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Title: Axoglial interactions in myelin plasticity - Evaluating the relationship between neuronal activity and oligodendrocyte dynamics

Running title: Axoglial interactions in myelin plasticity

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Main Points

- 1) Axonal activity modulates the generation of myelinating cells
- 2) The myelination of individual axons can be in part determined by their level of activity
- 3) A range of signaling mechanisms influence these regional and juxtacrine myelination effects.

Abstract

Myelin is a critical component of the vertebrate nervous system, both increasing the conduction velocity of myelinated axons and allowing for metabolic coupling between the myelinating cells and axons. An increasing number of studies demonstrate that myelination is not simply a developmentally hardwired program, but rather that new myelinating oligodendrocytes can be generated throughout life. The generation of these oligodendrocytes and the formation of myelin are influenced both during development and adulthood by experience and levels of neuronal activity. This led to the concept of adaptive myelination, where ongoing activity-dependent changes to myelin represent a form of neural plasticity, refining neuronal functioning and circuitry. Although human neuroimaging experiments support the concept of dynamic changes within specific white matter tracts relevant to individual tasks, animal studies have only just begun to probe the extent to which neuronal activity may alter myelination at the level of individual circuits and axons. Uncovering the role of adaptive myelination requires a detailed understanding of the localized interactions that occur between active axons and myelinating cells. In this review, we focus on recent animal studies that have begun to investigate the interactions between active axons and myelinating cells and review the evidence for – and against – the ability of neuronal activity to alter myelination at an axon-specific level.

Key Words

- 1) Myelin plasticity
- 2) CNS myelination
- 3) Neuronal activity
- 4) Axoglial interactions
- 5) Activity-dependent myelination
- 6) Adaptive myelination

7) Neuroplasticity

1. Introduction

Myelin is a highly specialized cellular structure in which glial cells (oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system) make concentric wraps of membrane around the axons of neurons. These wraps, which generate the myelin internode, electrically insulate axons and limit voltage gated sodium channels to the nodes of Ranvier established at the gaps between myelin segments. The myelination of an axon dramatically increases its conduction velocity relative to an unmyelinated axon of the equivalent caliber; conduction velocities increase with axonal diameter in a linear fashion for myelinated axons but as a function of the square root of axonal diameter for unmyelinated axons (Waxman, 1980). Myelination therefore allows for more rapid transfer and processing of information within a limited space. Although glial ensheathing structures are not entirely specific to vertebrates - some individual shrimp and worms species have independently evolved insulating structures analogous to myelin that increase the speed of axonal conduction (Xu and Terakawa, 1999) - the unique extent of myelin in the nervous system of jawed vertebrates almost certainly allowed the increase in size and complex behaviors seen in vertebrate species during evolution (Hartline and Colman, 2007; Zalc, 2016).

In humans, myelination is a remarkably prolonged process. Myelination does not peak in the human brain until the fifth decade, with progressive loss of myelin and myelin abnormalities seen thereafter (Bartzokis et al., 2010; Kohama et al., 2011; Bartzokis et al., 2012). In particular, myelination of late-maturing brain regions such as the connections between the frontal and temporal lobes continue well into the third decade of life (Lebel et al., 2008). Similarly in mice, continuous differentiation of resident oligodendrocyte progenitor cells (OPCs) gives rise to new oligodendrocytes capable of myelination throughout life, albeit at lower rates as the animal ages (Rivers et al., 2008;

Zhu et al., 2011; Hughes et al., 2013; Young et al., 2013). Intriguingly, a number of human neuroimaging studies found evidence of structural alterations within the white matter of adults in response to juggling, piano practice or working memory tasks (Bengtsson et al., 2005; Scholz et al., 2009; Takeuchi et al., 2010). The alterations seen in these studies have been interpreted as being most likely to reflect task-induced increases in myelination, although other cellular changes such as axonal diameter and packing could also contribute to the fractional anisotropy measurements common to these studies (Beaulieu, 2002; Zatorre et al., 2012). Together, these studies raise the important question of whether myelin could be modified in the human brain on an ongoing basis in response to patterns of neuronal activity, perhaps representing a form of plasticity (a concept commonly referred to as adaptive myelination).

A range of animal studies support the notion of a link between neuronal activity and myelination, a link first described in early studies of the developing optic nerve. Gyllenstein and Malmfors (1963) found that dark-rearing mice delayed the formation of myelin within the optic nerve. Conversely, premature eye opening within rabbits caused precocious expression of myelin proteins (Tauber et al., 1980). Since these early studies in the visual system, a wide range of animal models have been used to investigate the responsiveness of myelination to either environmental input or neuronal activity. These diverse approaches include stimulating or blocking activity in myelinating co-cultures (Demerens et al., 1996; Stevens et al., 2002; Wake et al., 2011; Lundgaard et al., 2013), social isolation or environmental deprivation (Liu et al., 2012; Makinodan et al., 2012; Hughes et al., 2018; Narducci et al., 2018), motor training (Sampaio-Baptista et al., 2013; McKenzie et al., 2014), optogenetic, electrophysiological or chemogenetic stimulation of neurons in the mouse brain (Li et al., 2010; Gibson et al., 2014; Mitew et al., 2018; Stedehouder et al., 2018) or genetic modulation of neuronal firing and vesicular release in the zebrafish (Hines et al., 2015; Mensch et al., 2015; Koudelka et al., 2016).

