Myelin plasticity modulates neural circuitry required for learning and behavior

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Abbreviations: DRG, dorsal root ganglion; M1, primary motor cortex; MBP, myelin basic protein; MRI, magnetic resonance imaging; MyRF, myelin regulatory factor; NMDAR, N-methyl-D-aspartate receptor; OLs, oligodendrocytes; OPCs, oligodendrocyte precursor cells; PLP1, proteolipid protein 1; TTX, tetrodotoxin

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Abstract

Oligodendrocytes, which form the myelin sheaths that insulate axons, regulate conduction velocity. Myelinated axons make up the brain's white matter and contribute to the efficiency of information processing by regulating the timing of neural activity. Traditionally, it has been thought that myelin is a static, inactive insulator around the axon. However, recent studies in humans using magnetic resonance imaging have shown that structural changes in the white matter occur during learning and training, suggesting that 1) white matter change depends on neural activity and 2) activity-dependent changes in white matter are essential for learning and behavior. Furthermore, suppression of oligodendrocytes and their progenitor cells leads to deficits in motor learning and remote fear memory consolidation, suggesting a causal relationship between glial function and the learning process. However, for technical reasons, it remains unclear how myelin-generating glia modulate neural circuitry and what underlying mechanisms they employ to affect learning and behavior. Recent advances in optical and genetic techniques have helped elucidate this mechanism. In this review, we highlight evidence that neural activities regulated by myelin plasticity play a pivotal role in learning and behavior and provide further insight into possible therapeutic targets for treating diseases accompanied by myelin impairment.

Keywords: behavior, learning, myelin plasticity, myelination, neural activity, neural circuitry, oligodendrocyte progenitor cell, oligodendrocyte

Introduction

Myelinated axons form white matter and act as cables to propagate information to distinct brain regions (Nave, 2010). Accumulating evidence from magnetic resonance imaging (MRI) studies in humans has shown that learning and training in skills, such as playing the piano and juggling, induce structural changes in white matter (Bengtsson et al., 2005; Sampaio-Baptista and Johansen-Berg, 2017; Scholz et al., 2009; Wang et al., 2014; Zatorre et al., 2012). Furthermore, a recent study in rodents has demonstrated that the structural changes detected by MRI during motor learning positively correlate with increases in the expression of myelin basic protein (MBP), which is one of the myelin-related proteins (Sampaio-Baptista et al., 2013), implicating myelin formation in the white-matter structural plasticity. Indeed, motor learning and fear memory induce proliferation of the oligodendrocyte precursor cells (OPCs) and promote their maturation into oligodendrocytes (OLs), resulting in increased myelin formation, which is required for learning and spatial memory (Gibson et al., 2014; McKenzie et al., 2014; Wang et al., 2020; Xiao et al., 2016). Thus, activity-dependent processes of OPCs and OLs affect myelin regulation and contribute to learning and behavior. In contrast, impaired regulation of myelination is frequently associated with learning deficits (McKenzie et al., 2014; Xiao et al., 2016), cognitive decline, and aging (Bennett and

Madden, 2014). In adults, social isolation causes impaired myelination in the prefrontal cortex (Liu et al., 2012; Makinodan et al., 2012). However, it remains unknown what changes in neural circuitry are associated with myelin plasticity. In the present review, we focus on the question of whether myelin plasticity affects neural activity and the extent to which such modifications are important for learning and behavior.

Activity-dependent functions of OPCs and OLs

In the central nervous system, OPCs proliferate and differentiate into premyelinating oligodendrocytes during the embryonic period, and subsequent myelination is initiated by contact between axons and premyelinating oligodendrocytes through various mechanisms (Nave and Werner, 2014), generating myelinating oligodendrocytes (**Figure 1**). For example, stabilization of these contacts can involve the Fyn tyrosine kinase component of lipid-rich membrane microdomains (Czopka et al., 2013), Rho A activity (Baer et al., 2009), and mRNA transport followed by local translation to MBP (Wake et al., 2011). Across the lifespan, the majority of myelination occurs during postnatal development, coinciding with secondary axonal elongation (Simpson et al., 2013). However, the OPCs continue to proliferate and differentiate, with the production of myelinating OLs, into adulthood (Rivers et al., 2008; Young et al., 2013). Indeed,

