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1 **On myelinated axon plasticity and neuronal circuit formation and function**

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21 **Abstract**

22

23 Studies of activity-driven nervous system plasticity have primarily focused on the gray matter.  
24 However, MRI-based imaging studies have shown that white matter, primarily composed of  
25 myelinated axons, can also be dynamically regulated by activity of the healthy brain. Myelination in  
26 the central nervous system (CNS) is an ongoing process that starts around birth and continues  
27 throughout life. Myelin in the CNS is generated by oligodendrocytes and recent evidence has shown  
28 that many aspects of oligodendrocyte development and myelination can be modulated by extrinsic  
29 signals including neuronal activity. Since modulation of myelin can, in turn, affect several aspects of  
30 conduction, the concept has emerged that activity-regulated myelination represents an important  
31 form of nervous system plasticity. Here we review our increasing understanding of how neuronal  
32 activity regulates oligodendrocytes and myelinated axons in vivo, with a focus on the timing of  
33 relevant processes. We highlight the observations that neuronal activity can rapidly tune axonal  
34 diameter, promote reentry of oligodendrocyte progenitor cells into the cell cycle, or drive their direct  
35 differentiation into oligodendrocytes. We suggest that activity-regulated myelin formation and  
36 remodeling that significantly change axonal conduction properties are most likely to occur over  
37 timescales of days to weeks. Finally, we propose that precise fine-tuning of conduction along already-  
38 myelinated axons may also be mediated by alterations to the axon itself. We conclude that future  
39 studies need to analyse activity-driven adaptations to both axons and their myelin sheaths to fully  
40 understand how myelinated axon plasticity contributes to neuronal circuit formation and function.

41

42 Approximately half of the volume of the human central nervous system (CNS) is white matter (WM),  
43 which is largely composed of myelinated axons. The presence of concentric wraps of myelin  
44 membrane around axons in our nervous system can greatly increase their conduction velocity (CV)  
45 compared to unmyelinated axons of the same size (Waxman and Bennett, 1972). Furthermore,  
46 variation in myelin sheath length and thickness has predictable effects on CV (Hursh, 1939; Smith and  
47 Koles, 1970; Waxman, 1980; Seidl, 2014; Arancibia-Carcamo et al., 2017). Additionally, myelin enables  
48 energetically efficient impulse propagation by restricting the regeneration of action potentials to the  
49 unmyelinated gaps between consecutive sheaths called nodes of Ranvier (Sherman and Brophy, 2005;  
50 Hartline and Colman, 2007; Chiu, 2011). However, the generation of myelin itself is costly, and it is  
51 thought that it takes months to recoup the initial energy invested in making a myelin sheath from  
52 savings in conduction efficiency (Harris and Attwell, 2012). Indeed, not all axons in our CNS are  
53 myelinated, and those that are, can be myelinated at different times in life. For example, histological  
54 studies have indicated that spinal cord axons, essential for basic motor functions, are myelinated  
55 around birth in humans; whereas cortical axons, involved in executive functions, may be myelinated  
56 decades later (Flechsig, 1896; Yakovlev and Lecours, 1967; Benes et al., 1994; Miller et al., 2012). This  
57 is supported by magnetic resonance imaging (MRI) analyses, which show ongoing growth and  
58 development of WM tracts well into adulthood (Giedd et al., 1999; Sowell et al., 2003; Lebel et al.,  
59 2008; Glasser and Van Essen, 2011; Krogsrud et al., 2016). The life-long importance of myelin for circuit  
60 formation and function is underscored by the severity of neurodevelopmental, neurodegenerative  
61 and neuropsychiatric diseases associated with its disruption, such as leukodystrophies, schizophrenia,  
62 multiple sclerosis, and amyotrophic lateral sclerosis, among an increasing number of others  
63 (Compston and Coles, 2008; Fields, 2008; Lee et al., 2012b; Philips and Rothstein, 2014; Pouwels et  
64 al., 2014; Zeidan-Chulia et al., 2014; Huang et al., 2015; Mighdoll et al., 2015; Miyata et al., 2015;  
65 Olmos-Serrano et al., 2016).

66 In the CNS, myelin is made by oligodendrocytes, which can make numerous myelin sheaths on multiple  
67 axons (Sherman and Brophy, 2005). Oligodendrocytes derive from oligodendrocyte progenitor cells  
68 (OPCs), also known as NG2 cells, which are present throughout our CNS from birth through death  
69 (Bergles and Richardson, 2015; Nishiyama et al., 2016). This persistence of OPCs allows not only the  
70 generation of new myelinating oligodendrocytes in the healthy adult brain, but also the regeneration  
71 of myelin following damage or disease (Zawadzka et al., 2010; Dimou and Gotz, 2014). Recent  
72 evidence has indicated that myelin made in adulthood in humans arises from a combination of the  
73 production of new oligodendrocytes and the remodeling of existing myelin (Yeung et al., 2014).  
74 Supporting the possibility that myelin sheath remodeling may take place is evidence that mature  
75 myelin sheaths can be stimulated to renew growth in the adult, long after their initial formation (Flores

76 et al., 2008; Snaidero et al., 2014; Jeffries et al., 2016). It is now clear that neuronal activity regulates  
77 many aspects of CNS myelination (Demerens et al., 1996; Makinodan et al., 2012; Gibson et al., 2014;  
78 Mensch et al., 2015). Indeed, the concept has recently emerged that activity-regulated myelination  
79 might play an important role in dynamically modulating neuronal circuit function. Supporting evidence  
80 has derived from two principal lines of investigation: MRI-based studies of how physiological brain  
81 activity relates to WM structure, and mechanistic investigations of myelination in vitro and in vivo.  
82 Here we review recent insights into how neuronal activity regulates WM, the oligodendrocyte lineage  
83 and myelinated axons in the healthy nervous system from development through adulthood. We then  
84 focus on how such interactions might affect the formation and function of neuronal circuits in vivo.

85

### 86 **The healthy WM is more dynamic than previously thought**

87 Many MRI-based studies of neural plasticity in humans have focused on gray matter (GM) and  
88 revealed significant structural and functional plasticity in response to neuronal activity, now thought  
89 to underlie cognitive functions such as learning and memory (Zatorre et al., 2012). Attention to WM  
90 has been more recent, and to date has focused on structural MRI-based analysis. Over the past decade  
91 or so, we have begun to understand that WM structure is significantly dynamic and responsive to  
92 physiological experience, and that WM adaptations in the healthy brain may represent a hitherto  
93 unappreciated form of neural plasticity (Fields, 2005; Wang and Young, 2014; Fields, 2015).

