Review

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Functional Myelin in Cognition and Neurodevelopmental Disorders

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ABSTRACT: In vertebrates, oligodendrocytes (OLs) are glial cells of the central nervous system (CNS) responsible for the formation of the myelin sheath that surrounds the axons of neurons. The myelin sheath plays a crucial role in the transmission of neuronal information by promoting the rapid saltatory conduction of action potentials and providing neurons with structural and metabolic support. Saltatory conduction, first described in the peripheral nervous system (PNS), is now generally recognized as a universal evolutionary innovation to respond quickly to the environment: myelin helps us think and act fast. However, the function of myelin in the CNS, particularly in the brain, is not necessarily to act quickly, but rather to act correctly. In this respect, myelin should primarily play a role in synchronizing the different neuronal networks, a synchrony that occurs in the form of oscillations (or rhythms) relevant for specific information processing. Interestingly, myelin has been directly involved in different types of cognitive processes relying on brain oscillations, and myelin plasticity is currently considered to be part of the fundamental mechanisms for memory formation and maintenance. However, despite ample evidence showing the involvement of myelin in cognition and neurodevelopmental disorders characterized by cognitive impairments, the link between myelin, brain oscillations, cognition and disease is not yet fully understood. In this review, we aim to highlight what is known and what remains to be explored to understand the role of myelin in high order brain processes.

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INTRODUCTION

In the central nervous system (CNS), oligodendrocytes (OLs) are responsible for the production and maintenance of the myelin sheath. OLs originate from oligodendrocyte precursor cells (OPCs), which arise in the embryonic (ventral OPCs) and postnatal (dorsal OPCs) mouse telencephalon in distinct successive waves [1,2]. OPCs also persist as a major pool of progenitors in the adult brain long after oligodendrogenesis, and promote remyelination when necessary [3–9]. However, they should not be constrained to their OL progenitor function as they are arising as circuit regulators in the parenchyma with functions ranging from neuronal migration to glial scar formation [10]. Along the same line, an extensive body of evidence links OLs to a variety of roles such as energy metabolism, neuroprotection, axonal maintenance and information processing [11–14], all of which have often been highlighted by studying myelin.

The myelin sheath is a highly specialized multilamellar membrane that wraps axons. Central myelin is structured by an ensemble of compact interconnected lamellae of membrane that contact the axon through terminal loops forming the axo-glial paranodal junction directly followed by the juxtaparanode located beneath the compacted myelin of the internode [15,16]. What we usually refer to as the myelin sheath is the single entity formed by the paranodes, juxtaparanodes and the internode. Adjacent myelin sheaths are separated by nodes of Ranvier (NORs) [17], unmyelinated regions where the nerve fiber is laid bare and frequently contacted by other glial cells including astrocytes [18,19], OPCs [20] and microglia [21,22]. Myelin's high compartmentalization allows a distinctive sheath-axon interaction that serves various functional ends such as the delivery of glial

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metabolites [16,23]. In conjunction with the unmyelinated segments or NORs, the myelin sheath enables action potential regeneration and propagation along fibers of varying lengths, resulting in saltatory conduction, an energy-, space- and time-saving phenomenon.

The function of myelin can be approached at two different levels: at the local level, which consists of isolating axons, supporting them and ensuring bidirectional axo-glial communication, and at the general level, which orchestrates the interconnection of neuronal assemblies and functional brain hubs for complex information processing. In this review, we will first introduce some well-established concepts about the role of myelin in action potential conduction and axonal metabolism. Next, we will discuss the implications of myelin in cortical function and cognition, and assess whether myelination might modulate neuronal network activity and brain oscillations during the execution of cognitive processes. Finally, we will address the relevance of myelin defects in neurodevelopmental disorders associated with cognitive deficiencies.

