter abnormalities and symptoms of the disorder [13–16]. It is not known whether the abnormalities observed to date reflect a decrease in number of axons, decreased axonal diameter, thinner myelin sheaths, or less coherent fibers.

Morphometric studies revealed prominent deficit of oligodendrocytes in different brain regions, including gray and white matter of the prefrontal cortex in schizophrenia [17–22]. The first stereological study estimated the length of myelinated nerve fibers in the whole brain, as well as in the prefrontal cortex of subjects with schizophrenia did not find significant group differences [23]. Postmortem electron microscopy revealed ultrastructural alterations of myelinated nerve fibers, damage and degeneration of oligodendrocytes in layer VI of the prefrontal cortex in schizophrenia [24]. Dysfunction and reduced proliferation of these cells were proposed to explain these findings. Oligodendrocytes were found to be the most severely affected cell type in schizophrenia and bipolar disorder as compared to normal controls [24], and deficit of oligodendrocytes was found in layers V and VI of the prefrontal BA10 and in underlying white matter

[21, 22]. However, it remains unknown whether alterations of myelinated fibers in white matter differ from those in gray matter, whether myelin abnormalities are associated with aging, schizophrenia, and medication effects.

Previously, we reported alterations of myelinated fibers in layer V of the prefrontal cortex in schizophrenia using small sample size [25]. Here, we present (1) the results of qualitative and morphometric studies of myelinated fibers in layer V of the prefrontal cortex, using rather big sample size, and in adjacent white matter in schizophrenia as compared to normal controls and (2) the results of qualita-tive study of oligodendrocytes in gray and white matters in schizo-phrenia as compared to normal controls. Since deficit of oligodendrocytes was found both in gray matter of the prefrontal BA10 and in underlying white matter in the subgroup of schizophrenia subjects with predominantly negative symptoms [21, 22], we expected more severe alterations of myelinated fibers in this subgroup as compared to the subgroup with predominantly positive symptoms.

The aim of the study was to detect ultrastructural abnormalities of myelinated fibers and oligodendrocytes in gray matter of the prefrontal cortex (layer V, BA10) and in underlying white matter in schizophrenia. Our study addressed the following questions: (1) What kind of ultrastructural abnormalities of myelinated fibers and oligodendrocytes differ schizophrenia subjects from controls, particularly, whether an axonal degeneration and loss of myelin occur in schizophrenia? (2) Do the ultrastructural alterations of myelinated fibers in gray matter differ from those in white matter? (3) Are the changes of myelinated fibers associated with age, gender, age at onset, and duration of illness? (4) Is there a link between abnormalities of myelinated fibers and symptoms of schizophrenia and neuroleptic exposure?

2. Materials and Methods

2.1. Materials. The study was performed using the Mental Health Research Center (MHRC) brain collection. Prefrontal cortex (BA10, layer V) was studied in 40 cases of schizophrenia and 40 normal matched controls with a short postmortem delay. White matter underlying prefrontal BA10 was studied in 12 cases of schizophrenia and 12 normal controls available. Clinical records were obtained. ICD-10 and DSM-IV-R diagnoses were made by psychiatrists from MHRC. The Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) were used by psychiatrists to rate negative and positive symptoms during the last hospitalization in schizophrenia subjects. Summary scores of negative and positive symptoms were determined on the basis of the ratio of the percentage of negative and positive scores in summary scores. Basic demographic and clinical data are given in Table 1. Cases were coded for morphometric blind study.

2.2. Methods

2.2.1. Electron Microscopy. For electron microscopy, small tissue pieces from gray matter of BA10 (left hemisphere) and from underlying white matter were obtained perpendicular to cortical surface. The tissue pieces were fixed by immersion with mixture of 2,5% glutaraldehyde and 4% paraformaldehyde in 0,1 M phosphate buffer for 1 week, then postfixed in 1% osmium tetroxide for 1 hour, stained with uranyl acetate for 1 hour, dehydrated in ethanol series and embedded in Araldit epoxy resin. Sections were cut using Reichert ultramicrotome, and semithin 1 μm sections stained with toluidine blue were used for orientation in cortical layers. Small pyramids were trimmed on layer V (layer of big pyramidal cells) and on adjacent white matter. Ultrathin sections were cut, put on formvar-coated, slot-type grids, counterstained with lead citrate and viewed with the electron microscope Philips EM 420.

2.2.2. Light Microscopy. Besides, for all the cases, histological standard methods were used: Nissl staining, hematoxilin-eosin staining, Van Gieson staining, Bielshowsky, and Congo red. No histological evidence of neurodegenerative, inflammatory, and ischemic diseases were found.

2.2.3. Morphometry. Morphometric study was performed to estimate the number of myelinated fibers per unit tissue area and the frequency of normally myelinated and pathological myelinated fibers in control and schizophrenia groups. 3 tissue blocks from layer V and 3 tissue blocks from white matter per each case were randomly selected. Systematic random sampling was used to estimate the number of myelinated axons present. The starting point for making photos was determined as the leftward top point of the section. Series of photographs were made at the distance 40 microns until the rightward edge of the section was reached. The camera was then moved 40 microns down, and photos of the myelinated fibers were taken in the same manner until the leftward edge of the section was reached. This process was repeated until 45 sampling fields in layer V and 48 sampling fields in white matter from each subject were systematically sampled and photographed under 4,000x magnification. Mean sample area per case was 14,850 μm^2 in gray matter and 15,800 μm^2 in white matter. Mean number of myelinated fibers per case counted in gray matter was 1,495 in control group and 1,438 in schizophrenia group; in white matter, it was 4,560 in control group and 4,056 in schizophrenia group. EM images of myelinated fibers were superimposed on the enlarger "Minolta" to get the final magnification 26,000x.

To quantify myelinated fibers, transversely sectioned nerve fibers were examined. Area density of myelinated fibers and the frequency of normal and pathological myelinated fibers were estimated. Area density of myelinated fibers was calculated as the number of fibers per unit tissue area (1000 μm^2). The frequency of normal and pathological myelinated fibers present was calculated as the number of normal or pathological fibers in unit tissue area per number of total myelinated fibers in unit tissue area expressed in percentages.

2.2.4. Statistical Analyses. Statistical analysis was performed using STATISTICA 6 software package for Windows (StatSoft Inc, Tulsa, OK, USA). Area density of myelinated fibers,

Table 1: Basic demographic characteristics (Means, SD).

Subjects	Number per group	Gender	Age (years)	PMI (hours)	Duration of illness (years)	Age at onset of illness (years)
Gray matter						
Controls	$N = 40$	29 M, 11 F	55,5 ± 14,2	5,9 ± 1,2		
Schizophrenia	$N = 40$	15 M, 25 F	58,7 ± 15,6	6,3 ± 1,8	25,1 ± 12,8	33,1 ± 14,8
SPNS	$N = 20$	6 M, 14 F	59,7 ± 16,5	5,7 ± 1,4	27,4 ± 12,5	32,2 ± 14,8
SPPS	$N = 18$	8 M, 10 F	56,6 ± 15,2	6,7 ± 2,1	21,9 ± 14,5	34,7 ± 15,4
White matter						
Controls	$N = 12$	8 M, 4 F	51,1 ± 14,0	6,5 ± 1,2		
Schizophrenia	$N = 12$	7 M, 5 F	51,1 ± 19,0	6,5 ± 1,2	27,0 ± 12,8	24,1 ± 12,6
SPNS	$N = 6$	4 M, 2 F	55,5 ± 21,0	6,1 ± 1,0	30,0 ± 14,0	25,5 ± 13,5
SPPS	$N = 6$	3 M, 3 F	46,7 ± 17,6	7,0 ± 1,3	24,0 ± 12,0	22,7 ± 12,7

SPNS: schizophrenia with predominantly negative symptoms.
SPPS: schizophrenia with predominantly positive symptoms.

frequency of normal and all pathological myelinated fibers, and frequency of different types of pathological fibers were analyzed.

Correlation analysis was performed for control and schizophrenia group to examine the influence of postmortem delay, age, duration of disease, medication (expressed as chlorpromazine equivalents according to Davis [26]), and correlations between the parameters measured. Since the normal distribution of the data by Kolmogorov-Smirnov tests was obtained, the Pearson correlation coefficient was used. Age effects were also analyzed using one-way analysis of variance (ANOVA) comparison of young (≤45 y.o.) and elderly (>45 y.o.) control and schizophrenia patients taking Bonferroni correction.

Differences between control group and schizophrenia group, between control group and schizophrenia clinical subgroups of subjects with predominantly positive or predominantly negative symptoms were examined. Also these clinical subgroups were compared.

Group comparisons were made using one-way ANOVA. Differences between the subgroups with predominantly positive or predominantly negative symptoms were examined using one-way ANOVA, followed by post hoc test, taking the Bonferroni correction. Two-way ANOVA followed by post hoc test with the Bonferroni correction was used to detect gender effects.

3. Results

3.1. Gray Matter

3.1.1. Qualitative Study. Qualitative study demonstrated that the ultrastructure of myelinated nerve fibers was well preserved in both schizophrenia and control subjects. The study of myelinated fibers revealed six types of pathological fibers demonstrating ultrastructural alterations of myelinated fibers in schizophrenia subjects and in controls (Figure 1). Myelinated fibers of type 1 (P1) were characterized by focal lysis of myelin sheath lamellae, sometimes with the formation of concentric lamellar bodies. This type of pathology often appeared in close apposition to astrocytic processes or inside them (Figure 1(a)). Fibers of type 2 (P2) exhibited the presence of myelin-like figures of unknown origin in swollen periaxonal oligodendroglial processes though myelin sheaths looked well preserved. (Figure 1(b)). Type 3 (P3) fibers demonstrated swelling of periaxonal oligodendroglial processes, atrophy of inner axon, and preserved myelin sheath. These types of alterations of myelinated fibers were seen mostly in myelinated fibers of small caliber, containing few myelin sheath lamellae (Figure 1(c)).

Besides, three types of degenerating myelinated fibers were rarely seen in gray matter in schizophrenia and controls. They demonstrated dark degeneration of myelinated fibers (type 4, P4) (Figure 1(f)), degeneration of myelin sheaths: splitting and decompaction of myelin sheath lamellae (type 5, P5) (Figure 1(d)), and inclusions of dense cytoplasm with vacuoles resembling the cytoplasm of microglial cell between myelin sheath lamellae (type 6, P6) (Figure 1(e)). Importantly to note is that all these types of pathological alterations of myelinated fibers demonstrated deformations of fibers (Figure 1). P4–6 fibers were seen mostly in white matter, in gray matter they were observed very rarely in schizophrenia and in controls, so they were counted only in white matter.

The changes of myelinated fibers were accompanied by prominent alterations of the ultrastructure of oligodendrocytes in schizophrenia as compared to controls (Figure 2). Electron lucent chromatin and small rim of cytoplasm were characteristic features of oligodendrocytes in control brains (Figure 2(a)). In schizophrenia subjects, oligodendrocytes demonstrated dystrophic and destructive alterations. The most prominent changes were chromatin condensation (Figures 2(b) and 2(d)) and swelling of cytoplasm (Figures 2(b)–2(d)). Destructive alterations of oligodendrocytes were rarely seen in control brains.

3.1.2. Morphometry

(1) Effects of Disease and Age. Morphometric study showed that the area density of myelinated fibers did not differ significantly: (mean ± SEM) 101 ± 6,0 per 1000 μm^2 in control group and 105 ± 6.4 per 1000 μm^2 in schizophrenia group.

Frequency of all pathological myelinated fibers was significantly increased in schizophrenia group as compared

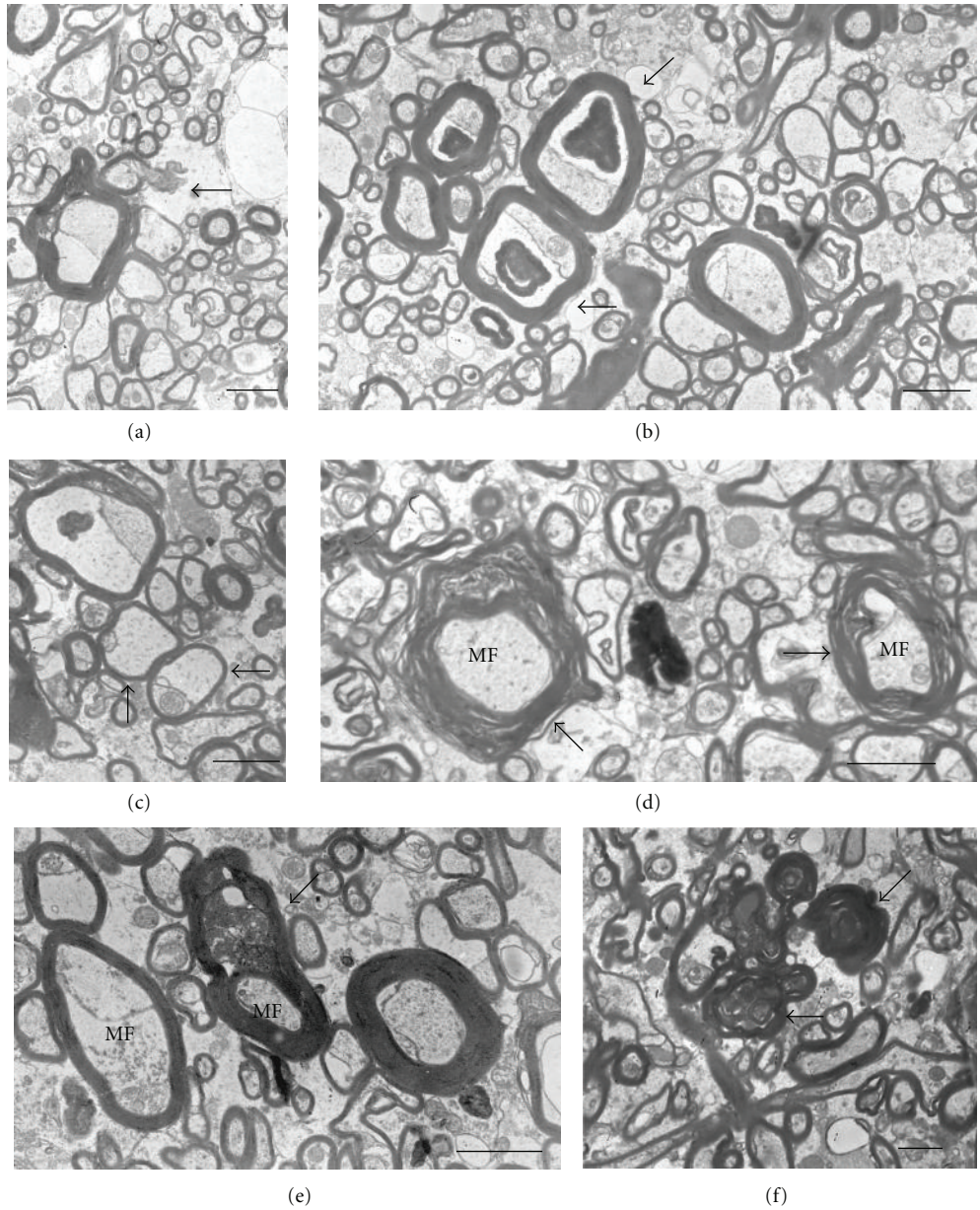

Figure 1: Six types of pathological myelinated fibers. Descriptions in the text. Scale bars = 2 μm.

to the control group ($F = 12.9$, $df = 1.78$, $P = .0006$). Frequency of P1 fibers did not differ significantly from controls. A significant increase in the frequency of both P2 fibers ($F = 8.6$, $df = 1.78$, $P = .004$) and P3 fibers were found in schizophrenia as compared to controls ($F = 62.6$, $df = 1.78$, $P < .0001$), (Figure 3(a)).

Comparison of the subgroups with predominantly positive symptoms, predominantly negative symptoms, and the control group demonstrated a significant differences in the frequency of all pathological myelinated fibers ($F = 6.25$, $df = 2.75$, $P = .003$) as well as in the frequencies of P2 fibers ($F = 6.49$, $df = 2.75$, $P = .0025$) and P3 fibers ($F = 30.3$, $df = 2.75$, $P < .0001$). Post hoc showed that the frequency of all pathological myelinated fibers and of P2 fibers significantly increased in the subgroup of patients with predominantly positive symptoms ($P = .002$). The frequency of P3 fibers increased both in the subgroup with predominantly positive symptoms ($P = .0001$) and with predominantly negative symptoms as compared to controls ($P = .0001$) (Figure 3(a)).

The frequency of P2 fibers correlated negatively and significantly with the frequency of P3 fibers in schizophrenia group ($r = -0.36$, $P < .05$) in contrast to the control group where no significant correlations were found ($r = -0.06$, $P = .7$).

No correlations with age of the estimated parameters were found in schizophrenia and control groups. However, comparison of young (≤45 y.o.) and elderly (>45 y.o.)

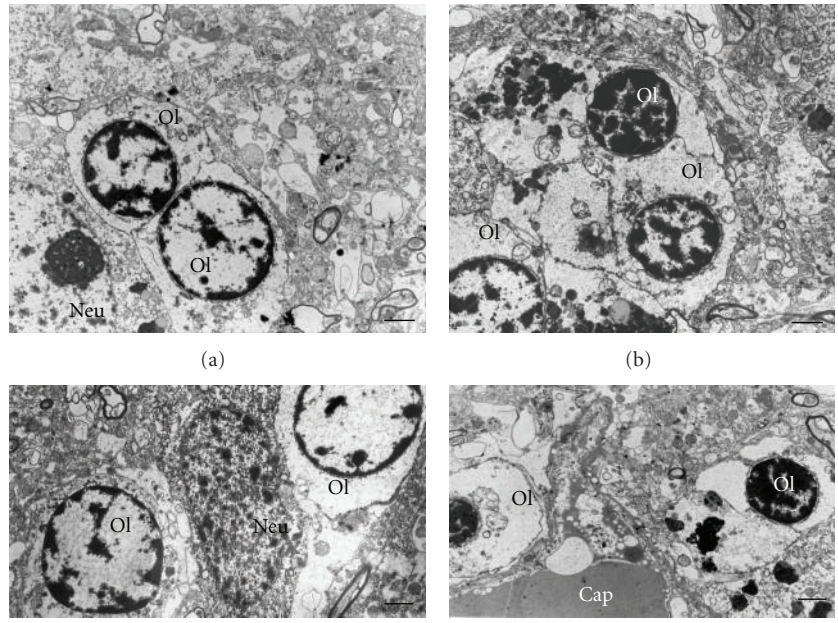

Figure 2: Electron micrographs of oligodendrocytes in gray matter from control subject (a) and from subjects with schizophrenia (b–d). Dystrophic alterations of oligodendrocytes, Ol, (b, c) and destructive changes of oligodendrocytes (d). Scale bars = 2 μm.

subgroups of patients with young and elderly control subjects demonstrated that both young and elderly schizophrenia patients differed from two control subgroups in the frequency of P3 fibers (Figure 4(a)). There were no significant differences between the age subgroups in other types of fibers.

We did not find the effects of gender in either control or schizophrenia group. There were no correlations between the parameters of myelinated fibers and age at onset or duration of schizophrenia.

(2) Effects of Other Confounding Variables. We did not find the effects of postmortem delay and neuroleptic exposure on the frequency of myelinated fibers.

3.2. White Matter

3.2.1. Qualitative Study. Three types of myelinated fibers described in detail in gray matter were also seen in the white matter (Figure 1). Besides, degenerating myelinated fibers were observed in white matter, and they demonstrated dark degeneration of myelinated fibers (type 4, P4) (Figure 1(f)) and degeneration of myelin sheaths of two types: splitting of myelin sheath lamellae (type 5, P5) (Figure 1(d)) and inclusions of dense cytoplasm with vacuoles resembling the cytoplasm of microglial cell in between myelin sheath lamellae (type 6, P6) (Figure 1(e)). The ultrastructural pathological findings were present mostly in large- and medium-sized myelinated fibers.

Myelinated fibers in white matter varied in size in control (Figure 5(a)) and schizophrenia brains (Figures 5(b)–5(d)). However, in schizophrenia brains both thinly myelinated (Figure 5(b)), axons with focal lysis of myelin sheath (Figure 5(d)) as well as some axons with abnormally thick myelin sheaths (Figure 5(b)), were often observed in contrast to controls. The second important finding was that myelinated fibers were often located in close apposition to numerous swollen astrocytic processes in schizophrenia subjects (Figures 5(c) and 5(d)) in contrast to controls where such swollen processes were not observed (Figure 5(a)).

The alterations of myelinated nerve fibers in white matter were accompanied by prominent dystrophic changes of oligodendrocytes in schizophrenia brains but not in controls. Oligodendrocytes in subjects with schizophrenia looked swollen and vacuolated as compared to controls (Figures 6(a) and 6(b)). No destructive changes of oligodendrocytes were found in white matter in either schizophrenia or control brains. Microglial cells were often located in close apposition to oligodendrocytes in control subject (Figure 6(a)) and in schizophrenia subject (Figure 6(b)) and apposed to myelinated fibers in schizophrenia subject (Figure 6(b)). Activated microglial cells containing invaginated nucleus and vacuolated cytoplasm were observed in close apposition to swollen astrocytic processes containing membranous debris (Figure 6(c)). Microglial cell participates in phagocytosis of myelin membranous debris in schizophrenia (Figure 6(d)). This type of activation of microglial cells was not seen in control subjects.

3.2.2. Morphometry

(1) Effects of Disease and Age. Morphometric study showed that the area density of myelinated fibers was nonsignificantly decreased (−7%) in schizophrenia: 323 ± 29.07 per 1000 μm^2 as compared to normal controls: 345 ± 31,1 per 1000 μm^2.

