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Wrapped to adapt: experience-dependent myelination

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Activity of the nervous system has long been recognized as a critical modulator of brain structure and function. Influences of experience on the cytoarchitecture and functional connectivity of neurons have been appreciated since the classic work of Hubel and Weisel (Hubel and Wiesel, 1963; Wiesel and Hubel, 1963a, b). In recent years, a similar structural plasticity has come to light for the myelinated infrastructure of the nervous system. While an innate program of myelin development proceeds independent of nervous system activity, increasing evidence supports a role for activity-dependent, plastic changes in myelin-forming cells that influence myelin structure and neurological function. Accumulating evidence of complementary and likely temporally overlapping activity-independent and activity-dependent modes of myelination are beginning to crystallize in a model of myelin plasticity with broad implications for neurological function in health and disease.

From a cellular perspective, the development of myelinating oligodendrocytes is among the most recent features of the vertebrate central nervous system. By reducing the transverse capacitance and increasing the transverse resistance along the axis of axonal membrane in concert with clustering of voltage-gated sodium channels at nodes between adjacent sheaths, myelin enables rapid saltatory conduction at speeds that would otherwise require prohibitively large axons to achieve. (Hartline and Colman, 2007) Two primary structural parameters of myelin that contribute to the rate of axonal transduction have been extensively described: the relative diameter of the myelin sheath compared to the wrapped axon (g-ratio), and the length and spacing of adjacent myelin sheath segments (internodes). Pioneering electrophysiological studies establishing support for saltatory conduction predicted an optimal internode spacing, at which a flat maximum conduction velocity would be achieved (Huxley and Stämpeli, 1949), predictions that are supported by recent studies in peripheral axons (Wu et al., 2012a). Longstanding observations by multiple groups that g-ratios are tightly controlled in the central nervous system also support established theoretical predictions of a narrow, optimal g-ratio window in which conduction velocity is maximized. In short, several decades of theoretical and experimental data suggest that, from the perspective of conduction velocity alone, an ‘optimum profile’ of myelin throughout the nervous system exists, a process that was thought to be achieved during development. In some regions of the nervous system such as the optic nerve, the parameters of myelin

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microstructure do approach these ideal proportions (Honjin et al., 1977). In other regions, however, such as the cortex and subcortical projections, myelin profiles are sub-“ideal” (Peters and Sethares, 1996; Tomassy et al., 2014), a state that may render these regions more amenable to plastic, experience-dependent changes.

Intriguingly, converging evidence from a growing cohort of investigators suggest that myelination is a far more dynamic process than this traditional model of innate myelination alone would suggest. A new model, recently proposed by ffrench-Constant and colleagues (Bechler et al., 2015), posits that adaptive myelination throughout life continues to shape an innate myelin infrastructure patterned during development. The adaptive model is defined by the continuation of myelin alterations into adulthood, a role for an animal’s experience and neuronal activity in shaping the cellular and ultrastructural properties of myelin, and the capacity for non-pathogenic myelin changes to modify network dynamics and animal behavior (See Fig 1). In this review, we weigh the evidence in support of this adaptive model of circuit-specific myelin changes in response to experiences that are beneficial to the function of the relevant circuit, report on hypothesized regulatory mechanisms, and consider the roles adaptive myelination might play in continuing studies of systems neuroscience.

Myelination is a dynamic process in the adult brain

For decades, the formation of myelin has been described almost exclusively in a developmental context, in mammals as a postnatal process that proceeds to completion over the course of juvenile development. In the mammalian CNS, this process is characterized by the late prenatal and postnatal emergence and expansion of oligodendrocyte precursor cells (OPCs)(Kessaris et al., 2006; Lu et al., 2002), and their subsequent differentiation into myelinating oligodendrocytes. The developmental origins of these cells have been extensively studied, and we direct interested readers to excellent reviews elsewhere (Bergles and Richardson, 2015; Emery, 2010; Lyons and Talbot, 2015; Nishiyama et al., 2009; Richardson et al., 2006). OPCs persist and proliferate in the CNS well into adulthood (Hughes et al., 2013; Young et al., 2013), an observation that has stimulated study of adult oligodendrogenesis and myelination. The development of genetic mouse models enabling selective manipulation and fate-mapping of OPC and oligodendrocytes has conclusively supported previous speculation that OPCs continue to proliferate and differentiate into myelinating oligodendrocytes in adult rodents (Clarke et al., 2012; Kang et al., 2010; Rivers et al., 2008; Simon et al., 2011; Young et al., 2013; Zuccaro and Arlotta, 2013). Adult-born myelinating oligodendrocytes in the optic nerves of mice form many more internodes than those generated early in development, and these internodes are dramatically shorter (Young et al., 2013). The rate of OPC proliferation and maturation in the adult CNS varies with age and by region, with estimates ranging from 5% to greater than 20% of the total oligodendrocyte population generated after P45 in the mouse (Kang et al., 2010; Rivers et al., 2008; Young et al., 2013). What axonal segments are available for adult-born oligodendrocytes to ensheath? In striking contrast to the predicted optimal profiles of axonal myelination, recent high-throughput 3D electron microscopy reconstructions have identified highly variable patterns of myelination along axons arising from pyramidal neurons in the adult (postnatal day 60) mouse neocortex (Tomassy et al., 2014). In particular, this study demonstrated many neurons exhibit a long pre-myelinating axon segment (PMAS), whose

length is correlated with cortical layer, and many axons arising from layer II/III pyramidal neurons exhibited intermittent myelination profiles that could not be explained by local differences in OPC density. Intriguingly, multiple classes of myelination profile could be found within each cortical layer, and while the functional significance of this heterogeneity remains unclear, it is suggestive that significant unmyelinated axonal territory remains in a diverse array of adult neocortical projections. Similarly, subcortical association projections such as the corpus callosum exhibit variable myelination, with as many as 30% of corpus callosum fibers unmyelinated in the adult rodent brain (Olivares et al., 2001). Theoretically non-ideal myelin profiles provide opportunity for optimization by adult myelin remodeling, possibly in response to experience. Therefore, adult myelination provides a plausible mechanism for significant alteration of conduction velocity in the mammalian cortex.

Myelin is altered by experience

If myelination is to be termed ‘adaptive’, the factors to which myelination adapts must be determined. From the perspective of neural plasticity, it is intriguing to suppose that an animal’s experience might modulate cellular and ultrastructural features of myelin, thereby conceivably altering conduction velocity in active circuits. Here, we highlight the exciting findings of several groups that have recently described paradigms in which experience resulted in adaptive myelin changes.

