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# Disturbed Oligodendroglial Maturation Causes Cognitive Dysfunction in Schizophrenia: A New Hypothesis

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**Background and Hypothesis:** Cognitive impairment is a hallmark of schizophrenia, but no effective treatment is available to date. The underlying pathophysiology includes disconnectivity between hippocampal and prefrontal brain regions. Supporting evidence comes from diffusion-weighted imaging studies that suggest abnormal organization of frontotemporal white matter pathways in schizophrenia. **Study Design:** Here, we hypothesize that in schizophrenia, deficient maturation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes substantially contributes to abnormal frontotemporal macro- and micro-connectivity and subsequent cognitive deficits. **Study Results:** Our postmortem studies indicate a reduced oligodendrocyte number in the cornu ammonis 4 (CA4) subregion of the hippocampus, and others have reported the same histopathological finding in the dorsolateral prefrontal cortex. Our series of studies on aerobic exercise training showed a volume increase in the hippocampus, specifically in the CA4 region, and improved cognition in individuals with schizophrenia. The cognitive effects were subsequently confirmed by meta-analyses. Cell-specific schizophrenia polygenic risk scores showed that exercise-induced CA4 volume increase significantly correlates with OPCs. From animal models, it is evident that early life stress and oligodendrocyte-related gene variants lead to schizophrenia-related behavior, cognitive deficits, impaired oligodendrocyte maturation, and reduced myelin thickness. **Conclusions:** Based on these findings, we propose that promyelinating drugs (e.g., the histamine blocker clemastine) combined with aerobic exercise training may foster the regeneration of myelin plasticity as a basis for restoring frontotemporal connectivity and cognition in schizophrenia.

**Key words:** oligodendrocytes/oligodendrocyte precursor cells,/myelination/cognition/hippocampus/prefrontal cortex

## Introduction

Each year, more than one-third of the European population experiences a mental disorder.<sup>1</sup> Among those disorders, schizophrenia (SZ) has the most unfavorable long-term outcome, and SZ is one of the 10 leading medical causes of years lived with disability worldwide.<sup>2</sup> The disease primarily affects young adults and leaves many of them with lifelong, untreatable deficits that are socially detrimental and cause high direct and indirect costs.<sup>3</sup> The costs are high because more than 50% of individuals with SZ develop residual symptoms, namely negative symptoms and, in particular, cognitive dysfunction, for which no effective pharmacological or psychotherapeutic treatment is available.<sup>4,5</sup> In addition, cognitive deficits are present before the onset of SZ and persist after symptomatic remission, further supporting the view that SZ is a cognitive illness.<sup>6</sup> Although individuals with SZ show deficits in all cognitive domains, the greatest deficits are seen in working and episodic memory, executive functioning, attention, and processing speed.<sup>7</sup>

Together, these symptoms lead to severe social disabilities and, ultimately, unfavorable social outcomes. In observational long-term studies, only 20% of patients show recovery, i.e., can maintain an unimpaired life despite residual symptoms, including cognitive dysfunction.<sup>8</sup> Although this finding emphasizes the critical role of cognitive deficits in SZ, we neither understand their pathophysiology nor

have a psychopharmacological treatment for them.<sup>9,10</sup> Unfortunately, the initial hope that second-generation antipsychotics would substantially improve cognitive and negative symptoms was not fulfilled.<sup>4,11</sup> Furthermore, over the past decade the pharmacological industry has largely withdrawn from the mental health field.<sup>12</sup> Thus, there is clear a need for drugs that (1) have a mode of action strongly rooted in the pathophysiology of SZ, (2) target symptom domains not really accessible with antipsychotics, and (3) are of no financial interest to pharmaceutical companies because the drugs are repurposed and thus lack commercial potential, allowing academic psychiatry to study them in preclinical and clinical research. Psychopharmacological treatment should be combined with evidence-based add-on treatment approaches, e.g., cognitive remediation or aerobic exercise, which have been shown in meta-analyses to have beneficial effects on global cognition, everyday functioning, and negative symptoms.<sup>13–15</sup> Overall, delivering an understanding of the pathophysiology of cognitive dysfunction and introducing mechanistically informed, causal treatments may turn SZ from a devastating mental illness that leads to social disability into a treatable disease with a fair outcome for many patients.