MYELIN IN CONDUCTION AND METABOLIC COUPLING

Saltatory conduction has long been held as the main phenomenon resulting from myelin sheaths wrapping around electrically active axons [24,25]. In electrophysiological terms, myelin works such wonders by decreasing the capacitance of the axolemma while increasing resistance to ion flow. This achieves two important features: (1) conduction speed of action potentials is increased while (2) electrical properties are maintained throughout the traveled distance. Beyond physical insulation of the axon, the segregation of crucial proteins by the various segments of the sheath directly impacts impulse conduction. Voltage-gated sodium channels (Na_V channels) are exclusively stabilized at the NORs by the paranodal axo-glial junction [26,27]. In this small, well-defined region of the axon, an increase in membrane potential up to the threshold potential induces Na_V channels opening, generating the strong depolarization (or rising phase) characteristic of the action potential. These channels are then rapidly inactivated allowing potassium channels to repolarize the axon. Different voltage-gated K^+ channels ($K_V3.1b$ and $K_V7.2$ channels) as well as mechano- and thermo-sensitive K^+ channels (two-pore-domain potassium K2P channels), actively drive repolarization (or falling phase) at the NORs [28–30], wherein K_V1 channels located in the juxtaparanode contribute to the refractory period enabling high frequency firing [31,32]. Directly underneath the sheath, OL expression of inwardly rectifying potassium (K^+) channels (K_{ir} channels) allows K^+ buffering which probably underlies the establishment of axolemma resting potential and excitability, especially relevant in white matter tracts where astrocytes have limited access to axons [33]. Furthermore, a recently uncovered type of conduction termed "sub-myelin conduction", i.e. potential beneath the myelin sheath through the periaxonal and paranodal spaces, is primordial to the spatiotemporal outline of action potential saltation [34], further supporting the notion of an electrophysiological coupling between the axon and its myelin sheaths.

Beyond their promotion of fast saltatory conduction, myelin sheaths have emerged as central players in axon metabolism [14]. Axonal access to energy-rich extracellular metabolites is limited by myelin insulation and, consequently, the sheath itself has to ensure their supply. Reminiscent of the astrocytic "lactate shuttle", OLs transport lactate, a product of aerobic glycolysis, into the axon *via* a pair of specialized monocarboxylate transporters (glial MCT1 and axonal MCT2) allowing a myelin-axon metabolic crosstalk that is relevant both in health and disease [14,35,36]. This axo-glial coupling is highly plastic and follows axon energy needs through the retroactive action of axons on their myelin sheath. Notably, myelin senses axon signals such as glutamate which, by activating NMDA receptors enriched in OL processes, enables these glial cells to tune their energy production to neuronal activation [37,38]. Myelinating cells participate in other forms of axo-glial communication that have metabolic repercussions. The activity-dependent release of glutamate triggers the secretion by OLs of exosomes carrying a specific protein and RNA cargo which are internalized by neurons, improving viability and maintaining axonal integrity [39]. Moreover, exosomes released by OLs contribute to antioxidant protection of neurons by secreting ferritin heavy chain (FTH1), a strong iron chelator protein, into the adjacent extracellular space, preventing ferroptosis in neurons [40]. Although the functional and metabolic coupling between myelin sheaths and axons is important for the dynamics of myelin-axon interactions, its significance goes far beyond local crosstalk, as it determines the action potential waveform and affects neuronal coding and activity in a network, ultimately influencing information processing in the brain. Over the last decade, myelin has emerged

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as an important component of plasticity, memory and learning, moving away from its primary function associated with the transmission and velocity of action potentials.

MYELINATION HETEROGENEITY IN THE CORTEX

The cortex contains a patchwork of differentially myelinated axons belonging to both excitatory and inhibitory neurons. Presence and extent of myelination relies on axon diameter, as OLs tend to extensively myelinate larger axons [41,42] although complex patterns of myelination are also present in sub-diameter threshold axons hinting at other factors driving myelination heterogeneity. OL intrinsic properties [43], neuronal activity [44], as well as neuronal localization and type, all constitute major players in the myelination patterns of the CNS. Amongst these factors, the last of the aforementioned has sparked great interest in the myelin properties of local GABAergic interneurons and long projection neurons and their functional effects. High throughput electron microscopy which individually traces pyramidal cell proximal axons in the mouse somatosensory cortex uncovered a myelin gradient, with deep layer (V/VI) pyramidal cells displaying a higher myelin coverage compared to superficial layer (II/III) pyramidal neurons. Furthermore, superficial layer pyramidal cells display a distinct longitudinal myelin pattern with myelin sheaths being separated by long unmyelinated gaps (much longer than NORs) (Figure 1A, right; [45]). Local GABAergic fast-spiking parvalbumin-expressing interneurons (PV interneurons) are also highly myelinated and contribute to a large proportion of gray matter myelin content [46–48]. PV interneuron myelin topography is dictated by axonal diameter and interbranch distances in both human and rodent neocortex [49]. However, this myelination is limited to the proximal part of the axon (<3%), so that most of the axon is myelin free [47], suggesting the existence of other subtle interactions between OLs and specific axonal regions (Figure 1A, right). This myelination serves various purposes during cortical network activity as it is required to sustain high frequency firing and feedforward inhibition, both of which are cardinal to somatosensory processing [50]. Moreover, a flawed myelination of interneurons early in development impairs their autaptic self-inhibitory transmission and results in long-lasting functional defects [51]. Another compelling function of PV interneuron myelin sheaths is the clustering of mitochondria along the axon to adapt metabolic requirements during axonal activation [52]. Although white matter myelin has been extensively studied both in health and disease, we should exert caution when extending such findings to gray matter myelination which is protracted, sparse and, as shown above, has topographical and functional specificities not found in white matter tracts [53].