94 Most MRI studies on WM to date have used Diffusion Tensor Imaging (DTI), a method that provides  
95 quantitative measures of the directionality of water diffusion. In WM, water does not diffuse  
96 unconstrained in all directions; instead it occurs preferentially along myelinated axons  
97 (anisotropically). Myelin contributes to anisotropy since it prevents water diffusion transversally to  
98 the axon. Thus, an increase in anisotropy can be inferred to reflect an increase in myelination (Zatorre  
99 et al., 2012; Roberts et al., 2013); although modulation of numerous components of WM can influence  
100 anisotropy, as will be discussed below. A seminal cross-sectional WM diffusion MRI study found that  
101 expert pianists had significantly increased anisotropy in important tracts mediating bimanual motor  
102 coordination and connecting auditory regions (Bengtsson et al., 2005). Long-term practice in other  
103 cognitive modalities, such as attention and working memory, has also been associated with anisotropy  
104 changes in relevant WM tracts (Lee et al., 2010; Hu et al., 2011).

105 Given the years-long duration of repetitive training-induced neuronal activity, such cross-sectional  
106 studies are not informative about physiological alterations occurring on shorter time-scales.  
107 Furthermore, these analyses cannot disentangle whether physiological activity actually cause  
108 structural WM changes or whether prior WM structural differences facilitate learning and  
109 performance. In contrast, longitudinal studies examine brain structure before and after learning a task

110 to study shorter-term activity-induced structural changes. Seminal longitudinal studies employed  
111 juggling, a complex visuo-motor skill that requires bimanual coordination, grasping and visual tracking,  
112 and showed that a week of training induces an increase in volume in cortical GM (Draganski et al.,  
113 2004; Boyke et al., 2008; Driemeyer et al., 2008). Interestingly 6 weeks of training increased anisotropy  
114 in the underlying WM, which lasted for at least 4 weeks after training stopped (Scholz et al., 2009).  
115 Learning a computer-based task that required similar skills also increased anisotropy in the same  
116 region (Lakhani et al., 2016). Training in other cognitive modalities, such as working memory (Takeuchi  
117 et al., 2010), spatial learning (Hofstetter et al., 2013), reading ability (Keller and Just, 2009) or language  
118 acquisition (Schlegel et al., 2012), also elicited WM changes after days to weeks of training.  
119 A remarkable finding of some longitudinal studies is that structural WM plasticity can also occur in  
120 response to brief stimuli and over short time-scales. For instance, two 45-minute sessions of training  
121 in a whole-body balancing task, spaced a week apart, induced changes in volume in frontal and parietal  
122 brain areas and in the adjacent WM regions after the second session (Taubert et al., 2010). In other  
123 studies, subjects scanned just before and just after 2 hours of training in a computer game that  
124 stimulates spatial learning showed changes in the hippocampus (Sagi et al., 2012), and in its main WM  
125 projection, the fornix (Hofstetter et al., 2013). Similar changes occurred in rats trained for one day in  
126 the Morris water maze (Hofstetter et al., 2013). In both humans and rats, the extent of WM changes  
127 correlated with GM changes in associated regions (Hofstetter et al., 2013), suggesting that activity-  
128 regulated adaptations take place in connected regions, potentially along specific circuits, which span  
129 GM and WM.  
130 Collectively, these studies highlight how dynamic the healthy WM can be – responsive within hours,  
131 following even moderate stimuli. If WM changes were due solely to myelin dynamics, this would imply  
132 a very high rate of myelin synthesis and/ or turnover, which is not easy to reconcile with the high  
133 energetic demand of myelin biosynthesis and with the timing of myelination (discussed below). This  
134 begs the question: what are the cellular correlates of WM structural changes?

135

### 136 **From WM to cells**

137 In addition to allowing inference on the myelination status of WM tracts, changes in anisotropy can  
138 also, in principle, be caused by alterations to axonal diameter, axon density, and to WM components  
139 beyond myelinated axons, such as astrocytes, OPCs, microglia and the vasculature (Zatorre et al.,  
140 2012; Walhovd et al., 2014). MRI analyses provide only a low resolution signature that includes all of  
141 these components: for instance, a WM volume of a typical human DTI voxel size ( $2\text{mm}^3$ ) has been  
142 roughly estimated to contain up to 5 million axons (which can be quite diverse in morphological and  
143 functional properties), 700,000 oligodendrocytes, 180,000 astrocytes (whose processes may occupy

144 as much volume as myelin), 52,000 OPCs and 76,000 microglia (Walhovd et al., 2014). Furthermore,  
145 essentially all of these respond to changes in neuronal activity (Hawrylak and Greenough, 1995;  
146 Ishibashi et al., 2006; Braun et al., 2009; Schafer et al., 2012; Yuen et al., 2014; Sun et al., 2016; Hasel  
147 et al., 2017). Thus, it remains challenging to define what the precise underlying cellular correlates of  
148 these MRI changes occurring in response to brain activity are. Nevertheless, studies in animal models,  
149 which enable histological analyses to follow-up on specific MRI changes, have supported the premise  
150 that alteration to myelin does indeed occur following stimulus-induced neuronal activity. Rats scanned  
151 the day before and the day after a 5 day-long spatial learning task show increased anisotropy in the  
152 corpus callosum (Blumenfeld-Katzir et al., 2011). Similarly, rats trained in a skilled reaching task over  
153 the course of 11 days also show increased anisotropy in the relevant subcortical WM region (Sampaio-  
154 Baptista et al., 2013). In both cases, histological follow-up show increased Myelin Basic Protein (MBP)  
155 staining in the relevant areas. These studies suggest that broad changes in myelination are indeed  
156 likely to represent one component of WM plasticity, at least over days-long timescales. How might  
157 activity-regulated myelination be mediated at a cellular level to regulate nervous system function?

158

#### 159 **Neuronal activity regulates multiple stages of oligodendrocyte development and myelination.**

160 In parallel to MRI-based approaches, mechanistic studies have now revealed that neuronal activity  
161 can regulate many aspects of oligodendrocyte lineage behaviour and myelination (Baraban et al.,  
162 2016; Mount and Monje, 2017). These studies encompass those carried out in vitro and in vivo, in  
163 developing systems and in adulthood, and with both physiological and non-physiological  
164 manipulations of activity. Together these analyses reveal many cellular interactions between axons  
165 and the oligodendrocyte lineage that could contribute to WM plasticity in the human brain.