MRI studies in adult humans reveal structural plasticity in the myelin after learning and training, suggesting that the proliferation and differentiation of OPCs, which results in increased myelination, are associated with improved cognition and behavior (Sampaio-Baptista and Johansen-Berg, 2017). Furthermore, many experiments have addressed the regulation of OPC proliferation and differentiation, as well as myelination by the resultant mature OLs (Kato et al., 2018). Traditional experiments employing the application of tetrodotoxin (TTX) to the retina demonstrated that reductions in neural activity inhibit OPC proliferation in the optic nerve, suggesting that spontaneous activity can regulate the number of OLs (Barres and Raff, 1993). Electrical stimulation of the rat medullary corticospinal tract was shown to enhance OPC proliferation and differentiation via the N-methyl-D-aspartate receptor (NMDAR) (Li et al., 2010). More recently, optogenetic stimulation of layer-5 pyramidal neurons in the premotor cortex expressing channelrhodopsin-2 promoted the proliferation and differentiation of OPCs (Gibson et al., 2014). Moreover, chemo-genetic activation of somatosensory neurons proved sufficient to produce the same effect in the white matter (Mitew et al., 2018). However, in the motor cortex, voluntary exercise enhanced OPC differentiation but inhibited OPC proliferation (Simon et al., 2011), suggesting that different mechanisms regulate proliferation and differentiation. In the rodent, after experimental sensory

105 deprivation (whisker removal during development), a reduction in glutamatergic inputs
106 from the thalamus to the developing barrel cortex occurs, suppressing the proliferation
107 of OPCs within the affected barrel and altering their distribution (Mangin et al., 2012).
108 These findings indicate that neural activity regulates the proliferation and differentiation
109 of OPCs and their maturation into OLs. Indeed, synapse-like structures, composed of
110 OPCs and presynaptic elements, and non-synapse like structures, composed of OPCs
111 and axons, are known to respond to neural activity (**Figure 2a**), which causes the OPCs
112 to be distributed differently in different brain regions, such as the white matter (Doyle et
113 al., 2018; Kukley et al., 2007), cerebral cortex (Chittajallu et al., 2004), hippocampal
114 CA3 region (Bergles et al., 2000), and cerebellum (Lin et al., 2005). Furthermore, OPCs
115 express various types of neurotransmitter receptors, enabling them to respond to neural
116 activity, which regulates the proliferation and differentiation of these cells. This
117 regulation is mediated by Ca^{2+} signaling, which is downstream from neurotransmitter
118 receptors, such as the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
119 receptor (Bergles et al., 2000; Kukley et al., 2007; Ziskin et al., 2007), NMDAR
120 (Káradóttir et al., 2008), and gamma-aminobutyric acid type A receptor (Lin and
121 Bergles, 2004).
122

Regulation of myelin formation by neural activity

Whether oligodendrocytes require neural activity to myelinate axons has long been debated (See **Figure 1**). For example, OPCs can build myelin around dead axons that have been fixed with paraformaldehyde (Rosenberg et al., 2008) or around engineered nanofibers (Lee et al., 2012). These findings suggest that OPC differentiation and myelination is possible in the absence of dynamic signaling between OPCs and axons. However, when OLs are cultured without neurons, they produce myelin-related proteins and myelin sheath-like structures (Dubois-Dalcq et al., 1986) but with ultrastructural features insufficient for function (Lubetzki et al., 1993), suggesting that neural activity from axons is necessary for the proper formation of myelin sheaths. Consistent with this, reducing the firing of neurons with ocular TTX injections decreased the number of myelinated axon segments in the optic nerve (Demerens et al., 1996). In contrast, stimulation of repetitive action potential propagations promoted an increase in the extent of myelin formation (Wurtz and Ellisman, 1986), suggesting that myelin formation is activity-dependent. Moreover, in humans, MRI studies using diffusion tensor imaging revealed increases in the fractional anisotropy of the white matter that were associated with juggling (Scholz et al., 2009), reading (Carreiras et al., 2009), and playing the piano (Bengtsson et al., 2005), implying that neural activity contributes to

141 the formation of myelin in the adult brain.