#### *SZ is a Dysconnectivity Disorder*

Functional neuroimaging and neurophysiology findings led to SZ being considered as a disorder of dysconnectivity.<sup>16</sup> A meta-analysis of more than 8000 patients and 8000 controls across psychiatric disorders, including SZ, provided evidence for alterations of resting-state functional connectivity in brain networks underlying cognitive dysfunction.<sup>17</sup> In animal models and patients with SZ, a disturbance of prefrontal-hippocampal functional connectivity underlies working memory deficits<sup>18,19</sup>; and in patients, reduced volumes of the dorsolateral prefrontal cortex (DLPFC) and hippocampus, including its subfields, are associated with disturbed cognition.<sup>20,21</sup>

Supporting evidence comes from diffusion-weighted magnetic resonance imaging (dMRI) studies that characterize structural connectivity and white matter microstructure.<sup>22</sup> Most dMRI studies in SZ report lower fractional anisotropy (FA) across the lifespan<sup>23,24</sup> and interpret findings as indicators of abnormal fiber density, myelination, or tract coherence.<sup>25</sup> White matter abnormalities are widespread,<sup>24</sup> but findings suggest that FA reductions are particularly pronounced in the white matter of the left frontal and temporal lobes,<sup>26</sup> as well as in frontolimbic and frontotemporal circuitries.<sup>27,28</sup> Notably, white matter microstructural abnormalities are more pronounced in individuals with lower cognitive performance,<sup>29,30</sup> are associated with the level of functioning,<sup>30</sup> and indicate a deficit subtype of SZ.<sup>31</sup>

At the cellular level, macro-connectivity in the central nervous system is mediated through oligodendrocytes (OLs), which form myelin sheaths around multiple axons,

facilitate rapid excitation conduction, and maintain axonal integrity.<sup>32</sup> OLs arise from maturation and differentiation of oligodendrocyte precursor cells (OPCs) during development and are also critical for efficient regeneration of myelin in demyelinating diseases.<sup>33</sup> Myelination of axons and development of white matter occur at a high rate in the first years of childhood<sup>34</sup> and continue until young adulthood.<sup>35</sup> Myelination depends on proper OL function at all stages of neurodevelopment. Consequently, OL dysfunction leads to disturbances in myelination and connectivity, and—at the functional level—may also lead to cognitive deficits.<sup>36</sup> We hypothesize that disturbed neurodevelopment involving genetic and environmental factors may negatively modulate connectivity-related adaptations, including OL function and myelination. This pathophysiological process may also contribute to the failure of circuit functions at later stages of experience-dependent shaping of higher-order neural networks.

#### *OL-Related Genetic Variants in SZ*

SZ has a multifactorial origin, and genetic and environmental factors are important risk factors that may interact during neurodevelopment to induce symptoms of the disease in early adulthood.<sup>37</sup> Over the last few years, large-scale genomics approaches have examined 69 369 patients and 236 642 controls and identified 270 independent genetic risk loci for SZ.<sup>38</sup> OL-related risk variants are not among the top associations in genome-wide association studies. However, in an enrichment analysis study of cell type-specific gene expression in humans, OLs and OPCs showed enrichment in genes associated with SZ.<sup>39</sup> In a dMRI study, OL-related gene variants, such as myelin-associated glycoprotein (MAG), were associated with white matter microstructure and cognitive performance in patients with SZ.<sup>31</sup> Interestingly, a single nucleotide polymorphism of the gene OL lineage transcription factor 2 (*OLIG2*), which is predominantly expressed in and required for the maturation of OPCs, was also associated with reduced white matter FA, indicating impaired myelination in SZ.<sup>31</sup> Single nucleotide polymorphisms in the *OLIG2* gene have been identified as risk factors in Caucasian patients with SZ.<sup>40</sup> An *OLIG2* risk variant has been associated with abnormal white matter structure<sup>41</sup> and reduced whole-brain functional connectivity.<sup>42</sup> In the DLPFC, this risk allele predicted low expression of *OLIG2*.<sup>43</sup> In patients with SZ, the density of *OLIG2* immunoreactive cells was reduced in the white matter of the DLPFC,<sup>44</sup> suggesting that postmortem studies are important for understanding the underlying cellular pathology.