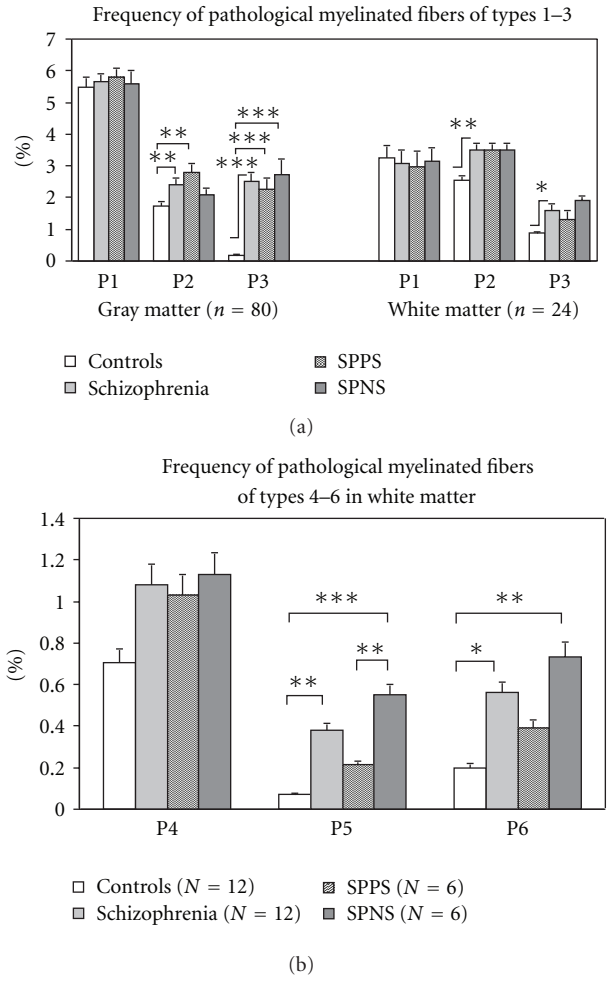

FIGURE 3: Frequency of pathological myelinated fibers present in gray matter and in white matter (mean ± SEM). SPPS: schizophrenia subjects with predominantly positive symptoms. SPNS: schizophrenia subjects with predominantly negative symptoms. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$.

Frequency of all pathological myelinated fibers increased in schizophrenia as compared to controls ($F = 5.33$, $df = 1.22$, $P = .03$). Among them, frequency of P1 fibers was nonsignificantly increased, frequency of P2 and P3 fibers increased significantly (Figure 3(a)), frequency of P4 fibers tended to increase ($P = .08$), and frequency of P5 and P6 fibers increased significantly (Figure 3(b)). The frequency of P2 fibers was not correlated with the frequency of P3 fibers in either schizophrenia or control group in contrast to gray matter where these parameters significantly correlated.

Comparison of the subgroups with predominantly positive symptoms, predominantly negative symptoms, and control group showed a significant differences in the frequency of P3 ($F = 3,6$, $df = 2,21$, $P < .05$), P5 ($F = 11.05$, $df = 2.21$, $P < .001$) and P6 ($F = 5.45$, $df = 2.21$, $P = .01$) fibers. Post hoc demonstrated a significant increase in the frequency of P5 ($P = .0004$) and P6 myelinated fibers in the subgroup with predominantly negative symptoms ($P = .006$) (Figure 3(b)). Also, frequency of P5 fibers was significantly higher in the subgroup with predominantly negative symptoms as compared to the subgroup with predominantly positive symptoms ($P = .005$).

The frequency of P1 and P6 fibers correlated significantly with age in schizophrenia group ($r = 0.74$, $P < .01$, $r = 0.62$, $P < .05$, resp.) but not in the control group, where only frequency of P5 correlated significantly with age ($r = 0.6$, $P < .05$). No other correlations of myelinated fibers with age were found. Comparison of young (≤45 y.o.) and elderly (>45 y.o.) subgroups of patients with young and elderly control subjects showed no significant differences between the subgroups in P3 fibers in contrast to significant changes of the parameter in gray matter (Figure 4). No significant differences between the age subgroups in other types of fibers were found. The frequency of pathological fibers was not correlated with age at the onset of disease.

The effects of gender were not found in the groups studied.

(2) Effects of Other Confounding Variables. We did not find the effects of postmortem delay and neuroleptic exposure on the parameters of myelinated fibers. However, the effect of duration of disease was found. The frequency of pathological myelinated fibers (P1, P4–6) correlated positively and significantly with illness duration (Figure 7).

4. Discussion

The present study provides evidence for alterations of oligodendrocytes and myelinated nerve fibers in the prefrontal cortex in schizophrenia as compared to controls. Comparative study of oligodendrocytes and myelinated nerve fibers in gray matter and in white matter showed both similarities and differences between gray matter and white matter in schizophrenia. In gray matter, dystrophic and destructive changes of oligodendrocytes were observed in schizophrenia, and in white matter, only dystrophic changes of oligodendrocytes were found in schizophrenia. Morphometric study showed damage of myelinated fibers including altered oligodendrocyte/axon interaction and myelin/axon integrity, axonal atrophy, and focal damage of myelin sheaths in gray matter in schizophrenia as compared to controls. The same changes were found in white matter in schizophrenia. Besides, frequency of degenerating myelin sheaths was significantly increased in white matter, while in gray matter they were rarely observed. In white matter, both astrocytic cell processes and microglial cells were involved in the phagocytosis of degenerating myelin sheaths in schizophrenia. Since myelin is produced by oligodendrocytes, these data suggest that the pathology of myelinated nerve fibers in schizophrenia might be due to oligodendrocyte abnormalities. The data are consistent with the results of our previous studies reported ultrastructural changes and deficit of oligodendrocytes in lower layers of the prefrontal BA10, and in adjacent white matter in schizophrenia [21, 22, 24] and with prominent deficit of oligodendrocytes in gray and white matters of the dorsolateral prefrontal cortex in schizophrenia [17, 18], though Segal et al. [27] found no significant differences in the oligodendrocyte distribution or density in the cingulum bundle in schizophrenia. However,

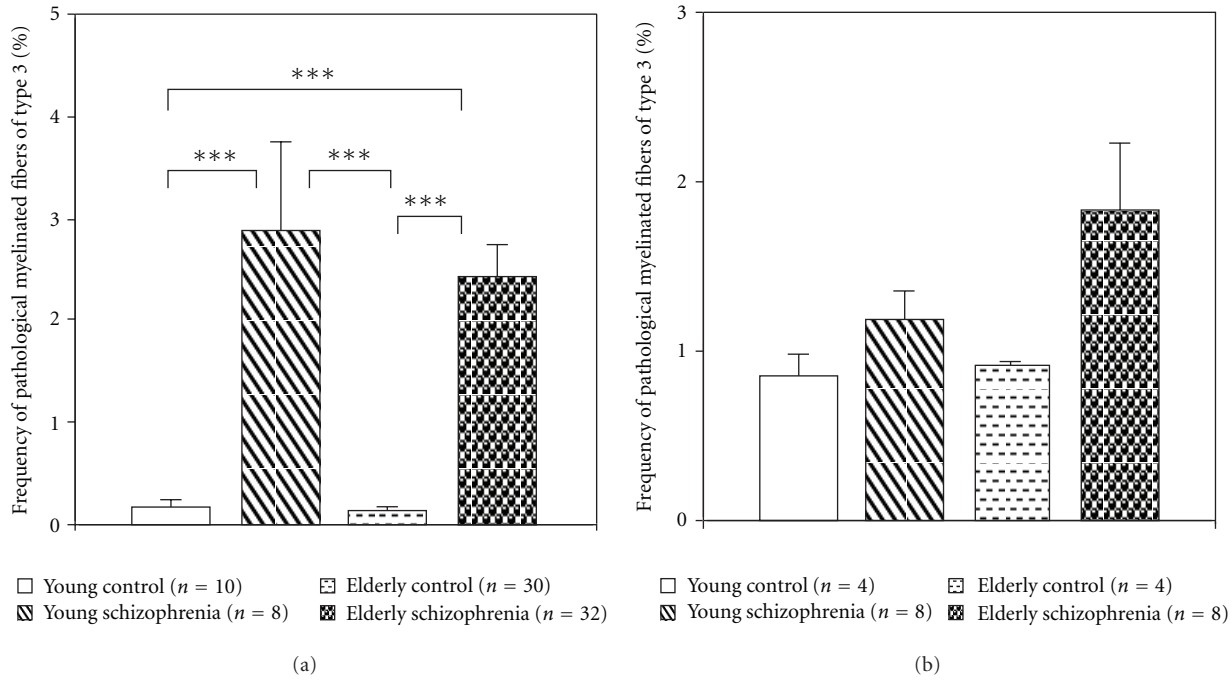

Figure 4: Histograms demonstrating the results of comparisons of the frequency of pathological myelinated fibers of type 3 in young and elderly patient subgroups with young and elderly controls. (a) Gray matter, (b) White matter (mean ± SEM).

the origin of the differences between gray and white matter abnormalities detected in schizophrenia remains uncertain.

We did not find significant changes in area density of myelinated fibers in either gray matter or in white matter in schizophrenia. It is important to note that there were no differences in the number and density of fibers in the uncinate fasciculus [28] and in the length of myelinated nerve fibers in the whole brain, as well as in the prefrontal cortex [23] reported in schizophrenia.

Frequency of normal fibers was decreased, and the frequency of pathological fibers was increased significantly in gray matter in young and elderly schizophrenia patients. In contrast, frequency of pathological fibers in white matter was increased significantly in elderly patients. These data suggest that alterations of myelinated fibers in white matter in schizophrenia might be followed by alterations of myelinated fibers in gray matter.

Do the alterations of myelinated fibers progress in the course of illness? In white matter, significant correlations of the frequency of pathological myelinated fibers with duration of illness were found in schizophrenia subjects. The results are in agreement with the progressive frontotemporal gray matter reduction and frontoparietal white matter expansion in schizophrenia associated with poor outcome during a chronic stage of illness [29] Mori et al. [30] found in white matter a significant negative correlation between FA and duration of illness. Progressive white matter loss may be a consequence of chronic disease [31–33]. We consider that the changes found in white matter in the present study might be a consequence of chronic disease including dystrophic and degenerative processes in oligodendrocytes and myelin sheaths. Degenerating myelin sheaths were found in medium and large-sized myelinated fibers suggesting that cortico-subcortical and cortico-cortical fibers might be involved in degenerating process of myelinated fibers in schizophrenia.

Do myelin alterations contribute to symptoms of schizophrenia? The present study demonstrated that in gray matter, the frequency of pathological fibers was increased significantly in the subgroup of patients with predominantly positive symptoms. On the contrary, in white matter the frequency of myelinated fibers containing degenerating myelin sheaths was increased significantly in subjects with predominantly negative symptoms. It is important to note that according to our previous data, cases with predominantly negative symptoms showed significant increase in the volume fraction of heterochromatin in layer VI, prominent deficit of pericapillary oligodendrocytes in layer V of the prefrontal BA10 and deficit of oligodendrocytes in adjacent white matter in schizophrenia [21, 22, 24]. These results also suggest that there is a link between alterations of oligodendrocytes and of myelinated fibers in schizophrenia.

Our data are in accordance with the results of neuroimaging studies that prefrontal white matter FA correlated with negative symptoms, impulsiveness, and aggressiveness [34, 35]. Reductions in prefrontal white matter may be associated with schizophrenia-negative symptoms [36]. Wible et al. [37] reported that schizophrenia subjects with high negative symptom scores had significantly smaller bilateral white matter volumes than those with low negative symptom scores. Decrements in prefrontal white matter related to higher levels of negative symptoms [38], increased density of interstitial white matter neurons in dorsolateral prefrontal cortex in the deficit group compared with the nondeficit as well as the control [39] have been reported in schizophrenia

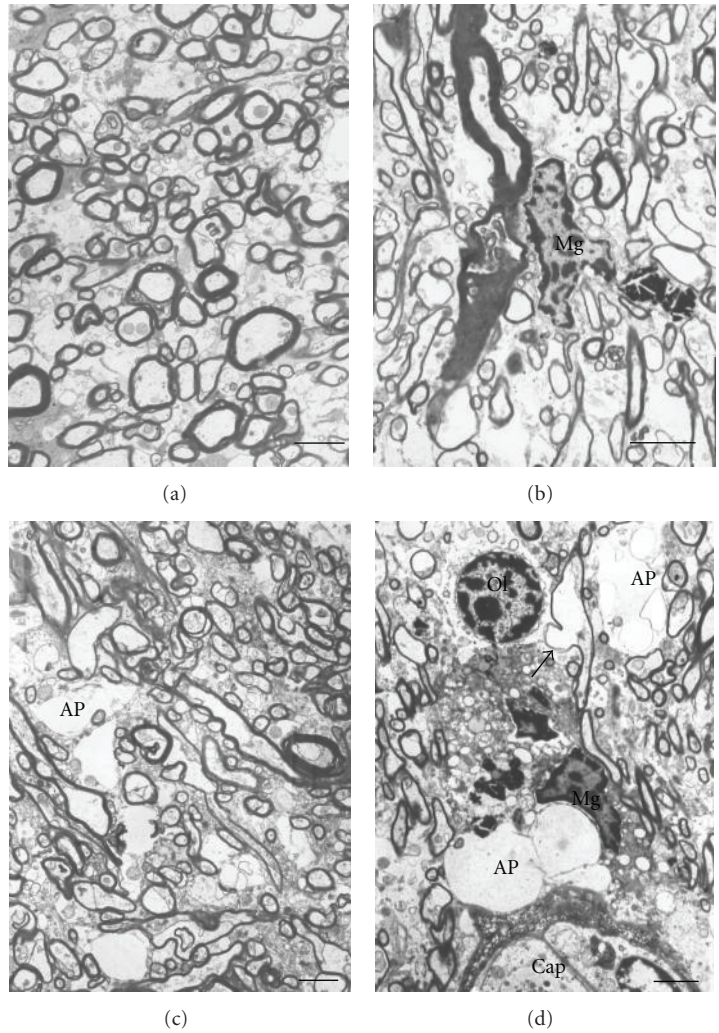

Figure 5: Electron micrographs of white matter from control brain (a) and from the brains of subjects with schizophrenia (b–d). Both thinly myelinated (b, c) and axons with focal lysis of myelin sheath (d) as well as some axons with abnormally thick myelin sheaths (Figure 1(b)) were observed in schizophrenia in contrast to controls. Ap: astrocytic process, Mg: microglial cell. Ol: oligodendrocyte. Scale bars = 2 μm.

patients. Negative symptoms may involve disruption of frontal-subcortical connections [40].

White matter might play a role in producing cognitive impairment in schizophrenia [6]. Cognitive deficit in schizophrenia is associated with the dysfunction of the prefrontal cortex [38, 41]. Myelinated nerve fiber degeneration plays a role in the pathogenesis of age-related cognitive decline [42]. In area 46 of monkey, the age-related alterations of myelinated fibers significantly correlate with the cognitive impairment index [42]. It is proposed that age-related correlations between frequency of myelin alterations and impairments in cognition occur because the conduction velocity along the affected nerve fibers is reduced, so that the normal timing sequences within neuronal circuits break down [42–45]. Our study detected positive correlation between age and the frequency of degenerating myelin sheaths in the white matter in control group (P5 myelinated fibers) and in schizophrenia group (P6 myelinated fibers), similar to those described in monkey during aging and correlated with cognitive impairment [46], though the effect of illness duration was more pronounced. These data suggest that degeneration of myelin sheaths in white matter found in the present study might be associated with cognitive impairment in schizophrenia.

Disturbed oligodendrocyte-axon relationships in schizophrenia. Our results support the hypothesis of Mitterauer [47] that decomposition of the oligodendrocyte-axonic system may be responsible for symptoms of incoherence (thought disorder, etc.) in schizophrenia. Our study detected prominent dystrophic alterations of oligodendrocytes, including their swelling in both gray matter and in white matter in schizophrenia, and destructive changes of oligodendrocytes in gray matter in schizophrenia. These data are in accordance with the most pronounced changes of P3 myelinated fibers in schizophrenia demonstrating swelling of periaxonal oligodendrocytic process and shrinkage of inner axon of myelinated fibers. Besides, the frequency of the P2 fibers in gray matter correlated negatively and significantly

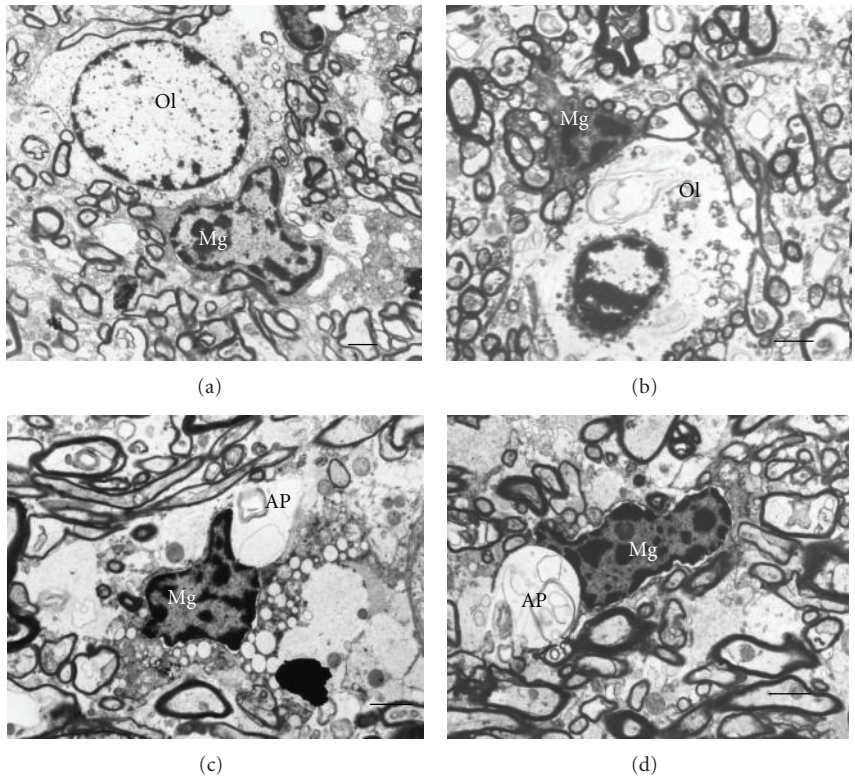

Figure 6: Electron micrographs of oligodendrocytes and microglia in white matter from control subjects (a) and from subjects with schizophrenia (b–d). Dystrophic changes of oligodendrocyte, Ol, (b). Activated microglia in close apposition to swollen astrocytic process (Ap) containing myelin debris in schizophrenia brain (c) Microglial cell participates in phagocytosis of myelin membranous debris in schizophrenia (d). Scale bars = 2 μm.

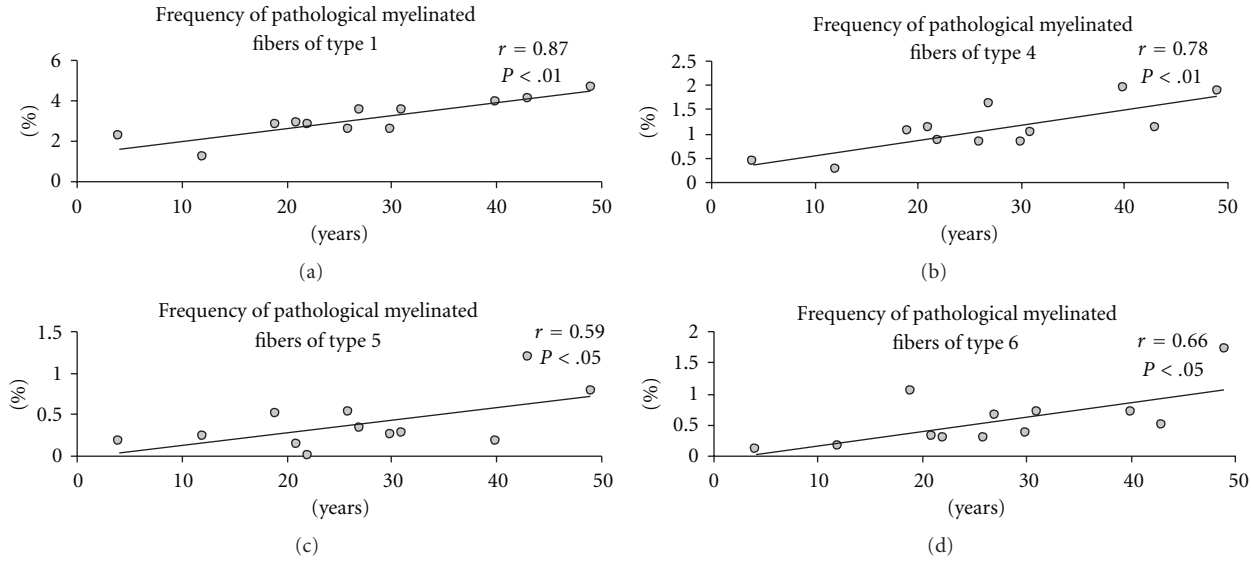

Figure 7: The association between frequency of pathological myelinated fibers in white matter and duration of schizophrenia.

with the frequency of P3 fibers in schizophrenia group in contrast to control group where no significant correlations were found. These data suggest that the P2 and P3 types of pathological myelinated fibers are interrelated. They might present a common type of alterations of myelinated fibers that might lead to axonal atrophy. P3 myelinated fibers had small size with thin myelin sheath. The data suggest that this type of pathological myelinated fibers might belong mostly to associative fibers or to axons of interneurons. A significant increase in the frequency of this type of myelin pathology has

been reported in the upper layers of the prefrontal and visual cortices [48], in the hippocampus [49] and in the caudate nucleus [25] in schizophrenia. The results are consistent with the ultrastructural damage of oligodendrocytes in the hippocampus [49] and in the caudate nucleus [24] in schizophrenia. The data suggest a widespread axonopathy due to injured oligodendrocyte-axon interactions in schizophrenia brains. These changes of myelinated fibers might cause changes in conduction velocity and might lead to the atrophy of presynaptic axon terminals reported in the prefrontal cortex in schizophrenia [50] and may contribute to altered connectivity in schizophrenia [51].