166

#### 167 ***OPCS***

168 OPCs are specified during embryogenesis in discrete neural tube domains from where they migrate  
169 and proliferate to colonise the CNS (Rowitch, 2004; Richardson et al., 2006). OPCs remain present  
170 throughout life, representing 3-10% of total cells in the CNS (Dawson et al., 2003; Nishiyama et al.,  
171 2009; Richardson et al., 2011; Dimou and Gotz, 2014). Interestingly, in vivo imaging based studies have  
172 indicated that the dynamic activity of OPCs appears conserved from the embryonic zebrafish spinal  
173 cord to the adult mammalian cortex (Kirby et al., 2006; Hughes et al., 2013), suggesting that  
174 developmental mechanisms regulating their lineage progression may be similar not only between  
175 species, but also at distinct times of life. Extrinsic factors, including neuronal activity, regulate OPC  
176 development (Barres and Raff, 1999; Bergles and Richardson, 2015). The ability of OPCs to sense and  
177 respond to neuronal activity is mediated by their expression of a variety of neurotransmitter receptors

178 (Karadottir and Attwell, 2007) and the formation of functional synapses between their processes and  
179 axons, observed from early stages of development through to adulthood, reviewed elsewhere  
180 (Paukert and Bergles, 2006; Sakry et al., 2011; Almeida and Lyons, 2014; Dimou and Gallo, 2015). OPCs  
181 appear to remain responsive to activity not only in development, but also in the mature CNS. For  
182 example, high-frequency electrical stimulation of corticospinal neurons in adult rats induced OPC  
183 proliferation and differentiation in the spinal cord (Li et al., 2010). More recently, optogenetic  
184 activation of motor cortex projection neurons both in juvenile and in adult mice promoted  
185 proliferation of OPCs and neural precursors in the premotor cortex and associated subcortical WM in  
186 the corpus callosum (Gibson et al., 2014). Remarkably, a 30-minute stimulation paradigm was  
187 sufficient to cause a significant number of OPCs to re-enter the cell cycle, 4-fold over unstimulated  
188 controls, detectable just 3 hours later. Given estimates of cell cycle time for OPCs at a similar stage  
189 (Young et al., 2013), this response would be predicted to lead to a significant increase in OPC number  
190 over the course of the following days. A more protracted period of stimulation additionally drove  
191 oligodendrocyte differentiation over a period of weeks, which was accompanied by increased myelin  
192 protein expression and myelin sheath thickness in the corpus callosum (Gibson et al., 2014). This  
193 suggests that distinct responses of oligodendrocyte-lineage cells to neuronal activity may occur with  
194 different timelines: a rapid re-entry of OPCs into the cell cycle within hours; and a more protracted  
195 oligodendrocyte differentiation-myelination response, occurring over days to weeks (Figure 1).

196

#### 197 *Additional roles of OPCs*

198 Emerging evidence suggests that at least some OPCs perform additional functions that are  
199 independent of generating differentiated oligodendrocytes. For instance, OPCs can contact nodes of  
200 Ranvier (Butt et al., 1999; Serwanski et al., 2017), as well as axon-dendritic synapses, where they may  
201 help maintain potassium homeostasis in the extracellular space during periods of high-frequency firing  
202 (Maldonado et al., 2013), and indirectly regulate glutamate homeostasis at synapses by modulating  
203 astrocytic glutamate uptake (Birey et al., 2015). OPCs have also been implicated in regulating neuronal  
204 long-term potentiation and postsynaptic neuron AMPA receptor (AMPA) composition via activity-  
205 driven cleavage of the NG2 proteoglycan (Sakry et al., 2014), or secretion of neuromodulatory factors  
206 (Sakry et al., 2015). Axon-OPC synapses may allow OPCs to perform their additional functions with  
207 high temporal and spatial precision, independent of or prior to differentiation and myelination itself.  
208 For instance, in the corpus callosum, additional OPCs generated by stimulus-induced proliferation may  
209 take days to start differentiating, but could in the meantime help buffer ion or neurotransmitter  
210 homeostasis near more actively firing axons (Figure 1). Alternatively, it is possible that a subset of



211 OPCs contribute to generating myelinating oligodendrocytes and other(s) to mediating these  
212 additional roles.

### 213 ***Oligodendrocyte differentiation***

214 The differentiation of OPCs into oligodendrocytes is regulated by intrinsic and extrinsic factors  
215 (Zuchero and Barres, 2013). Since oligodendrocytes have a default intrinsic propensity to differentiate,  
216 both in vitro (Zeller et al., 1985; Dubois-Dalcq et al., 1986; Kachar et al., 1986; Knapp et al., 1987; Tang  
217 et al., 2000) and in vivo (Ueda et al., 1999; Almeida and Lyons, 2016), extrinsic signals are generally  
218 considered as regulators of differentiation, rather than being completely required for differentiation.  
219 A lineage-tracing study in the young and juvenile rodent CNS identified a window of 3-8 days after  
220 OPC division in which each cell initiates differentiation (Hill et al., 2014), in line with the protracted  
221 period of differentiation following optogenetic stimulation of OPC proliferation. During this window,  
222 newly differentiating oligodendrocytes appear particularly sensitive to extrinsic regulation, including  
223 by neuronal activity: sensory-deprivation, for instance, reduced the survival of newly differentiating  
224 oligodendrocytes (Hill et al., 2014). A role for activity in regulating survival of newly differentiating  
225 oligodendrocytes has recently been supported by analysis of animals in which glutamate-mediated  
226 signaling through AMPARs was ablated in the oligodendrocyte lineage. This led to a transient 20-25%  
227 reduction in differentiated oligodendrocyte and myelinated axon number in the corpus callosum at  
228 postnatal days 14-21, following increased apoptosis of newly differentiating oligodendrocytes  
229 (Kougioumtzidou et al., 2017). Interestingly, the converse manipulation of increasing neuronal activity  
230 in the corpus callosum by electrical stimulation in young adults elicited distinct responses by  
231 oligodendrocytes according to firing frequency - promoting differentiation at lower frequencies and  
232 promoting OPC proliferation at higher frequencies (Nagy et al., 2017). Given that myelination can take  
233 place throughout life, it will be important to determine how cells of the oligodendrocyte lineage  
234 respond to different patterns of activity in yet other circuits at distinct stages.