Social Behavior

Prompted by observations that disturbances in social behavior in children and juvenile primates had been linked to white matter abnormalities, Makinodan and colleagues recently demonstrated that social isolation of juvenile mice following weaning results in dramatic alterations in white matter development of the medial prefrontal cortex (mPFC) (Makinodan et al., 2012). Following 4 weeks of isolation, animals displayed an expected deficit in a social interaction task, and microscopy in the mPFC revealed dramatically reduced ramifications of mature oligodendrocytes, reduced internodes per oligodendrocyte, and increased g-ratios, indicating thinning of myelin sheaths. Intriguingly, this change occurred only during a critical period during the first two weeks after weaning; mice isolated for the same total length of time but beginning at P35 displayed none of the myelin abnormalities noted in those isolated beginning at P21. Critically, myelin abnormalities generated by isolation beginning at P21 were not rescued by social reintroduction at P35, indicating that myelination in the mPFC is adaptive to social experience during a critical juvenile window. Additional study indicated that ErbB3 loss during this period phenocopied g-ratio alterations and social exploration deficits, and the finding that neuregulin type III expression is reduced in the mPFC following isolation contributes to a complex body of literature implicating neuregulin-ERBB signaling in oligodendrocyte development, recently reviewed in detail (Mei and Nave, 2014). In parallel, the team of Liu and colleagues generated corroborating evidence that social isolation resulted in increased mPFC g-ratios, without corresponding changes in other major white-matter tracts (corpus callosum), motivational regions (nucleus accumbens), or locomotor areas (cerebellum) (Liu et al., 2012). Are myelin alterations responsible for the observed social behavior deficit? Treatment during social isolation with clemastine, a H_1-receptor antagonist that enhances oligodendrocyte differentiation *in vitro*

and promotes remyelination after toxic injury *in vivo* (Mei et al., 2014), rescues social interaction along with mature oligodendrocyte densities and myelin g-ratios in the PFC (Liu et al., 2016). Taken together, these studies offer striking evidence that myelination in the mPFC adapts to social experience in a circuit-specific manner, and these adaptive changes may be necessary to support social behavior in rodents.

Motor Learning

Myelin has been an extraordinarily successful evolutionary innovation, and likely facilitated both predatory and escape behaviors in the earliest jawed fish (Zalc et al., 2008). Since then, an extensively myelinated peripheral nervous system has accompanied the extensive diversification of large body plans among vertebrates, establishing a clear link between rapid saltatory conduction and motor function. Beyond the well-established function of myelin in speeding motor commands from the CNS to the periphery, recent evidence has emerged suggesting that adaptive myelination may play a role in motor learning. Comprehensive discussion of the neural basis of motor learning is well beyond the scope of this review, but study has broadly focused on the complementary roles of the cerebellum, basal ganglia, and motor cortex in early adaptation and longer-term consolidation and improvement in motor tasks (Costa et al., 2004; Kawai et al.; Shmuelof and Krakauer, 2011; Yin et al., 2009). A potential link between adaptive myelination and motor learning has been suggested by structural imaging studies that identified white matter microstructural changes in human adult volunteers learning to juggle (Scholz et al., 2009), and who have undertaken musical training (Steele et al., 2013). Parenthetically, similar neuroimaging changes in white matter have been observed in humans following learning a second language (Schlegel et al., 2012), suggesting that such structural changes are not restricted to the motor system in humans. Initial follow-up studies in rats trained in a single-pellet reaching task revealed increased fractional anisotropy in the cingulum and external capsule, both rich in projections between regions involved in motor learning (Sampaio-Baptista et al., 2013). While changes in fractional anisotropy assessed in white matter can be a result of myelin alterations, the structural causes in these studies – myelination, axon diameter, density, and organization – must be inferred (Beaulieu, 2002).

Does adaptive myelination underlie fractional anisotropy changes present in white matter during motor learning? Several elegant studies in rodents now support a role for newly-generated oligodendrocytes in motor learning, although ultrastructural evidence of a requirement for new or remodeled myelin remains to be shown. Utilizing a ‘complex wheel’ task in which mice learn to run on a wheel with irregular rung spacing, the team of McKenzie and colleagues has recently shown that motor skill development in adult mice not only results in additional OPCs and mature oligodendrocytes in the corpus callosum, but that generation of new oligodendrocytes is required for consolidation of skill improvement (McKenzie et al., 2014). To demonstrate this requirement, the authors took advantage of the recent identification of myelin regulatory factor (*Mrf*) as a required transcriptional regulator for the generation of myelin (Emery et al., 2009). Conditional deletion of *Mrf* in OPCs of adult mice prevented the generation of additional myelinating oligodendrocytes without affecting expression of the gene in previously formed cells. Mice lacking the ability to generate new myelin spent a similar amount of time running on the complex wheel as

matched heterozygotes (which exhibit normal myelination), but at a consistently reduced speed. While conditional *Mrf* knockouts do improve on the complex wheel over time, the metrics of this improvement – average and maximum speed, along with total distance traveled – are consistently deficient relative to controls. Critically, if mice are trained on the complex wheel prior to *Mrf* knockout in OPCs, subsequent reintroduction to the wheel reveals no difference in performance between genotypes, suggesting that adaptive myelination is not required for recall of a previously learned motor skill. Recent follow-up study from this group has provided additional insight into the timecourse of adaptive myelination in this paradigm, demonstrating that significant reduction in performance on the complex wheel in conditional *Mrf* knockouts can be detected within several hours of introduction to the task, accompanied by accelerated differentiation of OPCs detectable within 4 hours in the motor cortex and 2.5 hours in the subcortical white matter (Xiao et al., 2016). No differences were detected between genotypes during the first two hours of training, in which rapid task improvement occurred in both cohorts. This is consistent with previous descriptions of biphasic patterns of motor learning, in which rapid initial improvement precedes longer-term consolidation of gradually improving performance (Costa et al., 2004). Moreover, it suggests that distinct phases of motor learning might be additionally classified as myelination dependent or independent. The role of task-induced oligodendrocyte generation in other centers of motor learning such as the basal ganglia and cerebellum remains to be elucidated, as does the potential balance of adaptive myelination occurring in cortical versus subcortical projections from motor cortex. While elevated neuronal activity in premotor areas has been shown to drive myelin remodeling in callosal projections (Gibson et al., 2014), ultrastructural features of adaptive myelination driven by behavioral motor learning paradigms remain to be explored.

Sensory experience

For all the benefit that enhanced conduction velocity in motor signaling can achieve, the potential advantages of rapid transmission of sensory information and subsequent processing are equally apparent. The direct impact of somatosensory input on adaptive myelination has recently been examined in the context of sensory deprivation by whisker trimming. Mangin and colleagues unilaterally removed the whiskers of mice at birth and examined oligodendrocyte lineage cell densities in the barrel cortex (Mangin et al., 2012). In this setting, NG2+ cell density was significantly increased in layer IV of the deprived hemisphere compared with the intact control, as was the percentage of proliferating NG2+ cells. Initially, these findings appeared to conflict with evidence in other systems that neuronal activity stimulated OPC proliferation and oligodendrocyte generation, but subsequent fate-mapping studies revealed that in this context, whisker deprivation significantly increases the rate of apoptosis in newly-generated NG2+ cells (Hill et al., 2014). Moreover, the total number of mature oligodendrocytes is reduced in this setting, suggesting that observed elevation in NG2+ cell division is a homeostatic response to the loss of differentiating and mature oligodendrocytes.