142 Although the cellular mechanism underlying activity-dependent myelination remains
143 unknown, several hypothetical mechanisms have recently been suggested. In co-cultures
144 of dorsal root ganglion (DRG) neurons and OPCs, adenosine triphosphate released from
145 axons in response to electrical stimulation led to OPC differentiation and myelin
146 formation (Stevens et al., 2002). Glutamate released axonally from DRG neurons
147 enhanced the production of MBP by OPCs specifically at non-synaptic junction sites
148 between the neurons and the OPCs, an effect mediated by activation of the Fyn kinase
149 (**Figure 2b**) (Wake et al., 2011). In addition, signaling by neuregulin and brain-derived
150 neurotrophic factor promoted NMDAR-dependent myelin formation around active
151 axons (Lundgaard et al., 2013). Furthermore, recent studies using *in vivo* two-photon
152 imaging in zebrafish have shown that axonal secretion of neurotransmitters induced by
153 neural activity is required for myelin sheath maintenance (Hines et al., 2015) and
154 regulates the myelin segment number of individual OLs (Mensch et al., 2015). The
155 above findings suggest that activity-dependent proliferation and differentiation of OPCs
156 may alter the behavioral output of the young-adult brain as newly matured OLs
157 differentiate from OPCs and synthesize myelin (Rivers et al., 2008). However, two
158 observations indicate that OPC differentiation and myelination may be distinct

159 processes: the presence of mature oligodendrocytes without myelination in the adult
160 corpus callosum and the extent of myelination correlating with the numbers of mature
161 oligodendrocytes (Yeung et al., 2014).
162 Lastly, evidence suggests that neural activity induces spatiotemporal regulation of
163 myelination and oligodendrogenesis. First, a recent report has shown that newly local
164 MBP translation in OPC processes occurs after 40 minutes of electrical stimulation in
165 co-cultures of DRG neurons and OPCs (Wake et al., 2011). Second, during a 15 hour
166 imaging session in the zebrafish brain, it has been shown that activity-dependent
167 secretion of neurotransmitters from axons is required for the maintenance of the myelin
168 sheath (Hines et al., 2015). Third, it has been shown using *in vivo* two-photon imaging
169 that sensory enrichment with whisker stimulation for 21 days does not affect myelin
170 remodeling, but rather enhances oligodendrogenesis in the somatosensory cortex of
171 middle-aged animals (around 12 months) (Hughes et al., 2018). Thus, little is known
172 about the mechanism of activity-dependent myelination *in vivo*. Future studies should
173 aim to elucidate the timescale and axon site associated with the occurrence of activity-
174 dependent myelination using *in vivo* two-photon imaging in the adult mammalian
175 cortex.
176 In the following section, we will focus on whether the activity-dependent processes of

177 OPCs, OLs, and myelination affect learning and behavior as well as the associated
178 neural circuitry.
179
180 **Myelin plasticity changes neural activities that promote behavioral learning**
181 Previous research has examined the behavioral effects of deleting the myelin
182 regulatory factor (MyRF), a transcription factor required by OLs for the initiation and
183 maintenance of myelination (McKenzie et al., 2014; Pan et al., 2020; Steadman et al.,
184 2020; Xiao et al., 2016). These results indicate that the inhibition of OPC
185 differentiation, and thereby myelination, leads to deficits in motor learning (McKenzie
186 et al., 2014; Xiao et al., 2016) and the consolidation of spatial (Steadman et al., 2020)
187 and fear memories (Pan et al., 2020). However, little is known about whether and how
188 myelin plasticity affects the neural circuitry related to learning and behavior.
189 Recent advances in optical and genetic techniques allow us to monitor and manipulate
190 neural activity, which makes it possible to demonstrate a causal relationship between
191 neural activity and learned behavioral changes in an awake animal (Campbell and
192 Marchant, 2018; Deubner et al., 2019; Yamamuro et al., 2020). In addition,
193 accumulating evidence suggests that myelin plasticity plays a pivotal role in learning
194 (Fields and Bukalo, 2020; Xin and Chan, 2020). Previously, it was reported that

195 impaired myelin regulation increases the conduction time of myelinated axons *in vivo*
196 (Bando et al., 2008; Tanaka et al., 2006). However, whether myelin plasticity and
197 regulation affect neural activity and properties is poorly understood. A recent report
198 suggests that an absence of proteolipid protein 1 (PLP1), which is one of the major
199 components of myelin, results in a compensatory enhancement of the proliferation of
200 OPCs in the subventricular zone, where new oligodendrocytes are generated,
201 concomitant with specific behavioral alterations (i.e., in cognitive function, anxiety, and
202 olfactory function). In young-adult *Plp-1* null mice, particularly with respect to the
203 behavior associated with olfaction, researchers also observed changes in neural
204 oscillations recorded using local field potentials from the piriform cortex (Gould et al.,
205 2018). These results indicate that impaired myelin regulation may affect neural
206 activities that contribute to learning. Unfortunately, a causal relationship between
207 changes in neural activity and changes in behavior and learning was not proven in that
208 study (Gould et al., 2018).
209 Fear is a behavioral response highly conserved in evolution, and the consolidation of
210 fear memories becomes stable through a process of neural network rearrangement that
211 occurs over several weeks. The mechanisms of this process, including the cellular and
212 synaptic aspects, have been elucidated (Tonegawa et al., 2018). However, it remains