The picture emerging from these studies is that neuronal activity represents an important aspect of the regulation of oligodendrocyte production and of their myelination within both the developing and adult CNS. Nevertheless, the picture is also biologically complex. Firstly, although these studies have highlighted the role of neuronal activity in regulating CNS myelination in some contexts, a range of studies have equally demonstrated that in other contexts myelination can proceed without any neuronal activity at all. *In vitro*, oligodendrocytes can form multilaminar myelin-like structures around chemically fixed axons or even inert rod or cone structures of the appropriate diameter (Rosenberg et al., 2008; Lee et al., 2013; Mei et al., 2014; Bechler et al., 2015). Similarly, in the developing visual system axonal diameter is a sufficient cue to drive successful myelination of axons that have been silenced by removal from the cell body (Mayoral et al., 2018). These studies highlight the fact that neuronal activity is likely to be an important, but definitely not universally required, regulator of myelination. Secondly, many studies investigating the role of neuronal activity have focused on relatively broad aspects of the myelination program, such as proliferation and subsequent differentiation of OPCs. Other studies have focused on local signaling mechanisms between the axons and the myelinating cells that potentially result in much more localized changes to myelination. The relative importance of these broad vs. highly selective effects of activity on myelination is often unclear. In this review we focus on recent advances in our understanding of the activity-dependent interactions between axons and myelinating cells and the implications of these interactions for development and neuronal circuitry.

2. Adaptive myelination: Why should neuronal activity influence myelination?

Why should myelination be responsive to levels of neuronal activity? A possibility receiving substantial interest is that activity-driven changes to myelination might

represent a form of neuroplasticity, fine tuning the functioning of neuronal circuits (for detailed review of these concepts see Fields, 2005; Pajevic et al., 2014; Fields, 2015; Purger et al., 2016; Almeida and Lyons, 2017). Certainly, even within the mature CNS considerable scope exists for the modulation of axonal conduction rates through changes to myelin. Firstly, not all axons are myelinated within many white matter tracts. For example, within the corpus callosum it has been estimated that only ~30-70% of axons are myelinated with even some theoretically receptive axons $>0.2\mu\text{M}$ remaining unmyelinated (Sturrock, 1980; Olivares et al., 2001). Within the cortex, many individual axons display isolated myelin segments interspersed with long unmyelinated regions (Tomassy et al., 2014). Here, the potential for *de novo* myelination of previously unmyelinated stretches becomes even more apparent. In addition to myelination of previously unmyelinated axons or stretches of axons (*de novo* myelination), conduction properties may be modified through changes in internode length, myelin thickness and nodal width, all of which have been shown either computationally or experimentally to change conduction velocity (Waxman, 1980; Wu et al., 2012; Ford et al., 2015).

Probably the best-described example of myelin tuning neuronal circuitry comes from the auditory system. Here, neurons of the cochlear nuclei project via different branches of the same axon to coincidence detection neurons in the ipsilateral and contralateral medial superior olivary nucleus. To allow the signals to reach the ipsilateral and contralateral postsynaptic nuclei simultaneously, the longer contralateral branches make use of both greater axonal diameter and longer internode lengths to increase conduction rates (Seidl et al., 2014; Seidl and Rubel, 2015). Similar use of variable myelin profiles along axons may compensate for differing axonal projection lengths and achieve isochronicity in thalamocortical projections (Kimura, 2009). An important caveat to these examples is that the patterns of myelin are often established developmentally, prior to the onset of hearing in the case of the collaterals from the cochlear nuclei to the medial superior

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olivary nucleus (Seidl and Rubel, 2015). It is therefore unclear whether they represent a specific example of a role for myelin in neuroplasticity so much as a genetically hardwired program.

Another potential role for adaptive myelination is to promote metabolic coupling between oligodendrocytes and axons. Oligodendrocytes are capable of producing lactate through glycolysis and providing it to axons via the MCT1 transporter for axonal ATP production (Funfschilling et al., 2012; Lee et al., 2013b; Meyer et al., 2018). This may help compensate for the logistical difficulty in transporting molecules between the soma and axons of neurons or from the extracellular environment to axons across the myelin sheath. Intriguingly, NMDA receptor signaling in oligodendrocytes enhances glucose transporter localization to the myelin sheath, providing a potentially elegant mechanism to link levels of neuronal activity to oligodendrocyte glucose uptake and subsequent axonal metabolic support (Saab et al., 2016). Many rapidly firing interneurons are myelinated in spite of this being unlikely to meaningfully alter the timing of signals reaching their postsynaptic targets; oligodendroglial metabolic support offers a potential explanation for the myelination of this neuronal population (Micheva et al., 2016; Stedehouder et al., 2018). Nevertheless, calculations show an axon may have to fire millions of times to offset the energy cost of producing the myelin sheath, and it remains unclear whether myelination necessarily confers a net energy benefit to the whole organism in addition to enhancing conduction velocity (Harris and Attwell, 2012).