#### *OL Deficit in SZ: Evidence From Human Postmortem Studies*

Over the last 15 years, our working group has focused on understanding the underpinnings of cognitive

dysfunction in SZ. In design-based stereology studies, we found a significant reduction of the number of OLs post-mortem in the cornu ammonis 4 (CA4) subregion of the hippocampus in SZ,<sup>45,46</sup> and we were able to replicate this finding in an independent sample.<sup>47</sup> This finding was not present in patients with bipolar disorder or major depression,<sup>48</sup> and in patients with SZ, it significantly correlated with a presence of “definite cognitive dysfunction” in the patients’ medical records.<sup>49</sup> A previous stereological study targeting the DLPFC in SZ revealed a loss of OLs, indicating a network problem involving frontotemporal regions.<sup>50</sup> Moreover, electron microscopy studies provided evidence of damaged myelin sheaths, myelin degeneration, and apoptosis/necrosis of perineuronal OLs in the prefrontal cortex of patients with SZ.<sup>51,52</sup> Transcriptomic studies showed decreased expression of myelin- and OL-related proteins, such as MAG and myelin basic protein (MBP).<sup>53,54</sup> In our own proteomic studies, we were able to replicate decreased expression of myelin- and OL-related proteins, such as myelin OL glycoprotein and MBP.<sup>55</sup> As a final point, postmortem studies have shown that a reduced number of OLs in the hippocampus correlates with a volume decrease in connected brain regions of the Papez circuit, particularly in the hypothalamus and mediodorsal thalamus, indicating that OLs are possibly to be essential for proper cognitive processing.<sup>49,56</sup>

#### *Animal Models Help to Understand the Molecular Basis of Myelin Plasticity and Cognition*

Myelination in the brain is experience dependent and can be influenced by environmental factors during neurodevelopment.<sup>37</sup> In nonhuman primates and mouse models, maternal immune activation induces mild inflammation and is known to cause SZ-related behavior (in early adulthood), demyelination, and alterations in synaptic and oligodendrocyte-related gene expression.<sup>57,58</sup> In a meta-analysis, obstetric complications were shown to be a risk factor for SZ<sup>59</sup> and to be accompanied by white matter injury, inflammation, impaired OL maturation, and myelin damage.<sup>60</sup> In addition, disturbances in myelination caused by stress during neurodevelopment have been hypothesized to play an essential role in SZ. Epidemiological studies clearly show that exposure to early life stress in the form of childhood abuse and neglect increases the risk for later development of SZ<sup>61</sup> and negatively influences cognition in patients with SZ.<sup>62,63</sup> A mouse model of juvenile social isolation (SI) mimics this feature and shows that application of SI immediately after weaning leads to SZ-related behavior (ie, deficits in prepulse inhibition of the acoustic startle response and in working memory), deficits in OL morphology, reduced myelin thickness, and decreased MBP and MAG expression.<sup>64,65</sup> Importantly, in contrast to the effects of SI in adults, this early induced phenotype cannot be rescued by later social reintegration,<sup>65</sup> which might reflect poor

functional remission rates in SZ. Besides the SI model, mutant mouse models also support the role of OLs in the pathophysiology of SZ. One earlier study showed that in cortices of *Olig2* knockout animals, myelination was arrested at the progenitor stage.<sup>66</sup> Recently, another study in adult *Olig2* knockout mice showed that myelination was inhibited in the cortex and hippocampus, and importantly, that mutant mice had a pronounced working memory deficit.<sup>67</sup>

One of the most replicated SNP-associated SZ risk genes is transcription factor 4 (*TCF4*),<sup>68</sup> a gene that is also related to cognitive deficits.<sup>69</sup> *TCF4* encodes a class I basic helix-loop-helix transcription factor. If combined with social defeat in mice, *Tcf4* single nucleotide polymorphisms significantly contribute to SZ-relevant endophenotypes, such as deficits in prepulse inhibition and cognitive flexibility.<sup>70–74</sup> Recently, in double heterozygous *Tcf4/Olig2* null mutant mice, TCF4 was shown to be the preferred heterodimerization partner for OLIG2 in OLs and required for oligodendrocyte precursor cells (OPC) differentiation.<sup>75</sup> Double heterozygous *Tcf4/Olig2* mice have defects in OPC generation and display reduced numbers of OLs.<sup>75</sup>

