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Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia

Nagahide Takahashi, Takeshi Sakurai, Kenneth L. Davis, and Joseph D. Buxbaum

Conte Center for the Neuroscience of Mental Disorders and the Department of Psychiatry, Mount Sinai School of Medicine, New York, New York 10029, USA

Abstract

Multiple lines of evidence in schizophrenia, from brain imaging, studies in postmortem brains, and genetic association studies, have implicated oligodendrocyte and myelin dysfunction in this disease. Recent studies suggest that oligodendrocyte and myelin dysfunction leads to changes in synaptic formation and function, which could lead to cognitive dysfunction, a core symptom of schizophrenia. Furthermore, there is accumulating data linking oligodendrocyte and myelin dysfunction with dopamine and glutamate abnormalities, both of which are found in schizophrenia. These findings implicate oligodendrocyte and myelin dysfunction as a primary change in schizophrenia, not only as secondary consequences of the illness or treatment. Strategies targeting oligodendrocyte and myelin abnormalities could therefore provide therapeutic opportunities for patients suffering from schizophrenia.

Keywords

myelin; gene expression; genetic association; brain imaging; oligodendrocyte; synaptic plasticity; dopamine; glutamate

1. Introduction

Schizophrenia is a severe and chronic psychiatric disorder with a lifetime risk of ~1%, characterized by positive symptoms (i.e., delusions and hallucinations), negative symptoms (i.e., social withdrawal, anhedonia, and blunted affect) and cognitive dysfunction (i.e., deficits in attention, working memory, and executive function). Population, family and twin studies indicate that schizophrenia is highly heritable, and both genetic and environmental factors are involved in this disease (Harrison and Weinberger 2005). It is widely accepted that these genetic factors and environmental insults affect developmental processes of the brain that then play an important role in the pathology of this disorder (Rapoport et al 2005). Most studies have focused on alterations in neurons and gray matter; however, recent evidence suggests that neurodevelopmental problems also occur in white matter, especially in oligodendrocytes and in the myelin that these cell produce. The formation of myelin structures in humans occurs postnatally and is completed in young adulthood, at around the same time period where the incidence of schizophrenia is at its peak. It is becoming

Correspondence should be addressed: Joseph D. Buxbaum, Ph.D., Department of Psychiatry, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1668, New York, New York, 10029, USA, Tel: (212)-241-0026, Fax: (212) 828-4221, joseph.buxbaum@mssm.edu.

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increasingly clear that myelination is important in neuronal signaling, ultimately contributing to cognitive functions, such as attention, learning and memory (Fields 2008). Disruption of such cognitive function can be considered to be a core dysfunction in schizophrenia, and has been identified as an intermediate phenotype in schizophrenia (Gottesman and Gould 2003). In addition to the role of myelination in neuronal signaling, recent evidence supports a role for oligodendrocytes and myelin in alterations in dopaminergic and glutamatergic circuitry, which are two pathways that have been shown to be altered in the disease.

In this review, we first outline the evidence showing that there are abnormalities in oligodendrocytes and myelin in schizophrenia. We then describe the function of oligodendrocytes and myelin in the synapse and in neuronal circuits relevant to schizophrenia, and discuss how oligodendrocyte and myelin deficits could affect these functions. Finally, we introduce relevant animal models based on an oligodendrocyte/myelin hypothesis in schizophrenia.

2. Background: Oligodendrocyte/myelin dysfunction in schizophrenia

There is increasing evidence that oligodendrocytes and myelin abnormalities are involved in schizophrenia. The evidence comes from imaging, postmortem and genetic studies.

2.1 White matter changes in schizophrenia—imaging studies

Over the past several years, diffusion tensor imaging (DTI) has become an important technique for the in vivo examination of white matter in schizophrenia (Liddle 1996; McClure et al 1998). To date, many DTI studies in schizophrenia have been carried out, most of which demonstrated decreased fractional anisotropy (FA) --- evidence of impaired white matter integrity, in several brain regions, including prefrontal and temporal lobes, as well as some of the fiber bundles connecting these regions, such as uncinate fasciculus, (Andreasen et al 1997), cingulum bundle (Benes 2000; Carlsson et al 2001; Grace 2000), and arcuate fasciculus (Andreasen et al 1997), as well as parietal, prefrontal, and occipital lobes (Heimer 2000; Kanaan et al 2005; Kubicki et al 2007; Middleton and Strick 2000). Importantly, it has been reported that these changes are observed in individuals with prodromal symptoms who were at very high risk for schizophrenia as well as patients in early stage of their illness (Witthaus et al 2008). However, there is little evidence that disease progression correlates with changes in FA (Steen et al 2006). These data suggest that white matter abnormalities present even before the onset of the illness, but may be a stable characteristic of the disease. Decreased FA implies disorganized white matter, i.e., tracts, that can be caused either by disorganized axonal components and/or by dysmyelination.

2.2 Altered expression of oligodendrocyte/myelin related genes in schizophrenia

Reduced expression of genes associated with oligodendrocytes and myelin (the main component of white matter), has also been widely replicated in schizophrenia, using a variety of samples and methods (see Table 1 for a summary of oligodendrocyte/myelin genes differentially expressed in schizophrenia).

Hakak et al carried out microarray analyses in a clinically well-characterized postmortem cohort of chronic unremitting schizophrenia and matched controls, and found that the expression of a series of genes related to oligodendrocytes and myelin were consistently down-regulated in dorsolateral prefrontal cortex (DLPFC) samples in schizophrenia (Hakak et al 2001). These initial observations have been replicated several times, in DLPFC and in additional regions, using a variety of samples and methods including cDNA arrays, quantitative PCR (qPCR), and gene ontology studies (Aston et al 2004; Aston et al 2005; Dracheva et al 2006; Katsel et al 2005; Tkachev et al 2003), with a few exceptions (Mitkus

et al 2008). In these reports, the largest changes in the expression of oligodendrocyte and myelin-related genes were observed in the cingulate cortex, the superior temporal gyrus, and the hippocampus.