MYELIN IN COGNITIVE PROCESSING

Myelination in the CNS happens in a specific spatial and temporal order in both humans and rodents, and remains plastic and adaptive throughout life [54]. Myelin maturation in the brain progresses in a protracted fashion, from caudal to rostral, so that the prefrontal cortex (PFC) in both humans and rodents is still undergoing myelination well into early adulthood [55–60]. It is tempting thus to parallel this “late” maturation of the PFC in terms of myelination with the establishment of higher cognitive functions such as self-identity, sociability and decision making. In fact, correlation between white matter changes and cognitive functions over the course of human life establishes a link between myelin plasticity and cognitive development. Maturation of fronto-parietal and fronto-striatal white matter pathways correlates with protracted development of cognitive processes during adolescence and early adulthood [61]. Moreover, longitudinal brain imaging studies have shown that white matter volume –reflecting the myelin content and axonal caliber [62]– have a linear volume increase throughout childhood and adolescence [63]. As reported by fractional anisotropy in diffusion tensor Magnetic Resonance Imaging (MRI), an increase of myelin thickness in frontal white matter positively correlates with increased working memory scope in children [64]. In mice, sociability is related to myelination of the medial PFC (mPFC) as shown by the deleterious effect of social isolation immediately after weaning on both adult mPFC function and myelination [65]. Myelination is therefore a long-lasting process that represents a perfect “substrate” for the maturation and adaptability of cognition and behavior. However, although myelination and cognitive development correlate, the underlying mechanisms that link these two processes are not fully understood. Among a possible mechanism, early neuron-OL interactions may play a decisive role in both developmental myelination and neuronal maturation. In the developing neocortex, OPCs

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receive transient synaptic inputs from GABAergic interneurons, mainly PV interneurons, that disappear in juvenile mice [66,67]. The genetic inactivation of these neuro-glial synapses at an early stage of postnatal development does not have a major impact on OPC proliferation and differentiation, but leads to significant defects in interneuron myelination and in the maturation of cortical inhibitory circuits, affecting sensory discrimination [48,50]. Furthermore, early $GABA_B$ receptor-mediated signaling on OPCs induces the apoptosis of interneuron *via* the cytokine TWEAK pathway, resulting in the proper PV interneuron density and myelination in the adult CNS [68]. The specific ablation of these receptors in OPCs is associated to a hypo-activity of inhibitory networks causing an excitation-inhibition imbalance in the mPFC and severe social behavioral defects [68]. These studies highlight an important role of early interneuron-OPC communication and interneuron myelination in the establishment of cortical inhibitory circuits and cognitive function (Figure 1A).