unknown whether the proliferation and differentiation of OPCs and new myelin formation are involved in the consolidation of remote fear memory. To address this question, a recent study examined contextual fear memory during conditioning and during retrieval sessions 24 hours and 30 days after conditioning in *Myrf* $^{loxP/loxP}$*;NG2CreERT+* mice, in which new myelin formation is genetically prevented. In the medial prefrontal cortex, fear learning induced OPC proliferation and differentiation into myelinating OLs, which form the myelin sheaths around axons. Fiber photometry was used to obtain *in vivo* Ca^{2+} images of neuron population activity, which underlies remote fear memory consolidation. Thirty days after conditioning, the knockout mice showed suppressed population neural activities and consequent behavioral deficits (i.e., reduced freezing in a conditioned context), which were not observed in the control mice (Pan et al., 2020). This impairment of behavior could be rescued by administering clemastine, a drug that induces oligodendrogenesis and the formation of new myelin. Consistent with these observations, the consolidation of spatial learning also promotes oligodendrogenesis, which is essential for this process. Local field potentials recorded from the anterior cingulate cortex and hippocampus revealed that oscillatory activity synchronized between these two areas, which are considered important for memory consolidation (Pajevic et al., 2014; Xia et al., 2017), are decreased by a disruption of

231 oligodendrogenesis (Steadman et al., 2020). Taken together, both reports indicate that
232 oligodendrogenesis, which is required in the adult for memory consolidation, can
233 change neural activity patterns across brain regions by regulating conduction velocities.
234 Regarding this hypothesis, we have recently employed *in vivo* two-photon Ca^{2+}
235 imaging, *in vivo* electrophysiology, and optogenetics to provide new insights into
236 activity-dependent myelination and its contributions to motor learning by promoting
237 synchronized spike-time arrivals (Kato et al., 2020). Motor learning is one of the most
238 intensively studied paradigms in myelin plasticity research. For example, genetic
239 deletion of Myrf was shown to impair the proliferation and differentiation of OPCs and
240 the ability to learn a modified running wheel with irregularly spaced rungs (McKenzie
241 et al., 2014; Xiao et al., 2016). In addition, neural activities in the primary motor cortex
242 (M1) have been shown to actively change during motor learning processes (Huber et al.,
243 2012; Masamizu et al., 2014). Therefore, to assess whether impaired myelin regulation
244 results in abnormal neural activities in M1, we performed two-photon imaging on *PLP-*
245 *tg* mice (Kagawa et al., 1994) during the learning of a lever-pulling task. These mice
246 have extra copies of the *PLP1* gene and show reduced conduction velocity in the
247 pyramidal tract due to a subtly abnormal myelin structure (Tanaka et al., 2009). In WT
248 mice, activity-dependent myelination correlated with motor learning performance,

249 which was not observed in the *PLP-tg* mice. In the latter, *in vivo* two-photon imaging
250 and electrophysiology detected increased spontaneous neural activities in M1, which
251 correlated with a deficit in motor learning (**Figure 3**). In line with this observation, high
252 spontaneous cortical activity was also observed in a mouse model of Alzheimer's
253 disease (Busche et al., 2008) and fragile-X syndrome (Gonçalves et al., 2013).
254 Furthermore, dispersion of axonal conduction velocities was observed in the
255 thalamocortical axons of the *PLP-tg* mice. When this was compensated by the repetitive
256 pairing of forelimb movements with optogenetic stimulation of these axon terminals,
257 motor learning was restored (Kato et al., 2020). These findings suggest that precise
258 regulation of myelin helps to maintain synchronous spike arrivals over long-range axons
259 and facilitates the information processing that contributes to motor learning. Indeed,
260 impaired myelin regulation can cause abnormal information processing, eventually
261 resulting in psychiatric and neurological disorders (Nave and Ehrenreich, 2014). For
262 example, a genome-wide analysis of patients with schizophrenia found that their
263 expression levels of myelin-related genes were significantly different from that of
264 healthy controls (Hakak et al., 2001) and, a diffusion-tensor MRI study in elderly people
265 demonstrated that abnormal signals from the white matter are associated with cognitive
266 decline (Bennett and Madden, 2014). These findings suggest that myelin regulation

affects information processing in an activity-dependent manner, and its disruption may be associated with the development of neuropsychiatric disorders.