Haroutunian et al. [52] has reported that some of the genes affected in schizophrenia are associated with the regulation of axoglial contacts, axon calibre, and the integrity of functional elements involved in signal propagation. In KCC3 knockout mice, an animal model of agenesis of the corpus callosum associated with peripheral neuropathy, some fibers accumulate fluid periaxonally. The swelling pathologies are followed by axon and myelin degeneration in adult nerves, leading to reduction in nerve conduction velocity [53]. To maintain axonal integrity, mammalian myelin-forming cells require the expression of some glia-specific proteins, including CNP, PLP, and MAG, as well as intact peroxisomes, none of which is necessary for myelin assembly. Loss of oligodendroglial support causes progressive axon degeneration and possibly local inflammation, both of which are likely to contribute to a variety of neuronal diseases in the central and peripheral nervous systems [54]. Axoglial interactions underlie the clustering of ion channels and of cell adhesion molecules, regulate gene expression, and control cell survival. Rasband et al. [55] reported that Cnp1-null mice, lacking expression of the myelin protein cyclic nucleotide phosphodiesterase (CNP), have disrupted axoglial interactions in the central nervous system. However, Mitkus et al. [56] did not find altered expression of MAG, CNP, and OLIG2 in the gray or white matter in patients with schizophrenia.

Benes [57] hypothesized delayed myelination in the prefrontal cortex in patients with schizophrenia. Abnormalities of myelination in the frontal cortex in schizophrenia were detected *in vivo* with MRI, and postmortem with analysis of oligodendrocyte proteins [2, 58–62]. Decreased expression of the glial gene *Quaking (QKI)*, encoding an RNA binding essential for myelination, has been reported in schizophrenia brain. These data support the notion that dysmyelination occurs in the brain of patients with schizophrenia.

MRS studies of patients with chronic schizophrenia as well as at first episode prior to treatment showed alterations in neuronal membrane biochemistry, including the prefrontal cortex [63]. The results of both metabolomic and proteomic studies pointed to energy metabolism and lipid biosynthesis [64], alterations of free fatty acids, phosphatidylcholines, and ceramides [65], cytoskeleton, oligodendrocyte, energy metabolism and cell-signalling proteins being impaired in schizophrenia [66]. Tkachev et al. [67] provide evidence for altered myelin biosynthesis and glutamatergic dysfunction in the prefrontal cortex in schizophrenia. Cerebral white matter, composed of myelin-containing oligodendrocytes, is highly sensitive to glutamate excitotoxicity, abnormally expressed NMDA receptor subunits in elderly patients with schizophrenia [68]. NMDA receptors have been shown to have an important role in mediating Ca^{2+}–dependent injury of oligodendrocytes and the myelin sheath. Together, these data suggest that oligodendrocytes and myelin abnormalities might be among the major components of the neurobiology of schizophrenia.

5. Conclusions

Abnormalities of myelinated fibers in schizophrenia include altered oligodendrocyte/axon interaction and myelin/axon integrity, axonal atrophy, damage of myelin sheaths in gray matter and in white matter, and degeneration of myelinated sheaths in white matter. Alterations of myelinated fibers in schizophrenia are accompanied by dystrophic and destructive changes of oligodendrocytes. Damage of myelinated fibers in gray matter is present in cases with predominantly positive symptoms. Degeneration of myelinated sheaths in white matter occurs in cases of schizophrenia with predominantly negative symptoms and progress in the course of illness. Damage of myelinated fibers in white matter in schizophrenia might be followed by alterations of myelinated fibers in gray matter. Alterations of myelinated fibers and oligodendrocytes in schizophrenia might contribute abnormalities of neuronal connectivity in schizophrenia.

The present study has few limitations. First, small sample size for the study of white matter, it is necessary to repeat the study of white matter using bigger sample size. Second, we did not find the effects of neuroleptic exposure on myelin abnormalities in schizophrenia. However, imaging data suggest that neuroleptic exposure influence white matter in schizophrenia. Further studies using big sample size are needed to estimate size of myelin sheaths and frequency of small-, medium- and large-sized myelinated fibers, to study the role of astrocytes and microglia and the effects of drug therapy on white matter changes in schizophrenia, and to better understand the nature of pathological process and the presence of regeneration in white matter in schizophrenia.

The results of the present study provide evidence for morphological basis of myelin abnormalities in schizophrenia that might be useful for better understanding the pathophysiology and pathogenesis of schizophrenia and for interpretation of neuroimaging data, to develop new, more precise neuroimaging techniques of white matter visualization and to create new therapeutic strategies directed to myelin abnormalities in schizophrenia.

Conflict of Interests

The authors have no conflict of interest with any commercial or other associations in connection with this article.

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Research Article

Age-Related Increase in the Number of Oligodendrocytes Is Dysregulated in Schizophrenia and Mood Disorders

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The postnatal maturation of the human prefrontal cortex is associated with substantial increase of number of oligodendrocytes. Previously, we reported decreased numerical density of oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders. To gain further understanding of the role oligodendrocytes in pathogenesis of schizophrenia and mood disorders, we examined the effect of the age on the number of oligodendrocytes in the prefrontal cortex in schizophrenia, bipolar disorder, and major depressive disorder. We revealed the age-related increase in numerical density of oligodendrocytes in layer VI and adjacent white matter of BA10 and BA 9 in normal controls but not in schizophrenia, bipolar disorder, and major depressive disorder. The absence of normal increase in the number of oligodendrocytes in gray and white matter with age in schizophrenia and mood disorders suggests that age-related process of oligodendrocyte increase is dysregulated in schizophrenia and mood disorders.

1. Introduction

Disconnection among different brain regions is believed to contribute to the abnormal functioning of neural networks and has been postulated to be central to the pathophysiology of schizophrenia [1–3]. The neurobiological substrate of these connectivity abnormalities remains unknown, but recent evidence suggests that abnormalities in myelination and altered oligodendrocyte number and function may be prominent contributors to schizophrenia. Indirect evidence for disturbed structural connectivity in schizophrenia has been obtained from functional neuroimaging and electrophysiologic studies. Imaging and postmortem studies provide converging evidence that patients with schizophrenia have a dysregulated process of frontal lobe myelination.

With growing evidence of disturbed connectivity in schizophrenia, myelin pathology has been a target of recent postmortem studies. As oligodendrocytes are essential for the production of myelin, disturbed myelination might be caused by dysfunctional oligodendrocytes or a reduced number of oligodendroglial cells. Many postmortem studies are focusing on the investigation of numerical density of oligodendroglial cells and structural alterations of myelin sheets. Evidence for the involvement of oligodendrocytes and myelin in the pathophysiology of schizophrenia has come from analysis of postmortem tissue subjects with schizophrenia using protein [4, 5] and gene expression studies [5–11], light, and electron microscopic studies [12–14], and in vivo neuroimaging studies [15–19].

The first direct evidence of oligodendrocyte deficit in schizophrenia was obtained from a series of studies performed in our laboratory [12, 13, 20].

We used the Stanley brain collection to estimate Nv of oligodendrocytes in the prefrontal cortex (BA9) in schizophrenia, bipolar disorder and major depression and our own Mental Health Research Center brain collection to estimate numerical density (Nv) of oligodendrocytes in the prefrontal cortex (BA10) in schizophrenia. Reduced Nv of oligodendrocytes was detected in BA9 in layer VI in schizophrenia, bipolar disorder and major depression [13] and in layer VI of BA10 and in adjacent white matter in schizophrenia [21]. Similarly, conducting a stereologic analysis of numbers, densities, and spatial distribution of oligodendrocytes, Hof et al. [22] also found a decrease in total number in cortical layer III and white matter in the superior frontal gyrus in schizophrenics compared to control cases.

In another morphometric study, we demonstrated decreased number of pericapillary oligodendrocytes in layer V BA10 of prefrontal cortex in schizophrenia [23]. We also found that the number of pericapillary oligodendrocytes per unit capillary length positively and significantly correlated with age in control group but not in schizophrenic group [23].

There are only few data on the effect of age on Nv of oligodendrocytes in normal controls and mental illnesses. Byne et al. [24] using the Stanley brain collection demonstrated a significant deficit of oligodendrocytes in thalamic nuclei in schizophrenia and in bipolar disorder. Both psychiatric groups compared to normal controls exhibited an attenuation of an age-related increase in the number of oligodendrocytes.

There is an apparent temporal relationship between myelination and the onset of schizophrenia. Myelination in the frontal and temporal lobes, brain regions consistently implicated in the pathophysiology of schizophrenia, occurs during late adolescence to early adulthood corresponding closely to the peak incidence of schizophrenia onset [25–30].

We hypothesized that the effect of age on Nv of oligodendrocytes might be different in controls and psychiatric groups. The aim of the study was to reveal the effect of age on numerical density of oligodendrocytes in the prefrontal cortex in two brain collections—Stanley Foundation Neuropathology Consortium (SFNC) and Mental Health Research Center (MHRC) collections to learn more about the origin of previously found deficit of oligodendroglial cells in the prefrontal cortex in major psychiatric disorders.

2. Methods

The SFNC consisted of 60 subjects: 15 schizophrenia, 15 bipolar disorder, 15 major depression, and 15 unaffected controls. Clinical records were obtained and DSM-IV diagnoses were made by psychiatrists from the SFNC. Routine neuropathological examinations were also conducted on each case by neuropathologists from the SFNC. Demographic data are given in Table 1.

The MHRC brain collection consisted of 64 subjects: 32 schizophrenia and 32 normal controls subjects matched by age, gender, and postmortem delay. Brains for this collection were obtained within short postmortem delay (mean 6 h). Ethical considerations in obtaining and using human autopsy material were informed by the Ethics Committee of the MHRC, the Russian Academy of Medical Sciences. Consent for autopsy and research was taken from family members. Demographic data are given in Table 2. Clinical records were obtained, and ICD-10 diagnoses were made by psychiatrists from MHRC. Causes of death in the schizophrenia group were the same as those in controls: coronary vascular disease, pulmonary embolism, myocardial infarction, pneumonia, and cardiac failure. Brains were excluded from the study if there was evidence of neurological damage, stroke, substantial drug, or alcohol abuse, or if there were changes characteristic of Alzheimer's disease or Parkinson's disease. Only the left hemispheres of brains were taken for study.

For estimation Nv of oligodendrocytes in BA9 and BA10 paraffin sections of 10 μm thickness were obtained from each case using systematic random sampling [31]. Sections were Nissl stained according to the standard method. BA9 and BA10 were verified by us using the morphological criteria established by Rajkowska and Goldman-Rakic [32]. Layer VI was identified by its location between layer V, which contains large pyramidal neurons, and adjacent white matter. Oligodendroglial cells were identified as profiles with a small round nucleus, with densely and homogenously staining and a narrow rim of cytoplasm [33]. In a similar study [22], close agreement was found between such profiles and immunocytochemically identified oligodendrocytes. Ten sections from each brain were used for estimation of the Nv of oligodendrocytes in layer VI and adjacent white matter. Nv of oligodendrogliocytes was estimated by optical dissector method [34]. Sections were viewed using a Carl Zeiss Axio Imager M1 light microscope with 100 × (N.A. = 1.40) oil immersion objective lens, which was connected via AxioCam MRc5 digital camera to a video monitor. Optical sectioning by AxioVision Module Z-stack was used for creation series Z-stack images. An unbiased sampling frame (frame size 0.05 × 0.065 mm = 0.00325 mm^2)was superimposed on the images of layer VI and of adjacent white matter with random start, 10 fields with equal interval (three frames) between fields were counted from each section, and 100 fields per each case were counted. One hundred dissectors were counted per layer VI and 100 dissectors per white matter per case. The thickness of the counting brick was 0.75 μm, and the total depth of the optical dissector was 6.75 μm with guards above and bellow ~0.5 μm.

Numerical density (Nv) of oligodendroglial cells was estimated using the formula: Nv = Q/v (dis), where Q is the average number of cell nuclei counted per dissector and v(dis) is the volume of the disector: $v(\text{dis}) = a[\text{frame}] \times h$, where "$a$" is area of frame and "$h$" is dissector height. Nv of oligodendroglial cells was estimated as number of oligodendroglial cells in 0.001 mm^3. Values for coefficient of error of the oligodendroglial density estimates in layer VI and adjacent white matter were consistently low, with group mean scores of <2.5% for layer VI and <1% for white matter.

For estimation of number of pericapillary oligodendrocytes in BA10 (layer V) the 30 paraffin sections of 20 mm thickness were prepared from each case. Ten sections from the series were sampled in systematic random manner for analysis. These sections were stained with Luxol-fast blue and cresyl violet for visualization of capillaries and of pericapillary oligodendrocytes. BA10 was verified, and layer V was identified as containing large pyramidal neurons. A Carl Zeiss Axio Image M1 light microscope with a 25/0.45 objective, which was connected via AxioCam MRc5 digital camera to a video monitor, was used. Ten rectilinear capillary segments from layer V were systematically random sampled from each section. In this manner, 100 rectilinear capillary segments were sampled per brain, and a total of 3200 capillary segments per group were sampled. The length of each segment was measured, the number of oligodendrocytes visible alongside each segment was counted, and

Table 1: Demographic data of SFNC brain collection.

	Schizophrenia $n = 15$	Bipolar disorder $n = 15$	Major depression $n = 15$	Normal controls $n = 15$
Age (mean ± SD)	44.5 ± 13.1	42.3 ± 11.7	46.5 ± 9.3	48.1 ± 10.7
Gender	9M, 6F	9M, 6F	9M, 6F	9M, 6F
Duration of disease (years) (mean ± SD)	20.6 ± 11.6	20.9 ± 10.2	12.7 ± 11.1	0
Age of onset (mean ± D)	23.2 ± 7.9	21.5 ± 8.3	33.9 ± 13.3	
PMI (h) (mean ± SD)	33.7 ± 14.6	32.5 ± 16.1	27.5 ± 10.6	23.7 ± 9.9
Side of brain	6R, 9L	8R, 7L	6R, 9L	7R, 8L
TF (m) (mean ± SD)	11.2 ± 8.4	9.6 ± 3.6	8.4 ± 6.6	4.4 ± 3.8

M: male; F: female; W: white; B: Black; A: Asian; PMI: postmortem interval in hours; L: left; R: right; TF: time in formalin in months.

Table 2: Demographic data of MHRC brain collection.

	Controls ($n = 32$)	Schizophrenia ($n = 32$)
Age (mean ± SD)	55.9 ± 15.2	51.4 ± 13.9
Gender	16M, 16F	19M, 13F
Duration of disease (years) (mean ± SD)	—	24.9 ± 10.5
Age of onset (mean ± SD)	—	26.7 ± 10.6
PMI (h) (mean ± SD)	6.0 ± 0.9	10.1 ± 7.7
TF (m) (mean ± SD)	1.3 ± 0.3	1.3 ± 0.4

M: male; F: female; PMI: postmortem interval in hours; TF: time in formalin in months.

oligodendrocyte densities were expressed as the number of oligodendrocytes per 0.01 mm of capillary length.

Statistical analysis was performed using STATISTICA 6 software package for Windows (StatSoft. Inc, Tusla, Okla, USA). Comparisons of number of oligodendrocytes to age in schizophrenia and normal controls were performed using multiple linear regression analysis. Statistical group comparisons between patients and the control groups were made using one-way analysis of variance (ANOVA).

3. Results and Discussion

Regression analyses examining the relationship between age and Nv of oligodendrocytes showed in controls a significant diagnosis by age interaction in layer VI of BA9 ($F = 10.05$, $df = 1.13$, $P = .007$) and in adjacent white matter ($F = 5.48$, $df = 1.13$, $P = .03$). In contrast, none of age-related changes were showed in schizophrenia, bipolar disorder, and major depression (all $P > .05$) (Table 3) (Figure 1).

Regression analyses of the relationship between neuroleptics dosage and Nv of oligodendrocytes in schizophrenic cases showed no significant neuroleptics by age interaction in layer VI of BA9 ($F = 0.6$, $df = 1.12$, $P = .5$) and in adjacent white matter ($F = 0.15$, $df = 1.12$, $P = .7$). Also, there was no significant neuroleptics by age interaction in bipolar disorder in layer VI of BA9 ($F = 0.01$, $df = 1.10$, $P = .9$) and in adjacent white matter ($F = 3.44$, $df = 1.10$, $P = .09$).

Regression analyses examining the relationship between age and Nv of oligodendrocytes showed in controls a significant diagnosis by age interaction in layer VI of BA10 ($F = 6.55$, $df = 1.30$, $P = .015$) and adjacent white matter ($F = 20.44$, $df = 1.30$, $P < .001$). In contrast, none of meaningful age-related change showed in schizophrenia ($F = 0.02$, $P = .9$, $F = 0.90$, $P = .34$, resp.) (Table 4) (Figure 2).

Table 3: Regression of Nv of oligodendrocytes on age in BA9.

	F	df	P
Controls			
layer VI	10.05	1.13	.007
white matter	5.48	1.13	.03
Schizophrenia			
layer VI	2.15	1.13	.16
white matter	0.14	1.13	.7
Bipolar disorder			
layer VI	0.51	1.13	.5
white matter	4.63	1.13	.051
Major depression			
layer VI	0.01	1.13	.9
white matter	1.34	1.13	.26

Regression analyses examining the relationship between neuroleptics dosage and Nv of oligodendrocytes in schizophrenia showed no significant neuroleptics by age interaction in layer VI of BA10 ($F = 3.15$, $df = 1.30$, $P = .09$) and in adjacent white matter ($F = 0.18$, $df = 1.30$, $P = .7$).

Comparisons of young (<50 years) and elderly patient subgroups (>50 years) with young and elderly controls showed that only elderly patients with schizophrenia had

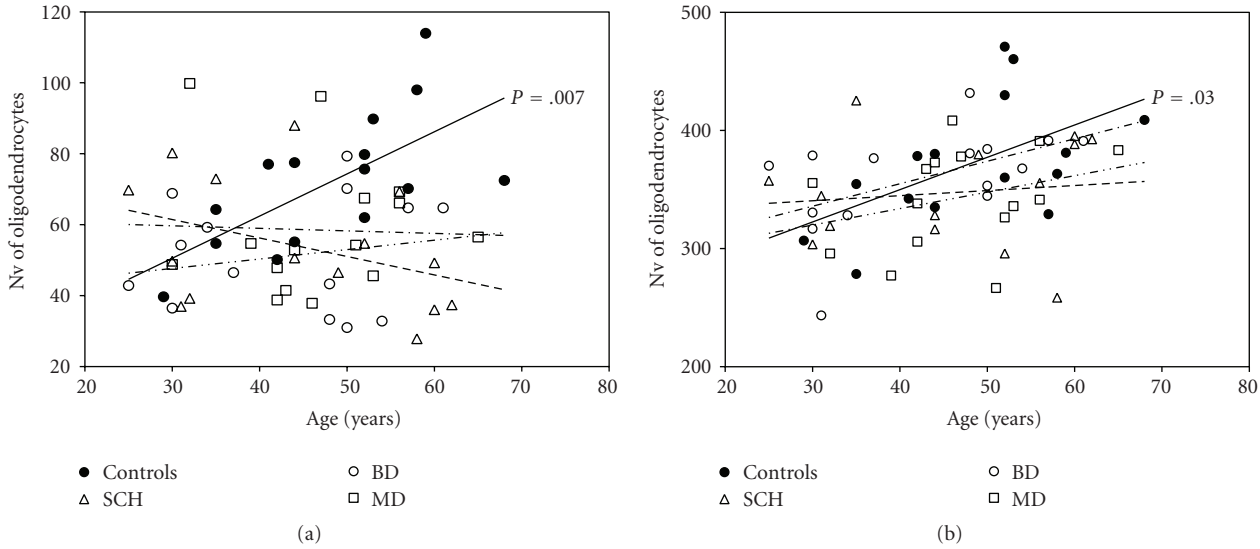

Figure 1: Plots summarizing results of regression analysis in BA9. There is a significant positive correlation between Nv of oligodendrocytes and age in controls in layer VI ($P = .007$) (a) and in adjacent white matter ($P = .03$) (b) but no significant correlations in schizophrenia, bipolar disorder, and major depression.

Table 4: Regression of Nv of oligodendrocytes on age in BA10.

	F	df	P
Controls			
layer VI	6.55	1.30	.015
white matter	20.44	1.30	<.001
Schizophrenia			
layer VI	0.02	1.30	.9
white matter	0.90	1.30	.34

significantly lower oligodendrocyte number as compared to elderly controls (in BA10 layer VI ($F = 26.78$, $df = 1.36$, $P < .001$)), in adjacent white matter ($F = 51.24$, $df = 1.36$, $P < .001$), in BA9 layer VI ($F = 7.28$, $df = 1.12$, $P = .02$) (Figures 3(a), 3(b) and 3(c)).

Significant reduction of oligodendrocyte density only was found in young patients with bipolar disorder as compared to young controls ($F = 11.30$, $df = 1.14$, $P = .005$) (Figure 3(d)).

Results of our study revealed a significant age-related increase in Nv of oligodendrocytes in layer VI and in white matter both in BA9 and BA10 in control groups. It is of interest to note that previously the age-related increase number of pericapillary oligodendrocytes in layer V in BA10 was also revealed in controls [23]. Of note, such an increase was not observed in age-matched psychiatric groups.