Animal models do not entirely map SZ phenotypes but may express species-overlapping phenotypes of specific behavioral domains, including cognition. The mouse models described above are thus context-specific and possibly to be suitable for mirroring the disturbed neurodevelopmental trajectories in OPC development and OL differentiation, forming the basis for developing new treatment strategies targeting myelin plasticity in SZ.

#### *Human-Induced Pluripotent Stem Cells as a Novel Tool to Assess OL Plasticity*

Until the last decade, cellular-level research in biological psychiatry was restricted to postmortem investigations. The advent of human induced pluripotent stem cell (hiPSC) technology in 2008 enabled the reprogramming of stem cells from peripheral tissue (eg, blood and fibroblasts) and their differentiation into any cell type of the body, including brain cells (ie, neurons, astrocytes, OPCs, and OLs). This approach now enables personalized disease modelling<sup>76,77</sup> and allows OL biology to be studied in “living” and functional cells, thereby overcoming the limitations of postmortem studies, such as disease duration and confounding effects of treatment. hiPSC technology might enable the investigation of the presumed OL dysfunction and disturbed myelin plasticity in SZ.<sup>78</sup> So far, 2 studies in cohorts of sporadic SZ have highlighted a cell-autonomous OL deficit: In glial progenitor cells, Windrem et al.<sup>79</sup> revealed a disturbed transcriptome with impaired differentiation, maturation, and signaling pathways in patients compared with healthy controls; moreover, implantation of OPCs from patients into mice showed impaired myelination potential of these cells in

the mouse chimeras.<sup>79</sup> In a differentiation assay that compared hiPSC lines from patients with SZ and healthy controls, McPhie et al. found fewer O4-positive late OPCs and OLs and, in an MRI investigation, showed an association between individual white matter myelin content and the number of O4-positive cells.<sup>80</sup>

Initial differentiation protocols used cell culture media with chemical compositions that supported OL differentiation from hiPSCs<sup>81</sup> within 55 to 200 days. In contrast, recent and more efficient protocols have used the overexpression of lineage-determining transcription factors to achieve OL differentiation within 20 days.<sup>82–84</sup> These latter approaches may support the scalability and application of methods to study cellular disease mechanisms in translational SZ cohorts.

#### *Aerobic Exercise Improves Cognition and Hippocampal Plasticity in Patients With SZ*

Motivated by the seminal animal work by van Praag et al. showing that physical activity stimulates adult neurogenesis and enhances cognitive performance,<sup>85</sup> we performed the first 3-arm trial of physical exercise in patients with SZ. We found that 3 × 30 minutes of indoor cycling per week over 3 months significantly increased hippocampal volumes in patients with multi-episode SZ.<sup>86</sup> In parallel, we found that cognition improved in patients performing aerobic exercise and showed that this improvement was related to increased hippocampal volume.<sup>86</sup> Subsequently, several international groups performed exercise studies in SZ, which fueled meta-analyses.<sup>13,87</sup> These meta-analyses demonstrated that physical exercise improves cognition, including social cognition, and has the largest effects on global cognition, attention and vigilance, working memory, and verbal learning, all of which belong to the cognitive domains affected in SZ. In a second 3-arm study, we combined physical exercise and cognitive remediation and found that the combination—but not cognitive remediation alone—had a significant effect on everyday functioning as assessed by the global assessment of functioning.<sup>88,89</sup> Improvement in global assessment of functioning was related to a volume increase of the right hippocampal subfields CA3 and CA4.<sup>90</sup> In a multicenter aerobic exercise study in patients with SZ,<sup>91</sup> we detected a positive association of aerobic fitness with right hippocampal volume and white matter volumes in parahippocampal regions.<sup>92</sup> On the subfield level, we found associations between aerobic fitness levels and increases in hippocampal volumes, with the strongest effects for the right CA3 and CA4 head.<sup>93</sup> Furthermore, aerobic fitness in patients with SZ is related to widespread functional connectivity patterns across the whole brain, with the most pronounced links between the temporal lobe, basal ganglia, and cerebellum.<sup>94</sup> In addition, aerobic exercise was shown to improve white matter organization in patients with SZ,<sup>95</sup> suggesting a possible trophic effect

of aerobic exercise on myelin structure, possibly by stimulating plastic, regenerative mechanisms.