Myelin remodeling has taken the spotlight as one of the main drivers of plasticity (both neuronal and behavioral) in the last decade. Myelin establishment during critical periods of early postnatal life is indeed important but not immutable, as OLs drive different myelination patterns in response to neuronal activity and experience throughout the individual's life [44,69–74]. During development, exposure to an early stress caused by maternal separation in mice induces a premature differentiation of OLs in the mPFC along with emotional and object recognition impairments in the adult that can be rescued by the chemogenetic activation of mPFC neurons during the two first weeks of life [75]. Furthermore, a hypomyelination phenotype induced by social isolation in juvenile animals can be reversed in the adult by re-socialization with socially housed mice, but not socially isolated mice [65,76]. Interestingly, prolonged social isolation in the adult specifically induces a decrease in myelin thickness and nuclear heterochromatin in the mPFC accompanied by a social defeat phenotype, while social re-integration for four weeks resulted in a recovery of myelin transcripts and social interaction behaviors [77]. Recent data on other tasks involving cognition also reveal that myelin is plastic and necessary for a proper behavioral performance. For instance, spatial memory consolidation during a Morris water maze test, resulting from a complex dialogue between PFC areas, such as the anterior cingulate cortex (ACC), and the hippocampus is altered when *de novo* myelination is prevented in the adult [78]. Along the same line, fear learning and a working memory task (radial arm maze) increase OPC proliferation and myelination, in the mPFC and ACC, respectively [79,80], while the inhibition of myelin formation impairs fear memory recall [80]. In these cognitive processes, reciprocal interactions between myelin and neuronal activity probably comes into play. Myelin plasticity could lead to potentiation or depression of conduction velocity along the axon, which could give rise to differential spike timings that are essential for neuronal network activity [50,72,73]. Myelination also affects synaptic transmission and the excitation-inhibition balance [50,81,82], thus having a potential impact on cortical oscillations and cognition (Figure 1; see next section). It should be noted, however, that some of these interactions may involve subtle mechanisms that go beyond a simple increase or decrease in the amount of myelin, as they may primarily produce a marked change in the length of NORs. Such a change has been observed following a repetitive transcranial magnetic stimulation or the execution of 8-arm radial arm maze task [83]. It should also be considered that it is difficult to disentangle the molecular and cellular pathways as well as the exact role of each player of the myelination process (OPC, OL or myelin) in the observed cognitive processing performances; further investigations are thus needed.

BRAIN OSCILLATIONS, MYELIN AND COGNITION

The cerebral cortex is characterized by a sustained activity reflected by the existence of rhythms or oscillations that can be divided into different frequency bands from 0.05Hz to 500Hz [84]. Each band is associated with different neuronal elements, such as membrane properties, population activity or inhibitory state, and its power and frequency can be differentially modulated by cognitive processes. Slow oscillations between 0.05Hz to 30Hz result from the coordinated activity of widely distributed neuronal ensembles, as in the case of theta-frequency synchrony (4-12 Hz) between the hippocampus and the mPFC during a spatial working memory task [85]. By contrast, high-frequency oscillations (30-500Hz) involve a small tissue volume and fewer neurons, and are considered a local phenomenon (Figure 1B, left). This is particularly true for gamma oscillations (30-90Hz), which constitute one of the key elements of information coding in the brain and are modulated by cognitive mechanisms such as attention, working memory, cognitive flexibility and social cognition (Figure 1B

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and C; [86]). Oscillations in the gamma band arise from the fast synchronization of excitatory neurons spiking activity that results from an effective and rapid inhibition, mainly provided by PV interneurons [84,86]. The control of the activity of a population of excitatory neurons by PV interneurons acts like a pacemaker, timing the network for a simultaneous discharge (peak of the cycle) followed by a subsequent silent period (trough of the cycle) [84]. Curiously, gamma rhythm has the same frequency range in several species regardless of the brain size. Furthermore, low- and high-frequency rhythms can be produced at the same time and interact with each other. One of the most widely studied rhythm interactions is the phase-amplitude coupling (PAC), in which the phase of the cycle is modulated by the slow oscillation and the power by the high-frequency oscillation, as first described for theta and gamma rhythms [87]. For instance, an increase of theta-gamma PAC power in the mPFC was associated with a better performance in working memory [88].