In the auditory system, precise control of interaural delays is necessary for computing spatial information from auditory inputs (Carr and Konishi, 1990). Developmental studies in barn owls suggest that postnatal myelination of interdigitating delay axons may underly

developmental tuning of interaural time delay maps in the auditory brainstem nucleus laminaris (Cheng and Carr, 2007). Seidl and colleagues have recently shown that ipsilateral and contralateral projections from single monaural cells adjust conduction velocities individually, with ipsilateral projections having shorter internodes and smaller axon caliber than longer contralateral branches (Seidl and Rubel, 2016; Seidl et al., 2014) Local patterns of myelination may therefore not only act to globally increase conduction velocity, but act to promote specific patterns of temporal coincidence. This is supported by the finding in mammalian auditory brainstem axons that internode length decreases progressively along distal axon segments; simulations predict that the resulting decrease in conduction velocity along the length of the projection supports downstream depolarization of the Calyx of Held (Ford et al., 2015). Extensive evidence of crosstalk between axon diameter and myelin thickness (Bechler et al., 2015; Michailov et al., 2004) emphasizes the need to consider the contribution of axon caliber to effects on conduction velocity as both a regulator of myelination and an independent determinant of axonal resistance. As an additional layer of complexity, axon diameters at nodes and internodes appear capable of independent variance along individual fibers (Ford et al., 2015). Beyond these studies, the role of sensory experience on adaptive myelination remains largely unexplored, and many outstanding questions remain to be addressed. Is there a role for adaptive myelination in circuits where temporal coincidence is particularly crucial to downstream processing, such as in the visual and auditory systems? Or is a fixed conduction velocity of such importance in these pathways that experience-dependent alterations would interfere with sensory processing? The observation that new myelin internodes continue to be generated and inserted into the healthy adult mouse optic nerve suggests that conduction velocity may continue to be subtly tuned in highly myelinated sensory input pathways (Young et al., 2013). Future investigation relying on refined and ideally pathway-specific sensory manipulations will be needed to further elucidate the role of adaptive myelination in sensory experience.

Intrinsic and extrinsic myelination cues

What are the mechanisms by which experience might be translated into adaptive myelination? Are all experience-dependent myelin responses dependent on neuronal activity, or do less direct mechanisms such as experience-induced hormonal alterations affect myelin-forming cells? Is experience-dependent myelin remodeling mediated by direct interaction between the active neuron and local oligodendroglial lineage cells, or do additional cellular intermediaries play a role? Do these mechanisms operate at the level of the OPC, the oligodendrocyte, or in ultrastructural alterations of individual internodes? In the next portion of this review, we consider the balance of evidence for intrinsic and extrinsic cues for adaptive myelination, and provide an overview of the current understanding of potential effector mechanisms in response to these cues.

Intrinsic myelination cues and innate myelination

How are targets for myelination specified in the CNS? Considering the vast territory of vaguely filamentous targets that a newly-generated oligodendrocyte might choose to myelinate, the confinement of myelination to axons alone appears remarkably selective. Do oligodendrocytes possess intrinsic machinery to selectively identify axons, or are there

extrinsic inhibitory or permissive cues that regulate myelination targets? Early evidence that oligodendrocytes possess intrinsic myelinating capabilities arose from the observation that local spatial constraints acted as a powerful trigger for OPC differentiation (Rosenberg et al., 2008), and that newly-generated oligodendrocytes *in vitro* ensheath paraformaldehyde-fixed axons or even bare polymer filaments, subject to size constraints (Bechler et al., 2015; Lee et al., 2013; Redmond et al., 2016). Intriguingly, in the case of OPCs co-cultured with previously-fixed neuronal cultures, aberrant myelination of dendrites and neuronal soma has been described, with extensive follow-up studies identifying *Jam2* as a potential inhibitor of somatodendritic myelination (Redmond et al., 2016). Traditionally, electron microscopy is used as a gold standard to demonstrate 'compact myelin', a distinction from light microscopy evidence of myelin-associated protein expression that carries much weight in the field. Acknowledging that compact myelination remains to be demonstrated in these culture systems, the ability of cultured oligodendrocytes to elaborate processes along fixed dendrites and soma is remarkable evidence that these cells possess the intrinsic capability to initiate at least the initial steps of myelination. Moreover, the properties of myelin segments generated by oligodendrocytes in filament culture systems are partially intrinsic to the myelinating cell. This was recently demonstrated in the finding that oligodendrocytes generated from mouse spinal cord OPCs develop longer myelin sheaths on polymer microfilaments than those isolated from the cortex (Bechler et al., 2015). Cortical-derived oligodendrocytes also elaborated additional sheaths in the presence of laminin, while spinal cord-derived cells remained insensitive to this cue, a finding that contributes to a diverse and rapidly-expanding literature exploring intrinsic heterogeneity in the oligodendrocyte lineage (Hill et al., 2013; Marques et al., 2016; Tomassy and Fossati, 2014). While oligodendrocytes therefore exhibit the intrinsic capacity to initiate myelination and elements of myelin sheath elaboration appear to be subject to basal intrinsic regulation, recent evidence suggests that intrinsic cues alone are incapable of generating physiological myelin profiles observed in the CNS.

Extrinsic myelination cues: the role of neuronal activity

A diverse array of extrinsic factors have been shown to influence the development of the oligodendrocyte lineage and myelination *in vivo* (Bergles and Richardson, 2015; Lyons and Talbot, 2015; Michalski and Kothary, 2015), indicating that while an innate program of oligodendrocyte differentiation occurs in isolated culture settings, physiologic oligodendrocyte lineage dynamics and myelination are subject to extrinsic regulation. What are the sources of these extrinsic cues? In the context of experience-dependent changes in myelination, a compelling and longstanding hypothesis holds that neuronal activity governs myelination of active axons. Early support for this hypothesis arose from the finding that transection of the developing optic nerve or intraocular tetrodotoxin injection in developing mice dramatically reduces the rate of OPC proliferation (Barres and Raff, 1993), significantly reduced oligodendrocyte survival (Barres et al., 1993a), and reduced the degree of optic nerve myelination (Demerens et al., 1996). Recent studies in co-culture systems, zebrafish, and rodent models have provided converging evidence supporting these pioneering studies.

Much of the *in vitro* work examining the mechanisms by which neuronal activity might alter myelination has focused on the instructive roles that neurotransmitters and activity-regulated

factors play in the transition of OPCs to myelinating oligodendrocytes, with early evidence suggesting that glutamate inhibited OPC proliferation and differentiation (Gallo et al., 1996). In co-culture systems of dorsal root ganglion neurons and OPCs, stimulation of action potentials in neurons activates adenosine receptors in OPCs, stimulates differentiation, and promotes the synthesis of myelin (Stevens et al., 2002). Intriguingly, there is evidence that the initial induction of myelin synthesis may be regulated within the OPC process that is driven by vesicular glutamate release (Wake et al., 2011), although in this system the glutamatergic receptors on OPCs may be extrasynaptic (Wake et al., 2015).