Over the last few years, genome-wide association studies have provided solid and replicable results on the important role of common variation in SZ.<sup>38,68</sup> SZ polygenic risk scores (SZ-PRSs) represent additive weighted sums of SNP effects across different *P*-value thresholds and provide a measure of risk to develop SZ.<sup>96</sup> In an attempt to understand the underlying mechanisms of brain plasticity mediated by exercise, we performed a GWAS on all participants in our second exercise study and found that SZ-PRSs correlated negatively with the volume increase in the hippocampal subfields.<sup>97</sup> This finding suggests that high SZ-PRSs are related to reduced levels of brain plasticity; however, as described above, brain plasticity may be improved by physical exercise. A study on cell-specific PRSs showed that this effect is confined to OPCs and radial glia, indicating that the dysregulated maturation of OPCs might be central to understanding the pathophysiology of cognitive deficits in SZ.<sup>98</sup> Future longitudinal studies with a deeper investigation of hiPSCs and multimodal neuroimaging in larger cohorts will hopefully pave the way for a better understanding of OPCs as cellular treatment targets in SZ.

#### *Treatment Avenue: Repurposed Drugs Targeting Myelination*

To date, no treatment is available for the myelination and OL-related deficits that may underly cognitive deficits in SZ. In this context, drug repurposing is a promising tool to address new treatment targets, with the aim to improve illness outcomes in SZ in a shorter time than is required for the usual drug development process, which can take decades. New treatment strategies targeting deficits in OL-related pathological processes could aim to improve differentiation of OPCs. Because OPCs are responsible for remyelination, new myelinating OLs could rescue deficits of white matter structures, thereby promoting macro-connectivity and possibly also improving cognitive symptoms.

Clemastine is a safe, first-generation histamine H1 receptor antagonist with several hydrophobic functional groups that enable it to cross the blood-brain barrier. In fact, all H1 antihistamines easily cross the blood-brain barrier,<sup>99</sup> where they not only bind nonselectively to H1 receptors, but also interact with adrenergic, serotonergic, and cholinergic receptors.<sup>100</sup> High-throughput screening of a library containing small compounds approved by the Food and Drug Administration identified clemastine as a leading candidate for enhancing myelin formation,<sup>101</sup> and in mice with demyelinating lesions, clemastine was shown to promote OPC differentiation and remyelination.<sup>102</sup> In adult mice exposed to SI, clemastine enhanced OL differentiation and myelination and improved also social avoidance behavior.<sup>103</sup> In a cuprizone-induced mouse model of

demyelination, in which mice display SZ-like behavioral changes, clemastine enhanced myelin repair in demyelinated regions of the brain, increased the number of mature OLs and amount of MBP, rescued behavioral deficits, including those in working memory, and improved anxiety.<sup>104</sup> However, other cognitive domains need to be investigated in more detail in SZ-related animal models. Because of its good safety, good blood-brain barrier penetrance, and efficacy in promoting OPC differentiation and remyelination in animal models, clemastine was selected by a panel of experts and people with multiple sclerosis as a prioritized licensed drug for repurposing in the treatment of progressive multiple sclerosis.<sup>105</sup> In a cross-over design, patients with multiple sclerosis received 8 mg/day clemastine, corresponding to 10.72 mg/day clemastine fumarate, for a total of 90 days. Participants showed significant shortening of P100 latency in visually evoked potential, indicating myelin repair even after prolonged damage.<sup>106</sup>