Although only a few studies have examined any of the above genes at the protein level, CNPase protein detected by ELISA has shown to be decreased in prefrontal cortex in schizophrenia (Flynn et al 2003), and proteomic analysis of the Stanley cohort also identified a decrease in CNPase protein in schizophrenia (Dracheva et al 2006; Prabakaran et al 2004).

Importantly, these reproducible results were derived from different cohorts where the age at death and the cause of death varies, indicating that these changes did not arise from confounding factors, such as aging or hypoxia. It has been reported that some types of typical, but not atypical, antipsychotics induce reduced expression of subsets of these genes (Narayan et al 2007) (and see discussion of Konopaske et al below); however, there are data indicating that changes in the oligodendrocyte/myelin related genes in schizophrenia are a primary defect, not a secondary consequence of disease progression or of medication. Hakak et al looked at the subset of patients off medication for a prolonged period and still observed reduced expression of oligodendrocyte/myelin genes and, as discussed below, some of these genes have been implicated as genetic risk factors in schizophrenia. Altogether, it is fair to conclude that there is decreased expression of genes associated with oligodendrocytes and myelination in schizophrenia.

2.3 Oligodendrocyte and myelin abnormalities in schizophrenic brain

Unbiased stereological analyses to quantify the numbers of oligodendrocytes in schizophrenia have been carried out in order to gain insight into the underlying biological basis of the reduction in the white matter volume and reduced expression of genes related to oligodendrocytes and myelin.

In one study, postmortem materials from the superior frontal gyrus of schizophrenics and controls were analyzed, and the coefficient of variation in controls was reported to be higher than in matched schizophrenic subjects. This indicated a more dispersed arrangement of oligodendrocytes in schizophrenic patients (Hof et al 2003). The density of oligodendrocytes was lower in schizophrenics compared to controls in both in gray matter and the white matter underlying area 9 (Hof et al 2003) (Uranova et al 2004). Absolute numbers of oligodendrocytes were also significantly decreased in schizophrenia in area 9 (Hof et al 2003), area 24 (Stark et al 2004), and anterior thalamic nucleus (Byne et al 2008).

Furthermore, Uranova and colleagues, using electron microscopy (Uranova et al 2001), demonstrated apoptotic oligodendrocytes and damaged myelin sheath lamellae forming concentric lamellar bodies in schizophrenic brains, along with irregularities of heterochromatin and mitochondria in oligodendrocytes.

It is likely that these changes are a primary defect of the illness. Konopaske et al investigated the effect of chronic exposure of both typical and atypical antipsychotics in Macaque monkeys, and found that antipsychotics significantly reduce the number of astrocytes, but not oligodendrocytes (Konopaske et al 2008). Furthermore, using phencyclidine (PCP) treated mice, Lindahl et al revealed that in utero administration of PCP, which induces symptoms mimicking schizophrenia in human, causes delayed differentiation of oligodendrocyte (Lindahl et al 2008) suggesting that oligodendrocyte loss is a disease-related change.

These direct observations of oligodendrocyte aberrations in number, spacing, morphology, and myelin formation provide compelling evidence for oligodendrocyte abnormalities in schizophrenia, and likely explain why decreased expression of oligodendrocyte and myelin-related genes is such a robust and reproducible finding in the disorder.

2.4 Genetic association of oligodendrocyte/myelin related genes in schizophrenia

There is increasing evidence that oligodendrocyte and myelin related genes are genetically associated with schizophrenia (see Table 1 for a summary).

One of the most replicated findings in schizophrenia involves the neuregulin 1 (*NRG1*) gene (Stefansson et al 2003; Stefansson et al 2002; Williams et al 2003). *NRG1* and its receptor *ERBB4* are involved in several aspects of nervous system development including oligodendrocyte development (Calaora et al 2001; Corfas et al 2004; Sussman et al 2005). A genetic locus-locus interaction analyses between *NRG1* and *ERBB4* genes provided evidence for a significant interaction between the *NRG1* Icelandic schizophrenia risk haplotype and *ERBB4* (Norton et al 2006), supporting the view that *NRG1* may mediate its effects on schizophrenia susceptibility through functional interaction with *ERBB4*. We need to keep in mind, however, that since *NRG1* acts through *ERBB4* as well as other receptors and *NRG1/ERBB4* have multiple effects in nervous system development (including effects on interneurons that are shown to be affected in schizophrenia), this pathway may play a role in schizophrenia pathogenesis through other mechanisms aside from effects on oligodendrocytes and myelin.

Reticulon 4 (*RTN4*, also known as *NOGO*) is a myelin-associated protein that inhibits the outgrowth of neurites and nerve terminals. Novak and colleagues reported over-expression of *RTN4* in the brains of patients with schizophrenia as well as evidence for genetic association with a marker in the 3' UTR of the gene (Novak et al 2002). Several groups have subsequently failed to replicate these findings (Chen et al 2004; Covault et al 2004; Gregorio et al 2005; Xiong et al 2005), although a moderately large study (Tan et al 2005) demonstrated modest evidence for association. Interestingly, 3 rare non-synonymous variants have been reported in the *RTN4* receptor in schizophrenia cases but not in controls (Sinibaldi et al 2004). More recently, Budel et al reported that they confirmed haplotypic association of the *NOGO* receptor (*RTN4R*) and identified two non-synonymous SNP exclusively in schizophrenia (Budel et al 2008). Subsequently, they showed that in vitro, schizophrenia-associated *RTN4R* variants fail to respond to the growth inhibiting activity of myelin, and functioned as a dominant negative to disrupt endogenous *RTN4R* when expressed in cultured neurons.