Our results obtained in normal control groups are consistent with the results of imaging studies on myelination of normal subjects. Bartzokis et al. [19] reported that the normal age-related development of the frontal and temporal lobes in adulthood is dysregulated in adults with schizophrenia primary due to a lack of normal myelination. van Haren et al. [35] proposed that cerebral gray matter volume loss in patients with schizophrenia was characterized by the absence of the normal curved trajectory of volume change with age that was present in healthy subjects. These data together with the results of postmortem studies suggest that age-related increase in oligodendrocyte number and progressive myelination that are evidenced in normal controls may be disrupted in psychiatric patients. A significant age-associated reduction in fractional anisotropy, progressive decrement of white matter volume in frontal lobe, and the relationships between white matter alterations and severity of symptoms were found in patients with schizophrenia in contrast to controls [36–39]. Our results are also in agreement with the data obtained in the monkey neocortex [40] where a substantial increase in the numbers of oligodendrocytes was found over the monkey's life span. An increase in the number of oligodendrocyte with aging has been also reported in the optic nerve, in the visual cortex [41, 42]. Severity of age-related myelin alterations in visual cortex correlated significantly with cognitive impairment index due to reduced conduction velocity along the affected nerve fibers [42, 43].

The increase of oligodendrocytes number and extensive myelination of the human brain makes myelin maintenance and repair especially critical for supporting our high cognitive processing speed [19, 44]. Importantly, that reduction of fractional anisotropy in different white matter

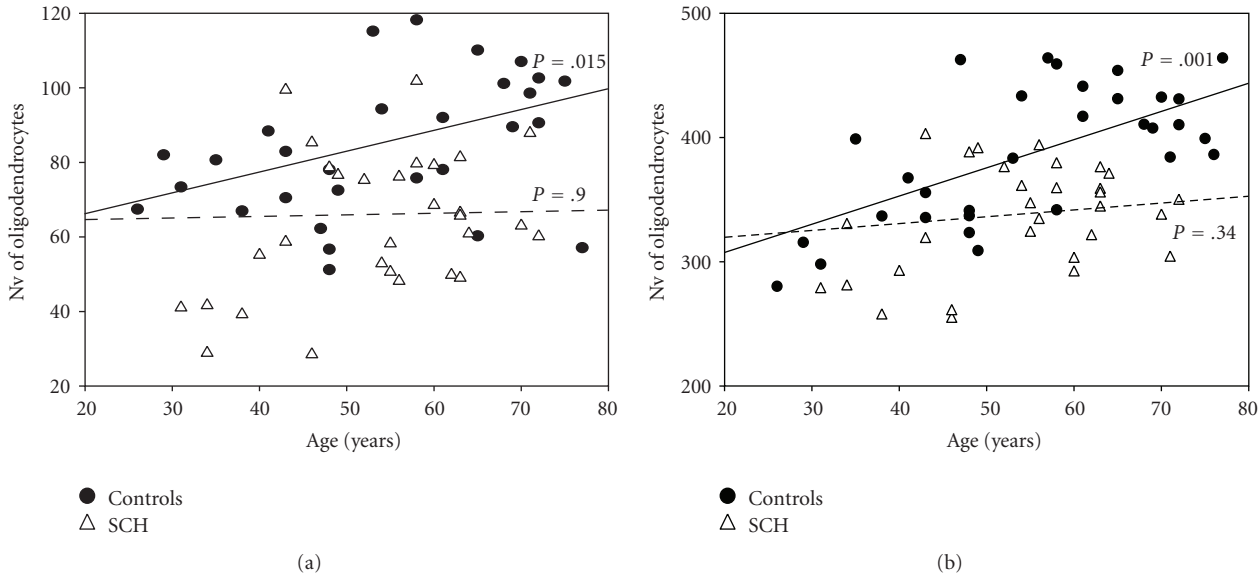

Figure 2: Plots summarizing results of regression analysis in BA10. There is a significant positive correlation between Nv of oligodendrocytes and age in controls in layer VI ($P = .015$) (a) and adjacent white matter ($P = .001$) (b) but no significant correlations in schizophrenia.

tracts was associated with cognitive deficits [45–49]. Thus, these data together with our results suggest that reduced oligodendrocyte density might be associated with cognitive dysfunction in schizophrenia and in bipolar disorder.

In the present study, only elderly patients with schizophrenia had significantly lower oligodendrocyte number as compared to elder controls. Elderly schizophrenia patients frequently develop more severe cognitive disturbances that younger ones. In these subjects reported reduced fractional anisotropy in frontotemporal clusters associated with frontal gray matter reduction and "frontal" cognitive deficits [50], though Frisoni et al. [51] found that orbitofrontal/cingulate region had low gray matter volume in elderly schizophrenia patients not associated with cognitive abnormalities. Neuroimaging studies demonstrated lower prefrontal gray matter volume in schizophrenia in chronic but not in first episode schizophrenia patients [52]. Patients with chronic schizophrenia showed widespread cortical thinning that particularly affected the prefrontal cortex [53–56], decreased fractional anisotropy in thalamofrontal white matter [57], lower levels of glutamate/glutamine and N-acetylaspartate compared to healthy controls and first-episode patients [58], abnormally expressed NMDA receptor subunits in elderly schizophrenia patients [59], and hypoperfusion of the prefrontal cortex [60].

On the contrary, gray and white matter volumes of prefrontal cortex were significantly smaller only in young adulthood bipolar disorder patients relative to healthy control subjects [61–64]. Decreased N-acetylaspartate was detected in the dorsolateral prefrontal cortex of young bipolar patients [65]. These findings suggest that prefrontal white matter abnormalities are present early in bipolar disorder and may consist largely of axonal disorganization, and white matter pathology may represent an early marker of bipolar disorder [66].

Our results that significant reduction of oligodendrocyte density was found in young patients with bipolar disorder as compared to young controls are in agreement with these in vivo data. They are also in line with the data obtained from other postmortem studies reported that patients with bipolar disorder demonstrated decreased neuronal size in the orbitofrontal cortex [67] and reductions in oligodendrocyte density in the prefrontal cortex [13, 14] and the number, size, and density of glial cells [68–70].

Maturity of oligodendrocytes is influenced by genetic and epigenetic factors. DNA microarray analysis repeatedly demonstrated downregulation of oligodendrocyte- and myelin-related genes [6, 8]. Most of these data were obtained on Mount Sinai and Stanley collections containing mostly elderly subjects. On the other side, Mitkus et al. [71] using brain collection containing younger cases of schizophrenia and controls did not confirmed downregulation of oligodendrocyte-related genes, but they found that individuals carrying risk-associated alleles in oligodendrocyte-related genes had relatively lower transcript levels. DTI studies of subjects at increased risk for bipolar disorder showed reduced fractional anisotropy in the superior frontal tracts [72] and decreased gray matter density. Bipolar disorder and schizophrenia share common chromosomal susceptibility loci and many risk-promoting genes. Thus, these data illustrate the importance of genetic factors in oligodendrocyte abnormalities in schizophrenia and in bipolar disorder.

Recently, epigenetic mechanisms facilitating oligodendrocyte development, maturation, and aging have been reported [73]. It is of interest to note that Iwamoto et al. [10] in BA10 of the prefrontal cortex of the Stanley brain collection detected reduced expression of SOX 10, an oligodendrocyte-specific transcription factor, and correlation between DNA methylation status of SOX 10 with its downregulation and oligodendrocyte dysfunction

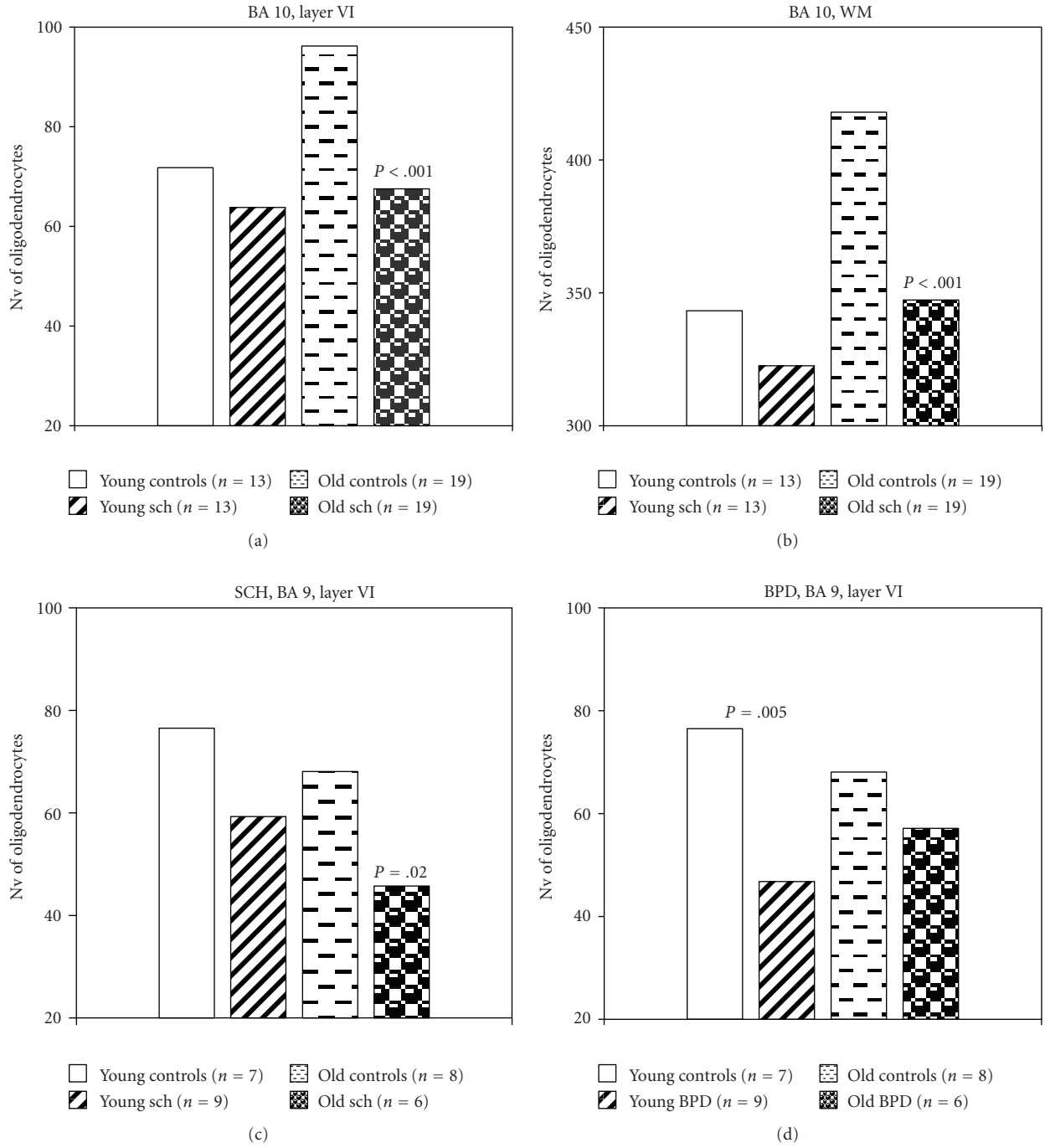

Figure 3: Plots summarizing results of comparisons of young and elderly patient subgroups with young and elderly controls.

in schizophrenia. It is known that oligodendrocytes are very sensitive to oxidative stress [69, 74, 75] and glutamate toxicity [69, 76]. Excess release of glutamate was found in schizophrenia patients [77] and especially in schizophrenic patients with cognitive impairment and negative symptoms [78]. Many genes modified in the brains of patients with schizophrenia are associated with glutathione and oxidative stress pathways [79]. The data provide evidence for epigenetic and intrinsic factors on oligodendrocyte dysfunction in schizophrenia.

Frontal and temporal lobe white matter volumes continue to increase in humans throughout the first five decades of life [80–82]. The convergence of natural and genetic risk factors on this area in schizophrenia and bipolar disorder may help to explain the apparent vulnerability of oligodendrocytes in these disorders [69]. Recent studies suggest that abnormal development of oligodendrocytes is involved in the pathophysiology of schizophrenia. Katsel et al. [83] suggest that oligodendroglial deficit in schizophrenia might be associated with disruption of normal patterns of cell cycle

gene and protein expression. Barley et al. [84] found that genes expressed after the terminal differentiation of oligodendrocytes tended to have lower levels of mRNA expression in subjects with schizophrenia compared to normal controls. Kern et al. [85] reported deficits in the expression of oligodendrocyte and myelin genes associated with a reduction in the number of oligodendrocytes and with abnormalities of cell cycle markers in some brain regions in schizophrenia.

Some of studies indicate that chronic treatment with antipsychotics may affect brain morphology [86–88]. However, we found no effect of neuroleptic treatment on Nv of oligodendrocytes in schizophrenia and bipolar disorder groups and revealed a lack of age-related increase in this parameter in major depression group without neuroleptic treatment. On the other hand, protective effects of neuroleptics on oligodendrocytes have been reported [89, 90]. Thus, we suggest that reported reductions in oligodendrocyte density in schizophrenia and mood disorder are related to the disease.

Oligodendrocytes form after wave of neurogenesis, and they show a selective vulnerability to cell death stimuli depending on their stage of development [91]. Gritti et al. [92] found age- and region-dependent quantitative changes in the cell composition of neural stem cells progeny (decreased quantity of neurons and oligodendrocytes; increased amount of astroglial cells). Aging had an effect on the morphological feature, number, and developmental regulation of oligodendroglial progenitors in rat CNS [93]. It is of interest to note that neural stem cell proliferation is decreased in schizophrenia, but not in depression [94], and haloperidol stimulate proliferation of oligodendrocytes precursors [90]. Benes [95] suggested delayed myelination in the prefrontal cortex in patients with schizophrenia. Akbarian et al. [96, 97] reported a maldistribution of the interstitial neurons in both prefrontal and temporal white matter in schizophrenia. The data suggested that neurodevelopmental abnormalities were present in at least a subgroup of psychiatric patients. Since young schizophrenia patients in the present study demonstrated decrease in Nv of oligodendrocytes, though no significant, we suppose that the deficit of oligodendrocytes might start during brain development and continue to become significant in elderly patients with schizophrenia.

Several limitations of the study must be noted. First, mean age in bipolar disorder was less than in schizophrenia group. Second, samples need to be comprised of both males and females, as there is clear evidence to suggest that the timing, course, and clinical features of schizophrenia are manifested quite differently in males and females, and this may be related to brain differences. Future studies will also need to include an evaluation of first episode psychotic patients, so as to provide a sample of patients who have limited exposure to psychotropic medications. It will also be important to evaluate a representative sample of normal controls across age, as white matter changes with age, and such changes may be quite different in pathological populations such as schizophrenia. Future DTI studies need also to include other imaging techniques, which highlight white matter pathologies, such as proton spectroscopy, magnetization transfer techniques, and relaxation times measurements. Moreover, such studies should be conducted in concert with functional MRI and PET imaging in order to characterize and to understand more fully both functional and structural abnormalities in schizophrenia. Although gender ratios were not precisely matched, previous studies have failed to correlate gender and measures of diffusion tensor imaging.

4. Conclusion

In conclusion, the study highlights the importance of inclusion of age effects in imaging and postmortem studies for further studies of white matter abnormalities in major psychiatric disorders.

Conflict of Interests

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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Review Article

White Matter Abnormalities and Animal Models Examining a Putative Role of Altered White Matter in Schizophrenia

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Schizophrenia is a severe mental disorder affecting about 1% of the population worldwide. Although the dopamine (DA) hypothesis is still keeping a dominant position in schizophrenia research, new advances have been emerging in recent years, which suggest the implication of white matter abnormalities in schizophrenia. In this paper, we will briefly review some of recent human studies showing white matter abnormalities in schizophrenic brains and altered oligodendrocyte-(OL-) and myelin-related genes in patients with schizophrenia and will consider abnormal behaviors reported in patients with white matter diseases. Following these, we will selectively introduce some animal models examining a putative role of white matter abnormalities in schizophrenia. The emphasis will be put on the cuprizone (CPZ) model. CPZ-fed mice show demyelination and OLs loss, display schizophrenia-related behaviors, and have higher DA levels in the prefrontal cortex. These features suggest that the CPZ model is a novel animal model of schizophrenia.

1. Introduction

Schizophrenia is a devastating mental disorder affecting about 1% of the population worldwide [1]. The onset of schizophrenia ranges from mid to late adolescence through early adulthood; the majority of cases occur between the ages of 16 and 30 years [2]. Clinically, this disorder is characterized by positive symptoms (psychosis, hallucinations, and paranoia), negative symptoms (flat affect, poor attention, lack of motivation, and deficits in social function), and cognitive deficits.

The positive symptoms of schizophrenia have been treatable since chlorpromazine was introduced into clinical practice in the early 1950s. Since then, a number of antipsychotic drugs have been developed, which are grouped into typical and atypical antipsychotics. All typical antipsychotics have high affinities for dopamine (DA) D_2 receptors, which correlate with the therapeutic doses of these drugs [3–6]. These observations, plus the psychotogenic effects of DA-enhancing drugs [7, 8], provided solid evidence for the DA hypothesis of schizophrenia that hyperactivity of DA transmission is responsible for the positive symptoms observed in this disorder [9].

In contrast to positive symptoms, negative symptoms tend to remain stable over time in patients with established illness [10] and have been found to persist despite of treatment [11, 12]. This phenomenon raised a critical challenge to the DA hypothesis. In addition, this hypothesis cannot account for why the symptoms of schizophrenia commonly first present in late adolescence and early adulthood.

During adolescence and early adulthood, white matter volume expands while grey matter volume loss occurs [13]. This long-lasting development of the white matter is associated with the development of cognitive functions [14]. Given these and that schizophrenia present in adolescence or early adulthood, it is reasonable to infer that disruption to white matter development and/or damage to some white matter structures during this period are responsible for the development of psychotic symptoms. In line with this view, there are increasing human studies, especially those following the inspiring review by Davis et al. [15], showing white matter abnormalities and altered oligodendrocyte- (OL) and

myelin-related genes in schizophrenic patients. On the other hand, abnormal behaviors are reported in patients with white matter diseases. In this paper, we will briefly review some of these human studies. Following that, we will selectively introduce some animal models that examine a putative role of white matter abnormalities in schizophrenia. The emphasis will be put on the cuprizone-fed mouse, a novel animal model of schizophrenia.

2. White Matter Abnormalities in Schizophrenic Patients

2.1. Imaging Evidence. Lateral ventricular enlargement is the best replicated anatomic abnormality detected in the brains of patients with schizophrenia both in earlier computed tomography (CT) studies and in many magnetic resonance imaging (MRI) investigations [16]. The boundaries of the cerebral ventricles are largely made up of white matter structures. Therefore, ventricular enlargement may be due in part to volumetric reduction of adjacent white matter tracts. However, conventional MRI findings in earlier studies for cerebral white matter volume in schizophrenia have been mixed. Some of them found no differences in white matter volume between schizophrenic patients and normal subjects [17–21], while some reported white matter reductions in schizophrenia [22–24].

Foong's group [25] for the first time used magnetization transfer imaging (MTI), a technique sensitive to myelin and axonal abnormalities, to investigate the white matter in patients with schizophrenia. They found that the magnetization transfer ratios (MTRs) significantly reduced in the right and left temporal regions in schizophrenic patients compared with controls. The same group also used diffusion tensor imaging (DTI), another new MRI technique capable of examining water diffusion in different tissues and the organization of white matter tracts, to investigate the neuropathology of the corpus callosum in patients with schizophrenia [26]. The mean diffusivity (MD) increased and fractional anisotropy (FA) reduced in the splenium of the corpus callosum in the schizophrenic group compared with controls. These results confirmed the findings in an earlier study, which reported a reduction in FA in the corpus callosum in a small group of schizophrenic patients [27].

A number of recent DTI studies in patients with schizophrenia [28–33] reported FA reduction in various brain regions/structures, including the frontal white matter, the deep frontal perigenual region, the medial occipital lobe, the inferior parietal gyri, the middle temporal gyri, the parahippocampal gyri, the corpus callosum, the internal capsule, the cingulum bundle, the fornix, the superior occipitofrontal fasciculus, the frontal longitudinal fasciculus, the right inferior occipitofrontal fasciculus, the right medial temporal lobe adjacent to the right parahippocampal gyrus, the left arcuate fasciculus, the left superior temporal gyrus, and the left uncinate fasciculus. Moreover, significant FA reductions were reported in all white matter regions bilaterally in schizophrenic patients of a recent study [34]. Lower FA values were also seen in never-medicated, first-episode schizophrenia [35–38]. More significantly, white matter abnormalities in specific brain regions were associated with different dimensions of schizophrenia symptoms. For example, widespread decrements in prefrontal white matter in schizophrenic patients were related to higher levels of negative symptoms, as measured by the Scale for the Assessment of Negative Symptoms (SANS) [39]; inferior frontal white matter FA inversely correlated with the SANS global ratings of negative symptoms [40]; a significant reduction of white matter in parietal cortex of right hemisphere was found in a subgroup of patients with pronounced negative symptoms [41]. In a more recent study, there were significant positive correlations between volumes (larger) in anterior callosal, cingulate and temporal deep white matter regions and positive symptoms, such as hallucinations, delusions and bizarre behavior. Negative symptoms were negatively related to volumes (smaller) in occipital and paralimbic superficial white matter and posterior callosal fiber systems [42].

2.2. Postmortem Evidence. Decreased (MTR) found in schizophrenic patients suggests decreases in the myelin or axonal membrane integrity. Similarly, FA decrease reflects the reduction in the coherence of white matter. These suggestions are in line with the results from postmortem studies, exemplified by reduced myelin basic protein (MBP) immunoreactivity [43] and myelin pallor and myelin loss [44] in brains of chronic schizophrenic patients. Moreover, ultrastructural evidence of reduced myelin sheath compactness, including bodies and lamellar bodies, has been shown in postmortem electron microscopy studies [45–47]. In addition, a delayed myelination in the PFC was reported in patients with schizophrenia, suggesting the developmental nature of this change [48].