Irrespective of whether adaptive myelination directs oligodendroglial metabolic support to highly active axons, conserves energy or modulates circuitry, these functions would seem to be best achieved through preferential targeting of myelin changes to the active population of axons. Unsurprisingly, therefore, many of the reported changes in myelination driven by experience or neuronal activity appear relatively specific to discrete anatomical regions or circuits. For example, rodent studies show social isolation

is associated with reductions in myelin in the prefrontal cortex but not in the corpus callosum or cerebellum (Liu et al., 2012; Makinodan et al., 2012). Rodent studies also show that running on a complex wheel is associated with increased oligodendrogenesis in the motor cortex and subcortical white matter but not the optic nerve (Xiao et al., 2016). In addition, skilled reaching tasks drive differences in the Fractional anisotropy (FA) signal in white matter areas underlying the sensorimotor cortex contralateral but not ipsilateral to the trained limb (Sampaio-Baptista et al., 2013). These findings are consistent with human neuroimaging studies that also show preferential changes in FA signal to anatomical regions relevant to the task. For example, juggling practice drives changes in the white matter regions connecting visual to motor cortex and piano practice driving changes in the pyramidal tract (Bengtsson et al., 2005; Scholz et al., 2009). However, adaptive myelination is still typically described at the level of broad anatomical regions or tracts rather than at the level of individual axons. At present, only a handful of studies approached this level of nuanced analysis; imaging studies in the developing zebrafish largely lead the way, but some tissue culture and mouse studies have also taken on the challenge.

3. Influences of neuronal activity on myelination: Regional and axon-specific responses

3.1 Activity-mediated oligodendrogenesis

A number of cellular processes dictate the available pool of differentiating oligodendrocytes available to myelinate. Generally speaking, proliferation of the OPC population increases the number of cells available to either continue proliferation or terminally differentiate into pre-myelinating oligodendrocytes. Live imaging studies within the adult mouse cortex found that the differentiation of one OPC tends to be

associated with subsequent proliferation of an adjacent OPC in order to replace it (Hughes et al., 2013), so in practice the processes of differentiation and proliferation are tightly coupled. In addition to the differentiation of OPCs, cell death also contributes to the ultimate number and location of myelinating oligodendrocytes; a large proportion of the newly differentiated pre-myelinating oligodendrocytes undergo apoptosis during both development and adulthood (Barres et al., 1992; Trapp et al., 1997; Hughes et al., 2018). Genetically blocking apoptosis causes increased myelination, including of axonal populations that usually remain unmyelinated (Sun et al., 2018). Current evidence suggests that neuronal activity influences the final density of myelinating oligodendrocytes through all three of these processes; proliferation, differentiation and cell death.

Substantial experimental evidence links stimulation of neuronal firing to OPC proliferation. For example, direct electrical stimulation of the corticospinal tract in adult mice leads to increased OPC proliferation (Li et al., 2010). Similarly, optogenetic stimulation of the premotor cortex leads to increased OPC proliferation 3 hours after stimulation within the cortex and underlying white matter; an increase that is reduced but detectable 4 weeks after a week of stimulation (Gibson et al., 2014). Chemogenetic stimulation of cortical neurons using excitatory DREADDs results in increased OPC proliferation within the corpus callosum, albeit with much longer latency between stimulation and detectable increases in proliferation (Mitew et al., 2018). Some of these differences in timing may reflect the frequencies and activity patterns generated by the optogenetic and chemogenetic approaches, given recent findings that high frequency stimulation (25-300 Hz) has greater effects on OPC proliferation within the corpus callosum than low-frequency stimulation (Nagy et al., 2017). Compared to these stimulation experiments, sensory deprivation experiments have yielded more mixed results. An early study sought to examine the effect of decreased neuronal activity on

oligodendrogenesis within the developing optic nerve of early postnatal rats using the Na⁺ channel blocker tetrodotoxin (TTX) to block retinal ganglion cell action potentials. Injection of TTX into one eye resulted in a substantial decrease in the number of mitotic OPCs in the optic nerve after two days (Barres and Raff, 1993). A more recent study sutured the eye shut to reduce coordinated activity between P15-32 found only a minor decrease in OPC proliferation over this longer time period, however (Etxeberria et al., 2016), and sensory deprivation via whisker trimming has even been linked to increased OPC proliferation in the somatosensory cortex (Hill et al., 2014).

The differentiation of the progenitor population represents an important cellular process, as this newly differentiated pool may potentially myelinate previously unmyelinated regions of axons. The above studies increasing neuronal activity in the brain or corticospinal tract via electrical, optogenetic or chemogenetic stimulation all noted increased differentiation of EdU or BrdU-labeled OPCs into post-mitotic oligodendrocytes within the stimulated regions (Li et al., 2010; Gibson et al., 2014; Nagy et al., 2017; Mitew et al., 2018). In contrast, the effect of decreasing firing of the retinal ganglion cells (RGCs) within the optic nerve during development suggests relatively limited influences of activity on differentiation. Reduced RGC firing at P4 via TTX injections resulted in decreased myelin segments within the optic nerve when examined at P6 (Demerens et al., 1996), but the density of myelin basic protein (MBP) expressing oligodendrocytes remained unchanged (suggesting that myelination but not the preceding step of differentiation was sensitive to activity). A recent monocular deprivation model examining the optic tract at P32 surprisingly reported an increase in mature oligodendrocytes generated between P15-32 in the deprived optic nerve and tract (Etxeberria et al., 2016). Given the strong apparent drive for the visual system to fully myelinate, these slightly disparate findings could perhaps be reconciled if an early

decrease in myelin formation resulted in a compensatory increase in oligodendrocyte differentiation at later time points.