As mentioned before, myelin plasticity, as another form of activity-dependent plasticity, is relevant not only to nervous system development but also to complex information processing tasks. By its capacity to speed up action potentials and mediate proper spike-timing, it has been widely assumed that myelin influences the synchronization of neuronal ensembles (Figure 1B, right). On a broader scale, myelin architecture in humans correlates strongly with functional connectivity mediated by neuronal oscillations in the beta and low-gamma bands, reinforcing the idea of a close relationship between myelination and specific functional networks [89]. However, despite emerging evidence for the role of myelin in cognitive processes involving coupling and synchrony, few studies have attempted to disentangle its impact on the generation and maintenance of brain oscillations [90]. Mathematical modeling and simulations have addressed this question and propose that myelin facilitates the synchronization of axon spikes coming from a distant population of neurons whose activity is correlated [91]. The model predicts that myelin plasticity in response to local action potentials of myelinated axons adjusts the spike temporal dispersion that occurs across these individual axons, thereby optimizing the precision of axonal discharges and promoting synchrony. Although this work supports a role for myelin in the generation of cortical oscillations, the mechanism linking myelination and neuronal synchronization is probably more complex. In fact, it has been shown that OL-dependent metabolic deficits, independently of myelin content, also alter the temporal precision of neuronal spikes in the auditory system in vivo [12]. Moreover, the heterogeneity of myelination patterns, which is patchy in pyramidal cells [45] and restricted to the proximal part of the axon in PV cells of the cortex (Figure 1A, right; [47]), probably has an impact on axonal conduction and needs to be taken into account. In an experimental study using a cuprizone-induced demyelination mouse model, Dubey et al., assessed the role of myelin in the generation of oscillations in the primary somatosensory cortex [82]. They observed that demyelination selectively amplifies theta power during periods of quiet wakefulness (but not active states) and proposed that this effect was caused, at least in part, by a decrease in the excitability of PV interneurons and fast inhibitory transmission. Furthermore, in vivo optogenetic stimulation of PV interneurons at a low gamma frequency of 30 Hz maintains an oscillatory activity at this frequency in controls, but not following demyelination. By simultaneously recording the ACC region and the hippocampus immediately after contextual fear conditioning, Steadman et al. show that the coupling between spindle oscillations in the prefrontal cortex and sharp wave ripple oscillations in the hippocampus was increased in controls but unchanged in mice with a disrupted oligodendrogenesis [78]. These results indicate that the production of new OLs is required for learning-induced increases in coordinated hippocampal-cortical activity. However, this effect is probably not due to myelin deficiencies as it occurs just after training.

Despite sparse studies on the role of myelin in the synchronization of neuronal networks and brain rhythms, how myelin influences different brain oscillations during cognitive processes is largely underexplored. Local in vivo electrophysiological recordings in behaving mice with genetically determined or induced alterations in myelination would be necessary to unravel how myelin is involved in behaviorally modulated cortical rhythms. The detection and quantification of brain oscillations is an advanced field of neuroscience that allows multiple brain areas to be recorded simultaneously, in some cases using more than a thousand electrodes, while the animal performs a cognitive task. This type of study represents a major challenge and a future line of research in the field of myelin.