Another gene reported to be associated with schizophrenia is *MAG*. *MAG* is a myelin associated glycoprotein that plays important roles in myelination (Dracheva et al 2006; Hakak et al 2001). Support for a role for *MAG* in schizophrenia susceptibility has been reported in both family-based and case control studies in Han Chinese populations (Wan et al 2005; Yang et al 2005).

Additional genes genetically associated with schizophrenia are *OLIG2* and *CNPI*. *Olig2* is a basic helix-loop-helix (bHLH) oligodendrocyte transcription factor that, together with *Olig1*, is necessary and sufficient for the formation of oligodendrocytes (Ross et al 2003; Sauvageot and Stiles 2002). Association analysis revealed strong evidence for association. Of 6 informative single nucleotide polymorphisms (SNPs) analyzed, 4 were associated (best $p=0.0001$) (Georgieva et al 2006). *CNPI*, which encodes CNPase is important for process formation of oligodendrocytes. The CNPase gene maps to a region which contains a previously reported significant linkage to schizophrenia in a single large pedigree. Significant association of a SNP was observed, and interestingly, this SNP is shown to be

associated with low CNPase expression using allelic expression analysis in human brain (Peirce et al 2006).

There have also been reports of association with schizophrenia for the myelin-oligodendrocyte glycoprotein gene (*MOG*) (Liu et al 2005), the proteolipid protein 1 gene (*PLP1*) (Qin et al 2005), the gelsolin gene (Xi et al 2004), and the transferrin gene (*TF*) (Qu et al 2008). The gene encoding QKI, the quaking homologue KH domain RNA binding, is located in 6q25–27, the region which was shown to be a susceptibility locus for schizophrenia in a large pedigree from northern Sweden (Lindholm et al 2001).

PTPRZ1, a gene encoding receptor protein tyrosine phosphatase beta (RPTP β) is a newer candidate gene for schizophrenia (Buxbaum et al 2008). RPTP β is expressed in oligodendrocytes (Harroch et al 2002) and dephosphorylates substrates of ERBB4, counteracting ERBB4 kinase activity in the cells. Association analysis of *PTPRZ1* showed highly significant association of this gene to schizophrenia ($p=0.0003$).

Disrupted-in-schizophrenia 1 (DISC1) was initially identified through the striking segregation of a chromosomal translocation (that disrupts the DISC1 gene) with schizophrenia and other major mental illness in a large Scottish pedigree (Millar et al 2000). Several lines of genetic evidence show this gene is also involved in sporadic cases of schizophrenia (Chubb et al 2008). It is interesting to note that DISC1 controls development of oligodendrocytes and neurons from olig2-expressing precursor cells in zebrafish (Wood et al 2009), though this has not been shown in mammals as of yet.

The recent demonstration that copy-number variation (CNV), a major source of structural and genetic variation in the human genome, is involved in the risk for schizophrenia also highlights oligodendrocyte and myelin genes. Walsh et al first reported a 400 kbp deletion in the gene encoding *ERBB4* in a child-onset schizophrenic patient (Walsh et al 2008). Subsequently, Kirov et al reported 17 p12 deletions schizophrenia cases but not in controls, and this region contains another myelin related gene, *PMP22* (Kirov et al 2009). Of note, although PMP22 is a known peripheral myelin protein, it has been shown that PMP22 is expressed in the CNS (Ohsawa et al 2006). Furthermore, neurological disorders caused by PMP22 duplication has been reported to have CNS phenotype (Tackenberg et al 2006), consistent with a role for PMP22 in CNS. Furthermore, other CNVs including myelin/oligodendrocyte related genes have been reported including *RTN4R*, (Kirov et al 2009) and *LINGO-1* (Ikeda et al 2009).

2.5 Demyelinating disease and psychosis

The onset of schizophrenia is most typically in the late teens to early twenties. Myelination processes in humans take place postnatally and are completed within the same time period as schizophrenia onset. Leukodystrophies and leukoencephalopathies are diseases characterized by progressive degeneration of the white matter, and frequently present with psychotic symptoms, sometimes indistinguishable from those of schizophrenia (Davis et al 2003; Denier et al 2007; Walterfang et al 2005). Similarly, patients with multiple sclerosis who have white matter lesions in the frontal and temporal lobes, which are brain regions implicated in schizophrenia, frequently display cognitive and psychiatric symptoms (Davis et al 2003).

In summary, there is increasing evidence that oligodendrocytes and myelin abnormalities are involved in schizophrenia. However, it is not clear how altered oligodendrocytes and myelin contribute to the development of schizophrenia. In the next section, we focus on the recent evidence showing the role of oligodendrocytes and myelin in synaptic function and

information processing, which may be disrupted in schizophrenia and shed some light on this question.

3. Oligodendrocyte and myelin dysfunction leads to altered synaptic function and information processing with relevance to schizophrenia

Oligodendrocyte abnormality and subsequent myelin dysfunction could contribute to the development of schizophrenia by altering synaptic function and information processing.

Changes in synapse formation and plasticity have been implicated in schizophrenia (Harrison and Weinberger 2005; Stephan et al 2006). Although it is challenging to measure synaptic function directly in humans, it has become possible to measure long-term potentiation non-invasively in human by using electroencephalogram (EEG) brain oscillations in the low-frequency range (De Gennaro et al 2008) and impaired synaptic plasticity has been noted in patients with schizophrenia (Daskalakis et al 2008; Stephan et al 2009).

Myelination has long been suspected to be involved in synaptic plasticity (Fields 2005). For example, it has been known that the number of oligodendrocytes increases by 27% to 33% in the occipital cortex of young rats raised in an enriched environment (Szeligo and Leblond 1977) and an increase in the number of myelinated axons in the corpus callosum also occurs in these circumstances (Juraska and Kopcik 1988). Recently, increased myelination associated with extensive piano playing in humans has been reported (Bengtsson et al, 2005), suggesting that increased conduction through enhancement of myelination along long tracts may enhance efficient integration of information in the relevant brain regions. These data support the idea that myelination may be a mediator of activity-dependent brain plasticity.