In other models, studies suggest that experience-driven oligodendrocyte differentiation precedes changes in proliferation. McKenzie et al. (2014) and Xiao et al. (2016) provided mice with a complex running wheel task and found little change in OPC division in the first 2 days of running (measured by incorporation of EdU), though OPC proliferation was subsequently increased at 4 days. In subsequent experiments where the OPCs were pre-labeled with EdU prior to introduction to the wheel, they observed a reduction in the density of EdU-labeled OPCs at two days after introduction to the wheel, suggesting that they may have begun to differentiate. Using the expression of Ectonucleotide Pyrophosphatase/Phosphodiesterase 6 (*Enpp6*), a gene highly enriched in newly formed oligodendrocytes, they reported a significant increase in this population in as little as two hours after exposure to the running wheel, confirming a rapid differentiation response. This result raises the possibility OPCs may typically respond to increases in activity first by differentiation, followed by a subsequent homeostatic proliferative response. A broadly similar enhancement of differentiation (at the expense of OPC proliferation) has been reported in response to running on a non-complex wheel (Simon et al., 2011) as well.

These studies show that changes to neuronal activity can lead to changes in the number of OPCs, newly formed oligodendrocytes, and mature oligodendrocytes, but are these newly generated pools transient or do they represent a cell population stabilized over time? Recently published work shows that the majority of oligodendrocytes that differentiate in the adult cortex fail to stably integrate, however placing adult mice in an enriched environment that provides frequent whisker stimulation results in an increase number of number of newly generated oligodendrocytes within the barrel cortex after 20 days

(Hughes et al., 2018). Conversely, whisker trimmed mice show increased death of newly generated oligodendrocytes within the developing somatosensory cortex, without changes in the rate of cell death of mature oligodendrocytes (Hill et al., 2014). Collectively, these studies suggest that increases to neuronal activity can lead to an increased pool of newly generated oligodendrocytes, capable of surviving and myelinating.

3.2 Do relative levels of activity in axons bias their selection for myelination?

The above studies indicate that neuronal activity is capable of modulating myelination at a broad level through the promotion of oligodendrogenesis. Broad levels of activity or environment also influence the total number of myelin segments produced per oligodendrocyte, again leading to an overall increase in myelin within the vicinity of the active axons (Makinodan et al., 2012; Mensch et al., 2015). If the electrical activity of axons modulates the total amount of myelin in their vicinity, does it also bias the axonal selection for myelination such that individual active axons are more likely to be myelinated than their less active neighbors? A number of groups have addressed this question, either altering activity within subsets of axons or preventing the vesicular release of signaling molecules from active axons (see below for discussion of these cues). These studies have generated surprisingly conflicting results.

Blocking vesicular release in a subset of electrically stimulated dorsal root ganglion neurons in culture, Wake et al. (2015) found that oligodendrocytes preferentially myelinated the control population of axons in which vesicular release had not been inhibited. OPCs in these cultures were more likely to make contacts with the axons capable of vesicular release, with localized MBP translation more likely to occur along the control than the inhibited axons. These findings are consistent with previous reports by the group that glutamate release from active axons enhances local MBP translation in

adjacent oligodendrocyte processes (Wake et al., 2011). The first *in vivo* evidence that neuronal activity could bias axonal selection came from developmental zebrafish studies. Hines et al. (2015) focused on the early-myelinated population of *Phox2b*⁺ axons in the zebrafish spinal cord. This study inhibited either the firing of this neuronal population via selective expression of the Kir2.1 inward rectifying channel or inhibited their vesicular release by selective expression of tetanus toxin (TeNT). Silenced *Phox2b*⁺ axons showed a reduced probability for myelination, while the myelination of adjacent sheaths remained unaffected. In addition, where the TeNT-expressing axons were myelinated, it tended to be with shorter sheaths. The reduction in sheath length could be rescued by inhibiting the activity of surrounding axons with TTX, suggesting a program of activity-based competition between axons for myelination. Although the initial contact between oligodendrocyte processes and axons did not seem to be influenced by activity, the oligodendrocyte contacts on silenced axons were more likely to be retracted, presumably leading to their competitive disadvantage (Hines et al., 2015).