235 In complement to studies that directly manipulate neuronal activity by genetic, optogenetic or  
236 electrophysiological approaches, behaviour-driven manipulations provide the most physiologically  
237 relevant way to assess the effect of activity on myelinated axons. Two recent behaviour-driven studies  
238 examined how motor learning affects oligodendrocyte lineage behaviour in vivo. McKenzie et al.  
239 studied adult mice learning how to run in a complex wheel with irregularly spaced rungs. Initially, mice  
240 have great difficulty running in a complex wheel, but become proficient over a week with voluntary  
241 training. Remarkably, mice that are genetically prevented from differentiating new myelinating  
242 oligodendrocytes in adulthood, with no disruption of developmental myelination or locomotor  
243 abilities, were impaired in their performance on the complex wheel (McKenzie et al., 2014). Thus,  
244 oligodendrocyte differentiation may underlie some aspects of the motor learning process. In an

245 important follow-up study, Xiao et al showed that these mice had impaired performance on the  
246 complex wheel within a matter of hours. Using a novel marker of newly differentiating  
247 oligodendrocytes, Xiao et al showed that when control mice learn to run in a complex wheel, G1-  
248 paused OPCs rapidly transition into newly differentiating oligodendrocytes without proliferation,  
249 specifically in task-relevant regions, e.g. within 2.5h in the subcortical WM (Xiao et al., 2016). Over the  
250 course of the training week, the OPC population did exhibit an increase in proliferation, which  
251 generated a later secondary wave of oligodendrocyte differentiation, in line with the previously noted  
252 days-long timeline of differentiation following OPC division. Importantly, myelination remains to be  
253 assessed in the context of such motor training, both in the hours-long response mediated by G1-  
254 paused OPCs that undergo rapid differentiation (Figure 1), and in the more protracted days-long  
255 proliferation-differentiation response. It will be interesting to determine what proportion of OPCs  
256 exist in a G1-paused state (potentially poised to differentiate), in different WM tracts and over the  
257 life-course.

258

#### 259 *Additional roles for differentiated oligodendrocytes*

260 Although differentiated oligodendrocytes produce myelin sheaths that regulate conduction, recent  
261 evidence suggests that they may also perform additional roles. In the mouse GM, for instance, a  
262 significant proportion of myelin is deposited on inhibitory interneurons in small discontinuous patches  
263 (Micheva et al., 2016; Stedehouder et al., 2017), and it remains to be determined if or how such myelin  
264 would impact conduction. A fundamental emerging concept is that oligodendrocytes also provide  
265 significant metabolic support to the axons they myelinate. Oligodendrocytes are thought to shuttle  
266 the glycolytic by-products lactate and pyruvate to the associated axon, via oligodendroglial  
267 monocarboxylate transporters MCT1 and axonal MCT2, where they serve as substrates for aerobic ATP  
268 production (Funfschilling et al., 2012). Indeed, MCT1 loss-of-function causes axonal pathology while  
269 sparing oligodendrocytes (Lee et al., 2012b). Remarkably, a recent study uncovered a link between  
270 axonal activity and metabolic support, whereby NMDA receptor (NMDAR) activation in  
271 oligodendrocytes stimulates glucose uptake by promoting surface localization of the glucose  
272 transporter Glut1, increasing glycolysis (Saab et al., 2016). The authors propose that the resulting  
273 lactate and pyruvate are then shuttled to axons via MCT1/2 to maintain energy supplies. Interestingly,  
274 axonal tracts with NMDAR-deficient oligodendrocytes have essentially normal myelination (De Biase  
275 et al., 2011), but they recover poorly from energy deprivation or increased energy demand (e.g. in  
276 response to high-frequency firing) and also develop age-related axonopathy (Saab et al., 2016). These  
277 results suggested the hypothesis that NMDARs in oligodendrocytes serve to sense glutamate in order  
278 to regulate the transfer of metabolic substrates to the axon. Further additional functions for

279 oligodendrocytes have been suggested by two recent studies, namely regulating potassium  
280 homeostasis near the somas of pyramidal neurons (Battefeld et al., 2016), and inducing clustering of  
281 sodium channels along axons into ‘pre-nodes’, which can speed up conduction independently of  
282 myelination (Freeman et al., 2015). It will be important in future studies to consider all of these  
283 additional roles. For instance, in the corpus callosum, oligodendrocytes that differentiate rapidly  
284 following motor learning may not fully myelinate entire axons within hours, but their initial  
285 interactions with axons may provide important metabolic support (Figure 1) to help facilitate a higher  
286 firing rate (Krasnow and Attwell, 2016; Saab et al., 2016; Trevisiol et al., 2017), or begin clustering ion  
287 channels to accelerate conduction.

288

### 289 ***Myelin sheath formation, growth and remodelling***

290 Oligodendrocytes exhibit a default propensity to make myelin: in vitro, they can extend flat sheets  
291 with extensive myelin protein expression (Bradel and Prince, 1983; Rome et al., 1986; Knapp et al.,  
292 1987), or even actual myelin sheaths around inert axon-shaped plastic fibers in the absence of specific  
293 molecular cues (Lee et al., 2012a; Bechler et al., 2015). In vivo, the environment is more complex: only  
294 some axons are myelinated, and axons of distinct neuronal subtypes can be myelinated by different  
295 mechanisms (Koudelka et al., 2016) and at very different times. The fact that axons are myelinated in  
296 a stereotyped manner over time, and that WM structure appears responsive to neuronal activity  
297 suggests that extrinsic axonal cues are likely to coordinate if, when and to what extent specific axons  
298 should be myelinated, both during early development and in the adult. Newly differentiated  
299 oligodendrocytes extend numerous highly dynamic processes that interact with multiple prospective  
300 axons in their environment. Live imaging studies in the developing zebrafish spinal cord have shown  
301 that individual oligodendrocytes initially over-produce short (~5µm long) myelin sheaths, some of  
302 which become stabilized and others retracted during a critical dynamic window of ~5 hours (Czopka  
303 et al., 2013), a similar timescale to initial sheath generation by individual mammalian oligodendrocytes  
304 in vitro (Watkins et al., 2008). After this period of axonal selection, no new sheaths are made by  
305 individual oligodendrocytes and very few are retracted. There is now good evidence that vesicular  
306 release of neurotransmitters (and possibly other signals) can bias myelin sheath formation and axon  
307 selection by oligodendrocytes. For example, preventing vesicular release from individual neurons can  
308 reduce the number of sheaths made on their axons in zebrafish (Hines et al., 2015; Koudelka et al.,  
309 2016), which was also observed in mammalian neurons in vitro (Wake et al., 2015). Interestingly, this  
310 functional regulation of myelination by activity appears specific to only some neuronal subtypes in  
311 vivo (Koudelka et al., 2016). In addition to biasing myelination to certain axons, activity-driven  
312 vesicular release may also regulate the total amount of myelin made by individual oligodendrocytes,