OLs are myelin sheath producing cells. Therefore, myelin sheath changes reflect OLs alterations. Indeed, OLs were first implicated in schizophrenia in 1938 when swollen OLs were observed in schizophrenic brains postmortem [49]. In recent years, the group of Uranova and Orlovskaya carried out a series of postmortem studies and reported solid evidence of disturbed structure and function of OLs [45, 46, 50–53], found reductions in density and size of OLs in prefrontal and striatal regions [52, 54, 55], and showed a deficit of OLs in PFC and adjacent white matter [56] in schizophrenia. Loss and altered spatial distribution of OLs were also found in the superior frontal gyrus in schizophrenia [57].

3. Altered OL- and Myelin-Related Genes in Schizophrenia

In a groundbreaking study, Hakak et al. [58] found that the expression of a series of genes related to OLs and myelin significantly decreased in the dorsolateral prefrontal cortex (DLPFC) samples of schizophrenic patients. Another microarray study measured expression of approximately 12,000 genes in the middle temporal gyrus and found significant decreases in the expression of some myelin-related genes in subjects with schizophrenia [59]. In a more recent study [60], variations in myelin- and OL-related gene expression were found in multiple brain regions of postmortem schizophrenic brains. The downregulated

myelin- and OL-related genes include neuregulin 1(*NRG1*), CNP (2′, 3′-cyclic nucleotide 3′-phosphodiestase), CLDN11 (claudin 11, an OL specific protein), OLIG2 (OL lineage transcription factor 2), MAG (myelin associated glycoprotein), MAL (myelin and leukocytes protein), OKI (quaking homolog, KH domain RNA binding (mouse)), TM4SF11 (trans-membrane 4 superfamily 11), and GELS (gelsolin). In the following, we will selectively review evidence for changes in some of the above mentioned genes.

3.1. NRG1. This is a family of proteins containing an epidermal growth factor-like domain that specifically activate receptor tyrosine kinases of the erbB family: erbB2, erbB3, and erbB4 [61]. NRG1-mediated erbB signaling has important roles in neural and glial development, as well as in the regulation of neurotransmitter receptors thought to be involved in the pathophysiology of schizophrenia. In the study by Hakak et al. [58], a significant reduction in the level of *erbB3* expression was found in PFC of schizophrenic patients. This decrease was confirmed by quantitative and differential-display RT-PCR analysis [62]. In a genome-wide scan, Stefansson et al. [63], by means of haplotype analysis, identified *NRG1* as a candidate gene for schizophrenia. This association of *NRG1* with schizophrenia was confirmed by the same group in a Scottish population [64] and by an independent study in a large sample of unrelated Welsh patients [65]. Strong association between *NRG1* and schizophrenia was also found in Chinese population [66, 67], but not in Japanese population [68]. In a more recent study [69], schizophrenic patients with the T allele for a single-nucleotide polymorphism (SNP8NRG221533) showed significantly decreased anterior cingulum FA compared with patients homozygous for the C allele and healthy controls who were T carriers, suggesting that *NRG1* variation may play a role in the white matter abnormality of this brain region in patients with schizophrenia.

3.2. CNP. This gene maps to 17q21.2, a region of the genome in which genome-wide evidence for linkage to schizophrenia was observed in a single pedigree [65]. CNP (protein) can be detected early in development, in the precursor cells to OLs. In adulthood, CNP shows a high turnover compared with other myelin-associated proteins [70]. Postmortem studies of anterior frontal cortex demonstrated less immunoreactivity of CNP in schizophrenia [71]. This result confirmed the downregulation of *CNP* gene in the schizophrenic brain [58]. Compatible with the underexpression of *CNP* mRNA in schizophrenia, the low-expressing A allele was significantly associated with schizophrenia in a case-control sample. All affected individuals in the linked pedigree were homozygous for the low-expression allele [72]. In a recent human study, reduced CNP protein in the hippocampus and anterior cingulated cortex of patients with schizophrenia was also reported [73].

3.3. MAG. This is a minor but important component of myelin that is expressed only in myelin-forming cells and is involved in the initiation of myelination in the CNS [74, 75]. Microarray studies reported decreased MAG mRNA expression in the DLPFC and the middle temporal gyrus of postmortem schizophrenic brains [58, 62]. In studies using quantitative PCR analysis, decreased MAG mRNA was found in the anterior cingulated cortex and the hippocampus, in addition to DLPFC [59, 76]. These findings were confirmed in a recent study that reported a decrease in the expression of MAG in white matter in schizophrenia using a probe that detected mRNAs for the large and small MAG splice variants. However, expression of MAG did not differ between patients with schizophrenia and controls in the grey or white matter in another study [77]. Discrepancy was also seen in genetic association analyses; some, but not all, of the analyses, linked MAG gene to schizophrenia [78–80].

3.4. OLIG2. This gene maps to 21q22.11 and encodes a transcription factor central to OL development. Strong association of *OLIG2* and schizophrenia has been reported. There are reports of deletion in this region in patients with schizophrenia [81] and of a low risk of schizophrenia in people with trisomy 21 [82]. In the postmortem schizophrenic brain, *OLIG2* mRNA reduced [60, 62, 83]. *OLIG2* expression in cerebral cortex significantly correlated with *CNP* and ERBB4, suggesting interaction effects on disease risk between *OLIG2* and *CNP* [84].

3.5. QKI. In a genome scan of a single large family from northern Sweden with high frequency of schizophrenia and schizophrenia-spectrum disorders, Lindholm et al. [85] detected a maximum LOD (logarithm of data) score of 6.6 on chromosome 6q25. This region contains only one gene described in the literature and the human databases, quaking homolog, KH domain RNA binding (mouse) (*QKI*) [86], pointing to the potential involvement of *QKI* in schizophrenia. In support of this suggestion, expression of *QKI* mRNA decreased in seven cortical regions and the hippocampus in the schizophrenic subjects [87], and relative mRNA expression levels of two *QKI* splice variants clearly downregulated in schizophrenic patients [88]. Moreover, mRNA levels of the tightly coexpressed myelin-related genes including *PLP1, MAG, MBP, TF, SOX10,* and *CDKN1B* decreased in schizophrenic patients, as compared with control individuals. Most of these differences (68–96%) can be explained by variation in the relative mRNA levels of *QKI*-7 kb. The same *QKI* splice variant was shown to be downregulated in patients with schizophrenia. Therefore, the authors suggested that decreased activity of some myelin-related genes in schizophrenia may be caused by disturbed *QKI* splicing [89].

3.6. The Other Myelin-Related Genes. In addition to the aforementioned genes, there have also been reports of association with schizophrenia for the myelin-oligodendrocyte glycoprotein (*MOG*) [90], the proteolipid protein 1 gene (*PLP1*) [91], and the transferring gene (*TF*) [92]. Of these, *PLP1* warrants to be emphasized here. Proteins (PLP1 and its splicing variant DM20) encoded by this gene are synthesized by OLs as the two major integral proteins of myelin membranes of CNS [93]. Point mutations of human *PLP* have been recognized as

the molecular basis of one form of leukodystrophy, the X-chromosome-linked Pelizaeus-Merzbacher disease (PMD). And a novel mutation in the *PLP* gene has been reported to lead to PMD [94]. Lower levels of *PLP1* mRNA have been reported in schizophrenia [59, 62, 95]. There is also evidence for a genetic association of *PLP1* with schizophrenia [91]. However, in Japanese population, no association was found between *PLP1* and schizophrenia [96].

4. Abnormal Behaviors in Patients with White Matter Diseases

The third line of evidence for the involvement of white matter abnormalities in schizophrenia came from studies reporting abnormal behaviors in human sufferers from white matter diseases.

4.1. Agenesis of Corpus Callosum (ACC). The corpus callosum is the largest white matter tract in the brain. Two developmental malformations of the corpus callosum associated with psychosis are partial or complete ACC and callosal lipoma [97]. When psychiatric disturbance presents in ACC sufferers, it is psychotic in nature in at least half of the patients [98]. Psychosis is also seen in Andermann's and Apert's syndrome at a higher rate, compared to healthy controls. Both Andermann's and Apert's syndrome are accompanied with ACC [99, 100]. On the other hand, undiagnosed ACC has been detected in schizophrenic patients at a significantly higher rate [101].

4.2. Metachromatic Leukodystrophy (MLD). This is a devastating demyelinating disease caused by a deficiency of the enzyme sulfatide sulfatase, also known as arylsulfatase A (ASA). Patients with MLD have abnormalities predominantly in the frontotemporal white matter. Up to 50% of patients with adolescent or early-adult onset present with psychotic symptoms such as auditory hallucinations, though disorder, affective disturbance, formal thought disorder, and catatonia [102]. In many cases of MLD, the behavioral abnormalities are the first symptoms. Some of these forms have been diagnosed as schizophrenia. Very seldom, neurological symptoms, especially ataxia, occur without cognitive or psychiatric disturbances [103]. On the other hand, a large number of adult patients with varying psychiatric manifestations have low levels of ASA-CS activity, suggesting that such patients may be asymptomatic carriers of the sulfatidase defect (heterozygotes for MLD) [104].

4.3. The Adult Onset Form of Niemann-Pick Type C (NPC) Disease. This is a lipid storage disorder. In the early stage of NPC, only white matter is affected [105, 106]. Patients show white matter disruption in the corpus callosum [107] and periventricular white matter [108]. Up to 40% of cases, a rate comparable with MLD, present initially with psychosis [108–112].

4.4. Multiple Sclerosis (MS). This is a demyelinating disease of CNS. The onset of most cases occurs between 20 and 40 years of age [113], reminiscent of the onset of schizophrenia that occurs mainly between the ages of 16 and 30 years [2]. In addition to the cardinal pathological features of focal areas of demyelination and immune-mediated inflammation, patients with MS show a number of different behavioral syndromes, which may be broadly divided into two categories: those pertaining to mood, affect, and behavior and those impairing cognitive functions [114]. Recent epidemiological studies estimated that the prevalence of psychosis in MS patients is two to three times those in the general population [115]. More interestingly, the prevalence is the highest (about 4.2%) in the 15- to 24-year age group in MS patients, again, which reminds us of the early onset of schizophrenia.

In patients with clinically definite MS, cognitive abnormalities can be detected in 40–60% of patients [116]. Memory and executive functions are often impaired to an extent that cannot be explained as a result of the general intellectual decline [117]. Moreover, impairment in sustained attention, processing speed, and verbal memory in MS patients negatively correlated with MS lesion volume in frontal and parietal regions at baseline, 1-year, and 4-year followup, suggesting a contribution of the frontoparietal subcortical networks disruption to these cognitive impairments in MS [118].

5. Oligodendrocyte-Related Genetic Animal Models of Schizophrenia

Although a number of biologically related genes have been reported to be downregulated in schizophrenia as reviewed above, only a few genetic animal models have been reported that show white matter development disruption and schizophrenia-related behaviors thus being used as potential animal models of schizophrenia.

5.1. Plp1 Transgenic Mice Show Schizophrenia-Related Behaviors. The first animal study that showed both white matter development disruption and abnormal behaviors was done by Boison and Stoffel [119]. They produced transgenic mice carrying a target alteration of the *plp* gene containing a deletion within exon III, mimicking DM20, and a neocassette in reverse orientation within intron III. The ultrastructure of the multilayer myelin sheath of all axons in the CNS of hemizygous male or homozygous female PLP/DM20-deficient mice is highly disordered. This disrupted assembly of the myelin sheath was accompanied with profound reduction of conductance velocity of CNS axons, impairments in neuromotor coordination, and reduced spontaneous locomotor activity. In a more recent study, Tanaka et al. [120] analyzed a transgenic mouse line harboring extra copies of the *plp1* gene ($plp1^{tg/-}$ mice) at 2 months of age. Although the $plp1^{tg/-}$ mice showed an unaffected myelin structure, the conductance velocity in all axonal tracts tested in the CNS greatly reduced. Moreover, the $plp1^{tg/-}$ mice showed altered anxiety-like behaviors, reduced prepulse inhibitions (PPI), spatial learning deficits and working memory deficit. These abnormal behaviors are schizophrenia-related behaviors, suggesting that the $plp1^{tg/-}$ mice may be used as a potential animal model to examine the role of altered *plp1* gene in schizophrenia.

5.2. Functional Consequence of Perturbing NRG1/erbB4 Signaling. In the functional studies, mutant mice heterozygous for either *NRG1* or its receptor erbB4 showed a behavioral phenotype that overlaps with mouse models for schizophrenia. Furthermore, *NRG1* hypomorphs had fewer functional NMDA receptors than wild-type mice. More interestingly, the behavioral phenotypes of the *NRG1* hypomorphs were partially reversible with clozapine, an atypical antipsychotic drug used to treat schizophrenia [63]. Since then a number of mutant mice with heterozygous deletion of transmembrane domain NRG1 have been replicated in independent laboratories [121], including hyperactivity in a novel environment [122, 123], mild disruption of PPI [124], and social interaction deficits [123, 125]. But both spatial learning and memory, assessed in the Barnes maze, and spatial working memory, as measured by nondelay Y-maze alternation, kept intact [123]. Similarly, there was no effect of *NRG1* genotype on performance in either test of emotionality/anxiety [125].

To test whether erbB signaling contributes to psychiatric disorders by regulating the structure or function of OLs, Roy et al. [126] analyzed transgenic mice in which erbB signaling was blocked in OLs *in vivo*. Loss of erbB signaling led to changes in OL number and morphology, reduced myelin thickness, and slower conduction velocity in CNS axons. Furthermore, these transgenic mice exhibited increased levels of DA receptors and transporters and behavioral alterations including reduced locomotion and social dysfunction. More interestingly, *BACE1* (β-site APP-cleaving enzyme 1) knockout mice, in which *NRG1* processing was altered, exhibited deficits in PPI, novelty-induced hyperactivity, hypersensitivity to a glutamatergic psychostimulant (MK-801), cognitive impairments, and deficits in social recognition. Some of these manifestations were responsive to clozapine, an atypical antipsychotic drug. Although the total amount of ErbB4 did not change in *BACE1* knockout mice, binding of erbB4 with postsynaptic density protein 95 significantly reduced in the brains of these mice [127]. Together, the above studies suggest that altered *NRG1*/erbB4 signaling plays an important role in the pathogenesis of schizophrenia.

5.3. Nogo-A Deficient Mice. In addition to the above two animal models, a mouse model of constitutive genetic Nogo-A deficiency deserves to be emphasized here. In a comprehensive series of behavioral tests with specific relevance to schizophrenia pathopsychology, the Nogo-A deficient mice showed deficient sensorimotor gaiting, disrupted latent inhibition, perseverative behavior, and increased sensitivity to the locomotor stimulating effects of amphetamine. Moreover, these behavioral changes were accompanied by altered monoaminergic transmitter levels in specific striatal and limbic structures, as well as changes in D_2 receptor expression in the same brain regions [128]. Therefore, the authors concluded that Nogo-A may bear neuropsychiatric relevance, and alterations in its expression may be one etiological factor in schizophrenia and related disorders.

6. Cuprizone-Fed Mouse: A Novel Animal Model of Schizophrenia

6.1. A Murine Model of Demyelination/Remyelination. Cuprizone (CPZ: biscyclohexanone oxalyldihydrazone) is a copper chelator used as a reagent for copper analysis. In early studies [129, 130], higher doses (0.3, 0.5, and 0.75%) of CPZ were administered to animals via diet. These treatments were extremely toxic to mice, manifested with severe growth reduction, posterior paresis, and high mortality early in the feeding period. Convulsion and seizures were also seen in later stages (6-7 weeks after CPZ-feeding). Pathological alterations include severe status spongiosus, astrogliosis, demyelination, and hydrocephalus. Under electron microscopy, there are many large vacuoles within the myelin sheaths and swollen glial cells. The vacuoles, which resulted from giant mitochondria, were also seen in the hepatocytes [129]. Later studies [131, 132] administered a lower dose (0.2%) of CPZ to mice. The animals have no evident toxic effects and neurological symptoms; consistent demyelination and mature OLs loss are main pathological alterations. When allowed to recover on a normal diet, remyelination begin within a week and progresses until all axons are myelinated. For these features, the CPZ models have been extensively used to define issues important to understanding of the pathophysiology of demyelination and to gain understanding of the mechanisms involved in remyelination.

6.2. Behavioral Deficits in CPZ-Fed Mouse. Given that demyelination and mature OLs loss are main pathological alterations in brains of mice exposed to the lower dose (0.2%) of CPZ, examining possible behavioral deficits in the CPZ-fed mice should provide informative data relating specific behaviors to regional white matter abnormality. In the first report by Liebetanz and Merkler [133], central motor deficits were observed in mice fed the CPZ-containing diet by using a novel murine motor test, the motor skill sequence. This test was designed to detect latent deficits in motor performance. In a first step, mice were habituated to training wheels composed of regularly spaced crossbars till maximal wheel-running performance was achieved. Then, the animals were exposed to wheels with irregularly spaced crossbars demanding high-level motor coordination. Demyelinated mice showed reduced running performance on the training wheels as compared to controls. This deficit was even more pronounced when these mice were subsequently exposed to the complex wheels. Interestingly, remyelinated animals after CPZ withdrawal showed normal performance on the training wheels but abnormal performance on the complex wheels.

The poor motor coordination of the CPZ-fed mice was also detected in the rota-rod analysis [134]. In addition, in the 3rd and 4th weeks after 0.2% CPZ treatment, the mice exhibited an increase in CNS activity, that is, an increase in climbing during the functional observation battery (FOB) tests, and an inhibited anxiogenic response to the novelty challenge (open-field) test. The FOB protocol consisted of 18 endpoints which evaluate CNS activity and excitability, neuromuscular and autonomic effects, and sensorimotor

reactivity [135]. The results related white matter abnormality to emotional behavior and reminded us of the previous finding that transection of the rat's corpus callosum induces an increased number of rearing and activity in the centre of the open field [136, 137].

6.3. A Novel Animal Model of Schizophrenia. In 2008, we, for the first time, examined effects of quetiapine, an atypical antipsychotic drug, on OLs [138]. We started from the *in vitro* effects of quetiapine on OL development. Quetiapine was shown to increase the proliferation of neural progenitor cells (NPCs) in the presence of growth factors, direct the differentiation of NPCs into OL lineage through extracellular signal-related kinases, upregulate the expression of MBP, and stimulate the myelination of axons by OLs in rat embryonic neocortical aggregate cultures. In the last experiment of this study, chronic administration of quetiapine prevented the CPZ-induced myelin breakdown and spatial working memory impairment in C57BL/6 mice. This protective effect of quetiapine on the CPZ-induced white matter abnormality was further substantiated in a following animal study. This drug dramatically decreased the numbers of activated microglia and astrocytes teemed in demyelinated sites, in addition to ameliorating myelin breakdown and MBP decrease in the brain [139].

Inspired by the above studies, we further characterized the behavioral and neurobiological changes in the CPZ-fed mice [140]. Mice exposed to CPZ for 2 and 3 weeks displayed more climbing behavior and PPI deficits. In addition, they showed lower activities of monoamine oxidase (MAO) and DA beta hydroxylase (DBH) in the hippocampus and PFC and had higher DA but lower NE levels in PFC. Mice exposed to CPZ for 4 to 6 weeks, when demyelination, myelin breakdown, and OL loss were evident, showed less social interaction compared to controls. At all time points, the CPZ-exposed mice spent more time in the open arms of an elevated plus-maze and exhibited spatial working memory impairment. The social interaction decrease and spatial working memory impairment were also reported in an independent study from other investigators [141]. These abnormal behaviors are reminiscent of some schizophrenia symptoms seen in human patients, thus suggested that the CPZ-fed mouse may be used as a novel animal model of schizophrenia to explore roles of white matter abnormalities in the pathophysiology and treatment of this mental disorder.

More significantly, the CPZ-induced behavioral changes showed different responses to typical and atypical antipsychotics [142]. All tested antipsychotics (haloperidol, clozapine, and quetiapine), when coadministered with CPZ to mice, effectively blocked the PPI deficits (Figure 1); clozapine and quetiapine, but not haloperidol, prevented CPZ-fed mice from spatial working memory impairment (Figure 2); clozapine and quetiapine, but not haloperidol, ameliorated social interaction decrease (Figure 3). These different effects of typical and atypical antipsychotics on abnormal behaviors seem to be related to their effects on the CPZ-induced white matter abnormalities as clozapine and quetiapine, but not haloperidol, ameliorated the myelin breakdown and MBP decrease in PFC, hippocampus, and caudate putamen (Figure 4). These results provide experimental evidence for the protective effects of antipsychotics on white matter abnormalities and the concurrent behavioral changes in CPZ-fed mice.

In a more recent study, we observed the time courses of behavioral abnormalities and remyelination in mice after CPZ withdrawal and examined effect of antipsychotics on the recovery processes [143]. The CPZ-induced abnormal performance on the elevated plus-maze recovered to the normal range within two weeks after CPZ withdrawal. In contrast, alterations in social interaction showed no recovery within the three-week postwithdrawal recovery period. And the social interaction deficit did not respond to any one of the antipsychotics (clozapine, haloperidol, olanzapine, and quetiapine) tested in this study. Altered performance in the Y-maze showed some recovery in the vehicle group; clozapine, olanzapine, and quetiapine, but not haloperidol, significantly promoted this recovery process. None of the drugs affected the recovery of damaged white matter within the three-week recovery period. These ineffective results may be due to inappropriate doses of tested drugs in this study and/or reflect the intractable feature of these abnormalities. In the latter case, a reasonable suggestion would be that the damage to OL/myelin in early phase could leave permanent damage on neural connectivity and/or its functions. To test this hypothesis, future studies should investigate the remyelination and functional recovery processes in longer recovery periods by means of various experimental approaches including electron microscopy and electrophysiological techniques.