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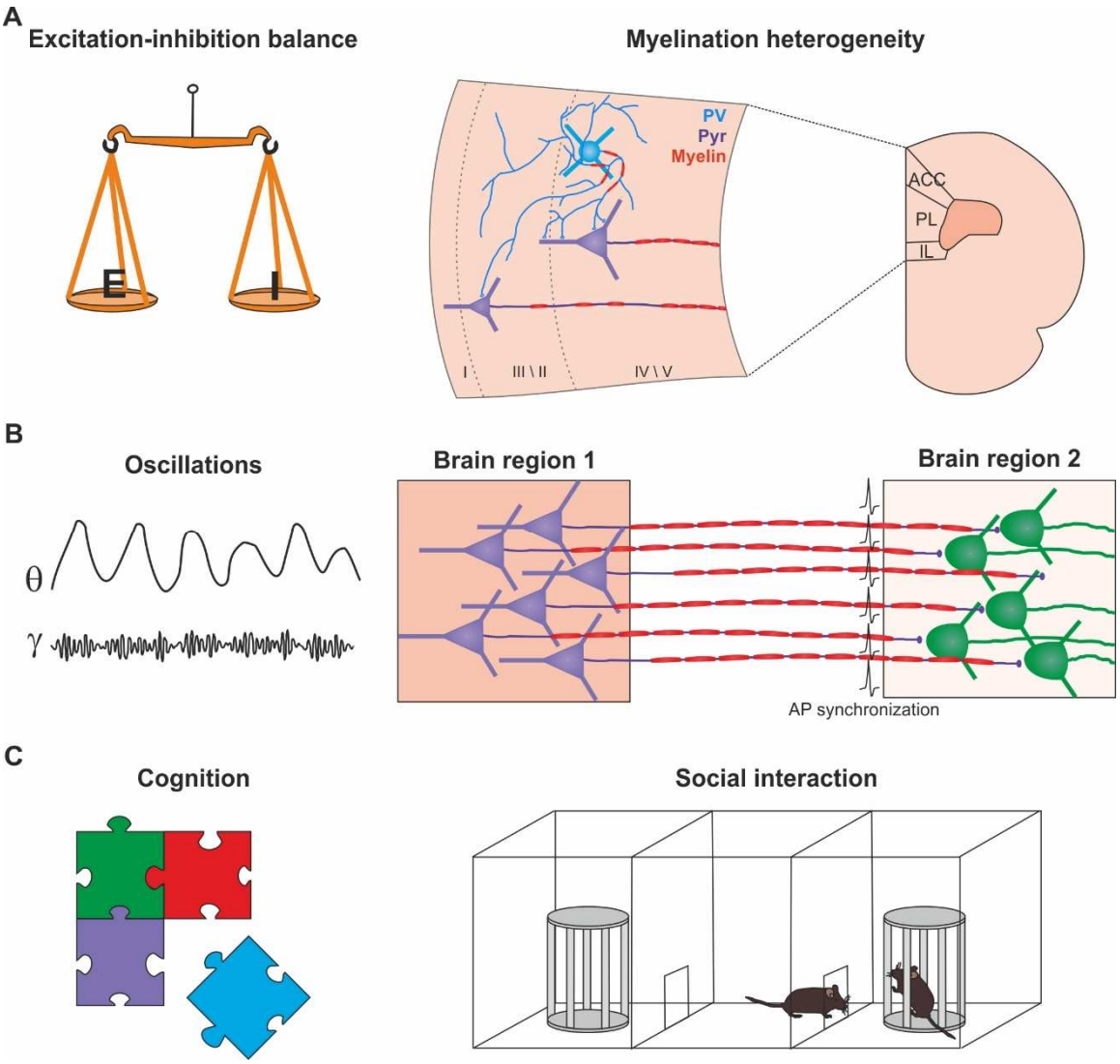

Figure 1. Summary of myelination effects at cellular, network and cognitive levels. A. Myelination patterns (myelin in red) of pyramidal neurons (pyr, purple) and PV interneurons (PV, blue) are different in the cortex, probably including the mPFC (right). It has been shown that myelination can affect the excitation-inhibition balance (left, Benamer et al., 2020). However, it is unknown how myelination heterogeneity impact conduction and synaptic transmission. IL and PL: infralimbic and prelimbic regions of the mPFC; ACC: anterior cingulate. **B.** Myelin may adjust the synchrony between neuronal ensembles of two distant brain regions (right). The synchrony of local (intracortical) and inter-regional neuronal networks generates brain oscillations at different frequencies such as gamma and theta, respectively (left). **C.** Myelin appear to be important for the proper perfomance of cognitive tasks such as social interactions. Behavioral performance also highly depends on brain oscillations which, in turn, are influenced by myelination.

MYELIN IN NEURODEVELOPMENTAL DISEASES (NDDs)

As an early onset phenomenon with a protracted evolution throughout life, myelin has emerged as a potential key player in NDDs, disorders that have their onset during childhood and adolescence. These two critical periods of development represent sensitive time windows for environmentally induced modifications and damage to central myelin structure and functions. Here we discuss the involvement of myelin in Autism Spectrum Disorders (ASD) and schizophrenia, two major NNDs characterized by overlapping symptoms such as communication difficulties and social withdrawal.

Autism Spectrum Disorders

As a classic example of NDD etiology, consisting of a mix of genetic and environmental risk factors, an accumulating body of evidence demonstrates that myelin deficits underlie altered communication between major brain hubs in ASD individuals [92]. As demonstrated by MRI Diffusion Tensor Imaging (DTI), white matter disruptions are widespread in children and adolescents