313 at least during the initial period of myelin sheath formation. For example, global abrogation of  
314 vesicular release in zebrafish embryos reduces the number of sheaths made by individual  
315 oligodendrocytes during this period, whereas promoting neuronal activity increases myelin sheath  
316 number per cell (Mensch et al., 2015). However, it remains unclear whether these observations simply  
317 reflect a role of activity in regulating the local dynamics of myelinating processes, or whether activity  
318 can also influence a central programme in the oligodendrocyte that sets the overall gain of myelin  
319 production. Future studies that can accurately assess myelin sheath number, length and thickness and  
320 thus total myelin production of individual cells over time will be required to investigate these possible  
321 roles of activity. Although the studies noted here focus on developmental myelination, we suggest  
322 that the basic principles of activity-regulated myelination may apply throughout life, irrespective of  
323 an individual oligodendrocyte's date of birth (Figure 1) - although further studies in adults will be  
324 required to test this prediction.

325 Once formed, stabilized myelin sheaths grow around and along axons, with sheath growth occurring  
326 at the direct interface with the axon (Snaidero et al., 2014). In zebrafish, the formation and growth of  
327 myelin sheaths along the length of individual axons can now be followed over time using a novel  
328 reporter that indicates the position and length of myelin sheaths on axons (Koudelka et al., 2016). The  
329 analyses of the first axons myelinated in the zebrafish CNS have revealed myelination along the entire  
330 length of axons just 2-3mm long took several days (Koudelka et al., 2016). Although these are  
331 developmental timelines, de novo myelination of entire axons in adult is likely to take as long, or even  
332 longer, given that cellular processes tend to slow with age, as evidenced by the greatly increased cell  
333 cycle times of OPCs in adulthood (Young et al., 2013). Faster myelination of entire axons would require  
334 synchronous oligodendrocyte differentiation and myelination along the length of the axons, e.g. if G1-  
335 paused OPCs were poised to differentiate along a specific tract, but such a scenario has not been  
336 observed in vivo.

337 In addition to de novo myelination, changes to already myelinated axons, e.g. in myelin sheath length  
338 or thickness, may also affect circuit function. High-resolution 3D reconstruction of growing myelin  
339 sheaths revealed the presence of a network of cytoplasmic channels during myelination, which may  
340 be the transport routes for myelin components from the cell to the myelin sheath. These channels are  
341 not detected in mature sheaths, suggesting that they close as sheaths stop growing (Snaidero et al.,  
342 2014). Interestingly, forced activation of the Akt signaling pathway in adult myelinating  
343 oligodendrocytes in mice resulted in the reopening of cytoplasmic channels and the subsequent  
344 renewed growth of mature myelin sheaths (Snaidero et al., 2014). This occurred over days to weeks,  
345 and may very well be a mechanism co-opted by neuronal activity to induce sheath regrowth and  
346 remodelling. Myelin sheaths retain neurotransmitter receptors in the innermost layer at the site of

347 interaction with the axon, where they have been proposed to enable mature oligodendrocytes to  
348 sense neurotransmitter release (Micu et al., 2016). Indeed, abrogation of vesicular release from  
349 individual axons results in shorter myelin sheaths both in developing zebrafish (Hines et al., 2015;  
350 Koudelka et al., 2016) and rodents (Wake et al., 2015; Etxeberria et al., 2016), suggesting a second  
351 independent role of activity in regulating myelin growth, after formation. However, the dynamics of  
352 myelin remodeling in vivo are unclear, and it remains to be demonstrated whether mature sheaths  
353 are indeed responsive to neuronal activity and how any such changes would actually affect conduction  
354 properties or WM signatures.

355 Two recent behaviour-driven studies have indicated that physiological activity can also regulate myelin  
356 sheath formation and growth, and importantly that such changes in myelination impact circuit  
357 function. Makinodan et al. studied how social isolation affects CNS structure and function in juvenile  
358 mice. They identified a period from postnatal day P21 to P35 during which social isolation led to  
359 pronounced behavioural defects and disruption to oligodendrocyte morphology in the pre-frontal  
360 cortex (PFC). Although their number was normal, oligodendrocytes in the PFC of socially isolated mice  
361 had simpler morphologies, with fewer, shorter, and thinner myelin sheaths, and a corresponding  
362 decreased expression of myelin genes (Makinodan et al., 2012). These socially isolated mice had  
363 impairments in sociability and working memory, two PFC-dependent behaviours. Interestingly, the  
364 myelin alterations preceded the behavioural impairments, suggesting that patterns of myelination can  
365 affect neural circuit function. This suggestion was supported by a phenocopy experiment wherein  
366 conditional ablation of the receptor tyrosine kinase gene *erbb3* specifically in oligodendrocytes from  
367 P19 phenocopied both the PFC myelination defects and behavioural impairments of socially isolated  
368 animals (Makinodan et al., 2012). Interestingly, the ligand for the *erbb3* receptor, neuregulin1, is  
369 known to be regulated by neuronal activity and is downregulated following social isolation (Liu et al.,  
370 2011; Makinodan et al., 2012). Furthermore, neuregulin is capable of switching the myelination of  
371 oligodendrocytes to being responsive to neuronal activity in vitro (Lundgaard et al., 2013), suggesting  
372 a possible molecular basis for these observations.

373 A parallel study of how social isolation affects myelination showed that in adult animals, protracted  
374 isolation for 8 weeks also leads to alterations of myelin gene expression and myelination in the PFC  
375 (Liu et al., 2012). Remarkably, these phenotypes could be rescued by rehousing in a social  
376 environment, or, as shown in a follow-up study, by treating animals with the promyelinating drug  
377 clemastine (Liu et al., 2016). These studies indicate that activity regulates myelination in juveniles and  
378 adults in a similar manner, but over different time-scales. Future studies that monitor the myelination  
379 status of specific axons and circuits over time will be required to determine to what extent social  
380 isolation, or indeed any form of neuronal activity, affects de novo myelination or remodelling of

381 already-myelinated axons. Nonetheless, these studies of social isolation and myelination lend further  
382 support to the idea that neuronal activity dynamically modulates myelination; that this, in turn, affects  
383 neuronal circuit function, and thus that activity-regulated myelination represents a form of functional  
384 plasticity.