While most of animal studies applied CPZ to C57BL/6 mice, efforts were also made to develop a rat model of demyelination in the CNS. After exposed to CPZ for two and four weeks, rats showed a decrease in mRNA transcripts and protein levels of OL-specific genes in PFC [144]. Levels of myelin-related genes did not change in the striatum and hippocampus, two brain areas that should have been completely myelinated before the age of CPZ exposure. In addition, glial fibrillary acidic protein upregulated in PFC, indicating an activation of astrocytes. More interestingly, rats treated for two weeks with CPZ showed an increased difficulty to shift attention from one perceptual dimension to another in the extra dimensional shift phase of the attention set-shifting task, a modified version of the Wisconsin Card Sorting Test which depend on PFC [145]. Importantly, CPZ-treated rats did not exhibit locomotor problems and had normal weight gain. Thus, the CPZ rat model can be used to study developmental vulnerability of white matter, as well as the pathogenesis and behavioral consequences of dysmyelination [146].

6.4. Comparing CPZ Model with Genetic Models of Schizophrenia. To summarize the aforementioned animal models of schizophrenia, Table 1 listed the main observations done so far on these animal models. Of the transgenic animal models, the NRG1-erbB4 transgenic mouse seems to have more similarities to observations in patients with schizophrenia, while relatively few studies have been done in the other

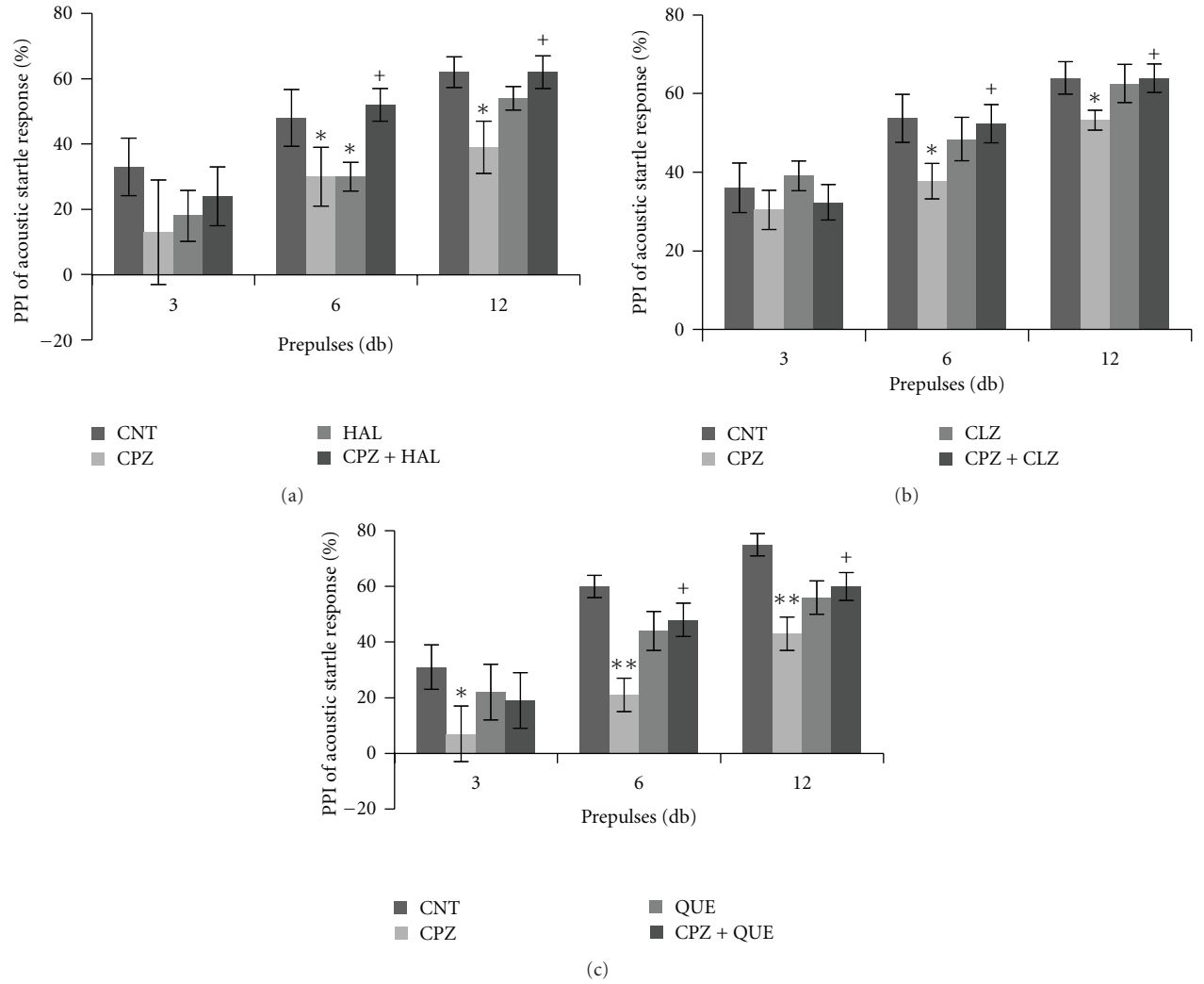

Figure 1: Effects of antipsychotics on the CPZ-induced deficits in PPI test. Control and experimentally treated C57BL/6 mice were subjected to PPI test on the same day (14th day after CPZ exposure). (a) The data of the HAL experiment. (b) The data of the CLZ experiment. (c) The data of the QUE experiment. Data were expressed as M ± SEM (n = 6 to 12/group). CNT: control group; CPZ: cuprizone group; CLZ: clozapine group; HAL: haloperidol group; QUE: quetiapine group; CPZ+CLZ: mice received both cuprizone and clozapine; CPZ+HAL: mice received both cuprizone and haloperidol; CPZ+QUE: mice received both cuprizone and quetiapine. PPI: prepulse inhibition; db: decibel. $^{*}P < 0.05$, $^{**}P < 0.01$, compared to the CNT group; $^{+}P < 0.05$, compared to the CPZ group.

two genetic animal models. However, studies have shown that both hypermorphic [147, 148] and hypomorphic [149–151] expression of the NRG1 gene may produce several common behavioral phenotypes in animals, which warrants further studies to address the underlying mechanisms on these behavioral abnormalities. The CPZ-fed mouse provided an alternative animal model showing white matter abnormalities in the brain- and schizophrenia-related behaviors. More interestingly, these CPZ-induced changes differently responded to haloperidol and atypical antipsychotic drugs.

7. Concluding Remarks

There is a great body of literature reporting white matter abnormalities in patients with schizophrenia, including imaging and postmortem evidence, suggesting a putative role of altered white matter in schizophrenia. Given its role as the primary infrastructure for long-distance communication in the brain, the evidence of altered white matter is agreeable to the disconnectivity theory of schizophrenia that emphasizes the role of abnormal interactions between brain regions [152]. Now, OLs and myelin dysfunction have been linked to neurocircuitry abnormalities in schizophrenia [153].

The white matter implication hypothesis can account for why the symptoms of schizophrenia commonly first present in late adolescence and early adulthood as the white matter development is still going on during these periods [13]. It is also consistent with the neurodevelopmental theory of schizophrenia [154]. According to this theory, the interaction of genetic vulnerability and early environmental exposures can induce a developmental trajectory which culminates

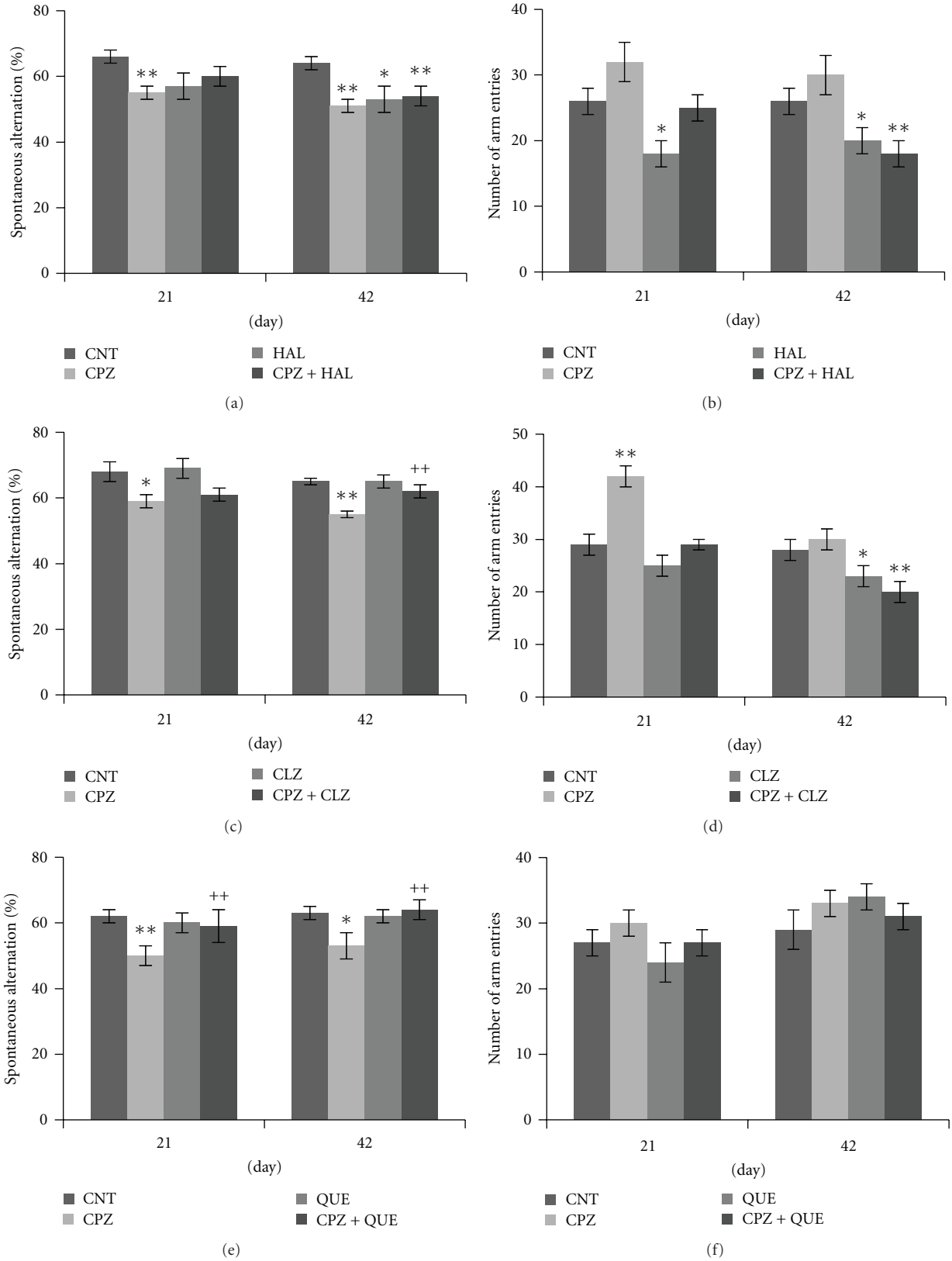

Figure 2: Effects of antipsychotics on the CPZ-induced abnormal performance in the Y-maze test. Control and experimentally treated C57BL/6 mice were subjected to Y-maze test on the same days (21st and 42nd days after CPZ exposure). (a) The data of the spontaneous alternation in the HAL experiment. (b) The data of the number of arm entries in the HAL experiment. (c) The data of the spontaneous alternation in the CLZ experiment. (d) The data of the number of arm entries in the CLZ experiment. (e) The data of the spontaneous alternation in the QUE experiment. (f) The data of the number of arm entries in the QUE experiment. Data were expressed as M ± SEM (n = 6 to 12/group). $^{*}P < 0.05$, $^{**}P < 0.01$, compared to the CNT group; $^{++}P < 0.01$, compared to the CPZ group.

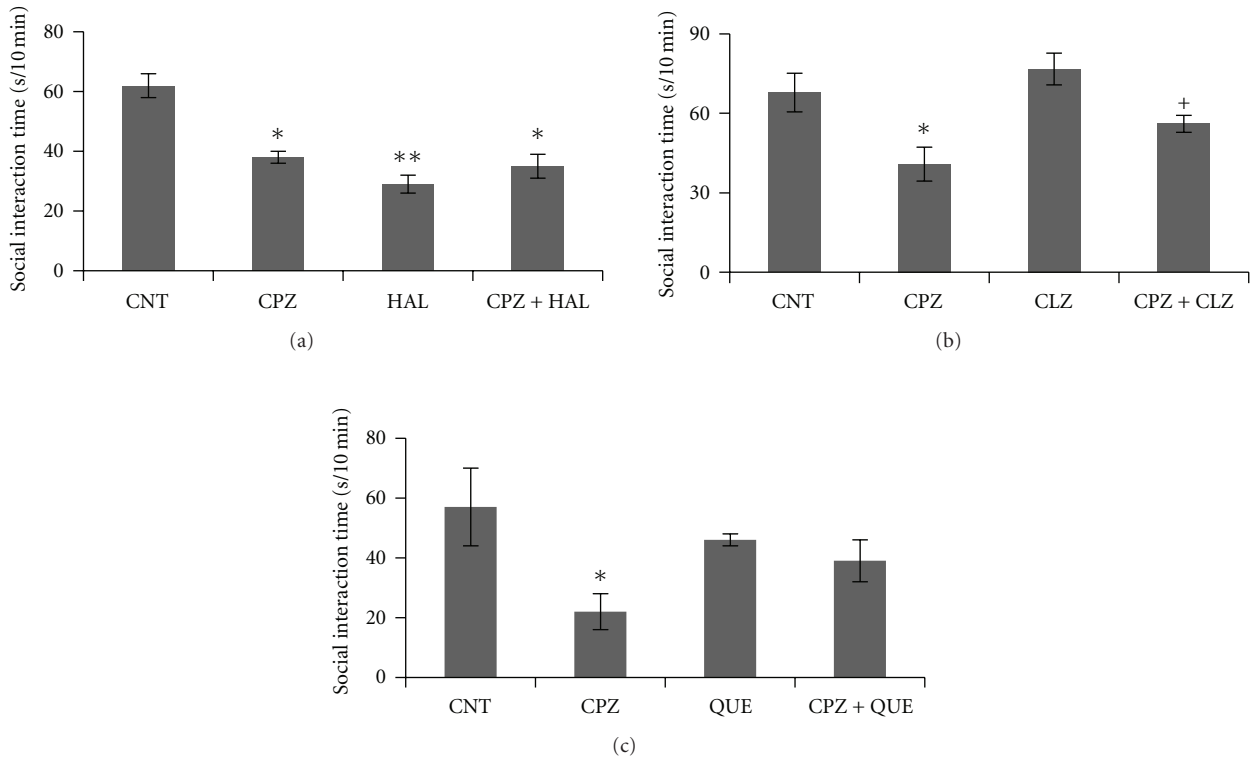

Figure 3: Effects of antipsychotics on the CPZ-induced deficits in the social interaction. Control and experimentally treated C57BL/6 mice were subjected to social interaction test on the same day (28th day after CPZ exposure). (a) The data of the HAL experiment. (b) The data of the CLZ experiment. (c) The data of the QUE experiment. Data were expressed as M ± SEM ($n = 6$ pairs/group). $^{*}P < 0.05$, $^{**}P < 0.01$, compared to the CNT group; $^{+}P < 0.05$, compared to the CPZ group.

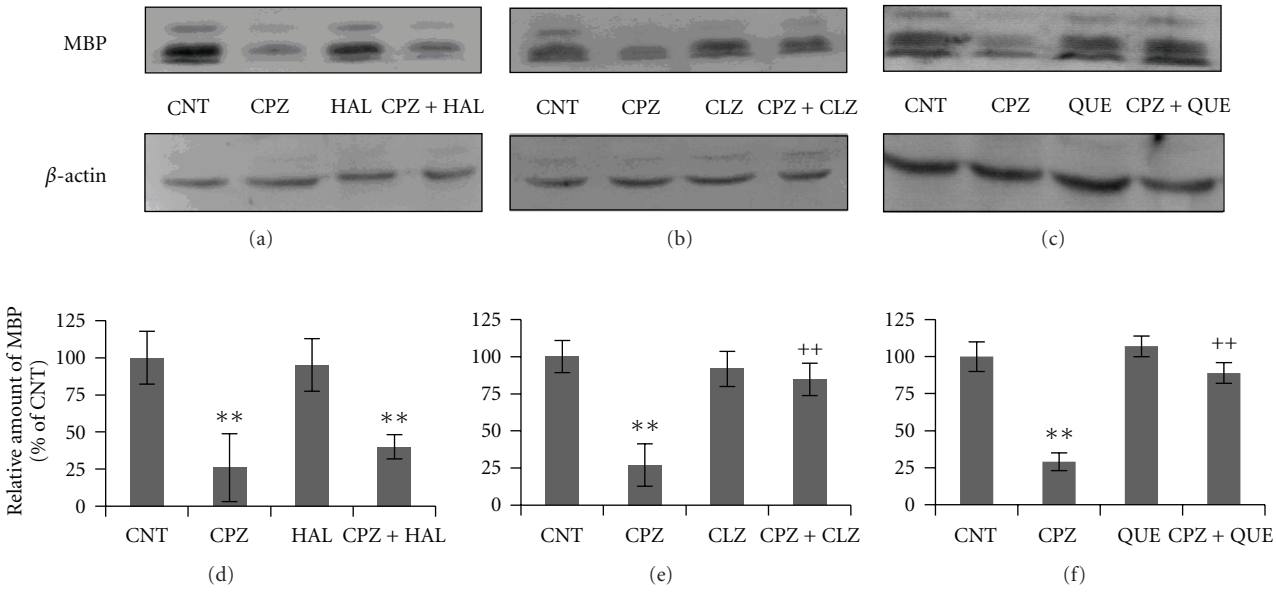

Figure 4: Effects of antipsychotics on the CPZ-induced decrease in MBP in CP. Control and experimentally treated C57BL/6 mice were sacrificed on 43rd day after CPZ exposure. The CP was dissected out of the brain and processed for Western-blot analysis to measure MBP levels. The upper photographs (a), (b), and (c) are representative of Western blots from the HAL, CLZ, and QUE experiments, respectively. The bar charts (d), (e), and (f) in the bottom panel are the statistical results of the amount of MBP relative to β-actin in the same corresponding lanes as labeled. Data were expressed as M ± SEM ($n = 6$/group). $^{**}P < 0.01$, compared to the CNT group; $^{++}P < 0.01$, compared to the CPZ group.

Table 1: Comparison of animal models examining a putative role of altered white matter in schizophrenia.

	$plp1^{tg/-}$ mice	NRG1-erbB4 transgenic mice	Nogo-A deficient mice	CPZ-fed mice
Altered myelin structure	—	√	No data	√
OL loss	No data	√	No data	√
Decreased axonal conductance	√	√	No data	No data
Dopamine level	No data	No data	↓	↑
D_2 receptors	No data	↑	↓	No data
NMDA receptors	No data	↓	No data	No data
Hyperactivity	No data	√	No data	√
Anxiety-like behaviors	√	√	√	√
Disrupted PPI	√	√	√	√
Spatial learning deficit	√	√	No data	√
Working memory deficit	√	√	No data	√
Impaired social activities	No data	√	—	√
Response to antipsychotics	No data	√	No data	√

later in the clinical syndrome [154, 155]. Indeed, molecular genetics analyses revealed altered OL- and myelin-related genes in schizophrenia.

Another line of evidence supporting the white matter implication hypothesis in schizophrenia came from patients with white matter diseases. As illustrated by ACC, MLD, NPC, and MS, white matter lesions are commonly accompanied with certain schizophrenia symptoms. These human studies warrant future experimental studies to examine a putative role of altered white matter in schizophrenia.

The use of transgenic and mutant animal models offers a unique opportunity to analyze OLs and relevant changes in schizophrenia [156]. Examples included in this paper are the *plp1* transgenic mice, mutant mice heterozygous for either *NRG1* or its receptor erbB4, and the Nogo-A deficient mice. These transgenic and mutant mice show both white matter development disruption and schizophrenia-related behaviors thus may be used as potential animal models of schizophrenia. More informative data are expected to come from further studies with these animal models.

Although CPZ is a neurotoxic compound, the white matter alterations seen in CPZ-fed mice are not conflict with the neurodevelopment theory of schizophrenia. Indeed, genetic and developmental factors, such as animal species, age, and developmental status of a white matter structure, have significant impacts on the white matter alterations in CPZ-fed animals [141, 143, 157]. Moreover, the abnormal behaviors seen in CPZ-fed mice and rats [140, 141, 143] are reminiscent of schizophrenia symptoms including positive and negative symptoms as well as cognitive impairment. In addition, CPZ-fed mice show higher DA levels in PFC and lower NE levels in the same brain region. These changes in DA and NE may account for the abnormal climbing behavior and PPI deficits occurred before the appearance of demyelination and myelin breakdown [140]. High levels of DA in PFC may also contribute to demyelination and myelin breakdown in this brain region. This notion is in accordance with the finding that chronic administration of amphetamine (1.0 mg/kg) to mice caused microstructural changes in the white matter of frontal cortex and induced higher locomotion and spatial working memory impairment [158]. The abnormal white matter, in turn, may affect DA neurotransmission in the brain and thus cause behavioral changes. In line with this view, a new hypothesis of schizophrenia has been proposed, which theorized that the abnormal myelination of late-developing frontal white matter is a single underlying cause of the three distinctive features of this disorder, namely, its excessive DA neurotransmission, its frequent periadolescent onset, and its bizarre, pathognomonic symptoms [159]. Extensive studies are necessary to further address the relationship of excessive DA neurotransmission and abnormal myelination in schizophrenia.