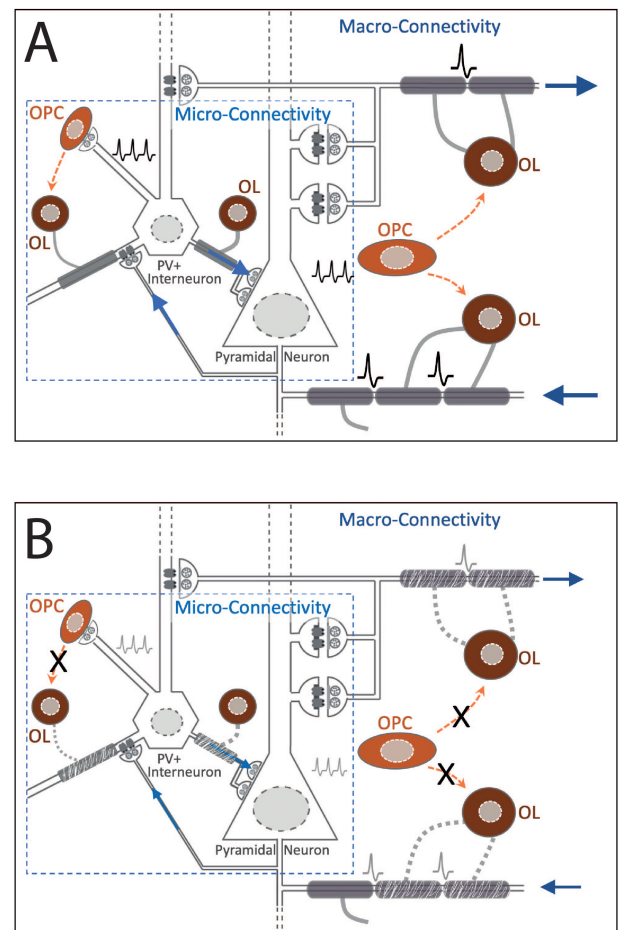
In addition to these promising clinical trials, animal models suggest that clemastine and aerobic exercise have positive bidirectional effects.<sup>107</sup> Ideally, in patients with SZ, combining these interventions should increase both the proportion of remyelinated axons and the thickness of myelin and thus accelerate the conduction of impulses along axons and, consequently, improve cognition, and everyday functioning.

Besides clemastine, miconazole (an antifungal agent), and clobetasol (a corticosteroid) also improve remyelination and maturation of OLs: In a mouse toxin model of demyelination, both substances enhanced remyelination and increased the number of new OLs.<sup>108</sup> Moreover, in mouse pluripotent epiblast stem cell-derived OPCs, treatment with these drugs enhanced the generation of mature OLs and thus OPC differentiation.<sup>108</sup> However, their effects on human OPCs remain to be determined.

#### *A New Hypothesis for Cognitive Dysfunction in SZ*

SZ is a disorder of disturbed sensory and cognitive processing that is at least partially caused by a disconnection between frontotemporal brain regions, especially between the hippocampus and DLPFC. A body of evidence (see figure 1) suggests that cognitive deficits in at least a subgroup of patients with SZ may be related to a reduced number of OLs in the CA4 subregion of the hippocampus and in the DLPFC.<sup>45,46,109</sup>

Cell-specific PRS data show that a fraction of the genetic risk for SZ is linked to OPCs and radial glia in the CA4 subregion<sup>98</sup> and that it likely mediates impaired regenerative mechanisms in the hippocampus.<sup>110</sup> The OL-associated deficit in hippocampal CA4 has been linked to volume decreases in connected brain regions that are crucial for cognitive processes.<sup>56</sup> For several reasons, we hypothesize that disturbed maturation of OPCs and