385

### 386 **Neuronal activity also regulates axon structure**

387 In addition to the fact that neuronal activity can regulate oligodendrocytes and myelination, there is  
388 now emerging evidence that the structure and molecular composition of the axon itself is responsive  
389 to experience. For example, unmyelinated axons were recently observed to be dynamically regulated  
390 by both high-frequency and physiological firing *ex vivo*, wherein increased activity led to a progressive  
391 enlargement of axons in diameter over tens of minutes (Chereau et al., 2017) (Figure 1). Interestingly,  
392 axon diameter is now known to be a core determinant of myelination in the CNS (Almeida et al., 2011;  
393 Lee et al., 2012a; Goebbels et al., 2017), as has long been known in the peripheral nervous system  
394 (Voyvodic, 1989). Thus, primary and rapid regulation of axon diameter in response to neuronal activity  
395 may in fact trigger later *de novo* myelination (Figure 1), which will be important to investigate in the  
396 future.

397 In addition to the observation that neuronal activity can regulate the diameter of unmyelinated axons,  
398 an increase in axonal diameter has also been observed along myelinated axons of the auditory  
399 brainstem, coincident with the onset of hearing. Indeed, when the onset of auditory stimuli is  
400 experimentally delayed, the growth in diameter of the same myelinated axons is prevented, until later  
401 restoration of sensory input (Sinclair et al., 2017), demonstrating a role for activity in regulating the  
402 diameter of myelinated axons as well. Thus, activity may contribute to the dynamic regulation of both  
403 *de novo* myelination and myelinated axon remodelling via modulation of axon diameter (Figure 1).

404 Indeed, alterations to axonal diameter may also contribute to the WM signatures observed by MRI  
405 following physiological brain activity in humans. For example, in a longitudinal study of WM plasticity  
406 following meditation, anisotropy-based measures thought to reflect an increase in axon diameter  
407 were observed prior to those reflecting an increase in myelination (Tang et al., 2012). However, how  
408 changes in axonal organisation and diameter affect various aspects of MRI-based signatures is  
409 complex and context dependent (Beaulieu, 2002). Furthermore, if changes in axon diameter lead to  
410 subsequent changes in myelination along WM tracts, the anisotropy-based signatures reflecting such  
411 changes are likely to dynamically change over time. Given the importance of dynamic changes in WM  
412 structure in both the healthy nervous system and in disease (Beaulieu, 2002), there is an important  
413 drive in the community to develop increasingly refined structural MRI analyses (Stikov et al., 2015;

414 Lerch et al., 2017; Wu and Miller, 2017) and to better correlate MRI signatures with actual cellular  
415 alterations. Furthermore, the emergence of functional MRI analysis of WM tracts (Gawryluk et al.,  
416 2014; Peer et al., 2017; Warbrick et al., 2017) will further reveal the full extent of WM dynamics and  
417 the relative contribution of myelin and non-myelin adaptations.

418 **How does regulation of myelination and axonal structure and composition affect neuronal circuit**  
419 **function?**

420 In principle, myelinated axon structure and composition can regulate neuronal circuit function in  
421 several ways. Myelination is primarily thought to regulate conduction velocity (CV). For instance, de  
422 novo myelination of previously unmyelinated axons accelerates CV. In addition, regulation of the  
423 number, distribution, length, and thickness of myelin sheaths along myelinated axons could be  
424 employed to fine-tune CV. This is because regulation of the geometric properties of myelin sheaths  
425 also regulate CV (Hursh, 1939; Smith and Koles, 1970; Waxman, 1980; Wu et al., 2012; Seidl, 2014;  
426 Arancibia-Carcamo et al., 2017). Recent studies have indicated surprising diversity in the pattern of  
427 myelination along the length of at least some axons, whereby myelin sheaths are irregularly spaced  
428 and often interspersed by very large unmyelinated stretches (Tomassy et al., 2014). How such a  
429 pattern of myelination relates to the axons' function remains to be determined. However, there is  
430 evidence that precise regulation of myelination occurs in at least some other specific circuits in vivo in  
431 order to meet specific conduction requirements (Lang and Rosenbluth, 2003; Salami et al., 2003; Ford  
432 et al., 2015; Seidl and Rubel, 2016). For instance, encoding the spatial location of an auditory stimulus  
433 requires uniform conduction times along the two main branches of individual cochlear neuron axons  
434 to coincidentally deliver action potentials to distinct target neurons in opposite hemispheres. In order  
435 to compensate for the different lengths of the collateral branches projecting to each hemisphere,  
436 longer myelin sheaths are found along the longer collateral, which is thought to help increase its CV,  
437 equalise conduction times along each collateral, and thus facilitate coincident impulse arrival (Seidl et  
438 al., 2010; Seidl and Rubel, 2016). Thus, dynamically changing CV along specific axons by refining  
439 myelination may alter the coincident arrival of action potentials in postsynaptic neurons. Changing  
440 the arrival of impulses at postsynaptic neurons may also change the balance between excitation and  
441 inhibition – in essence, regulating the firing probability of a neuron. In some circuits, the order and  
442 precise timing of pre- and post-synaptic potentials determine whether potentiation or depression is  
443 induced (Feldman, 2012; Markram et al., 2012). In addition to regulating the speed and timing of  
444 conduction, myelinated axons may also better sustain high-frequency firing compared to  
445 unmyelinated axons (Perge et al., 2012). This could be due to the possibility that myelin may help  
446 support metabolically demanding high-frequency firing of action potentials (Saab et al., 2016).  
447 Additionally, myelin restricts the regeneration of action potentials to the very small nodes of Ranvier,

448 which enables rapid repetitive cycles of axolemma depolarization and repolarization (Fields, 2008). At  
449 the network level, precise regulation of both conduction timing and firing frequency may be necessary  
450 between neuron populations to generate synchronous or time-locked firing patterns and oscillations,  
451 which have been associated with numerous higher cognitive functions such as attention, sleep, or  
452 memory (Pajevic et al., 2014). Future studies that combine high-resolution 3D analyses of anatomy  
453 with functional assessment of neurophysiology will provide important information to allow informed  
454 modelling of the role of myelin in regulating emergent properties of neural circuits.