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Research Article

Abnormal Behaviors and Microstructural Changes in White Matter of Juvenile Mice Repeatedly Exposed to Amphetamine

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Amphetamine (AMP) is an addictive CNS stimulant and has been commonly abused by adolescents and young adults, during which period brain white matter is still developing. This study was to examine the effect of a nonneurotoxic AMP on the white matter of juvenile mice. *d*-AMP (1.0 mg/kg) was given to young male C57BL/6 mice once a day for 21 days. The spatial working memory and locomotion of mice were measured at the end. Then, mice were sacrificed and their brains were processed for morphological analyses to examine the white matter structure and for Western blot analysis to measure three main proteins expressed in mature oligodendrocytes. AMP-treated mice displayed higher locomotion and spatial working memory impairment and showed lower levels of Nogo-A and GST-pi proteins in frontal cortex and lower MBP protein in the frontal cortex and hippocampus. They also had fewer mature oligodendrocytes and weak MBP immunofluorescent staining in the same two brain regions. But the striatum was spared. These results suggest that the late-developing white matter is vulnerable to AMP treatment which is able to increase striatal and cortical dopamine. Both the compromised white matter and increased dopamine may contribute to the observed behavioral changes in AMP-treated mice.

1. Introduction

Amphetamine (AMP) is a drug approved by FDA for the treatment of attention-deficit/hyperactivity disorder (ADHD) and narcolepsy. This drug, similar to the others in the same group (amphetamines) consisting of AMP, methamphetamine, and methylenedioxymethamphetamine (MDMA), produces its principal effects by increasing synaptic levels of the biogenic amines, dopamine, norepinephrine, and serotonin through multiple mechanisms [1, 2]. While the therapeutic efficacy of AMP on ADHD has been appreciated, this drug is also an addictive CNS stimulant and has been used illegally. In fact, amphetamines are the prescription drugs most commonly abused by adolescents and young adults. Abuse of amphetamines constitutes a serious public health concern with worldwide abuse of them surpassing that of cocaine and opiates combined [3, 4].

It is well established that exposure of experimental animals to acute, high doses of amphetamines produces damage, generally referred to as "neurotoxicity," to dopaminergic neurons innervating the dorsal striatum (caudate putamen) [4, 5]. Also, chronic intermittent administration of AMP to rodents produces a progressive and enduring increase in hyperactivity and stereotyped behavior [6–8]. This phenomenon, called behavioral sensitization, has been widely recognized as an animal model of lasting susceptibility to exacerbation of psychostimulant-induced psychosis [9]. Although these previous data are informative, the relevance of them to the consequences of low-dose, prescription use of amphetamines in humans is not clear.

Over the past years, some human studies examined the white matter of amphetamines abusers. For example, Thompson et al. [10] found significant hypertrophy of the white matter in the methamphetamine abusers. After partitioning the white matter into lobes, the authors found that methamphetamine abusers had hypertrophy of the temporal white matter and occipital white matter. This white matter abnormality was thought to result from altered myelination

and adaptive glial changes, including gliosis secondary to neuronal damage. Another white matter abnormality is white matter signal hyperintensities (WMH), which can be defined as patchy or diffuse white matter changes on T2-weighted magnetic resonance images (MRI) [11]. Methamphetamine abusers showed greater severity of WMH than the healthy subjects and severity of deep WMH correlated with total cumulative dose of methamphetamine [12]. More recent studies employed a new MRI technique, diffusion tensor imaging (DTI), to probe white matter microstructure with two useful indices: fractional anisotropy (FA) and mean diffusivity (MD). FA describes the directional variance of diffusional motion, and MD is an indicator of the overall magnitude of diffusional motion. Compared to healthy subjects, methamphetamine abusers showed significantly lower FA values in prefrontal white matter [13], genu of corpus callosum [14, 15], and mid-caudal superior corona radiata [16]. However, no information is available about effects of nonneurotoxic doses of amphetamines on white matter of animal brains.

On the basis of the aforementioned human studies, we hypothesized that chronic repeated administration of a nonneurotoxic dose of AMP could cause microstructural changes in white matter of mouse brain. To test this hypothesis, this study took advantage of juvenile C57BL/6 mice during the process of myelination, which continues to progress through adolescence in rodents [17]. The protracted time course for this process has been demonstrated to be vulnerable to perturbation in both rodents and humans [18–22]. We administered *d*-AMP once daily to C57BL/6 mice for three weeks. The spatial working memory of mice was measured two days after the last injection and the locomotion five days. After finishing behavioral tests, mice were sacrificed and their brains were processed for morphological analyses to examine the micro-structure of white matter, which is one of the two components of the central nervous system (CNS) and consists mostly of myelinated axons. The myelin sheath of myelinated axons is produced by oligodendrocytes located in both grey and white matter. The myelinated axons can be examined in brain sections immunohistochemically stained using the specific antibody to the myelin basic protein (MBP) believed to be a marker of myelin sheath. The oligodendrocytes can be labeled by specific antibodies to the pi form of glutathione-stransferase (GST-pi) or Nogo-A, two proteins expressed in mature oligodendrocytes In addition, Western blot analysis was performed to measure the amounts of all above-mentioned proteins of tissue samples from the brain regions of the frontal cortex, hippocampus, and striatum.

2. Materials and Methods

2.1. Animals and Treatments. All animal procedures in this study were in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care and Use Committee of Southern Illinois University at Carbondale.

Twenty-four male juvenile (postnatal day 28, P28) C57BL/6 mice (Charles River Laboratories, Wilmington, Mass, USA) were used in this study. They were kept in Plexiglas cages with free access to food and water, in a room with controlled temperature (22 ± 1°C) and on a 12 h light/dark cycle (lights on at 07:00 h). After one week acclimatization, the mice were randomly assigned to two groups of twelve each. Mice in the control group (CNT) received intraperitoneal (i.p.) injection of 0.9% saline (10 mL/kg) once a day for 3 weeks. During the same period (P36–56), mice in the experiment group (AMP) received i.p. injection of *d*-AMP sulphate (1.0 mg/kg, dissolved in saline) once a day (Sigma-Aldrich, St. Louis, MO, USA). This dosage is much lower than the neurotoxic doses (≥15 mg/kg, continuous systemic administration) in nonhuman studies [23] and may be comparable to the standard AMP treatment for core ADHD symptoms (0.1 to 0.5 mg/kg, oral administration), given the much higher basal metabolic rate in rodents than in humans [24]. The period P36–56 corresponds to puberty or adolescence in humans when myelination continues slowly at least in the prefrontal cortex [25, 26]. The AMP solution was prepared freshly and given to mice based on their body weight which was measured every day.

2.2. Y-Maze Test. The Y-maze test, a simple recognition test of measuring spatial working memory of rodents [27–29], was performed 24 hours after the last AMP/saline administration. Each mouse was placed at the end of one arm of a symmetrical Y-maze (15 cm of two shorter arms and 20 cm of the longer arm) and allowed to move freely through the maze for an 8-min test period. Alternation was defined as successive entries into the three arms on overlapping triplet sets. The maximum number of possible spontaneous alternations was determined as the total number of arms entered-2, and the percentage was calculated as the ratio of actual to possible alternations × 100.

2.3. Open-Field Test. The open-field was performed five days after the last AMP/saline administration. The open-field apparatus used in this study was a square wooden box (56 cm × 56 cm × 31 cm) with an open top and floor divided into 9 equal smaller squares (units). Fifteen minutes after a challenge injection of AMP (0.5 mg/kg; given to mice in both the control and AMP groups), a mouse was placed in the center of the open-field arena and allowed to move freely around the open field for 15 min. The moving path of the mouse was recorded by a video camera, which was placed above the arena and connected to the computer installed with the video tracking program SMART (San Diego Instruments, Calif, USA). Specifically, the following parameters were analyzed and compared between the groups in the present study.

Total ambulation frequency = number of any floor unit entered;

Peripheral squares ambulation frequency = number of entrances into the floor units close to the walls of the apparatus;

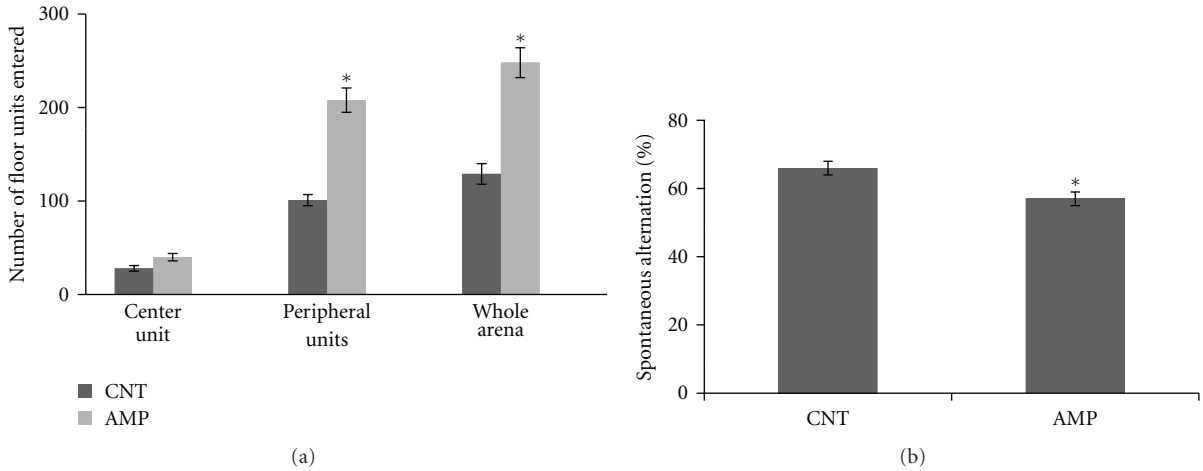

Figure 1: AMP-induced behavioral changes. Mice were administered intraperitoneally with 1.0 mg/kg d-AMP once a day for 21 days or a same volume of saline during the same period. The spatial working memory of mice was measured two days after the last injection and the locomotion five days. Data were expressed as means ± SEM. Comparisons were made between CNT and AMP groups. $^*P < 0.05$. For open-field test, all 12 mice in the AMP group entered the peripheral units more often than the average of CNT group. For Y-maze test, of 12 subjects in the AMP group, two mice showed spontaneous alternations (68 and 71%) above the average of CNT group (66%).

Central square ambulation frequency = number of entrances into the central unit of the apparatus.

2.4. Western Blot Analysis. Mice ($n = 6$ per group) were sacrificed under deep anesthesia. Their brains were rapidly removed; then the frontal cortex, hippocampus, and striatum were dissected out and stored at −80°C until use. Western Blot analysis was performed to assess the amount of MBP, GST-pi, and Nogo-A proteins in each brain region. Briefly, equal amounts of protein (10–30 μg) was separated by 12.5% (for MBP and GST-pi) or 8% (for Nogo-A) SDS-polyacrylamide gel electrophoresis and then transferred to polyvinylidene difluoride membranes in a Tris-glycine buffer with 20% methanol using a power of 20 V overnight. Membranes were then blocked in 5% skim milk in TBST (10 mM Tris, pH 7.5, 150 mM NaCl plus 0.05% Tween-20) and incubated overnight at 4°C with their primary antibodies diluted in TBST. The antibodies used were rabbit anti-NogoA (1 : 1000, Sigma-Aldrich, MO, USA), rabbit anti-MBP (1 : 4000, Chemicon, Calif, USA), rabbit anti-GST-pi (1 : 1000, Stressgen, Canada), and rabbit anti-β-actin (1 : 2000; Sigma-Aldrich, MO, USA). They were then washed three times in TBST and subsequently incubated in TBST buffer containing secondary antibody (Alexa Fluor 680, invitrogen, Calif, USA). Image was scanned with ODYSSEY (Li-COR, Biosciences) and analyzed with Image J software (NIH, Bethesda, MD, USA). Values of proteins of interest were normalized to β-actin, and the ratios were then used to perform statistical analysis.

2.5. Immunofluorescence. Animals ($n = 6$ per group) were deeply anesthetized with chloral hydrate (400 mg/kg i.p.) and perfused through the ascending aorta with 0.1 M phosphate buffered saline (PBS; pH 7.4), followed by 4% paraformaldehyde in PBS. Their brains were then removed and immersed in the same fixative overnight, followed by cryoprotection in 25% sucrose at 4°C for 24–48 h. Serial coronal sections (20 μm) of the brains were cut using a sliding microtome (Lipshaw, Detroit, Mich, USA) and collected in six well plates containing 0.01-M PBS. Free-floating sections were incubated in 1% H_2O_2/10% Triton X-100 in PBS for 10 min, and then washed with PBS. Sections were incubated overnight with anti-MBP (MAB 386; 1 : 200, Chemicon, Temecula, Cailf, USA) or anti-GST-pi (1 : 200, Stressgen, Canada). FITC-conjugated donkey anti-rabbit IgG (1 : 100; Chemicon, Temecula, Cailf, USA) visualized the GST-pi epitope and Rhodamine-conjugated donkey antimouse IgG visualized the MBP epitope. Controls obtained by omitting the primary antibody were run for each immunofluorescent staining. Images of stained mouse brain sections were acquired with a DMI 4000 B microscope (Leica, German) equipped with a digital capture system. Image-Pro Plus software (Version 6.0, Media Cybernetics, Inc., Bethesda, MD, USA) was used to count the number of GST-pi positive cells in the cerebral cortex (including frontal cortex and parietal cortex) and corpus callosum and to quantify pixel intensity values of MBP staining in the cerebral cortex, corpus callosum, and hippocampus. The values of the AMP group were normalized as the percentages of those in CNT group.

2.6. Immunohistochemistry. Free floating sections were pretreated with 0.5% hydrogen peroxide in methanol for 20 min, then washed with PBS, and incubated for 1 h at 22°C with a blocking solution composed of 0.2% Triton X-100 and 5% normal rabbit or goat serum in PBS. Sections were then incubated with rabbit anti-Nogo-A (1 : 100; Sigma-Aldrich, MO) in the blocking solution for 48 h at 4°C. After rinsed in PBS, sections were incubated in biotinylated secondary antiserum (1 : 200) of the Vectastain (Elite) ABC kits (Burlingame, Calif, USA) for 2 h at 22°C. Following

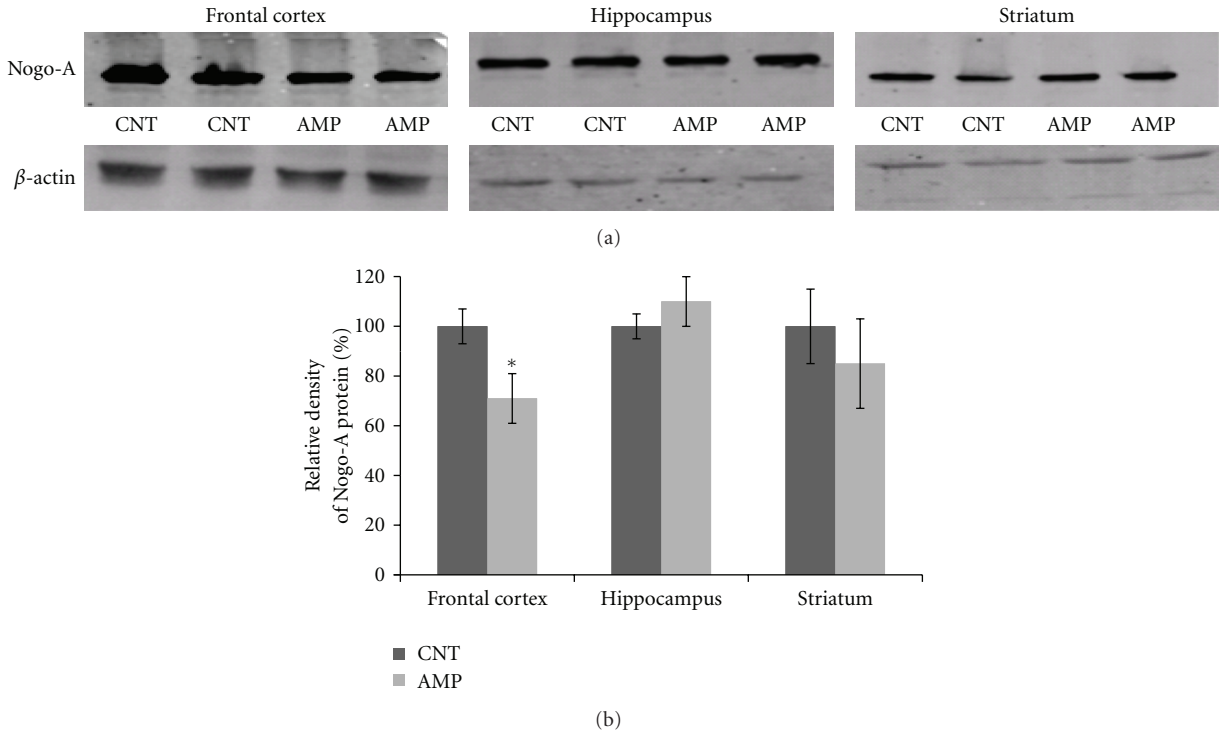

Figure 2: AMP reduced the amount of Nogo-A protein in the frontal cortex. After treating with d-AMP or a same volume of saline for 21 days and subjected to behavioral tests, mice were sacrificed, their brains were dissected, and tissue samples from specific brain regions were processed for Western blot analysis. The amount of Nogo-A protein in the frontal cortex, hippocampus, and striatum was measured. (a) shows representative Western blot images and (b) is a bar chart illustrating the statistical analysis of the Western blot results. Data were expressed as means ± SEM. Comparisons were made between CNT and AMP groups. $^*P < 0.05$. Of 6 PFC samples in AMP group, one showed a ratio (1.5) of Nogo-A protein/β-actin higher than the average of CNT group (1.4).

PBS rinses, the sections were incubated in an avidin-biotin-horseradish peroxidase complex (ABC) for 1 h at 22°C. Then the antigen antibody complexes were visualized using 0.025% 3,3′-diaminobenzidine (DAB, Sigma-Aldrich, St. Louis, MO, USA) as the chromogen. The immunohistochemically stained sections were examined under the DMI 4000 B microscope. The numbers of Nogo-A positive cells in the cerebral cortex (including frontal cortex and parietal cortex) and corpus callosum were counted using the Image-Pro Plus software.

The values of the AMP group were normalized as the percentages of those in CNT group.

2.7. Data Analysis. The data from Y-maze test and Western blot analysis were analyzed by *Student t*-test. Each Western blot test had samples from a same brain region of mice in CNT and AMP groups therefore, brain region was not considered as a factor (data from different brain regions were not combined). The other data were analyzed by two-way analysis of variance (ANOVA), followed by *Post hoc* comparisons of the Newman-Keuls test. When a P value was less than 0.05, the difference was considered significant.

3. Results

3.1. Behavioral Changes in AMP-Treated Mice. For open-field test, Two-way ANOVA analysis was performed and the result indicated a significant effect of areas (central, peripheral, and whole arena) on the numbers of floor units entered ($F_{5,71} = 116$; $P < 0.0001$). *Post hoc* comparisons suggested that AMP-treated mice had more locomotion in the peripheral zone of the open-field arena than the controls; the total locomotion of AMP-treated mice was also higher. But the difference in their locomotion in the center zone did not reach a significant level ($P = 0.07$) (Figure 1(a)). For Y-maze test, *Student t*-test indicated that the AMP-treated mice had decreased spontaneous alternation compared to controls that had never exposed to AMP (Figure 1(b)). The numbers of arm entrance of the two groups were comparable (not shown).

3.2. Decreased Nogo-A, GST-pi, and MBP Proteins in AMP-Treated Mice. Compared to the CNT group, AMP-treated mice showed a lower amount of Nogo-A in the frontal cortex but not in the hippocampus and striatum (Figure 2). Similarly, the AMP-treated mice had a lower level of GST-pi in the frontal cortex than the CNT group. In the same Western blot analysis, the AMP-treated mice showed lower levels of MBP protein in their frontal cortex and hippocampus but not in the striatum (Figure 3).