To assess the ability of neuronal activity to bias axonal selection in the intact mammalian CNS, our group recently stimulated neurons in the somatosensory cortex using the excitatory synthetic G protein-coupled receptor hM3Dq. Following a week of daily stimulation with the hM3Dq ligand clozapine-n-oxide (CNO), we assessed the myelination of hM3Dq-expressing and neighboring control axons in the corpus callosum (Mitew et al., 2018). Treatment of the mice with CNO enhanced the accumulation of newly generated oligodendrocytes approximately two-fold in both juvenile and young adult mice. This is consistent with previous studies indicating that stimulating neuronal activity promotes oligodendrogenesis (Li et al., 2010; Gibson et al., 2014; Nagy et al., 2017). In addition, the hM3Dq expressing axons in the corpus callosum (identifiable through co-expression of eGFP) showed a greater increase in myelination following the stimulation with CNO than their neighboring non-hM3Dq transduced axons. This suggests that the newly differentiated oligodendrocytes preferentially myelinated the

active axons. Conversely, expressing Kir2.1 in a subset of axons reduced the probability of myelination without affecting myelination of the surrounding population of axons. The stimulated hM3Dq expressing axons were also surrounded by thicker myelin, though it was not possible to distinguish whether this was restricted to myelin segments produced following the stimulation or whether pre-existing myelin may have also undergone remodeling. These results, together with the above *in vitro* and zebrafish studies (Hines et al., 2015; Wake et al., 2015), indicate that newly generated oligodendrocytes prefer to myelinate the more active axons within an available pool.

In contrast to these studies, several studies using sensory deprivation models in the developing visual system found no evidence for preferential myelination of active axons. Osanai et al. (2018) reduced coordinated activity within one eye by suturing the eyelid shut during the postnatal period of active myelination. The groups subsequently assessed individual oligodendrocytes within the optic chiasm where axons from both the intact and deprived eye were present and identified by labeling with different fluorescent proteins. They found that individual oligodendrocytes surrounded by both intact and deprived axons showed no preference for myelinating axons from the intact eye. Oligodendrocytes predominantly surrounded by axons from the deprived eye did tend to produce larger numbers of shorter internodes, indicating that silencing neuronal activity influenced myelination, but only at a population level. Using a similar monocular deprivation model Etxeberria et al. (2016) found that monocular deprivation did not reduce the probability of myelination in retinal ganglion cells, but did result in shorter myelin internodes. Etxeberria et al. also made use of the small number of ipsilaterally projecting axons within the optic tract to determine the fate of a small population of active axons within a population of silenced ones, or vice versa. They found that axons from the intact eye were myelinated with shorter internodes when surrounded by axons from the deprived eye. This is again consistent with global levels of activity determining myelin length in

oligodendrocytes within an activated region, rather than activity of an individual axon. Nevertheless, ipsilateral axons from the deprived eye still showed shorter internode lengths when projecting through the optic tract alongside more numerous axons from the control eye. Whether this reflected the cumulative effects of the ~10% ipsilaterally projecting axons from the deprived eye within that tract or whether it was consistent with some degree of axonal autonomy in the determination of internode length remains unclear. In either case, neither Etxeberria et al. (2016) nor Osanai et al. (2018) found a preferential myelination of active axons within this model.

One possible explanation for the discrepancies in the findings of the above studies is that activity is not a dominant signal for myelination in all axonal populations. Koudelka et al. (2016) found that not all types of neurons in the developing zebrafish rely on vesicular release for their myelination. After expressing TeNT in two populations of glutamatergic, large-caliber, early-myelinated axons, they found vesicular release strongly inhibited myelination in axons of reticulospinal neurons but did not affect axons of commissural primary ascending axons (CoPA). It is possible that the lack of preference for myelinating active axons in the above monocular deprivation experiments (Etxeberria et al., 2016; Osanai et al., 2018) reflects a dominant genetic program for myelination in the retinogeniculate pathway, which is nearly fully myelinated within the first month or two of life. (See Bechler et al., 2017, for further discussion of the potential for distinct default and activity-dependent programs of myelination.) Nevertheless, Osanai et al. (2018) obtained similar results with reduced activity in a subset of somatosensory neurons via unilateral whisker trimming. Individual oligodendrocytes within the corpus callosum surrounded by both control and deprived axons were as likely to myelinate either population, though they produce shorter segments if surrounded predominantly by silenced axons.

The contexts in which activity of individual axons regulates their own myelination therefore remains unclear. *In vitro* studies, developing zebrafish and our lab's chemogenetic studies in the mouse corpus callosum reveal a strong bias towards a developing oligodendrocyte myelinating the active axons at the expense of nearby relatively inactive axons. Other systems using sensory deprivation models found no preference for the myelination of active axons in spite of broader effects of the deprivation on myelination. It is also possible that the determination of whether activity-dependent or -independent mechanisms for axonal selection predominate depends greatly on the individual population of axons being examined, the developmental period, and the patterns of activity involved. With increasingly powerful techniques available to both image and manipulate neurons within the intact brain, it is likely that future *in vivo* longitudinal imaging studies will help clarify this issue.

3.3: Does neuronal activity promote remodeling of existing myelin?