Building upon these *in vitro* studies, technological advances have recently allowed unprecedented ability to examine the role of neuronal activity in myelination in an *in vivo* context. Several elegant studies in zebrafish have provided compelling support for the role of neuronal activity as a critical external cue for successful myelination during development. *In vivo* time-lapse microscopy has shown that myelination in this model follows a pattern of initial sheath wrapping followed by either process retraction or extension and stabilization of nascent sheaths (Czopka et al., 2013; Hines et al., 2015; Kirby et al., 2006). What determines whether a nascent sheath is stabilized? Tetrodotoxin block prior to the onset of myelination in zebrafish larvae reduces the proportion of sheaths that succeed in wrapping neurons (Hines et al., 2015; Mensch et al., 2015). Selective inhibition of activity by expression of tetanus neurotoxin light chain – a potent inhibitor of synaptic vesicle exocytosis – as well as the inward-rectifying Kir2.1 channel in *phox2b*$^{+}$ neurons reduces both the number of axons selected for myelination and the percentage of the axon that is myelinated (Hines et al., 2015). Intriguingly, nascent sheath retraction is markedly reduced when vesicular secretion is inhibited in neurons, suggesting a role for vesicular secretion in the selection of active neurons for sheath stabilization and subsequent myelination(Hines et al., 2015). Induction of ectopic activity, however, appears to have varying impacts on myelination depending upon the method and neurons targeted (Hines et al., 2015; Mensch et al., 2015), and elucidating the contributions of specific modes of activity to myelination in genetically-defined zebrafish circuitry is likely to become a rich field of study.

Technologies enabling selective manipulation of neuronal activity in mammalian systems offer enormous potential to expand our understanding of the link between physiologic patterns of activity *in vivo* and changes in myelin-forming cells. The use of optogenetics to drive physiomimetic patterns of neuronal activity has recently enabled the study of oligodendrocyte lineage dynamics in response to neuronal activity in vivo (Gibson et al., 2014). In this study, mice expressing channelrhodopsin in deep cortical projection neurons subjected to cycles of 20Hz optical stimulation in premotor cortex generated a rapid and robust proliferation of OPCs in the deep cortex and subcortical white matter within the stimulated circuit. A subset of these cells differentiates into mature oligodendrocytes, indicating activity-induced expansion of the oligodendrocyte lineage. Intriguingly, this oligodendroglial expansion was confined to callosal rather than corticofugal projections of the premotor circuit, suggesting as-yet uncharacterized regulatory mechanisms linking activity to cellular effectors of adaptive myelination. In this system, enhanced activity also increased the thickness of myelin in premotor subcortical projections and positively influenced motor system function. Activity-dependent alterations in neurological function can be explained by the response of a variety of activity-responsive cell types, not the least

of which are neurons themselves. To investigate the possibility that activity-regulated synaptic plasticity accounts for the observed functional change, pharmacologic inhibition of histone deacetylase activity was used. HDAC inhibition prevents oligodendrocyte differentiation (Shen et al., 2005; Wu et al., 2012b) but improves synaptic plasticity (Morris et al., 2013; Shi et al., 2011) thereby uncoupling synaptic from myelin plasticity. Optogenetic stimulation with concomitant HDAC inhibition prevented this activity-dependent promyelinogenic effect and abrogated the observed motor changes, indicating that the observed change in neurological functional depends upon adaptive myelin changes. Considered together, there is compelling evidence from in vitro models to zebrafish and mammalian systems that neuronal activity is an extrinsic regulator of myelination with important functional implications. Identifying the effectors of this regulation represents a significant challenge given the incompletely understood molecular mediators of direct neuron-oligodendrocyte lineage cell interactions and given the extensive communication between oligodendrocyte lineage cells and additional cell types that respond to activity such as microglia (Miron et al., 2013), astrocytes (Ishibashi et al., 2006; Watkins et al., 2008), and endothelial cells (Tsai et al., 2016; Yuen et al., 2014).

Effectors of adaptive myelination

What are the potential mechanisms linking neuronal activity to adaptive myelination? Here we review the signaling mechanisms hypothesized to regulate this interaction, and how oligodendrocyte lineage cells might transduce these signals into adaptive myelin changes (summarized in Table 1).

Neurotransmitters

Numerous in vitro studies have provided evidence that neurotransmitter signaling has functional consequences in oligodendrocyte lineage cells. While this signaling was originally thought to arise from tonic activation as reported in other glia (Bergles et al., 2010), the discovery that OPCs form bona fide synapses in the central nervous system stimulated great interest in synaptic communication as a potential regulator of adaptive myelination (Bergles et al., 2000). Both glutamatergic (Bergles et al., 2000; De Biase et al., 2010; Karadottir et al., 2008; Kukley et al., 2010; Mangin et al., 2008; Ziskin et al., 2007; Zonouzi et al., 2011) and GABAergic (Lin and Bergles, 2004a; Orduz et al., 2015; Velez-Fort et al., 2010) synaptic inputs to OPCs have been identified, the properties of which have been reviewed in detail (Bergles et al., 2010). These observations underlie a compelling hypothesis that neuron-OPC synaptic activity might guide patterns of adaptive myelination. Intriguingly, synapses formed by OPCs may be inherited by daughter cells (Kukley et al., 2008), although direct examination of neuron-OPC synapses through the process of differentiation has not yet been achieved.

An extensive body of evidence has established that oligodendrocyte lineage cells express a range of ionotropic and metabotropic glutamate receptors (Barres et al., 1990; Berger, 1995; Borges et al., 1994; Holzwarth et al., 1994; Liu and Almazan, 1995; Patneau et al., 1994; Sontheimer et al., 1989; Wyllie et al., 1991). Early studies in culture indicated AMPA and kainate inhibit oligodendrocyte progenitor proliferation (Gallo et al., 1996; Liu and

Almazan, 1995; Yuan et al., 1998), and trigger intracellular Ca^{2+} elevation (reviewed in (Butt, 2006)). Ca^{2+} elevation appears to be a common response to glutamate receptor agonists in OPCs and oligodendrocytes. OPCs express an expanded repertoire of glutamate receptors (Sontheimer et al., 1989), including calcium-permeable AMPA receptors lacking a GluR2 subunit (Liu and Zukin, 2007; Ziskin et al., 2007). During differentiation into mature oligodendrocytes, expression of glutamate receptors along with many other ion channels is downregulated (De Biase et al., 2010), a change that may be important to limit well-established calcium-induced excitotoxicity in mature oligodendrocytes (Hamilton et al., 2016; Karadottir et al., 2005; Micu et al., 2006; Salter and Fern, 2005). Glutamate may also play a role in the patterning of new myelin segments, as the stimulation of local myelin basic protein translation by neuronal activity in myelinating co-cultures is sensitive to glutamate antagonists (Wake et al., 2011). The use of conditional genetic manipulations is beginning to elucidate the roles of specific axes of glutamate signaling in oligodendroglial cells *in vivo*. For instance, although both OPCs and OLs express NMDA receptors (Burzomato et al., 2010; Karadottir et al., 2005; Ziskin et al., 2007), and their activation induces transient intracellular Ca^{2+} elevation (Micu et al., 2006), conditional deletion of the NMDA receptor NR1 subunit in OPCs and their progeny does not compromise cell development or myelination *in vivo* (De Biase et al., 2011). However, loss of NMDA receptors induces an increase in calcium-permeable AMPAR expression (De Biase et al., 2011), a reminder that overlapping and potentially compensatory roles for multiple routes of glutamatergic signaling will complicate interpretation of experimental manipulations testing the necessity of glutamate receptors.