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with ASD [93–95]. Intriguingly, the callosal white matter of autistic patients is overgrown during the first two years of life, but tends to be smaller than controls as they age [96]. These observations in humans were recently confirmed and termed "precocious myelination" in a murine model of ASD (BTBR mice) in which both the number of OLs and the myelin content in the frontal brain were shown to be increased in neonatal pups [97]. This accelerated postnatal development of the brain in ASD patients that tends to normalize (and worsen) with age might be more nuanced for gray matter myelination. It has been shown using T1w and T2w MRI that the overall spatial patterns of intracortical myelin distribution are similar between ASD children 1.5 to 5.5 years old and typically developing children, but that the age-related increase in intracortical myelination is impaired in ASD [98]. At the cellular level, OPCs cultured from a mouse model of ASD ($Pten^{m3m4}$) have an enhanced proliferation rate and a premature maturation into OLs [99]. This defect does not lead in vivo to a greater number of OLs in the adult, as these cells die by apoptosis and produce abnormal myelin which fails to ensheath axons [99]. In another mouse model of ASD induced by the prenatal exposure to valproic acid, OL density and myelin content is decreased in adult mice in some of the main brain regions linked to social behavior, such as the mPFC, pyriform cortex and basolateral amygdala [100]. Integrated transcriptomic analyses of both ASD mouse models and ASD patients tissues further stress OL genes dysregulation and myelination defects across species, as a highlight in both syndromic and idiopathic ASD [101,102]. Another area of interest concerns myelin proteins such as MBP, that has been put forward as targeted by an abnormal autoimmune reaction in the ASD brain [103]. However, while molecular and cellular alterations in OL biology and myelination are a hallmark of ASD, it is unknown whether these are responsible for social behavior deficits in the disease. Interestingly, frontal cortex myelin thickness reduction has been associated with a murine model of Williams syndrome (WS), a non-canonical NDD characterized by hypersociability [104], proving that conflicting behaviors, hypersociability in WS vs hyposociability in ASD, can arise from similar myelin abnormalities (hypomyelination), further stressing the complex etiology and symptomatology of such disorders.

These studies in ASD have singled out myelin and myelinating cells as potential therapeutical targets in a few preclinical studies. Myelination enhancing compounds such as clemastine - which promotes OPC differentiation into OLs and has been studied as a promyelinating agent in other myelin-related diseases such multiple sclerosis [105]- appear to rescue the cellular, structural and behavioral phenotype of the ASD mouse model of Pitt-Hopkins syndrome [106], opening new and exciting areas of investigation for future therapies. Furthermore, in a mouse model of perinatal hypoxia (a condition commonly associated with ASD in humans), which exhibits significant myelination impairments, early environmental enrichment was also shown to selectively promote endogenous myelin regeneration and functional recovery in the developing white matter [107]. Therefore, an alternative therapeutic strategy to improve myelination and overturn white matter dysfunction might be found in early behavioral intervention and environmental enrichment.

Schizophrenia

Schizophrenia (SCZ) onset coincides with adolescence and early adulthood, but its origins can be traced back to earlier stages of development as some cognitive impairments, depression and negative symptoms can occur during childhood [108].A growing body of evidence suggests that myelin alterations are as prevalent in this disease as they are in ASD. Although the neurobiological mechanisms underlying SCZ are not fully understood, it has been proposed that genetic and environmental risk factors during the perinatal period, either *in utero* or in infancy, contribute to neurodevelopmental abnormalities that may lead to impaired myelination in the adult brain [109]. The use of myelinating cells and myelin as a prism to look at this disorder is compelling because myelination is a protracted developmental process in most of the brain regions found to be dysfunctional in SCZ [109,110]. Myelination impairments during development have been considered to result in a defective maturation of neuronal networks connectivity (the 'dysconnectivity' hypothesis), which could explain some of the varying cognitive symptoms in SCZ patients, including cognitive flexibility [111–114]. Similarly to ASD, imaging studies questioning the structural integrity of white matter and the inter-connectivity of various brain regions have provided a better understanding of structural insults in SCZ patients [110]. Although most of the metrics used in imaging can be related to various structural components of white matter (axon diameter, fiber density,

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myelination), foundational work investigating both total and frontal white matter regions suggested an overall hypomyelination of the corpus callosum in human SCZ patients [115]. These findings were corroborated by post-mortem analyses of the anterior frontal cortex which showed a reduction in the expression of the two OL-associated proteins, MAG and CNPase, in SCZ patients [115]. It was subsequently observed that frontal white matter is indeed recurrently defective in chronic patients [116–118]. On the other hand, a recent study focusing on gray matter highlights more intricate changes as some regions exhibit higher and others lower myelin content in first-episode treatment-naïve SCZ patients [119].