If neuronal activity influences *de novo* myelination during oligodendrocyte differentiation, is there evidence that changes in environment or neuronal activity also modify existing myelin in the mature CNS? In rodents the half-life of myelin proteins and lipid components have been estimated to be in the order of months (Smith, 1968; Sabri et al., 1974). Similarly, a human study utilizing ^{14}C carbon dating indicates that the components of myelin are turned over relatively regularly, well in excess of the modest 0.3% per annum rate of oligodendrocyte addition calculated in the same study (Yeung et al., 2014). Although this turnover of myelin components seems to leave the door open for ongoing remodeling of myelin, direct evidence for changes to existing myelin internodes in the mature CNS in response to changes in neuronal activity remains sparse. One recent study of myelination in the auditory system showed that raising the auditory threshold by providing mice with ear plugs between P55-66 (after myelination in this tract reaches maturity) caused a decrease in myelin thickness on large diameter axons (Sinclair et al.,

2017). This decrease in myelination isn't necessarily an adaptive change, but it does provide evidence that mature myelin can be remodeled in response to physiological changes. Several genetic approaches in the adult mouse also suggest that mature oligodendrocytes can dynamically regulate the thickness of existing myelin internodes in response to intracellular signaling pathways. Conditional activation of either the Erk1/2-MAPK pathway (Ishii et al., 2016) or the PI3K/AKT/mTOR pathway (Snaidero et al., 2014) in mature oligodendrocytes cause increases in myelin thickness. Although stimulation of these pathways in mature oligodendrocytes has not yet been observed in responses to neuronal activity, localized stimulation of such intracellular pathways may modulate myelin thickness at the level of an individual oligodendrocyte or even individual myelin segment.

Clearly, observing the same internode over time represents the gold-standard in determining whether existing myelin segments undergo remodeling. Two recent studies used this exact approach (Hill et al., 2018; Hughes et al., 2018). Using an *in vivo* two-photon imaging approach with genetically labeled OPCs and oligodendrocytes in the adult mouse, Hughes et al. (2018) found that only ~0.9% of established myelin segments in the somatosensory cortex showed dynamic changes in their length over a 48 day period. Neither sensory stimulation (hanging beads in the home cage) nor sensory deprivation (whisker trimming) enhanced this low basal level of remodeling, in spite of oligodendrogenesis being altered by these same interventions. This suggests that remodeling of existing myelin may represent, at most, a limited component of plasticity. Using a broadly similar longitudinal imaging approach, Hill et al. (2018) observed a substantially higher proportion of extant myelin segments undergoing remodeling, with ~20% of segments displaying extension or retraction over a 30 day period. Intriguingly, individual internodes generated by the same oligodendrocyte could either be extended, retracted or remain stable, indicating that these remodeling events may be regulated at the

local axonal level rather than at the level of the whole oligodendrocyte. The reason for the apparent disparity between rates of remodeling in these two studies remains unclear, but may be in part due to the older ages utilized by Hill et al. (2018). Importantly, given the limitations of light microscopy neither studies addressed more subtle aspects such as myelin thickness or nodal width, both of which have the potential to alter conduction dynamics (Waxman, 1980; Ford et al., 2015).

Would plasticity of existing oligodendrocytes be restricted to modification of existing myelin internodes, or could mature oligodendrocytes extend new segments to ensheath previously unmyelinated regions of axon? Fate mapping experiments suggest that new myelin internodes are primarily generated by newly differentiated oligodendrocytes (Rivers et al., 2008; Zhu et al., 2011; Young et al., 2013) and it is questionable whether a mature oligodendrocyte is even capable of extending new myelin internodes. Both *in vitro* imaging of actively differentiating rodent oligodendrocytes (Watkins et al., 2008) and *in vivo* imaging of myelinating oligodendrocytes in zebrafish (Czopka et al., 2013) show that actively differentiating oligodendrocytes extend their myelin sheaths within a relatively short period of time (under a day) with only the occasional retraction of myelin segments seen thereafter. Longitudinal imaging studies of mature oligodendrocytes in the adult rodent cortex and genetic fate mapping approaches also failed to see any evidence of mature oligodendrocytes extending new myelin segments (Crawford et al., 2016; Hill et al., 2018; Hughes et al., 2018). Nevertheless, a recent electron microscopy study of remyelinating lesions in cat and monkey found many examples of single oligodendrocytes connected to both myelin internodes with both normal myelin thickness and internodes with very high g-ratios - a cardinal marker of remyelination (Duncan et al., 2018). This offers perhaps the strongest evidence yet for the notion that a mature myelinating oligodendrocyte potentially extends to form additional myelin internodes (at least in the context of injury). Until time-lapse imaging or genetic labeling approaches

show definitive evidence, the field is likely to remain skeptical that extant mature oligodendrocytes are a substantial contributor of new myelin segments. It does remain an intriguing possibility however, particularly in humans where the number of postmitotic oligodendrocytes seems to peak some decades before the maximum amount of myelin is established (Yeung et al., 2014).

4. Diffusible and local signals in adaptive myelination

Neuronal activity influences oligodendrocyte dynamics, affecting proliferation, differentiation, and survival and possibly altering myelin structure and axonal selectivity. What are the signaling mechanisms underlying this signal transmission?