One well-studied paradigm for activity-dependent brain plasticity involves ocular dominance column formation in visual cortex (for review, see Morishita and Hensch, 2008)). This paradigm is defined by both functional plasticity and structural plasticity, with the structural plasticity occurring in a critical period during which experience/environmental stimulus highly affects the neural circuits, directly correlated with functional outcomes. It has been shown that both Nogo-66 receptor 1 (NgR1) and paired immunoglobulin-like receptor B (PirB) knockout mice show a prolonged critical period (McGee et al, 2005; Syken, et al, 2006). Interestingly, both NgR1 and PirB serve as receptors for myelin-associated axon growth inhibitors, such as Nogo-A, MAG and OMgp (for review, see Voineskos 2009), which inhibit axon sprouting. These results support the view that myelination may be responsible for regulating experience-driven synaptic plasticity during the critical period.

3.1 Oligodendrocyte and myelin abnormalities and axonal degeneration in the adult

Several lines of evidence suggest that axonal degeneration occurs in patients with multiple sclerosis (MS). It has been proposed that lack of myelin-derived trophic support due to long term demyelination is responsible for the continuous axonal degeneration in MS (Bjartmar and Trapp 2003). Additionally, some oligodendrocyte-derived molecules, such as GDNF, are known to be essential for the enhancement of axonal length via the MAP/ERK pathway (Wilkins et al 2003). Therefore, oligodendrocyte/myelin abnormalities could result in alterations in the maintenance of axonal tracts, thus affecting basic brain wiring patterns. This would ultimately affect normal synaptic transmission.

3.2 Oligodendrocyte and myelin abnormalities and axon sprouting and pruning

Some oligodendrocyte/myelin proteins, such as Nogo-A (Chen et al 2000; GrandPre et al 2000), MAG (McKerracher et al 1994), and OMgp (Wang et al 2002), are reported to inhibit axonal sprouting, and this step is considered to be important for synaptic formation (Fields 2008). Alterations in axon sprouting and pruning could lead to abnormal synapse formation.

3.3 Oligodendrocyte and myelin abnormalities and conduction velocity

Conduction velocity along axons is regulated by axon diameter, thickness of the myelin sheath, the number and spacing of nodes of Ranvier, nodal structure, and the molecular composition of ion channels in the node and paranodal region (Fields 2008). In addition, intriguing possibility of modulation of conduction velocity by oligodendrocytes has been reported recently (Yamazaki et al, 2007). Altered conduction velocity has been implicated in various neurological and psychiatric disorders (Biancheri et al 2007; Defrin et al 2004; el-Mallakh et al 1996; Soontarapornchai et al 2008). There has been some evidence for altered conduction velocity in patients with schizophrenia (Thaker 2008). It has been proposed that precisely defined conduction velocity is necessary for many learning process (Fields 2008) and that disruption of conduction velocity could cause disorganized thought and the cognitive impairments observed in schizophrenia (Tanaka et al 2009). Altered conduction velocity should affect synaptic transmission.

In fact, some animal models for schizophrenia show altered conduction velocity and behavioral changes relevant to schizophrenia. For example, Plp transgenics, harboring one extra copy of Plp, showed reduced conduction velocity as well as neurocognitive deficits, including prepulse inhibition (PPI) deficit, and altered working and spatial memory (Tanaka et al 2009). An additional relevant study is of mice expressing dominant negative ERBB4 driven by the CNP-ase promoter. These mice also showed not only reduced conduction velocity, but altered behavior relevant to schizophrenia, including enhanced sensitization to amphetamine (Roy et al 2007) (discussed in detail below).

3.4 Oligodendrocyte and myelin abnormalities and neuronal structure and plasticity

Neuronal morphology is thought to reflect synaptic function. Recently, Höistad et al found that mice deficient in *MAG* showed alterations in morphology of layers II-III pyramidal cells in their anterior cingulate cortex (Sinibaldi et al 2004), such as basal dendritic integrity, even though they showed very subtle changes in myelination (Hoistad et al 2009). Another mouse model, quaking mice, which have a deletion 5' to the qk gene (the mouse homologue of *QKI*) and reduced expression of the gene product and severe hypomyelination (Lu et al 2003), show shorter dendritic length for both apical and basal dendrites in pyramidal neurons in layers II-III of the ACC (Hoistad et al 2009). Interestingly, apical dendrites were poorly developed, but increased number of dendritic spines was also observed in quaking mice compared to control littermates, suggesting the presence of compensatory mechanisms similar to sprouting (Hoistad et al 2009). These data support the idea that myelin deficiencies have substantial impact on the morphology of target neurons and possibly synapse.

Furthermore, several knockout mice of oligodendrocyte/myelin associated genes have been demonstrated to show alterations in synaptic plasticity by electrophysiological measures. Lee et al demonstrated that Nogo-66 receptor knockout mice show alterations in both long-term potentiation (LTP) and long-term depression of synaptic transmission at Schaffer collateral-CA1 synapses, showing that a myelin related gene is involved in synaptic plasticity (Lee et al 2008).

RPTP β is involved in oligodendrocyte differentiation (Takahashi et al, unpublished data). The mouse knock down of RPTP β has been reported to induce enhancement of LTP in mouse hippocampus (Niisato et al 2005). Conversely, over-expression of RPTP β reduces LTP in the region and induces spatial memory deficits in animals (Takahashi et al, unpublished data).

