Introduction to the Special Section:
Myelin and oligodendrocyte abnormalities in schizophrenia

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Abstract
A central tenet of modern views of the neurobiology of schizophrenia is that the symptoms of schizophrenia arise from a failure of adequate communication between different brain regions and disruption of the circuitry that underlies behaviour and perception. Historically this disconnectivity syndrome has been approached from a neurotransmitter-based perspective. However, efficient communication between brain circuits is also contingent on saltatory signal propagation and salubrious myelination of axons. The papers in this Special Section examine the neuroanatomical and molecular biological evidence for abnormal myelination and oligodendrogial function in schizophrenia through studies of post-mortem brain tissue and animal model systems. The picture that emerges from the studies described suggests that although schizophrenia is not characterized by gross abnormalities of white matter such as those evident in multiple sclerosis, it does involve a profound dysregulation of myelin-associated gene expression, reductions in oligodendrocyte numbers, and marked abnormalities in the ultrastructure of myelin sheaths.

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Schizophrenia, like most psychiatric disorders, is complex in origin. It typically manifests itself in late adolescence or early adult life with major, progressive and usually irreversible deterioration from a previous level of functioning. Neuropathological studies conducted during the past century have described a multitude of ‘soft’ abnormalities in many brain regions, but they have failed to identify a ‘smoking gun’. For the past 50 yr, neurotransmitter-based approaches have dominated research and treatment strategies in schizophrenia. These approaches have been guided almost entirely by the interpretation of therapeutic responses to pharmacological agents (dopamine- and serotonin-based approaches), or by the similarities of symptoms produced by some drugs of abuse (e.g. glutamate-based approaches) to schizophrenia. Neurobiological studies of these neurotransmitter systems in living subjects and in post-mortem specimens have generally yielded ambiguous or contradictory results or effect sizes that have been smaller and less robust than the ideal. Thus, although these neurotransmitter-based approaches have led to very significant advances in treatment efficacy and to equally great strides in our understanding of the neurobiology of dopamine, serotonin and glutamate neurotransmitter systems, to date, they have contributed less to our knowledge of the underlying biology of schizophrenia and its aetiology.

During the past decade, purely neurotransmitter-based models of schizophrenia have evolved into systems biology and connectivity-based hypotheses (Harrison and Weinberger, 2004; Stewart and Davis, 2004). Although these hypotheses have also invoked neurotransmitter system abnormalities, they have been informed by neuroimaging and neuropathology studies and have emphasized the interplay of neurotransmitters within and between different brain regions. Thus, the central tenet of this modern view has been that symptoms of schizophrenia arise from a failure of adequate communication between different
brain regions and disruption of the circuitry that underlies behaviour and perception.

Disruption of brain circuitry and even abnormalities in neurotransmitter function can be brought about by a variety of more basic factors. These factors can include, but are clearly not limited to, alterations in synaptic functions, synaptic proteins and G-protein coupling (Levitt et al., 2006; Mirnics et al., 2001), changes in energy metabolism and metabolic function (Middleton et al., 2002; Prabakaran et al., 2004), challenges to the structural integrity of central nervous system cellular components (Rosoklija et al., 2000) and alterations in the mechanisms that subserve signal propagation, including myelination (Davis et al., 2003).

White-matter and myelination abnormalities are high among the processes that must be considered in any hypothesis that posits abnormal communication within specific brain circuits and between brain regions. Initial studies of white matter by neuroimaging techniques failed to reveal profound deficits, but subsequent work with higher resolution methodologies has unveiled significant, albeit subtle, reductions and deficits (Wright et al., 2000). These studies and the multiple roles and functions of the myelin-forming glial constituents of the brain as they relate to schizophrenia have been reviewed recently (Stewart and Davis, 2004). More direct evidence for myelin-associated abnormalities in schizophrenia came first from broad-scale microarray gene expression studies (Hakak et al., 2001) that identified the down-regulation of the expression of a family of genes associated with myelination and oligodendrocyte function. This initial finding was soon confirmed by other investigators using similar and different tools and independent subject cohorts (Dracheva et al., 2006; Katsel et al., 2004; Stewart and Davis, 2004; see also Tkachev et al., 2007 and Haroutunian et al., 2007 in this Special Section). These findings have been extended and supported further by MRI and protein-based experiments (Dracheva et al., 2006; Flynn et al., 2003), light microscopic studies of post-mortem specimens (Hof et al., 2003; Orlovskaya et al., 2000; see also Segal et al., 2007 in this Special Section), and electron microscopic studies of the frontal cortex and the caudate nucleus (Uranova et al., 2004; see also Uranova et al., 2007 in this Special Section).

Developments in novel neurobiological techniques and technologies have allowed close scrutiny of many of these systems in post-mortem brain tissue specimens from persons with schizophrenia. These studies are now beginning to be reported and the papers in this Special Section describe and review some of these approaches and their initial results. Interrogation of gene expression profiles in single or multiple brain regions by high-throughput gene microarray technologies and the use of metabolomic techniques is the topic of three of the papers in this Special Section (Haroutunian et al., 2007; Sokolov, 2007; Tkachev et al., 2007). The other three papers in the Special Section take advantage of modern neuroanatomical methodologies to examine more closely the central nervous system elements that may be affected by some of the gene expression deficits described in schizophrenia. One of these papers focuses on the detection of myelin-tract abnormalities and their relationship to cognitive function in post-mortem human brain specimens from persons with schizophrenia (Dwork et al., 2007), the second examines the ultrastructure of myelin and oligodendrocytes in multiple brain regions in schizophrenia (Uranova et al., 2007), and the third explores the neuroanatomical consequences of the ablation of one of the myelin-associated genes involved in schizophrenia in mouse model systems (Segal et al., 2007).

The picture that emerges from the studies described here suggests that although schizophrenia is not characterized by gross abnormalities of white matter such as those evident in multiple sclerosis, it does involve a profound dysregulation of myelin-associated gene expression, reductions in oligodendrocyte numbers, and marked abnormalities in the ultrastructure of myelin sheaths. Since each myelinating oligodendrocyte myelinates as many as 40 axon segments (Baumann and Pham-Dinh, 2001; Larocca and Rodriguez-Gabin, 2002), it is easy to envision how changes in the number of oligodendrocytes, and/or in the integrity of myelin sheaths, and/or axoglial contacts can have a profound impact on signal propagation and the integrity of neuronal circuits. This picture of myelin-associated deficits influencing signal propagation and signalling through neural circuits that subserves emotion, cognition and thought processes is entirely consistent with the symptoms of schizophrenia and with the disconnection hypothesis alluded to above. The findings elaborated in this Special Section are also consistent with the view that it is no longer tenable to think only in terms of neuron–neuron connections but we must view connectivity and communication within the brain as the interplay between circuits where neurons and glia form functional units and interact to affect information processing (Haydon, 2001). This view makes it abundantly clear that further elaboration of the myelin-associated dysfunction in schizophrenia is imperative to the understanding of not only the neuropsychiatric
consequences of myelin and oligodendroglial deficits, but to the identification of the core factors that are responsible for these deficits and the development of corrective therapeutic approaches.

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Statement of Interest
None.

References