Recent genetic, epigenetic and biochemical analyses have corroborated OL dysfunction and abnormal expression of myelin-related genes and proteins [120,121] as well as a reduction in the density of OLs in layer V of the PFC in SCZ patients [122], hinting at possible insults to both the development and function of these cells in SCZ. One possible explanation could be found in OPC physiology, that was shown to be impaired in the PFC of SCZ patients [123]. Moreover, SCZ-like behaviors in juvenile mice such as impaired sociability can be elicited via a DNA hypermethylation, a hallmark risk factor of SCZ, that targets genes related to the OL lineage cells [124]. Overall, dysfunctional OL lineage cells could explain, to some extent, myelination damage in SCZ patients although the origins of such disorders and their temporal unfolding remain unsolved, ultimately interrogating if dysmyelination is a cause or a result of SCZ [109,117]. An important point of discord from human studies is the difficulty of untangling the mesh of possible myelin insults as studies include a heterogenous population of patients: chronic patients that have been medicated for years, first episode patients naïve for any treatment, high risk patients, familial genetic risk patients. They are usually age and gender matched with the controls but might still account for slight contradictory results. A standardization of patient cohorts is needed to confirm previous results and produce finer insight in the investigations. Although further research is needed in this regard, a recent report demonstrated that specific mutations in chondroitin sulfate proteoglycan 4 (CSPG4/NG2), a hallmark protein of OPCs, exhibited familial segregation in SCZ patients having significant abnormal white matter integrity [125], a finding in favor of a direct role of OL lineage cells in this disease.

All these studies confirm the importance of myelin in connecting functional hubs and synchronizing distant neuronal ensembles to generate optimal behavioral responses in a changing environment. Brain connectivity analyses indeed indicate that long-range connectivity is usually impaired in SCZ. Along with white matter integrity impairments, substantial evidence supports a causal role of local GABAergic interneuron dysfunction in linking cortical circuit and behavioral deficits in this disease [126]. Several reports have found that alterations in local oscillations, mainly gamma oscillations, occur during performance of cognitive control tasks [126–128]. As previously mentioned, synchronization of cortical networks in the gamma band frequency is highly dependent on the activity of PV interneurons, which provide robust perisomatic inhibitory control of excitatory neurons [129,130]. This probably explains why dysfunctions in PV interneurons and gamma oscillations have been associated with cognitive deficits characteristic of SCZ [126,131,132]. Interestingly, myelination defects occurred specifically in PV interneurons of the mPFC in a rat model displaying schizophrenia-like behaviours [133]. Considering these findings, the high levels of myelination of PV interneurons and the early and reciprocal interactions between cortical PV interneurons and OPCs, it might be possible that impairments in PV interneuron myelination compromise the integrity of precisely timed action potentials and local synchronization [134,135]. An interesting line of study in the field of myelin will be to investigate whether PV interneuron and OL lineage abnormalities can synergize to increase the risk of developing NDDs.

As for ASD, myelination could be a potential therapeutical target for SCZ. In accordance with this hypothesis, pro-myelinating drugs could be evaluated as precognitive interventions in first-episode patients. Antipsychotic drugs that could act on OL dysfunction by potentiating their differentiation and maturation, such as the NMDA receptor ligand D-serine, and lithium [136] are another area of excitement in terms of SCZ treatment, just like we previously discussed with promyelinating compounds as possible therapies for ASD.

CONCLUDING REMARKS

Myelin plays an undisputable role in cognitive processing due to its specific contribution in inter-regional as well as local connectivity. The recurrent mention of dysmyelination in various CNS

disorders characterized by cognitive and behavioral defects further underlines the importance of myelin. Deciphering the roots of flawed myelin in the complex landscape of brain diseases could be achieved by considering: (1) the extent to which OPCs and OLs are affected, (2) whether dysmyelination susceptibility is homogenous across neuronal populations, (3) the causal effects, is myelin programmed to be defective or is it defective due to its diseased environment?, and (4) the consequences of these defects on myelin function in the global and local connectivity of the CNS. It is clear that dysmyelination is most likely the result of a complex synergy of all aforementioned possibilities. Addressing each point separately will have the advantage of being technically straightforward, as discussed above, in addition to clearly delineating future therapeutical targets of interest, especially relevant for diseases such as NDDs.

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