NRG1 signaling, a parallel pathway to RPTP β , is known to be involved in myelination. The NRG1 receptor, ErbB4 plays a key role in activity-dependent maturation and plasticity of excitatory synapses (Li et al 2007) and *NRG1*^{+/-} mice have been reported to display reduced LTP in hippocampus (Bjarnadottir et al 2007). Since NRG1 is involved in NMDAR function as well (Bjarnadottir et al 2007), one cannot yet conclude that these changes are derived from altered myelination. This is especially true as the role of NRG1 in the CNS myelination is still controversial as Brinkmann et al reported that several mouse lines of elimination of NRG1 signaling did not cause dysmyelination in the CNS (Brinkmann et al 2008), which is inconsistent with previous study reporting hypomyelination in these mice (Taveggia et al 2008). However, Bace1, a molecule that is involved in the proteolytic processing of NRG1, influences the myelination of central axons (Hu et al 2006), and interestingly, Bace1 knockout mice also showed specific synaptic dysfunctions at Schaffer collateral to CA1 (Laird et al 2005) and CA3 synapses (Wang et al 2008).

Taken together, these data suggest that oligodendrocyte/myelin dysfunction could cause changes in conduction velocity of axons, in synapse formation, and in neuronal function (Figure 1). How these changes at the cellular level could lead to the development of schizophrenia is unknown. In the next section, we will focus on the circuitries relevant to schizophrenia and discuss how oligodendrocyte/myelin dysfunction could affect these circuitries.

4. Oligodendrocyte/myelin dysfunction leads to changes in the neuronal circuitry relevant to schizophrenia

One of the most challenging issues related to the oligodendrocyte/myelin hypothesis for schizophrenia is linking these changes to the circuitry abnormalities observed in schizophrenia. However, recent evidence supports a role for oligodendrocytes and myelin in alterations in dopaminergic and glutamatergic circuitry.

4.1 Oligodendrocyte/Myelin dysfunction leads changes in the dopaminergic signaling

Any covered hypothesis of the pathology of schizophrenia must integrate the fact all currently available antipsychotics have the ability to block the dopamine receptor D2 (DRD2). Thus, it is accepted that dopaminergic activity can modulate the symptoms of schizophrenia, although the degree to which dopaminergic activity is primary or a secondary consequence of disease is unresolved. However, elevated dopamine signaling in striatum apparently precedes the onset of schizophrenia (Howes et al 2009). Furthermore, these changes have been shown to be associated with hypo-prefrontal function, which is considered to be relevant to cognitive deficit in schizophrenia (Davis et al 1991; Fusar-Poli et al 2009)

Accumulating data support the notion that altered oligodendrocyte and myelin function could induce changes in the dopamine signaling. First, patients with multiple sclerosis (MS) frequently show psychiatric symptoms, and their psychotic symptoms can be treated by neuroleptics, including clozapine (Safferman et al 1994). In addition, experimentally induced demyelination has been shown to increase dopamine signaling. Experimental autoimmune encephalomyelitis (EAE) has been shown to have protective effects against MPTP, a compound known to cause Parkinsonism (Balkowiec-Iskra et al 2007b;

Balkowiec-Iskra et al 2003; Kurkowska-Jastrzebska et al 2005), and striatal dopamine levels have been shown to be significantly elevated in MPTP-treated mice compared to that of vehicle-treated controls (Balkowiec-Iskra et al 2007a). Since EAE has multiple effects on several cell populations, this elevated dopamine signaling after MPTP treatment may not be solely linked to oligodendrocyte and myelin defects taking place in EAE, however.

Furthermore, quaking mice display not only severe dysmyelination of the CNS due to defects in oligodendrocyte maturation, but also increased dopamine metabolism and increased dopamine D₂ receptor binding (Nikulina et al 1995). However, it should be noted that quaking mice are also deficient in other genes, such as *Parkin* and the *PARKIN* coregulated gene (*Pacrg*) which are implicated in Parkinson disease in human (Lorenzetti et al 2004).

Roy et al reported that mice expressing dominant-negative ErbB4 (DN-ErbB4) in oligodendrocytes (thereby inhibiting neuregulin signaling in these cells) exhibited oligodendrocyte and myelin abnormalities as well as elevated dopamine signaling and altered behaviors related to changed dopamine signaling (Roy et al 2007). In these mice, the expression of DAT and D1-like binding in the cortex and striatum were significantly increased, and amphetamine injection induced greater c-fos expression. Furthermore, evoked dopamine release in the striatum was significantly elevated in these mice. Interestingly, similar changes have been observed in mice over-expressing RPTP β , by which neuregulin signaling is inhibited, working similarly to DN-ErbB4 (Takahashi et al unpublished data).

Finally, mice treated with cuprizone, a drug which induces demyelination, demonstrated increased expression of dopamine in their PFC (Xu et al 2009). Furthermore, altered dopamine related behaviors, including impaired working memory (Tan et al 2009) and PPI deficits (Geyer 2008), have been found in these mice (Gregg et al 2009; Xiao et al 2008) (described in detail in the next section).

Several oligodendrocyte/myelin related molecules are known to function both in oligodendrocyte/myelin pathways and in dopamine signaling, and have been implicated in schizophrenia. Lingo-1, a component of the Nogo-66 receptor/p75 signaling complex (Mi et al 2004), is expressed in oligodendrocytes and negatively regulates myelination (Mi et al 2005). Lingo-1 exerts neuroprotective effects on midbrain DA neurons (Inoue et al 2007), suggesting that this molecule is important for both myelination and dopamine signaling. Furthermore, this molecule has been shown to be involved in GSK3 β activation (Zhao et al 2008). Interestingly, a duplicated region on chromosome 15q24.3 harboring the entire Lingo-1 gene has been found in a patient with schizophrenia (Ikeda et al 2009).

GDNF is expressed in oligodendrocytes, and is known to promote myelination in the peripheral nervous system (Hoke et al 2003) and to be involved in the survival of dopaminergic neurons (Lin et al 1993). Genetic association of a 3' UTR repeat in this gene has been reported in schizophrenia (Michelato et al 2004).