Conclusion

In this review, we have summarized evidence that neural activities modulated by myelin plasticity are important for learning and behavior, and that pathological cortical circuitry resulting from impaired myelin regulation shows an increase in asynchrony and spontaneous activity. We suggest that the disruption of myelin plasticity may have an effect on the progression of neuropsychiatric disorders. Indeed, special transcriptome analysis in patients with Alzheimer's disease identified the disruption of an oligodendrocyte gene (Chen et al., 2020), indicating that promoting oligodendrogenesis and ameliorating the neural activities associated with impaired myelin plasticity could be a therapeutic target in Alzheimer's disease.

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Author contributions

D.K. and H.W. designed the concept for the manuscript and wrote the manuscript.

Declaration of Interest

None.

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Figure legends

Figure 1. Roles of oligodendrocyte progenitor cells (OPCs) and oligodendrocytes in neural activity-dependent myelination

OPCs expressing specific antigens, such as NG2 chondroitin sulfate proteoglycan and the alpha receptor for platelet-derived growth factor (PDGFαR), have proliferative and differentiative potential, regulating myelination in the adult brain. Sensory deprivation, voluntary exercise, and alterations in neural activity modulate OPC proliferation, differentiation and, ultimately, myelination.

PDGFαR: alpha receptor for platelet-derived growth factor

PLP: proteolipid protein

CNP: 2', 3'-cyclic-nucleotide 3'-phosphodiesterase

MBP: myelin basic protein

L1: L1 cell adhesion molecule

F3: F3 neural adhesion molecule

NMDAR: *N*-methyl-D-aspartate receptor

mGluR: metabotropic glutamate receptor

Figure 2. Mechanism of communication between OPCs and axons

(**a**) OPCs receive direct neural inputs from presynaptic terminals and axons through vesicular and nonvesicular neurotransmitter release. (**b**) The underlying cellular mechanism of activity-dependent myelination has been revealed through the observation of local synthesis of the myelin basic protein at specific contact sites between the dorsal root ganglion neurons and OPCs, induced by glutamate release from axons and Fyn kinase activity.

Figure 3. Impaired myelination promotes high spontaneous activity

Impairment of myelin regulation causes high spontaneous activity in the motor cortex due to dispersion of axon conduction velocities in the thalamocortical projection, which results in motor learning deficits.