455 In addition to myelin-driven changes in conduction, activity-driven regulation of the axon itself can  
456 also affect function. In fact, to modulate conduction and circuit function, it is arguably simpler, faster  
457 and energetically cheaper to regulate the structure or composition of the axon, than to remodel  
458 myelin made by numerous independent cells along its length. For example, CV increases with axon  
459 diameter (Hursh, 1939; Matsumoto and Tasaki, 1977; Waxman, 1980). Furthermore, fine-tuning CV  
460 could be achieved by changing axonal domains. For example, in axons of the auditory brainstem, the  
461 diameter of nodes of Ranvier increases along the axon, which has been predicted to contribute to  
462 regulation of precise conduction times (Ford et al., 2015). Indeed, further anatomically-informed  
463 modelling studies have indicated that nodal size and composition can be regulated along myelinated  
464 axons to achieve comparable CV alterations to those of myelin changes, but at a fraction of the  
465 energetic cost (Arancibia-Carcamo et al., 2017). Dynamic alteration of node of Ranvier structure  
466 remains to be visualised in vivo, but nodal length actually can be fine-tuned by the axon via its own  
467 cytoskeleton during development, and not necessarily by the flanking myelin sheaths (Brivio et al.,  
468 2017). The axon initial segment, where the action potential is initiated, and which is similar in  
469 composition to nodes, can, in fact, be structurally remodelled in response to activity (Grubb and  
470 Burrone, 2010; Kuba et al., 2010; Yamada and Kuba, 2016), in order to control action potential firing.  
471 Thus, modulation of many aspects of myelinated axons are well poised to have profound effects on  
472 nervous system function (Figure 1).

473 To understand how dynamic alterations to myelin and myelinated axons regulate neuronal circuit  
474 function it will be necessary to concomitantly interrogate the morphological and functional  
475 development of entire individual axons over time in the context of de novo myelination and  
476 remodelling. Ongoing technical developments will allow detailed reconstruction of the morphology  
477 and ultrastructure of individual myelinated axons over time (Wang et al., 2005; de Vito et al., 2014;  
478 Schain et al., 2014; Tomassy et al., 2014), which will help bridge this gap, when integrated with  
479 detailed functional studies.

480

481 **Final Remarks and Perspectives**



482 In summary, mechanistic studies have provided numerous insights into the dynamic and adaptive  
483 nature of the oligodendrocyte lineage and myelination, particularly in response to neuronal activity.  
484 In parallel, MRI studies have provided compelling evidence that brain activity can regulate WM  
485 structure in a circuit-specific manner that implies a role in functional plasticity. In Figure 1 we provide  
486 an overview of the timelines of prospective activity-driven changes to axonal morphology, the  
487 oligodendrocyte lineage, and myelinated axon subdomains. We propose that the effects that occur  
488 acutely on the order of minutes to hours are most likely to represent initial changes to the axon and  
489 non-myelin related changes to OPCs and differentiating oligodendrocytes, and those that occur over  
490 longer time scales will represent de novo myelination of axons, myelin remodelling, and further  
491 dynamic alteration to the myelinated axon (Figure 1). It is essential to note that myelination is not  
492 restricted to WM. Many axons in the GM are myelinated (Tomassy et al., 2014; Micheva et al., 2016;  
493 Stedehouder et al., 2017). Neurons with myelinated axons that project through WM tracts will  
494 typically have their cell body, some of their axon and also their distal synaptic terminals in GM regions.  
495 Therefore, future analyses will need to focus on entire myelinated axons that traverse both GM and  
496 WM. Furthermore, a complete understanding of myelinated axon function will require study of the  
497 structure and composition of the domains of the axon itself. Therefore, we suggest that the term  
498 myelinated axon plasticity more completely conveys the range of potential adaptations within these  
499 functional units. Given that neuronal activity can regulate multiple stages of oligodendrocyte lineage  
500 behaviour through myelination as well as axonal structure, it is likely that myelinated axon plasticity  
501 plays a central role in many aspects of the formation and function of neuronal circuits that remain to  
502 be discovered.

503 Numerous fundamental questions remain to be addressed, for example:

504 *1. How does myelinated axon plasticity affect axonal conduction and function?* Changes to axonal  
505 diameter, myelination and the formation of associated axonal domains changes conduction from  
506 graded to saltatory, but we know little about how the functional properties of individual axons change  
507 throughout these processes. For example, does partial myelination already affect conduction or the  
508 ability to sustain high-frequency firing? Similarly, our knowledge of the functional impact of  
509 subsequent myelin remodelling and refinement of axonal domains along single axons remains unclear.  
510 Emerging technologies to map and manipulate individual neurons and their connections coupled with  
511 the ability to interrogate function in vivo will be essential to bridge this gap (Fosque et al., 2015; Joesch  
512 et al., 2016; Wanner et al., 2016; Forster et al., 2017; Hildebrand et al., 2017).

513 *2. Which neuronal subtypes and circuits exhibit myelinated axon plasticity?* In developing zebrafish,  
514 activity-regulated myelination has been shown to be a property of only specific neuronal subtypes  
515 (Koudelka et al., 2016). It will be important to define which neurons and circuits exhibit myelinated

516 axon plasticity throughout life, and in response to experience. In addition to neuronal diversity, there  
517 is increasing evidence of diversity in the oligodendrocyte lineage, which will be important to consider  
518 from the point of view of circuit formation and function in future studies (Butt et al., 2005; Karadottir  
519 et al., 2008; Nishiyama et al., 2009; Vigano et al., 2013; Bechler et al., 2015; Marques et al., 2016).

520 *3. How does myelinated axon plasticity relate to nervous system growth?* Myelination of certain axons  
521 occurs very early in life, long before the nervous system has grown to its mature adult size. This begs  
522 the question; how is function maintained along individual axons over time? Do axons grow in both  
523 length and diameter in-step with animal growth, and if so, do individual myelin sheaths follow suit?  
524 Or, do individual axons need to be actively remodelled over time to sustain function, e.g. by addition  
525 of new myelin sheaths as the animal grows? Again, longitudinal live imaging will address these  
526 questions.

527 *4. How flexible is myelinated axon plasticity?* Could adaptations to the structure and function of  
528 specific myelinated axons during development or following training in a specific task facilitate the  
529 subsequent learning or execution of a related task? For instance, could fine-motor skills acquired when  
530 learning to play piano also benefit subsequent learning of another musical instrument? Also, how  
531 stable are activity-regulated structural modifications to myelinated axons? Once made, are they stable  
532 for an indefinite period, or do they require continuous activity to be maintained, such that myelin  
533 sheaths may shrink or be retracted from axons in disuse (e.g. following social isolation)?