Trophic factors

Several diffusible signaling molecules have been identified that may promote oligodendrocyte proliferation or differentiation within a brain region. Using a combined proteomics and optogenetics approach, Venkatesh et al. (2015) identified a series of proteins released by activated neurons, including Neuroligin-3 and Brain-derived neurotrophic factor (BDNF). A role for Neuroligin-3 in myelination has not been shown, though Venkatesh et al. (2015) did find that it mediated much of the activity-induced proliferation of glioma cells in their model. Of the activity-induced proteins identified in that study, BDNF in particular represents an attractive candidate for mediating activity-induced oligodendrogenesis within active tracts as it acts through oligodendroglial TrkB receptors to promote both OPC proliferation and subsequent myelination (Xiao et al., 2011; Wong et al., 2013; Peckham et al., 2015). Current work seeks to address the exact contribution of BDNF in adaptive myelination. In addition to BDNF, a recent animal study implicated the secreted neuropeptide VGF in activity-mediated oligodendrogenesis. In a mouse genetic model of ataxia, voluntary exercise (running) both increased VGF

expression and improved cerebellar myelination. VGF promoted oligodendrogenesis *in vitro* and viral expression of VGF was able to increase myelination in the mouse ataxia model, suggesting it may contribute to the protective effects of exercise (Alvarez-Saavedra et al., 2016). As VGF is both downstream of BDNF and in turn modulates signaling through neurotrophin receptors (Alder et al., 2003; Bozdagi et al., 2008; Lin et al., 2015), considerable potential also exists for these two activity secreted factors to act in concert.

Neurotransmitters

Activity-regulated release of neurotransmitters also seems to have the potential to contribute to the activity-dependent myelination at either an axon-specific or at least highly localized level. In addition to synaptic release at their terminals, axons release vesicular neurotransmitters along their length during action potentials (Kukley et al., 2007). OPCs express voltage gated ion channels and many neurotransmitter receptors such as AMPA, NMDA, and GABA receptors (De Biase et al., 2010), also receiving direct synapse-like input from the axons of both excitatory and inhibitory neurons (Bergles et al., 2000; Lin and Bergles, 2003; Ziskin et al., 2007). Although the expression of many of these receptor subunits decreases in OPCs both during their differentiation and as the rate of myelination decreases with age (De Biase et al., 2010; Spitzer et al., 2019), post-mitotic oligodendrocytes still express detectable NMDA receptors, providing a potential mechanism to survey levels of activity in individual axons (Micu et al., 2016; Saab et al., 2016). As noted above, blocking axonal vesicular release in a subset of axons in the developing zebrafish reduces their myelin coverage (Hines et al., 2015; Mensch et al., 2015), a finding potentially attributable to vesicular release of glutamate acting to promote the stabilization or extension of developing myelin segments. Consistent with this possibility, although blocking glutamate release from mouse RGC axons did not prevent their myelination, it did result in reduced internode length in the optic nerve

(Etxeberria et al., 2016). Localized activity and synaptic release of glutamate also induces localized Ca^{2+} signaling and translation of MBP in oligodendrocyte processes (Wake et al., 2011; Krasnow et al., 2018), providing localized cellular mechanisms that could direct preferential myelin extension along active axons.

Nevertheless, the exact role of vesicular release of neurotransmitters in myelination remains unclear, with oligodendrocyte conditional knockouts of neurotransmitter receptor subunits showing only modest phenotypes. Myelination proceeds relatively normally in mice with deleted OPC specific NR1 subunit of NMDARs, with proliferation and differentiation being unaffected and at most a minor delay in myelination (De Biase et al., 2011; Saab et al., 2016). This argues for a modest role for NMDARs in myelination; so why express them at all? NMDA receptors demonstrate a higher affinity for glutamate than AMPA receptors, so it is possible that these receptors act more as a sensor, prone to respond to smaller changes in glutamate levels or possibly spillover from nearby active areas. Disruption of AMPARs in the oligodendrocyte lineage also results in relatively modest phenotypes, with a minor decrease in the myelinating oligodendrocytes caused by increased apoptosis of the differentiating cells (Kougioumtzidou et al., 2017). Interestingly, although oligodendroglial NMDAR were not essential for myelination, Saab et al. (2016) found that they did regulate the surface expression of glucose transporters and that in the absence of functional oligodendroglial NMDARs mice developed a late onset axonal pathology. This strongly implicates glutamate signaling through oligodendrocyte NMDARs as a mechanism to match oligodendrocyte metabolic support with axonal activity. At present, none of these studies address whether glutamate receptor mutant mice might display more subtle alterations in myelination of selective subtypes of axons.