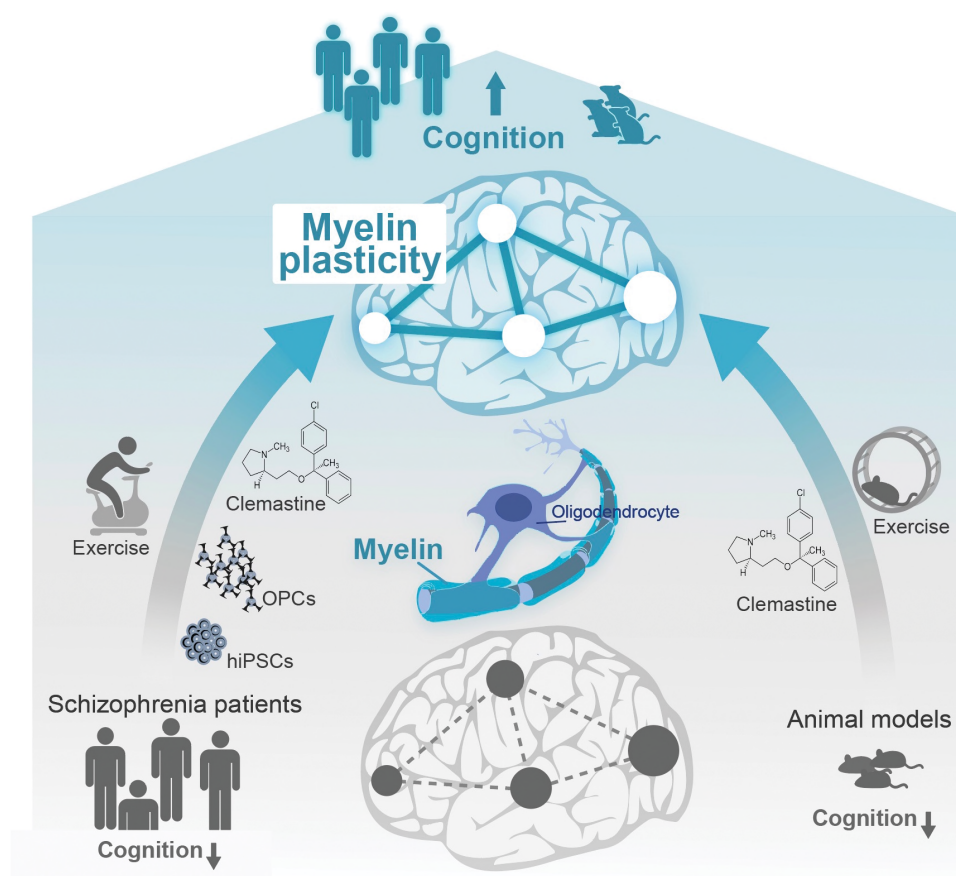


**Fig. 1.** Alterations of oligodendrocyte differentiation and myelination of axons from pyramidal neurons and interneurons as the basis of a new hypothesis of schizophrenia pathophysiology involving deficits in connectivity and cognition. (A) Oligodendrocytes (OL) function in healthy brains. OPC differentiate into OLs and are capable of myelination of parvalbumin-immunopositive (PV+) interneurons, a major subgroup of interneurons. OLs provide trophic support to interneurons in the form of lactate, thereby contributing to energy metabolism and enabling inhibitory properties of gamma-aminobutyric acid (GABA) ergic synapses on glutamatergic pyramidal neurons and micro-connectivity. OLs also provide trophic support by myelinating axons of pyramidal neurons, promoting rapid nerve cell conductance in long-range projecting axons in neuronal circuits and enabling proper macro-connectivity. (B) Proposed OL pathology in schizophrenia and link to the hypothesis of an inhibitory interneuron deficit. OPC differentiation into mature OLs is impaired, resulting in deficits in both myelination and trophic support of interneurons. The reduced number of mature OLs results in a functional deficit of inhibitory control of synapses from PV + interneurons and leads to impaired micro-connectivity. Impaired myelination of long-range projecting axons from pyramidal cells leads to deficits in macro-connectivity and is the basis of impaired structural and functional connectivity, thereby causing subsequent cognitive deficits in schizophrenia. OL, oligodendrocyte; OPC, oligodendrocyte precursor cell; PV+, parvalbumin-immunopositive.

OLs has widespread effects on the pathophysiology of SZ: (1) On the macrostructural level, there is evidence that disturbed OPC maturation may lead to abnormal structural macro-connectivity of myelinated white matter tracts between frontal and temporal brain regions (figure 1), (2) on the molecular level, studies have suggested that OLs are metabolically coupled to axons,<sup>111</sup> and indeed, support for the axonal neuron metabolism is provided by the finding that glycolytic OLs deliver lactate as an energy source to neuronal mitochondria,<sup>32</sup> and (3) OPCs are known to form a structured synaptic network with input from interneurons.<sup>112</sup> A functional deficit of hippocampal and prefrontal inhibitory interneurons, with decreased expression of parvalbumin, has been proposed as a core part of the pathophysiology of SZ.<sup>113,114</sup> The origin of the alteration of these interneurons may be the consequence of multiple factors, such as deficits in glutamate transmission,<sup>115</sup> oxidative stress,<sup>116</sup> and mitochondrial dysregulation.<sup>117</sup> However, myelination deficits may also play a role because parvalbuminergic interneurons in particular are myelinated in the cortex and hippocampus of