3.3. Decreased Mature Oligodendrocytes and MBP Staining in AMP-Treated Mice. In brain sections, mature oligodendrocytes were labeled by the specific antibodies to Nogo-A

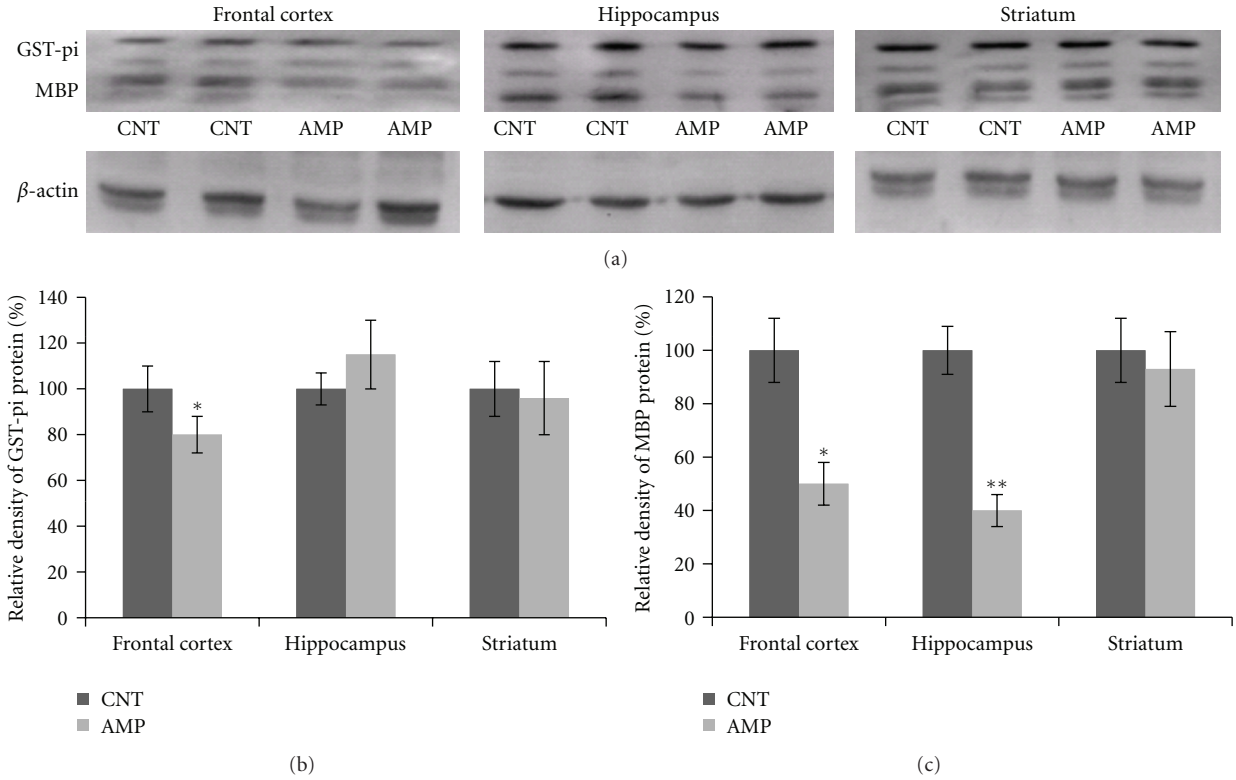

Figure 3: AMP reduced the amounts of GST-pi and MBP proteins in the frontal cortex and hippocampus. After treating with d-AMP or a same volume of saline for 21 days and subjected to behavioral tests, mice were sacrificed, their brains were dissected, and tissue samples from specific brain regions were processed for Western blot analysis. The amounts of GST-pi and MBP proteins in the frontal cortex, hippocampus, and striatum were measured. (a) shows representative Western blot images and (b) and (c) consists of two bar charts illustrating the statistical analysis of the Western blot results. Data were expressed as means ± SEM. Comparisons were made between CNT and AMP groups. $^{*}P < 0.05$; $^{**}P < 0.01$. In the measurement of GST-pi protein, all 6 frontal cortex samples in the AMP group showed lower levels than the average of CNT group. In the measurement of MBP protein, all frontal cortex and hippocampus samples in the AMP group showed lower levels than the average of CNT group.

or GST-pi and counted using the software Image-Pro Plus. The Nogo-A positive cells were in brown color as shown in Figure 4. Two-way ANOVA analysis was performed and the result indicated a significant treatment (AMP) effect on the number of Nogo-A positive cells in the brain regions ($F_{3,23} = 113$; $P < 0.0001$). Compared to the CNT group, the AMP-treated mice showed fewer Nogo-A positive cells in their cerebral cortex and corpus callosum (Figure 4). The GST-pi positive cells were labeled with green fluorescence and counted. Two-way ANOVA analysis was performed, and the result indicated a significant treatment (AMP) effect on the number of GST-pi positive cells in the brain regions ($F_{3,23} = 86$; $P < 0.0001$). The cerebral cortex and corpus callosum of the AMP-treated mice showed fewer numbers of GST-pi positive cells than the CNT group (Figure 5).

The MBP containing myelinated fibers were labeled with red color as shown in Figure 6 and the optical density of it was measured using the software Image-Pro Plus. Two-way ANOVA analysis was performed, and the result indicated a significant treatment (AMP) effect on the intensity of MBP immune-fluorescent staining ($F_{3,23} = 10.46$; $P < 0.01$). The AMP-treated mice showed much weaker MBP staining in the cerebral cortex, corpus callosum, and hippocampus, as compared to the CNT group (Figure 6).

4. Discussion

Chronic repeated administration of 1.0 mg/kg AMP to juvenile mice induced a behavioral sensitization and impaired the spatial working memory of subjects (Figure 1); in the meanwhile, this treatment caused microstructural changes in white matter of the subjects (Figures 4–6). This dosage is much lower than the neurotoxic doses in nonhuman studies [23] and lower than those used in most of rodent studies investigating the behavioral sensitization effect of this drug [30–35]. Therefore, this treatment regimen was not expected to be of "neurotoxicity". In fact, the averaged body weight changes of saline and AMP-treated mice during the experimental period overlapped perfectly (not shown). These results suggest that white matter is very vulnerable to AMP and that the microstructural changes in white matter of some brain regions contribute to the above-mentioned behavioral changes. These two suggestions have specific relevance to the uses of chronic low-dose AMP in adolescents

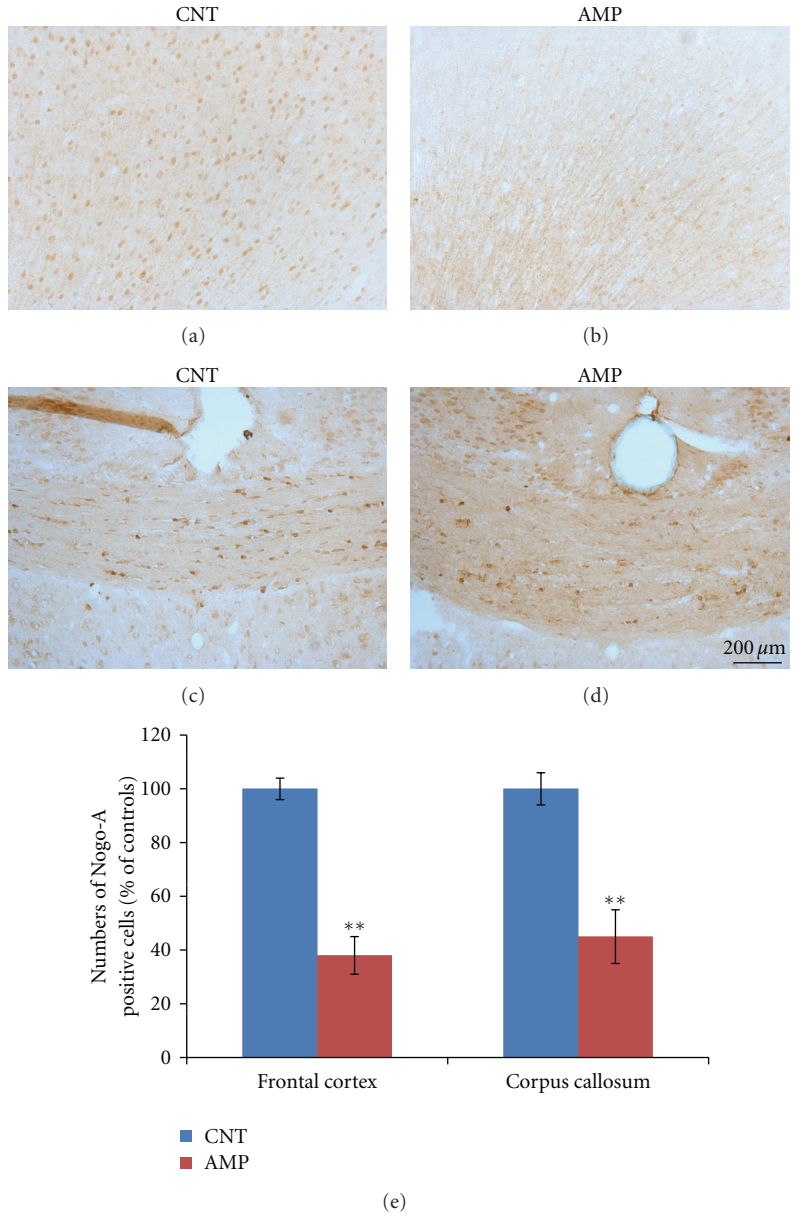

Figure 4: AMP reduced the numbers of Nogo-A positive cells in cerebral cortex and corpus callosum. After treating with d-AMP or a same volume of saline for 21 days and subjected to behavioral tests, mice were sacrificed and their brains were processed for immunohistochemical staining. The numbers of Nogo-A positive cells in cerebral cortex and corpus callosum were counted. All AMP-treated mice had decreased Nogo-A cells than the average of CNT group. Representative photographs were presented and labeled. Quantitative data were statistically analyzed and presented in a bar chart. Data were expressed as means ± SEM. Comparisons were made between CNT and AMP groups. $^{**}P < 0.01$.

and young adults considering the following conditions. First, in many cases AMP treatment of ADHD has been extended to adulthood from the initiation of it in adolescence as the disorder can persist into adulthood, with adverse occupational, academic, and interpersonal consequences [23, 36]; second, in newly diagnosed adults higher doses (0.9 mg/kg/day) are usually used for maximal benefit [37, 38]. Third, there is increasing illicit use of AMP among college students, who may not only take the drug orally but also dissolve and inject it [39]. Therefore, it should be aware of that chronic low-dose AMP may suppress the myelination process in brains of adolescents and young adults and thus causing behavioral problems.

Although high doses of AMP, comparable to amounts used by addicts, were shown to damage dopaminergic pathways [23], neurotoxicity was not usually seen in rats after administration of lower amounts, either by continuous exposure, when the doses were less than about 15 to 20 mg/kg/day, or when the exposure lasted for 3 days or less [40]. Therefore, the microstructural changes in the

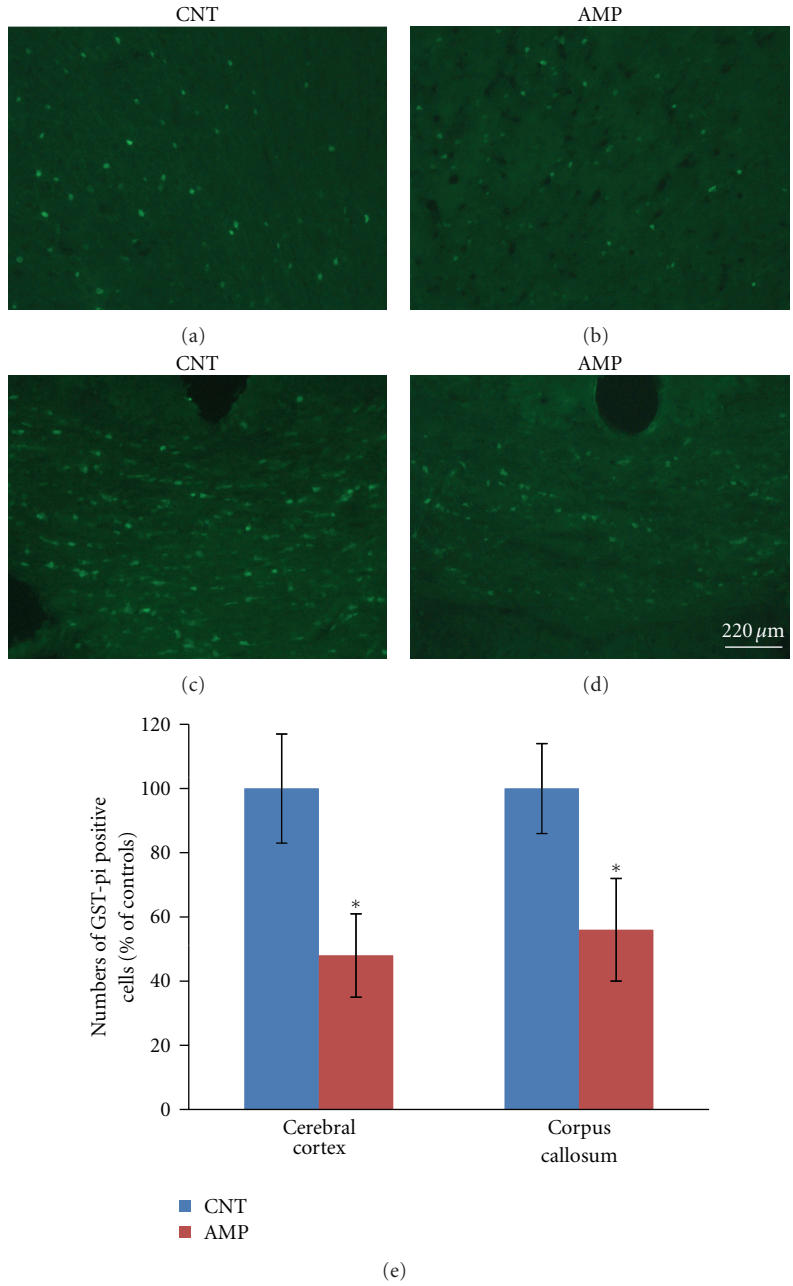

Figure 5: AMP reduced the numbers of GST-pi positive cells in cerebral cortex and corpus callosum. After treating with d-AMP or a same volume of saline for 21 days and subjected to behavioral tests, mice were sacrificed and their brains were processed for immune-fluorescent staining. The numbers of GST-pi positive cells in cerebral cortex and corpus callosum were counted. All AMP-treated mice had decreased GST-pi cells than the average of CNT group. Representative photographs were presented and labeled. Quantitative data were statistically analyzed and presented in a bar chart. Data were expressed as means ± SEM. Comparisons were made between CNT and AMP groups. $^*P < 0.05$.

white matter of mouse brain by a nontoxic AMP treatment regimen in the present study suggest that white matter is more susceptible to AMP than the grey matter. This finding is interesting but not surprising, since that white matter undergoes a much longer postnatal developmental period than the grey matter does. In humans, the white matter volume increases across the adolescent years, particularly in frontoparietal regions [25, 26, 41]. Also, the micro-structure of white matter undergoes developmental changes during adolescence. For example, studies of typically developing adolescents showed increases in FA (high FA reflects greater fiber organization and coherence, myelination, and/or other structural components of the axon) and decreases in MD (low MD values suggest greater white matter density). These trends continue through early adulthood [42–46].

Most of the studies employing repeated administration of AMP generally investigated the effects of this regimen on locomotor activity and stereotypes and attributed AMP-induced higher locomotor activity to increased striatal and cortical dopamine [6–8]. However, only a few previous

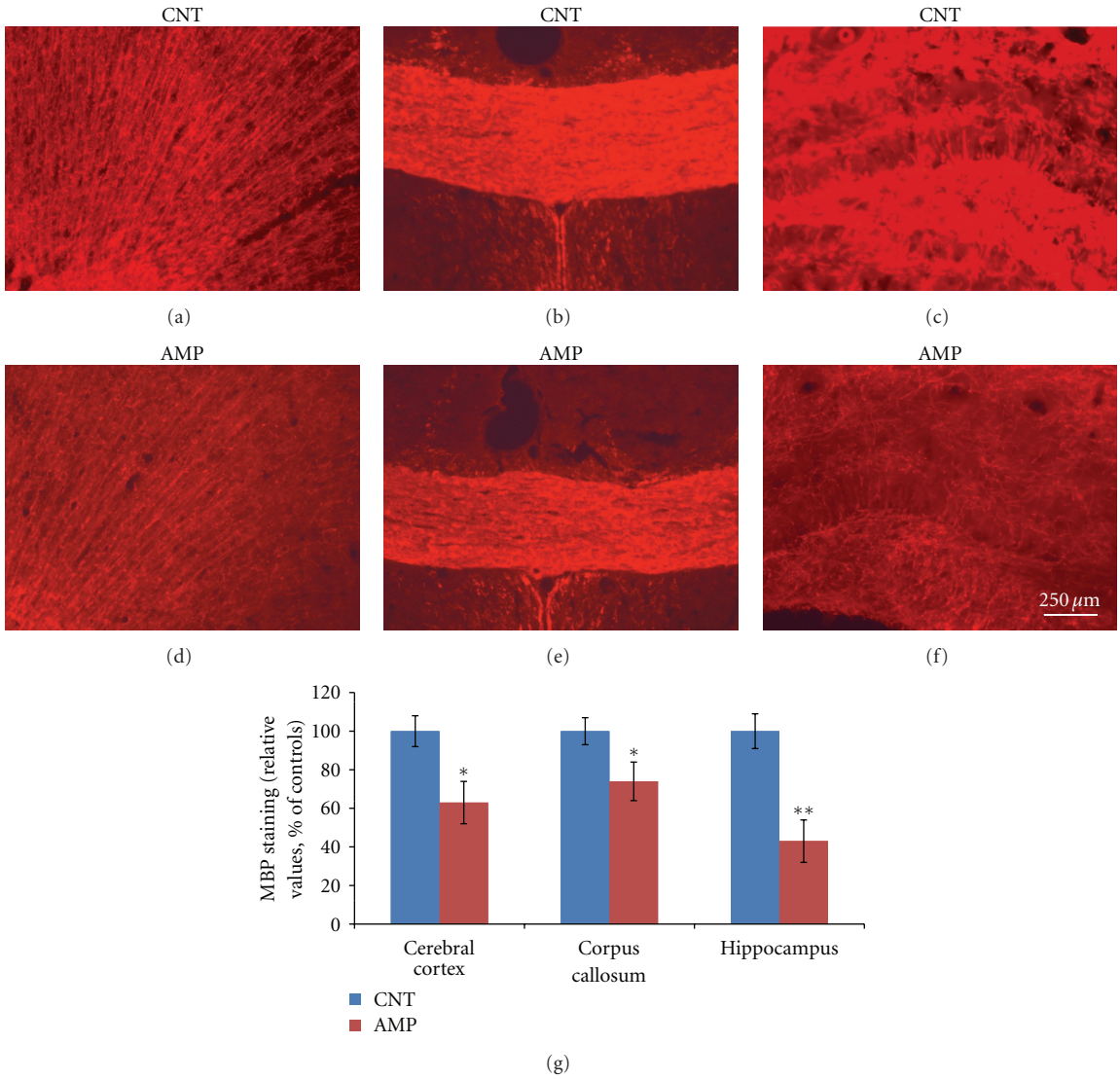

Figure 6: AMP reduced the MBP immune-fluorescent staining in cerebral cortex, corpus callosum and hippocampus. After treating with d-AMP or a same volume of saline for 21 days and subjected to behavioral tests, mice were sacrificed, and their brains were processed for MBP immune-fluorescent staining. Representative photographs were presented and labeled. Quantitative data were statistically analyzed and presented in a bar chart. All AMP-treated mice had decreased values of MBP staining than the average of CNT group. Data were expressed as means ± SEM. Comparisons were made between CNT and AMP groups. $^{*}P < 0.05$; $^{**}P < 0.01$.

studies [31, 47] assessed possible deficits in learning and memory of AMP-treated mice. In the study by Mandillo et al. [31], 5 days of repeated injections (i.p.) of AMP (2.5 and 5.0 mg/kg per day) impaired the ability of mice to a spatial change when tested on day 6. In the study by Stefani and Moghaddam [47], rats administered AMP (2.5 mg/kg, twice daily) for 5 consecutive days showed impaired alternation performance relative to their pretreatment baseline score. In the present study, mice administered 1.0 mg/kg AMP (once a day) for 21 days showed impaired spontaneous alternation in the Y-maze (Figure 1). These experimental results may have relevance to schizophrenia, in which dysfunctional dopamine systems are fundamental, the impairment of cognitive functions has been recognized as a core feature, and the cognitive impairment has been correlated with white matter abnormalities [48, 49].

Low doses (0.15 and 0.25 mg/kg) of AMP were reported to increase synaptic and extracellular dopamine in prefrontal cortex of rat [50], and therapeutic doses of AMP increase synaptic and extracellular dopamine in the striatum [51]. On the basis of these previous results, it is plausible to suggest that the AMP treatment regimen in the present study could increase striatal and cortical dopamine. The increased dopamine activity in frontal cortex might contribute to spatial working memory impairment. In line with this speculation, patients with schizophrenia have impairment of cognitive functions as discussed before. In animal studies [52, 53], high level dopamine in frontal cortex was accompanied by impaired spatial working memory in mice, and this impairment was prevented by antipsychotic drugs. In addition, high levels of dopamine were reported to be toxic via the formation of oxidative metabolites resulting from dopamine

degradation [54], which may kill oligodendrocytes and cause demyelination. In support of this speculation, high levels of dopamine in frontal cortex were seen to precede the demyelination in the same brain region of mice exposed to cuprizone [52], a copper chelator that was shown to induce demyelination [55]. Taken together, we suggest that the AMP-induced dopamine increases contribute to both impaired spatial working memory and the microstructural changes in white matter of mice.

It is noteworthy that no changes were found in the striatum white matter, whereas changes were significant in cerebral cortex, corpus callosum, and hippocampus. This regional difference may be explained as follows. First, it is known that the baseline of dopamine concentration in striatum is the highest among the brain regions. This feature may make the stratum most tolerant to dopamine increase. Therefore, we may speculate that the AMP-induced increases in striatal dopamine might be tolerable in this study, thus did not damage white matter in the brain region. Second, it is also known that the frontal cortex and hippocampus develop later than the striatum. These late-developing brain regions are expected to be more susceptible to the AMP-induced increases in dopamine compared to the early-developed striatum. In line with this explanation, the frontal cortex, corpus callosum, and hippocampus were demonstrated to be most susceptible to cuprizone-induced demyelination [56], where dopamine increases preceded demyelination [52].

In summary, repeated administration of 1.0 mg/kg AMP increased the locomotion, impaired the spatial working memory, decreased protein levels of Nogo-A and GST-pi in the frontal cortex, reduced numbers of mature oligodendrocytes in the frontal cortex and corpus callosum, and lowered MBP protein in the frontal cortex and hippocampus of mice. The striatum was spared from this treatment regimen. These results suggest that the late-developing white matter of frontal cortex and hippocampus is very vulnerable to AMP, treatment which is able to increase striatal and cortical dopamine. Both compromised white matter and increased dopamine in these brain regions may contribute to increased locomotor activity and impaired spatial working memory in the AMP-treated mice.

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