OLIG2 is a basic helix–loop–helix transcription factor and is necessary and sufficient for the genesis of oligodendrocytes and myelination (Jakovcevski and Zecevic 2005; Rowitch et al 2002). As we described above, genetic association and postmortem brain studies strongly implicated this gene in schizophrenia, and recent evidence shows that Olig2 is also expressed in adult stem cells in the subventricular zone (Hack et al 2005) as well as in the DA-depleted striatum (de Chevigny et al 2008), suggesting that Olig2 plays a role in the development of dopamine signaling. Further direct evidence was obtained from a zebrafish study, showing that Olig2 controls development of DA neurons through regulating the expression of Sim1, a transcriptional regulator expressed in diencephalic progenitors

(Borodovsky et al 2009). Thus, altered expression or function of these molecules could induce both hypomyelination and hyperdopaminergia. Direct evidence using gene-manipulated mouse models has yet to be reported.

Conversely, dopamine itself could modulate myelination (Belachew et al 1999). For example, in phenylketonuria (PKU), a disease characterized by hypomyelination, there is reduced dopamine levels and cognitive disabilities. Interestingly, when mice with PKU were kept on a low phenylalanine diet, they showed an increase in both dopamine and myelin-basic protein (MBP) levels (Joseph and Dyer 2003).

Meanwhile, Bongarzone et al showed that the D3 receptor is not only expressed in neurons, but also in immature oligodendrocytes before the peak of myelination (Bongarzone et al 1998). Mature oligodendrocytes do not express D3, but express D2 during the peak of myelination events. The D2/D3 agonist quinpirole led to an increase in the number of oligodendrocyte precursor cells and a decrease in the number of mature cells that produce myelin. When these cells were treated with the dopamine antagonist haloperidol, the number of mature cells increased (Bongarzone et al 1998).

In conclusion, there is an apparently close relationship between oligodendrocytes/myelin and dopamine signaling, and the evidence suggests altered oligodendrocyte and myelin function could induce elevation in the dopamine system; however, the underlying molecular and cellular mechanisms are still largely unknown.

4.2 Oligodendrocyte/myelin dysfunction leads to changes in glutamatergic signaling

An appreciation for altered glutamatergic signaling in schizophrenia arose in part from the findings that use of PCP, a glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist, could induce schizophrenia-like symptoms in humans (Goff and Coyle 2001). However, a relationship between glutamate and myelin is best elucidated in MS.

Glutamate levels are increased in the cerebrospinal fluid (Sarchielli et al 2003) as well as brains of MS patients (Cianfoni et al 2007). Furthermore, increased expression of glutamate receptors has been observed on the oligodendrocytes in MS patients brains (Newcombe et al 2008). Indeed, glutamate excitotoxicity of oligodendrocytes through glutamate receptors on these cells is thought to be responsible for demyelination in MS (Pitt et al 2000). Also, glutamate-mediated excitatory postsynaptic currents are enhanced during the early phase of EAE (Centonze et al 2009). Meanwhile, expression of the glutamate transporter is consistently shown to be up-regulated in the various regions of the MS brains, (Newcombe et al 2008; Vallejo-Illarramendi et al 2006), suggesting hypo-glutamatergia in the synapse.

On the other hand, in *NRG1*^{+/-} mice, reduced phosphorylation of NR2B, a subunit of NMDAR, has been reported (Bjarnadottir et al 2007). As we have discussed in the section of “synaptic plasticity” above, it is not clear whether this change is due to altered myelination or direct effects of NRG1 on neurons. However, considering the important role of NRG1 in myelination, NRG1 could affect NMDAR function through modulation of myelination. Also similar changes have been observed in mice over-expressing RPTP β (Takahashi et al unpublished data).

These findings demonstrate that oligodendrocytes/myelin dysfunction could alter neuronal circuitries considered to be important in the etiology of schizophrenia. In the next section, we will review various animal models with oligodendrocyte myelin dysfunction to appreciate the behavioral changes associated with this dysfunction, and to further elucidate the relationship between oligodendrocytes, myelin, dopamine and glutamate transmission.

5. Oligodendrocyte/myelin dysfunction leads to altered behaviors relevant to schizophrenia

Several lines of genetically modified mice, in which the expression of oligodendrocyte/myelin related genes has been modified, show altered behaviors relevant to schizophrenia.

Schizophrenia is characterized by three symptom clusters, positive, negative and cognitive. The positive symptoms refer to hallucinations, delusions and disorganized speech/thinking, the negative symptoms refer to social withdrawal, avolition (lack of motivation), anhedonia, and blunted affect, and the cognitive symptoms refer to deficits in attention, working memory, and executive function. To understand how genetic/molecular changes lead to schizophrenia, animal models in which molecules of interest are manipulated have been used. Although it is quite challenging to reproduce schizophrenic symptoms in rodents, especially positive symptoms, several behavioral paradigms have been developed and widely used (Table 2). Also, based on the findings that some psychostimulants, such as MK-801, ketamine, and amphetamine, could exacerbate the symptoms of schizophrenia (Tamminga and Holcomb 2005), sensitivity to these drugs has frequently been examined in these animals.

Using these behavioral paradigms, several mouse models where oligodendrocyte/myelin related genes are genetically modified have been examined, and accumulating evidence suggests that oligodendrocyte/myelin dysfunction leads to behavioral changes relevant to schizophrenia (see Table 3 for a summary of animal models for schizophrenia based on the oligodendrocyte/myelin hypothesis). It should be noted that most of these animal models do not show comprehensive deficits spanning all symptomatic domains.

A myelin-related mouse model for schizophrenia is *NRG1*^{+/-} and *ERBB4*^{+/-} mice (Stefansson et al 2002). In these mice, researchers found hyperactivity in *NRG1*^{+/-} and *ERBB4*^{+/-}, and prepulse inhibition (PPI) deficit in *NRG1*^{+/-}. Remarkably, these changes could be reversed by the antipsychotic clozapine. DN-ERBB4 mice also showed hyperactivity and increased sensitization to amphetamine (Roy et al 2007). Consistent with molecular evidence that RPTPβ inhibits NRG1 signaling (Buxbaum et al 2008), mice over-expressing RPTPβ showed a similar phenotype as that observed in *NRG1*^{+/-}, including PPI deficits and hyperactivity (Takahashi et al unpublished data).