OPCs also appear to be sensitive to GABAergic stimuli, although the functional consequences are less understood. $GABA_A$ currents in hippocampal OPCs are triggered by TTX-sensitive interneuron activity (Lin and Bergles, 2004b, c). The impact of $GABA_A$ activation on membrane potential depends on the resting potential and intracellular chloride concentration, and although $GABA_A$ reversal currents are elevated in OPCs it remains unclear whether these inputs are primarily depolarizing or play a larger role in regulating AMPA receptor responses by acting as a current shunt (Lin and Bergles, 2004b, c). Mice treated by whole-body administration of the GABA receptor antagonist bicuculline appear to exhibit marked increases in OPC proliferation and decreases in the quantity of mature oligodendrocytes in cerebellar white matter, an effect not seen with direct bicuculline treatment of purified OPC cultures (Zonouzi et al., 2015). Conditional deletion of the Na^+-K^+-Cl^- co-transporter 1 (NKCC1), which maintains elevated intracellular chloride concentrations in OPCs, phenocopies the impact on OPC proliferation and reduces the percentage of cells that differentiate, although notably an impact on the total number of mature oligodendrocytes is lacking (Zonouzi et al., 2015). Taken together, these findings suggest that GABA may also contribute to the regulation of OPC proliferation and daughter cell fate.

Considered as a whole, much remains to be understood about the functional roles of neurotransmitter signaling in oligodendrocyte development. In particular, direct evidence of the impact of signaling or its deprivation upon individual synapses, cells, and myelin in the native context have been limited by technical obstacles. Significant advances in our ability to

manipulate and observe neurotransmitter signaling *in vivo* are likely to enable far greater understanding of its mechanistic relevance in adaptive myelination.

Neurotrophins

The importance of neurotrophins in oligodendrocyte lineage development became apparent during original efforts to purify, culture, and characterize glial cell precursor populations. It is now well known that in culture settings ciliary neurotrophic factor (CNTF) supports oligodendrocyte survival, and neurotrophin 3 (NT3) supports OPC survival and proliferation (Barres et al., 1993b). In culture settings, nerve growth factor (NGF) has the capacity to regulate the degree axonal myelination via the TrkA receptor; intriguingly, the valence of this effect appears to differ between CNS oligodendrocytes and peripheral Schwann cells (Chan et al., 2004).

As attention has shifted to neuronal activity-regulated factors in oligodendrocyte development, the role of brain-derived neurotrophic factor (BDNF) in this capacity has attracted considerable interest. BDNF in the brain is produced primarily by astrocytes and neurons, and its production and secretion are regulated by neuronal activity (Ghosh et al., 1994; Tao et al., 1998). In BDNF heterozygotes (homozygous deletion is lethal), the quantities of OPCs and myelin-associated proteins are reduced (Vondran et al., 2010), effects that appear to be mediated through the TrkB receptor (Wong et al., 2013; Xiao et al., 2010). Conditional deletion of the TrkB receptor in the oligodendrocyte lineage of mice decreases the thickness of CNS myelin during development, but induces a transient increase in OPC density via TrkC-dependent signaling (Wong et al., 2013). The pro-myelinogenic effects of astrocyte-derived BDNF may offer an axis for therapeutic investigation in the context of demyelinating lesions (Fulmer et al., 2014; Tsiperson et al., 2015). Beyond its direct effects, BDNF may serve as a key co-stimulatory molecule for activity-dependent signaling. In myelinating co-cultures, application of BDNF has been reported to render myelination sensitive to the NMDAR antagonist MK-801, suggesting BDNF may regulate the sensitivity of oligodendrocyte lineage cells to activity-dependent glutamatergic signals (Lundgaard et al., 2013). Intriguingly, neuregulin – whose role in CNS myelination remains controversial (reviewed in (Mei and Nave, 2014)) – also appears to enhance NMDAR currents in oligodendrocyte lineage cells, suggesting multiple overlapping and potentially compensatory growth factors may influence sensitivity to activity-dependent signals (Lundgaard et al., 2013). Neurotrophins are thus well-established players in oligodendrocyte development, and there is mounting evidence suggesting their role in activity-dependent myelination.

Myelin sheath remodeling

Beyond oligodendrocyte lineage progression, adaptive myelination likely engages programs of direct myelin sheath remodeling that have recently been the subject of several pioneering studies. Discussion of the relative contributions of oligodendrocyte generation and turnover versus myelin sheath dynamics to adult myelination has recently been stimulated by striking ^{14}C labeling data in postmortem human oligodendrocytes (Yeung et al., 2014). By taking advantage of the sharp increase and subsequent decay of atmospheric ^{14}C resulting from mid-20th century nuclear weapons testing, the ^{14}C content of oligodendrocytes was used to approximate their date of origin. In this study, the ^{14}C levels of purified myelin

fractions were roughly equivalent to atmospheric levels at the time of death, suggesting myelin carbon exchange (and potentially sheath remodeling) continues throughout human life. By contrast, genomic ^{14}C levels predicted a stable annual turnover rate of less than 1% of oligodendrocytes in the corpus callosum after 5 years of age. These findings that suggest limited ongoing human oligodendrogenesis remain challenging to reconcile with immunohistochemical evidence of ongoing OPC proliferation in adult human brain (Geha et al., 2010), and evidence of adult oligodendrocyte population expansion in nonhuman primates. While early studies using thymidine analogues to study cell replication described low rates of incorporation in the white matter of adult rhesus monkeys (Rakic, 1985), immunohistochemical analyses of aging rhesus visual cortex suggest that over the course of adulthood, oligodendrocyte numbers may increase by as much as 50% (Peters and Sethares, 2004; Peters et al., 2008). In light of long-standing observations of adult oligodendrogenesis in rodents (Rivers et al., 2008; Young et al., 2013; Zhu et al., 2011), and these conflicting observations utilizing different techniques in non-overlapping brain regions, the dynamics of adult oligodendrogenesis in humans and nonhuman primates remains an open question. An important caveat to consider is that genomic ^{14}C dating in oligodendrocytes marks the date of origin of the OPC that later differentiated into the mature oligodendrocyte, and although stereological estimates indicate an approximately stable OPC population in adult corpus callosum (Yeung et al., 2014), the potential for limited ongoing direct differentiation of OPCs into oligodendrocytes in the adult human brain cannot be excluded on the basis of genomic ^{14}C data alone. Continuing efforts to model adaptive myelination in rodents would benefit greatly from a clearer understanding of primate oligodendrocyte dynamics.