Contact-mediated factors

In addition to vesicular release of neurotransmitters and trophic factors from axons, which would be expected to act over a relatively short range, an axon's level of activity could result in highly localized contact-mediated cues for myelination. For example, axonal expression of N-Cadherin, a cell adhesion molecule that promotes oligodendroglial-axonal interactions (Schnädelbach et al., 2001), is increased along axons of the developing zebrafish in an activity dependent manner. Blocking N-Cadherin in turn blocked activity-induced increases in myelination (Chen et al., 2017). Social isolation of juvenile mice during a critical period in brain development leads to decreased expression of the axonal ErbB3 ligand Neuregulin-1 type III, accompanied by decreased myelination within the prefrontal cortex (Makinodan et al., 2012). A similar decrease in prefrontal myelination (reflected by both increased g-ratios and decreased internode number per oligodendrocyte) is seen in both Neuregulin-1 type III heterozygotes and oligodendrocyte ErbB3 mutants (Taveggia et al., 2007; Makinodan et al., 2012), suggestive of a causal link between neuregulin signaling and isolation-induced hypomyelination. Neuregulin signaling decreases oligodendroglial expression of the inhibitory NR3A subunit of NMDAR, suggesting a mechanism by which an activity-influenced cell surface protein could signal to make oligodendroglia more responsive to vesicularly released glutamate (Lundgaard et al., 2013). Presumably, activity-induced regulation of N-Cadherin, Neuregulin-1 type III or additional adhesion molecules along individual axons could provide a highly selective juxtacrine selection signal for nearby differentiating oligodendrocytes to preferentially myelinate the active axons. Interestingly, the diameter of unmyelinated axons also transiently increases after high-frequency signaling (Chéreau et al., 2017). Given that the diameter of CNS axons plays a dominant role in promoting their myelination (Lee et al., 2013a; Goebbels et al., 2016; Mayoral et al., 2018) this could also provide an important cue for oligodendrocytes during axonal selection.

5. Future directions and challenges for the adaptive myelination field

Over the past several decades, the view of myelin has largely evolved from that of a static insulator to being a potentially plastic component of the brain. Nevertheless, a number of key challenges remain for the field. Firstly, as highlighted in this review, a greater understanding is required of which axonal populations use activity as a major contributor of their myelination and at what stages of development. How activity dependent and independent modes of myelination might interact and whether activity of one axon will influence primarily its own myelination or also that of the surrounding axonal population represent important yet open questions.

Secondly, so far only a handful of studies have sought to determine the functional consequences of blocking activity-dependent myelin changes. The Monje lab capitalized on the known role of histone deacetylases in oligodendrocyte differentiation, treating optogenetically stimulated mice with HDAC inhibitors to block myelination. This blocked the long-term effects of optogenetic stimulation of the motor cortex on forelimb swing speed on the CatWalk test (Gibson et al., 2014). The Richardson lab took a genetic approach, conditionally ablating the transcription factor *Myrf* from adult OPCs to prevent *de novo* myelination. This resulted in a reduction in the ability of these animals to adapt to a complex running wheel (McKenzie et al., 2014; Xiao et al., 2016). These studies provided the earliest proof-of-principle data that adult myelination is a functionally important component of plasticity, but still only scratched the surface of the forms of learning that adaptive myelination may be involved in. In addition, only some aspects of adaptive myelination were targeted in these studies (neither strategy would be predicted to disrupt any adaptations in existing myelin, for example.) As we learn more about the cellular basis of adaptive myelination and the neuronal signals driving it, better tools will

become available for determining the roles of specific myelin changes in altering neuronal conduction and function over a range of plasticity paradigms.

Finally, there is a great deal of justified interest in the concept of myelin plasticity as a mechanism for tuning neuronal circuits (e.g., Fields, 2005; Pajevic et al., 2014; Fields, 2015; Purger et al., 2016; Almeida and Lyons, 2017). Synchrony of spike timing between presynaptic inputs has long been considered a prerequisite for Hebbian synaptic plasticity (reviewed in Feldman, 2012); successful myelination is almost certainly vital for establishing this synchrony in many regions of the CNS. Nevertheless, the concept of how circuits may utilize changes in conduction velocity as a mechanism of (rather than a requirement for) synchrony-based plasticity remains relatively underdeveloped. As noted by Koudelka et al. (2016), the use of adaptive myelination to adjust synchrony within circuits seems to imply a feedback mechanism from the postsynaptic neuron to provide information that the impulses were arriving too slowly or quickly. How this information would then be transmitted back down the axon and provided to the oligodendrocyte is currently unknown. Again, with increasingly powerful tools available to both image and manipulate individual axons and their myelin, these important questions are becoming increasingly tractable and will be the focus for future work.

Figure 1: Model of paracrine and juxtacrine signals mediating adaptive myelination.

A: Axonal activity promotes the vesicular release of glutamate and BDNF to enhance proliferation and differentiation of OPCs, also promoting the survival of the newly differentiated oligodendrocytes. This provides a local pool of immature oligodendrocytes ready to myelinate. Vesicular release of these same molecules, or axonal expression of membrane-bound signaling molecules (N-cadherin, neuregulin), may then promote the preferential myelination of the active axons. Cooperativity also may exist between membrane-bound and secreted factors, for example neuregulin enhances OPC NMDAR expression, shifting the OPCs to an activity-dependent form of myelination.

B: NMDARs on mature myelin respond to vesicular release of glutamate into the periaxonal space or at the paranode. Signaling through these NMDARs enhances glucose import through the Glut1 transporter, allowing the oligodendrocytes to increase their lactate supply to active axons via monocarboxylate transporters. Whether signaling from active axons to the mature myelin also results in active modification of the myelin sheath remains unclear.

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