534 *5. How relevant is myelinated axon plasticity to disease?* It is now clear that disruption to myelinated  
535 axons is a feature of many CNS diseases. To what extent could myelinated axon plasticity be employed  
536 to maintain function during the disease course? For instance, if axons become demyelinated (e.g. in  
537 multiple sclerosis), could adaptations to that axon or to other axons in the circuit compensate to help  
538 maintain function? Furthermore, could disruption to the mechanisms underlying the plasticity of  
539 myelinated axons underlie defects in circuit-level communication that characterise neuropsychiatric  
540 conditions?

541 Future studies that bridge scales of analyses from ultrastructure to circuit, from molecule to  
542 behaviour, and from fish to man will illuminate how myelinated axon plasticity affects neuronal circuit  
543 formation and higher-order function.

544

545 **Figure 1: Potential timeline of activity-related changes to GM and WM**

546 *Minutes:* functional synaptic adaptations (e.g. potentiation and depression) as well as structural  
547 adaptations can occur within milliseconds to minutes of stimulus onset in GM (1). Axons can grow in  
548 diameter within tens of minutes, potentially both in GM and WM (2).

549 *Hours:* new oligodendrocytes can differentiate rapidly in the WM (3), and OPCs can also re-enter the  
550 cell cycle within several hours (4). MRI-detected WM changes likely reflect changes in non-myelin  
551 components, e.g. axon diameter and OPCs.

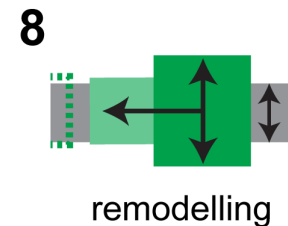
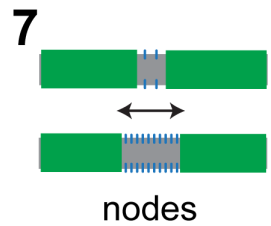
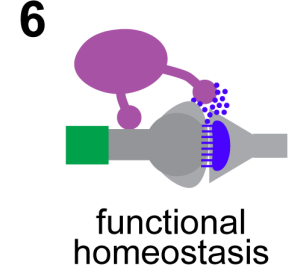
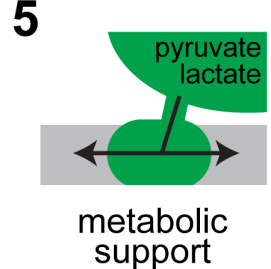
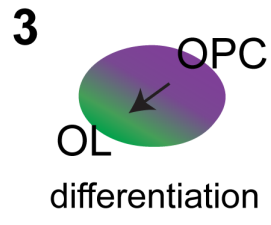
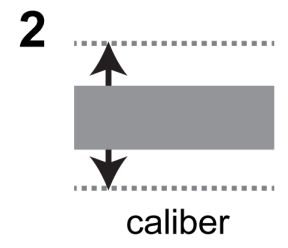
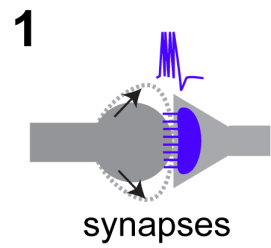
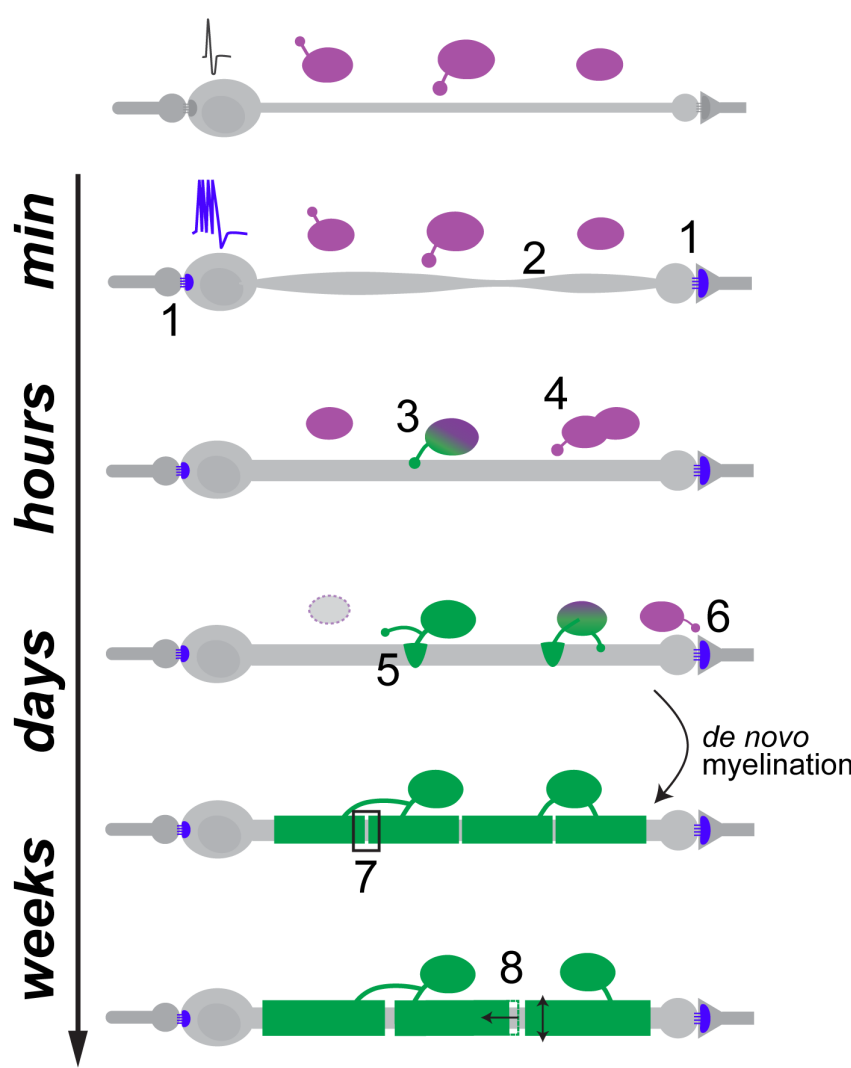
552 *Days:* Dividing OPCs differentiate over days, and together with rapidly differentiated oligodendrocytes  
553 may provide important metabolic support to axons (5). In parallel, OPCs can contribute to functional  
554 homeostasis at synapses (6). MRI-detected WM changes may reflect an increase in cell number  
555 following OPC proliferation, and/ or myelination.

556 *To be determined:* it remains unclear over what timescales dynamic changes to nodes of Ranvier (7),  
557 axon diameter and myelin remodelling (8) take place along myelinated axons or how such changes  
558 affect one another or corresponding MRI signatures.

559

560

561



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