What mechanisms mediate myelin wrapping and internode remodeling? Reasoning that myelin sheath remodeling depends upon membrane-trafficked biosynthesis pathways, the team of Snaidero and colleagues studied sheath dynamics *in vivo* using vesicular stomatitis virus, which expresses a glycoprotein (VSV-G) that can be used as a reporter of newly-synthesized membrane protein trafficking (Snaidero et al., 2014), In a remarkable technical achievement, immuno-electron microscopy of VSV-transduced developing myelin tracts exquisitely preserved by high-pressure freezing demonstrated VSV-G was primarily trafficked to the inner tongue membrane of the myelin sheath. Serial reconstructions revealed cytoplasmic channels leading to this leading edge which are regulated by phosphatidylinositol-3,4,5- trisphosphate (PI(3,4,5)P3) levels. PI3K/AKT/mTOR signaling, which has numerous recognized roles in myelin development (Flores et al., 2008; Goebbels et al., 2010; Tyler et al., 2009), may therefore play a critical role in adaptive modulation of myelin internodes. Recent support for this model arises from the discovery that conditional deletion of *Pten* in cerebellar granule neurons, thereby activating AKT1-mTOR signaling, triggers aberrant myelination of parallel fiber axons (Goebbels et al., 2017). Overlapping effects throughout the oligodendrocyte lineage in this model, including enhanced OPC proliferation and differentiation, along with increase in parallel fiber axon size emphasize the complex nature of molecular and mechanical cues neurons provide to oligodendrocytes. Much remains to be understood of the downstream targets of myelin-inducing neuronal cues, and in particular how they may regulate the progressive stages of oligodendrocyte recruitment, initial ensheathment, and ongoing sheath remodeling.

Myelin dysregulation: a ‘maladaptive’ context?

Myelin disorders, while diverse in etiology, are overwhelmingly categorized as conditions in which myelin is grossly lost or compromised. Identifying methods to recruit the mechanisms of adaptive myelination in the context of disease, which offer the potential to drive ongoing myelination in the healthy adult brain, are thus of great interest in the realm of regenerative medicine. Yet as the many layers of regulation to which myelination in subject continue to emerge, understanding the contextual roles of promyelinating signals is increasingly important. And despite its long-recognized role in mediating neural communication, there is extremely sparse direct molecular evidence of where myelin fits into the orchestra of glial effects being investigated in psychiatric disease.

Regeneration

Does neuronal activity contribute to myelin regeneration? Naturally, diverse models of myelin injury (considered in (Ransohoff, 2012)) complicate this question, but considerable evidence exists to suggest that activity-dependent signaling influences oligodendrocyte lineage progression in regeneration, although the valence of that impact appears highly contextual. Because many white matter lesions are infiltrated with OPCs that fail to differentiate (Franklin, 2002), considerable effort in this field is devoted to understanding dysregulation of OPC differentiation. In a chronic hypoxia mouse model of perinatal diffuse white matter injury, $GABA_A$ receptor inputs to OPCs are down-regulated and correspond with increased OPC proliferation but decreased differentiation, an effect reversed by blocking GABA uptake (Zonouzi et al., 2015). Glutamatergic signaling also appears to impact remyelination; natural repair of ethidium bromide-induced cerebellar lesions in mice is inhibited by both TTX block and AMPAR inhibition (Gautier et al., 2015). Under ischemic conditions, glutamate receptor block has long been recognized to reduce myelin damage (Bakiri et al., 2009; Karadottir et al., 2005; Micu et al., 2006; Salter and Fern, 2005), although recent surprising evidence suggests this could be a result of external $[K^+]$ elevation and activation of H^+-gated TRPA1 channels on oligodendrocytes (Hamilton et al., 2016). Diverse effects of activity-dependent signaling across myelin disease contexts highlight its importance in considering regenerative strategies, and suggest broad possibilities for therapeutic interventions as the mechanisms linking neuronal activity to myelination are elucidated.

Cancer

As resident cycling precursor cells, OPCs constitute a cell type that may be particularly susceptible to malignant transformation. As the genetic and cellular origins of CNS tumors are uncovered, converging lines of evidence place oligodendrocyte progenitors under increasing scrutiny as potential cells of origin for these cancers (Liu et al., 2011). Retained or induced sensitivity to neuronal activity-dependent signaling in malignant cell populations may therefore represent a deadly yet under-appreciated axis of glioma progression. Ironically, the contribution of neuronal activity in cancer progression is best-understood outside of the brain, where peripheral innervation has been shown to drive the progression of prostate (Magnon et al., 2013), gastric (Hayakawa et al., 2017; Zhao et al., 2014), skin (Peterson et al., 2015), and pancreatic (Stopczynski et al., 2014) cancers. Recent work has

demonstrated that, like healthy OPCs, high-grade glioma cells proliferate in response to active neurons in the tumor microenvironement and that elevated neuronal activity results in circuit-specific increased glioma growth (Venkatesh et al., 2015). A diverse range of high-grade glioma types, including pediatric diffuse intrinsic pontine glioma (DIPG), pediatric glioblastoma, adult glioblastoma and anaplastic oligodendroglioma, proliferate in response to factors secreted by active neurons. Robust neuronal activity-regulated glioma mitogens include a secreted form of neuroligin-3 (Nlgn3) and BDNF(Venkatesh et al., 2015). Beyond these findings, much remains to be explored regarding the potential roles of neuronal activity-dependent cues in CNS tumorigenesis and progression.

Psychiatric disease

While unraveling the pathophysiology of psychiatric disease remains an extremely formidable challenge, large-scale studies of patient genetic and phenotypic data are beginning to yield promising hypotheses to explore in model systems. The development of comprehensive and easily accessible cell type-specific CNS transcriptome databases (Zhang et al., 2014) has revealed that many genes found to be associated with psychiatric disorders are highly expressed in glia, including oligodendrocyte lineage cells, and has contributed to the efforts of several groups to explore the glial contribution to these highly complex diseases. A multitude of human imaging studies have identified white matter abnormalities in psychiatric conditions ranging from schizophrenia (Davis et al., 2003; Dwork et al., 2007) to attention disorders (Onnink et al., 2015). To date, there is little mechanistic evidence underlying these observations, yet they suggest a tantalizing possibility that dysregulated myelination of diverse cortical territories over the course of development might fail to properly tune conduction velocity (or induce maladaptive alterations) and impair cognitive function (Nave and Ehrenreich, 2014). While much additional work elucidating the role of adaptive myelination in normal circuit-specific contexts is necessary before model systems can be designed to test these hypotheses, the highly plausible role for myelin alterations in shaping cortical conduction velocity and circuit dynamics suggest myelination may be identified as a critical substrate of psychiatric disease.