mice and humans.<sup>118,119</sup> Therefore, a disturbed cross-talk between interneurons and OLs may partially underlie the reduced micro-connectivity in SZ (figure 1).<sup>120</sup>

In addition, we hypothesize that in at least a subgroup of SZ patients, number of mature OLs are reduced because of impaired differentiation of OPCs. This dysmaturation of OLs may be triggered by genetic and epigenetic processes at different stages of brain development and maturation. Although environment-induced epigenetic alterations in SZ may be independent of OLs, there is increasing evidence for their impact on OL dysfunction. OL differentiation is known to be regulated by histone deacetylases (HDACs) at the level of chromatin because pharmacological inhibition of HDAC activity causes a delay in OPC differentiation and myelination.<sup>121,122</sup> Conditional deletion of HDAC1 and HDAC2 in OLs leads to a loss of OLs and OPCs.<sup>123</sup> Small-coding RNAs such as microRNAs are considered to be the “epigenetic micromanagers” of gene expression and have roles in cellular differentiation and maintenance. Specific microRNA-target interactions are involved in the



**Fig. 2.** A proposed therapeutic approach to restore differentiation of oligodendrocyte precursor cells to oligodendrocytes and myelination in patients with schizophrenia. Aerobic exercise and clemastine treatment are combined to improve myelin plasticity in the brain, thus improving connectivity and cognitive function. The background and mechanisms of schizophrenia-related behavior and treatment effects can be assessed in more detail in patient-derived human pluripotent stem cells and animal models of oligodendrocyte pathology mirroring working memory deficits. hiPSCs, human pluripotent stem cells; OPCs, oligodendrocyte precursor cells.

differentiation of progenitor cells into neuronal or glial cells, and dysregulated expression of microRNAs has been reported in patients with SZ.<sup>124</sup> In SZ, research has identified a significant gene-microRNA interaction network that includes microRNA-92a, microRNA-134, and microRNA-495 and converges with differentially expressed genes involved in OL function. These microRNAs build a regulatory network with OL genes such as OL lineage transcription factor 1 (OLIG1) and myelin proteolipid protein (PLP).<sup>125</sup> MicroRNAs with predicted target genes enriched for OL function and myelination play an important role in OPC differentiation.<sup>126</sup> Disturbed OL maturation during vulnerable brain development periods may lead to reduced conduction velocities and feed into functionally disturbed micro- and macro-circuitry (figure 1). Other environmental stressors of the circuitry, such as obstetric complications<sup>127</sup> and trauma,<sup>63</sup> may also interrupt OL maturation.

Because OPCs are capable of remyelination upon differentiation to OLs,<sup>33</sup> they may be a promising cellular target for SZ treatment that addresses cognition, including social cognition (figure 2). When aerobic exercise is used as a regenerative stimulus, the maturational process is reactivated in approximately 40% of patients with SZ, enhancing recovery.<sup>90</sup> In the remaining 60% of patients in whom the process is not reactivated, the administration of drugs such as clemastine may enhance the proliferation and differentiation of OPCs, thereby improving the dysfunctions in regenerative processes underlying the pathophysiology of SZ.<sup>110</sup> In addition, animal models with impaired myelin plasticity may provide insights into the neurobiological processes of treatment effects on cognitive function (figure 2).

In summary, research has shown that disconnectivity in SZ may be related to myelination deficits. So far, physical exercise is the only existing non-pharmacological treatment to enhance myelin plasticity and consequently improve cognition in SZ. Stimulating myelin plasticity and enhancing OPC differentiation and as yet unidentified OL-based molecular mechanisms by combining aerobic exercise with repurposed drugs represents a promising and unexplored approach to assess cognitive domains affected in SZ, including social cognition.

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