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EDITORIAL

A new role for oligodendrocytes and myelination in schizophrenia and affective disorders?

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An important part of human brain development is myelination of axons and development of white matter, which occurs at a high rate in the first years of childhood and continues until young adulthood. Myelination is dependent on proper oligodendrocyte function at all stages of development. Consequently, oligodendrocyte dysfunction leads to disturbances in myelination and connectivity and—on the functional level—also to cognitive deficits. In a diffusion tensor imaging (DTI) study, oligodendrocyte-related gene variants, such as myelin-associated glycoprotein (MAG), were related to white matter tract integrity and cognitive performance in SZ patients. Interestingly, a single nucleotide polymorphism of the oligodendrocyte transcription factor Olig2, which is necessary for maturation of oligodendrocyte precursor cells (OPCs), has also been associated with reduced white matter fractional anisotropy in schizophrenia [1]. Several meta-analyses of voxel-based DTI studies revealed reduced fractional anisotropy as a measure of deficits in fiber density and myelination in left frontal and temporal lobe white matter in patients with schizophrenia and affective disorders. Using high-immersion oil microscopy, Williams et al. detected decreased myelin cross-sectional area per axon in the splenium of patients with major depression [2].

In the entorhinal cortex of schizophrenia patients, we detected a decreased intensity of myelin basic protein (MBP) staining and found that decreased myelination correlated with disorganization of pre-alpha cells [3], demonstrating that disturbed neurodevelopment in these disorders might be the basis of disturbed myelin-based connectivity. In the gray matter of the prefrontal cortex, Kolomeets and Uranova report a reduction of the density of oligodendrocytes in schizophrenia [4]. Moreover, previous electron microscopy studies from that group in cases with very low postmortem intervals (time from death to autopsy) provided evidence for damaged myelin sheaths, myelin degeneration, and apoptosis/necrosis of oligodendrocytes in gray and white matter of the prefrontal cortex of patients with schizophrenia and affective disorders. A recent review of neuropathological findings in affective disorders, namely bipolar disorder, summarizes a loss of oligodendrocyte density in the gray or white matter of the prefrontal cortex and fronto-limbic network [5]. In design-based stereological postmortem studies, our group showed a decreased oligodendrocyte number in the left cornu ammonis 4 (CA4) region of the anterior and posterior hippocampus in schizophrenia but no alterations in neuron or astrocyte number [6]. Interestingly, we found that the reduction of oligodendrocytes was confined to the CA4 region, a region that is now regarded as a polymorph layer of the dentate gyrus. The CA4 region connects the dentate gyrus, where in animals neurogenesis can be observed, with the CA3 region. Moreover, we found that patients with marked cognitive deficits had a decreased number of oligodendrocytes in CA4, CA2/3, and the subiculum of the anterior hippocampus [7]. This led to the hypothesis that the decreased number of oligodendrocytes is a result of a failure of maturation and also indicates disturbed regeneration in the CA4/dentate region underlying impaired long-term outcome. However, to date it is unknown whether a failure in differentiation of OPCs, which are still capable of myelination or a loss of mature oligodendrocytes, contributes to the loss of oligodendrocyte number.

In schizophrenia and affective disorders, the relationship of oligodendrocytes with interneuron pathology is unknown. A large fraction of myelinating oligodendrocytes ensheathes fast-spiking parvalbuminergic interneurons [8]. Intriguingly,

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myelin that is formed around these axons shows an unusual pattern, with a patchy distribution and myelinated segments preferentially localizing to the axon arbor near the cell body [8, 9]. Since this pattern of myelination is unlikely to support saltatory nerve conduction, it raises the question of its function. The fast-spiking and very high tonic activity of parvalbuminergic-positive inhibitory basket cells may require the function of myelin in supporting their high-energy demands. Energetic support of the axonal intermediate metabolism is provided by the delivery by glycolytic oligodendrocytes of lactate to axons. In fact, myelin deprives axons from rapid access to extracellular metabolites, which necessitates that lactate is delivered by oligodendrocytes to myelin and from there into the axon. This concept of metabolic coupling of myelin and axons is an important new development in neuroscience [10], but it remains to be established if all types of neurons need this metabolic support. In patients with schizophrenia and affective disorders, pathology of interneurons, including decreased expression of glutamic acid decarboxylase 67 (GAD67) and parvalbumin, has been detected in postmortem hippocampus and prefrontal cortex. In schizophrenia and affective disorders, the concept of metabolic coupling may link oligodendrocyte to interneuron pathology. Further studies in animal models and human brains are needed to shed light on this pathophysiological concept. If findings in preclinical studies are positive, similar to first clinical studies in multiple sclerosis new add-on treatment strategies targeting oligodendrocyte differentiation can be developed, which address treatment-resistant symptoms in schizophrenia and affective disorders.

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