Myelin plasticity? A case for systems-level thinking

Temporal precision on the order of milliseconds is widely-held to be critical to orchestration and integration of neural activity, and temporal coincidence is a central feature of numerous models of plasticity. Our understanding of the impact that axonal conduction velocities play in either contributing to or disrupting this synchronization is remarkably limited, and recent work suggests adaptive myelination may be necessary to maintain the complex overlapping patterns of oscillatory activity in mammalian brains (Pajevic et al., 2014). Direct evidence of discontinuous cortical myelination profiles elevates such considerations to plausible mechanisms for shaping diverse patterns of neural activity (Tomassy et al., 2014). Mounting evidence for the role of oligodendrocytes in axonal metabolism (Funfschilling et al., 2012) suggests myelin may additionally play a critical trophic support for neuronal plasticity. Does adaptive myelination represent an additional axis of brain plasticity? The pioneering efforts of the systems neuroscience community have generated remarkable tools to explore this question. Multiphoton microscopy *in vivo* has recently been used to great effect to elucidate

OPC dynamics in the superficial neocortex (Hughes et al., 2013), and live imaging in zebrafish is dramatically enhancing our understanding of the mechanisms regulating internode patterning in active neurons. High-throughput electron microscopy techniques have revolutionized our understanding of cortical myelination patterns and promise to offer unprecedented examination of myelination patterns throughout the brain and spinal cord. Increasing access to super-resolution microscopy is beginning to improve our understanding of the molecular ultrastructure of the internode and node (D'Este et al., 2016), while new spectroscopic imaging techniques offer the potential for label-free *in vivo* myelin imaging (Schain et al., 2014). Techniques for selective manipulation of neural activity, from optogenetics to chemogenetics (DREADDs), represent powerful tools to investigate the role of activity-dependent myelination under physiomimetic conditions *in vivo*, and targeting circuit-specific manipulations utilizing modern databases of neural connectivity will enable far greater precision in our evaluation of activity-dependent myelination and its potential impact on behavior.

The myelin biologist's toolkit: challenges and opportunities

As in any field, there are unique challenges to the study of adaptive myelination that will stimulate additional technique development and refinement in the future. The relatively deep location of most white matter tracts in the mammalian brain limit the ability of *in vivo* imaging techniques to study oligodendrocyte lineage dynamics in key myelinated regions of adult rodents. Combining the molecular information conveyed by immunostaining techniques with the ultrastructural resolution of electron microscopy has been a long-standing challenge that may be overcome by implementation of correlative microscopy techniques. Above all, a mechanistic understanding of the impact of adaptive myelination in circuit function will require the ability to measure conduction velocities with considerably greater resolution than currently achieved by compound action potential recordings, a challenge that will likely require innovative combinations of imaging and electrophysiological techniques. As the textbook refrain goes, we offer this as a challenge to the reader.

Taking a high-level view, while there is extensive evidence of the structural manifestations of adaptive myelination and emerging data to support hypothesized functional consequences, there remains no satisfactory toolset to directly measure the systems-level impact of adaptive myelination. Successful innovation in this space, particularly when amenable to use in awake and behaving animals, would offer unprecedented capability to dissect the role of myelin and oligodendroglial cell dynamics in cognition, and to distinguish the necessity of neuron-oligodendroglial communication for adaptive myelination in diverse systems.

Concluding remarks

From its early description as a highly useful but essentially static innovation, myelin is undergoing a renaissance of interest in the neuroscience community. Pioneering uses of diverse technologies are forging a new model of adaptive myelination that may have wide implications in development and adult experience-dependent behavior. While the role of neuronal activity in shaping myelination has become apparent, many mechanistic details

remain to be discovered. Development of techniques enabling more precise *in vivo* measurement of conduction velocities in circuit-specific pathways would represent a tremendous advance for the field and is vital to forging mechanistic links between dynamic alterations in oligodendrocyte lineage cells and functional consequences for neural circuits. In addition to the great potential within regenerative medicine, the possible contributions of myelin biologists to the study of cancer and psychiatric disease should not be overlooked.

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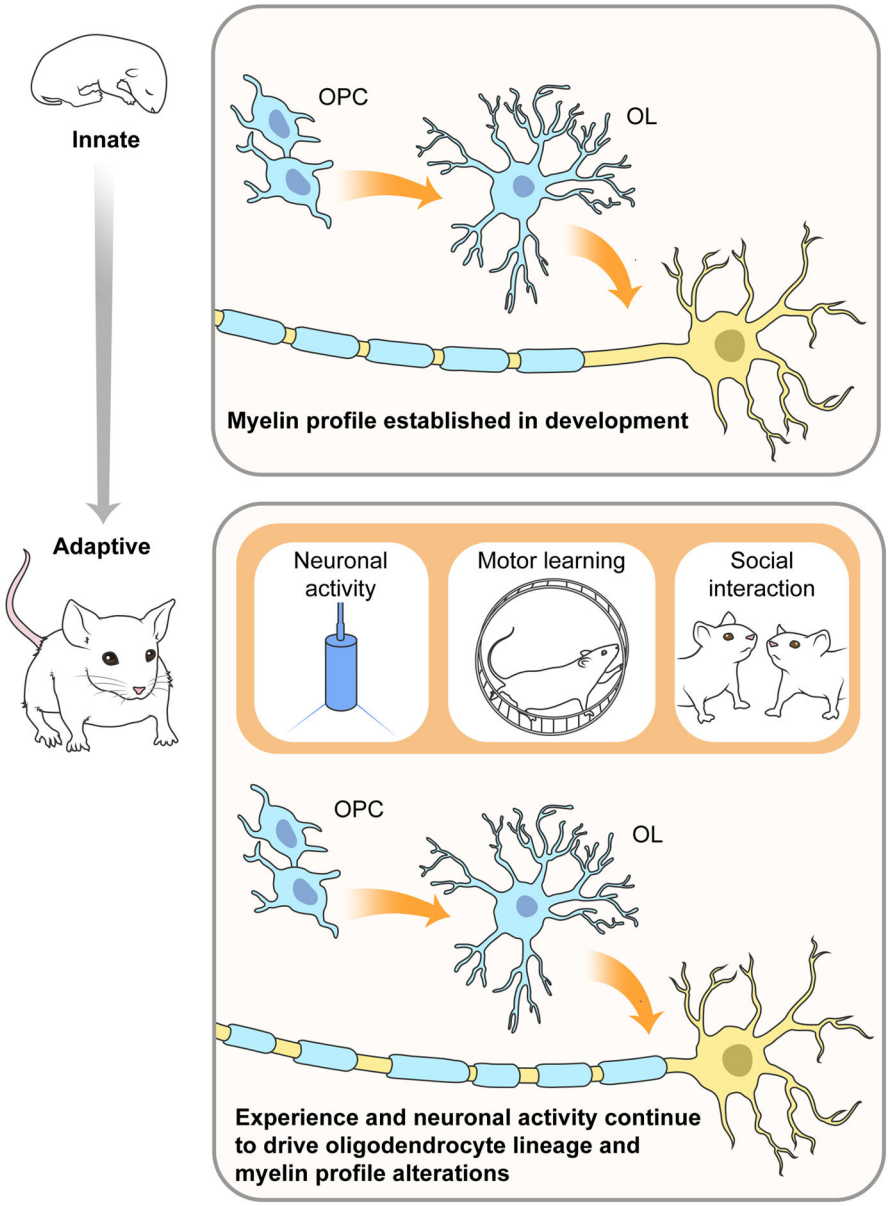

Figure 1. Innate and adaptive myelination

Traditional models of developmental myelination programs (top) emphasize an innate program of robust expansion of oligodendrocyte precursors (OPCs) during postnatal neurodevelopment, followed by widespread differentiation into oligodendrocytes (OLs) that myelinate target axons in a largely uniform pattern. Within the central nervous system (CNS), converging lines of evidence support an additional model of adaptive myelination (bottom). Defined as modulation of myelin in response to neuronal activity, adaptive myelination represents a program of continued myelination and myelin remodeling into adult life that is responsive to an animal's experience. Modulation of neuronal activity in optogenetic, motor learning, and social interaction paradigms, among others, variably stimulate alterations in OL lineage dynamics and myelin sheath microstructure. Ultrastructural analysis and lineage tracing experiments also indicate that patterns of

myelination in the adult brain may deviate significantly from the intrinsic model of continuous internode patterning, and that ongoing sheath remodeling or insertion of new sheaths may contribute to this discontinuity. A model recently proposed by ffrench-Constant and colleagues (Bechler et al., 2015) posits that adaptive myelination throughout life continues to shape an innate myelin infrastructure patterned during development.