Mice lacking the Nogo-66 receptor displayed reduced working memory function (Budel et al 2008) and locomotor activity (Hsu et al 2007). Bace1-null mice exhibited deficits in PPI, novelty-induced hyperactivity, hypersensitivity to a glutamatergic psychostimulant (MK-801), cognitive impairments, and deficits in social recognition. Importantly, some of these manifestations were responsive to treatment with Clozapine, (Savonenko et al 2008). Further, mice over-expressing Plp1 showed reduced PPI, spatial learning and working memory deficits (Tanaka et al 2009).

Cuprizone treated mice are a relatively new animal model for schizophrenia. Mice treated with Cuprizone, a neurotoxin known to induce demyelination, showed deficits in working memory, implicated in the pathophysiology of schizophrenia (Xiao et al 2008). Varying duration of Cuprizone treatment induces different phenotypes. For instance, mice exposed to Cuprizone for 2 and 3 weeks displayed more climbing behavior and lower PPI, but mice exposed to Cuprizone for 4 to 6 weeks had less social interaction, even though both Cuprizone treated groups showed consistent brain demyelination, myelin break down, and loss of oligodendrocytes (Xu et al 2009). A spatial working memory impairment in Cuprizone treated mice was found at all time points. Demyelination in the juvenile period had a more profound effect on working memory and social interaction at later stage of their

life (Makinodan et al 2009). Similarly, lysophosphatidylcholine, a potent demyelinating agent, injected into the ventral hippocampus of the 10-day-old rat caused deficits in PPI, motor hyperactivity in response to methamphetamine and anxiety-related behaviors (Makinodan et al 2008). These data suggest that the timing and duration of demyelination affect the development of schizophrenia and disease severity.

In conclusion, altered expression and function of oligodendrocyte and myelin display behavioral changes relevant to schizophrenia in mice, and some of them possess enough validity of animal models for schizophrenia.

6. Conclusion and future direction

The evidence clearly supports the hypothesis that oligodendrocyte and myelin dysfunction can be a primary cause for schizophrenia, rather than only a consequence of the illness. This in turn raises the possibility of novel therapeutic approaches as well as individualized medicine for the patients with oligodendrocyte and myelin dysfunction.

6.1 Link between oligodendrocyte/myelin dysfunction and neuronal circuitry affected in schizophrenia

An oligodendrocyte/myelin hypothesis of schizophrenia does not conflict with other current hypotheses for schizophrenia, including neurodevelopmental, or dopamine and glutamate hypotheses for this disease, but rather supports these concepts. Nevertheless, the mechanism of how altered oligodendrocyte/myelin function could induce changes in other signaling pathways, like dopamine and glutamate circuitries, is not clear. Since dopaminergic axons, at least in nigrostriatum pathway, are unmyelinated, (Griffin and Thompson 2008), oligodendrocyte/myelin deficits that affect dopaminergic signaling must be indirect. It has been suggested that reduced excitatory input into interneurons could increase dopamine release into the striatum (Balla et al 2009) and induce a schizophrenic phenotype in mice (Belforte et al). GAD67, the enzyme that synthesizes GABA, was shown to be significantly down-regulated in the brain of MS patients (Dutta et al 2006). Thus, one possible explanation for altered dopamine transmission is altered or reduced presynaptic signal inputs into inhibitory neurons due to dysmyelination of excitatory axons (Figure 2). In this model, activity of inhibitory neurons would be suppressed by reduced or altered input from dysmyelinated glutamatergic excitatory axons, and would induce elevated dopaminergic signaling around these inhibitory neurons, one of the most established findings in schizophrenia (Howes and Kapur 2009). Detailed analysis, including electrophysiological analysis of GABAergic signaling in mice with deficits in oligodendrocyte/myelin, would help to understand the mechanism of how these molecules regulate these signaling pathways.

6.2 Schizophrenia and oligodendrocyte/myelin dysfunction

Considering a significant role of oligodendrocyte/myelin in synaptic function, signal transduction, and working memory (Fields 2008), patients who have abnormalities in oligodendrocyte/myelin may show more severe cognitive dysfunction. In fact, the degree of change in fractional anisotropy (FA) in DTI imaging (and therefore, the degree of white matter integrity) is correlated with degree of performance in several cognitive domains, such as memory, attention and executive function (Cocchi et al 2009; Lim et al 2006; Nestor et al 2004). Keefe et al defined a group of patients, who either remain chronically hospitalized or totally dependent on others for basic necessities of life, as poor outcome patients or 'Kraepelinian' (Keefe et al 1987), and Mitelman and Buchsbaum found a pattern of white matter deficits within these patients (Mitelman and Buchsbaum 2007).

6.3 Neurodevelopmental oligodendrocyte/myelin hypothesis in schizophrenia and novel therapeutic approaches

Based on findings reviewed above, we propose that therapeutics need to be developed that can correct the oligodendrocyte/myelin abnormalities. This paper has elucidated numerous targets. However currently available medications for multiple sclerosis such as corticosteroids or interferons (Wiendl et al 2008) can even induce psychosis (Gonzalez-Burgos and Lewis 2008). Hence new approaches are essential.

In conclusion, imaging, anatomical, molecular, and genetic evidence indicate that there is an abnormality in oligodendrocyte/myelin in schizophrenia, and it is becoming clear that oligodendrocyte loss/dysmyelination is a primary deficit in the disorder and can lead to the several neuronal deficits observed in schizophrenia, such as altered synaptic function and altered circuitry. A further understanding of the role of oligodendrocyte/myelin in schizophrenia would provide new insights into the treatment of this disease.