Figure 1

Activity dependent proliferation, differentiation, and myelination

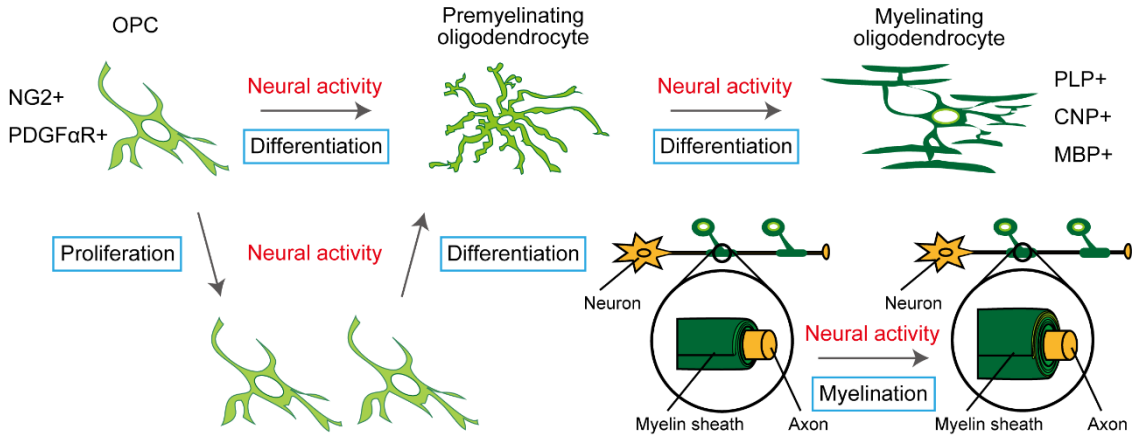


Figure 2

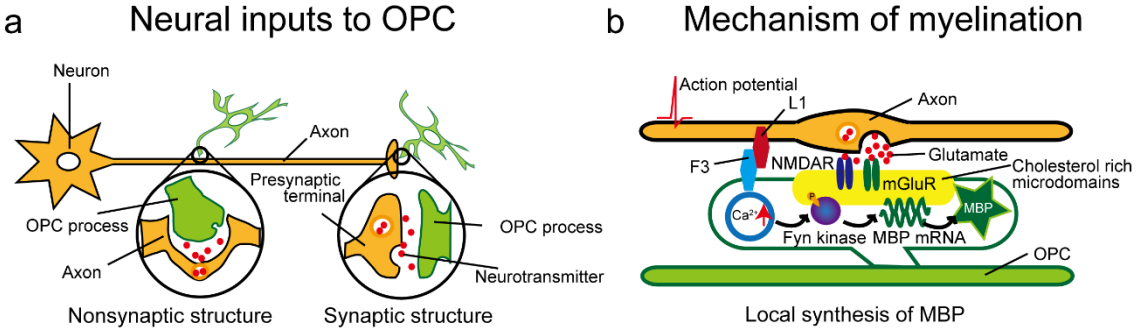
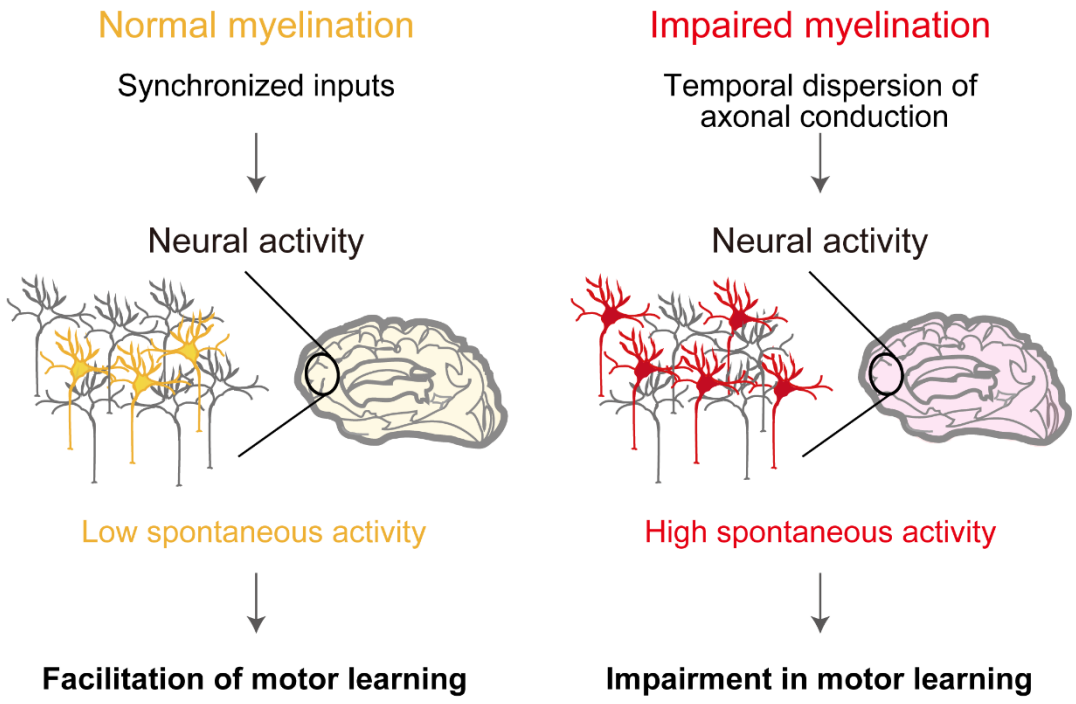

a
Neural inputs to OPC
Neuron
Axon
Presynaptic terminal
OPC process
Axon
OPC process
Neurotransmitter
Nonsynaptic structure
Synaptic structure
b
Mechanism of myelination
Action potential
L1
Axon
F3
NMDAR
Glutamate
Cholesterol rich microdomains
mGluR
Ca2+
MBP
Fyn kinase MBP mRNA
OPC
Local synthesis of MBP

Figure 3


Normal myelination
Synchronized inputs
Neural activity
Low spontaneous activity
Facilitation of motor learning
Impaired myelination
Temporal dispersion of axonal conduction
Neural activity
High spontaneous activity
Impairment in motor learning

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