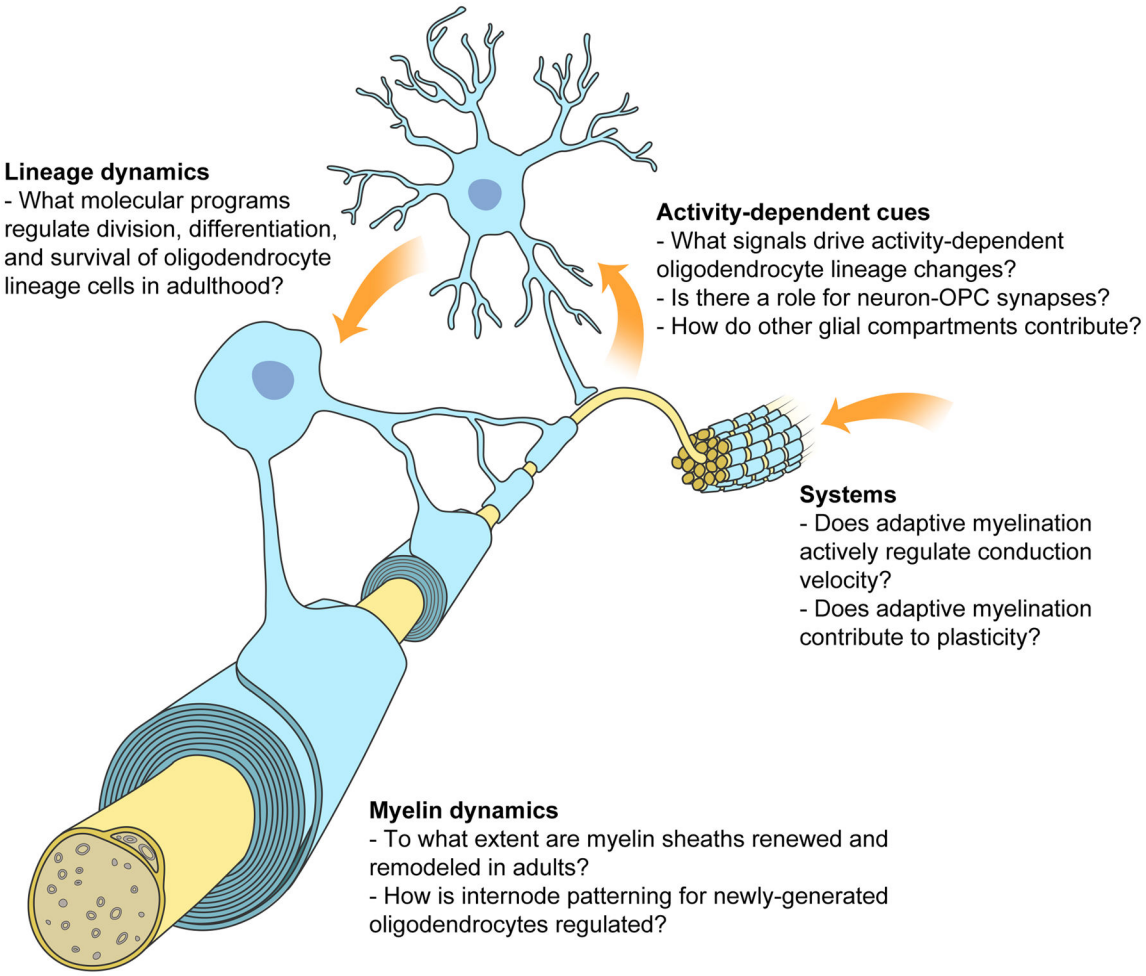

Figure 2. Adaptive myelination effectors: from molecules to systems

Decoupling adaptive myelination cues from intrinsic oligodendroglial programs represents a significant challenge for uncovering the mechanisms of this process. Several lines of inquiry are under active investigation. Neuronal activity-regulated molecular cues, including neurotrophins and neurotransmitters, have long been known to modulate oligodendrocyte lineage dynamics and are therefore leading candidates for mediating neuronal activity-dependent myelination. Neuron-OPC synapses offer a particularly compelling route by which effector recruitment might occur with high spatiotemporal specificity, although the functional relevance of these synapses remains unclear. Beyond oligodendrogenesis, there is significant potential for activity-dependent signaling to influence myelin sheath dynamics. Investigation in developing zebrafish support a role for neuronal activity in myelin sheath recruitment and stabilization, and evidence of ongoing myelin turnover in rodents and humans suggest this may represent an additional axis along which adaptive myelination occurs. Critically, the systems-level mechanisms linking molecular and cellular processes of adaptive myelination to observed behavioral changes are unknown. Several existing hypotheses include conduction velocity tuning, synchronization of parallel impulses, and metabolic support of underlying neuronal activity. Exploring these and other means by

which adaptive myelination can effect behavioral change represents an exciting ongoing challenge for the field.

Table 1

Summary of current evidence for proposed effectors of adaptive myelination.

Neurotransmitters	Glutamate	Triggers Ca^{2+} entry in OPCs and OLs (reviewed in (Butt, 2006)) Influences OPC differentiation *in vitro* (Gallo et al., 1996; Wake et al., 2011) Conditional NMDAR deletion does not substantially impact developmental myelin(De Biase et al., 2011)
	GABA	Bicuculline administration in mice increases OPC proliferation, decreases mature OLs in cerebellar white matter (Zonouzi et al., 2015)
Neurotrophins and other growth factors	BDNF	BDNF heterozygous mice have diminished OPC densities (Vondran et al., 2010) Conditional TrkB deletion in oligodendrocytes reduces myelin thickness and oligodendrocyte density during development (Wong et al., 2013) *In vitro*, renders myelin generation susceptible to NMDAR blockade (Lundgaard et al., 2013)
	Neuregulin	Enhances NMDAR currents in OPCs and OLs co-cultured with neurons (Lundgaard et al., 2013) Deletion of *Nrg1* in mice does not prevent developmental myelination; overexpression of Nrg1, I and III in mice causes developmental hypermyelination (Brinkmann et al., 2008) Conditional ErbB3 deletion in juvenile mice phenocopies hypomyelinating effects of social isolation (Makinodan et al., 2012)
	LIF	Astrocyte-derived LIF, secreted in response to axonal ATP release, promotes myelination in co-cultures (Ishibashi et al., 2006)
Mechanical cues	Axon diameter	Conditional deletion of *Pten* in mouse cerebellar parallel fibers caused axon diameter enlargement and aberrant myelination (Goebbels, 2017)