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Abbreviation list

DTI	diffusion tensor imaging
FA	fractional anisotropy
DLPFC	dorsolateral prefrontal cortex
qPCR	quantitative PCR
PCP	phencyclidine
SNP	single nucleotide polymorphism
CNV	copy-number variation
MS	multiple sclerosis
PPI	prepulse inhibition
LTP	long-term potentiation
CNS	Central nervous system
EAE	Experimental autoimmune encephalomyelitis
NMDA	N-methyl-D-aspartate

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Figure 1. Oligodendrocyte and myelin and synaptic function

Oligodendrocytes wrap axons and form electrical insulation, myelin that enhances conduction of nerve impulses. Altered oligodendrocytes and myelin reduces conduction velocity. Also impairment in oligodendrocytes and myelin alters axonal growth/sprouting and synaptic plasticity in the synapse.

Figure 2. A model that altered oligodendrocyte/myelin induces hyper-dopaminergic states

A. Healthy myelinated axon. Inhibitory neuron receives sufficient glutamatergic input from myelinated axon, and releases sufficient GABA to inhibit excess dopamine release at dopaminergic terminals.

B. Dysmyelinated axon. Inhibitory neuron receives insufficient glutamatergic input from unmyelinated axon, and fails to release sufficient GABA and disinhibits excess dopamine release.

This is a simplified model which includes only frontal cortex and striatum.

Table 1

Oligodendrocyte and myelin related genes implicated in schizophrenia from gene expression and genetic association studies..

Gene symbol	Altered gene expression (major or first study)	Genetic association (major or first study)
CLDN11	Tkachev et al. (2003)	
CNP1	Hakak et al. (2001).	Peirce et al. (2006)
DISC1		Millar et al (2000)
ERBB3	Tkachev et al. (2003)	
ERBB4		Norton et al. (2006), Walsh et al. (2008) *
MAG	Tkachev et al. (2003)	Wan et al. (2005), Yang et al. (2005)
MAL	Hakak et al. (2001).	
MBP	Tkachev et al. (2003)	
MOBP	Tkachev et al. (2003)	
MOG	Tkachev et al. (2003)	Liu et al. (2005)
NRG1		Stefansson et al (2002), Williams et al. (2003)
Olig2	Tkachev et al. (2003)	Georgieva et al. (2006)
PLP1	Tkachev et al. (2003)	Qin et al. (2005)
PMP22	Dracheva et al. (2006)	Kirov et al. (2009) *
PTPRZ1		Buxbaum et al (2007)
QKI		Lindholm et al. (2001)
RTN (NOGO)		Budel et al. (2008) **, Kirov et al. (2009) *
SOX10	Tkachev et al. (2003)	Maeno et al. (2007)
TF	Hakak et al. (2001).	Qu M et al. (2008)

* rare CNV in schizophrenic patients.

** rare variants in schizophrenic patients

Table 2

Behavioral models mimic psychotic symptoms of schizophrenia.

	Symptoms in human	rodent model
Positive symptoms	Delusions	N/A
	Hallucinations	N/A
	Disorganized speech/thinking	N/A
	Grossly disorganized behavior	N/A
	Catatonic	N/A
Negative symptoms	social withdrawal	Decreased interaction with a juvenile conspecific/place preference for a caged peer conspecific/preference for social novelty/nesting behavior, altered aggression behavior on intruder
	Anhedonia	reduced voluntary sucrose consumption
	Avolition	reduced swimming time in forced swim test, reduced hanging time in tail suspension
	Blunted affect	N/A
Cognitive symptoms	Working memory	impaired performance in T-maze/8-radial maze
	Spatial memory	impaired performance in Morris water maze
	Attention/sensory gating	decreased Prepulse inhibition (PPI)/latent inhibition
Sensitivity to psychostimulants	psychostimulants induce schizophrenia	locomotor response to psychostimulants
	psychostimulants exacerbate symptoms of schizophrenia	Increased effects of psychostimulants on PPI test

Table 3

Animal models for schizophrenia based on oligodendrocyte/myelin hypothesis

Animal name	Molecular findings related to oligodendrocyte/myelin	Molecular findings (others)	Behavioral findings	Reference
Bace1 knock out	Hypomyelination	Reduced spine density in hippocampal pyramidal neurons	Deficits in prepulse inhibition, cognitive function, and social recognition, novelty-induced hyperactivity, hypersensitivity to MK-801 hyperactivity	Hu et al. (2006), Savonenko et al. (2008)
ERBB4 heterozygotes				Stefansson et al. (2002)
DN-ERBB4	Impaired oligodendrocyte/myelin development, reduced conductance velocity	Elevated dopamine signaling	Increased sensitization to amphetamine	Roy et al. (2007)
MAG knock out	Subtle dysmyelination	Alterations in basal dendritic integrity		
NgR1 (Nogo receptor) knock out		Enhancement of long-term potentiation and attenuates long-term depression	Deficits in working memory, reduced locomotor activity	Hsu et al. (2007)
NRG1 heterozygotes	controversial	Reduced phosphorylation of NR2B, impaired LTP	Hyperactivity, reduced prepulse inhibition	Taveggia et al. (2008)Stefansson et al. (2002)
PLP1 transgenics	Reduced conductance velocity		Reduced prepulse inhibitions, spatial learning and working memory deficit.	Tanaka et al. (2009)
PTPRZ1 transgenics	Delayed oligodendrocyte development	Reduced phosphorylation of NR2B, impaired LTP, elevated dopamine signaling	Reduced prepulse inhibitions, spatial learning, hyperactivity, increased sensitization to amphetamine	Takahashi et al, in preparation
quaking	Severe dysmyelination	Shorter dendritic lengths distal from the soma, fewer numbers of branch radial intersections, fewer higher order branches were observed in apical dendrites Increased dopamine metabolism and dopamine D2 receptor binding,		Hoistad et al. (2009)
Cuprizone treated mice	Demyelination	Elevated dopamine signaling	Deficits in working memory, prepulse inhibition, and social interaction	Xiao et al (2008), Makinodan et al (2009)