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Dynamics and Mechanisms of CNS Myelination

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Summary

Vertebrate myelination is an evolutionary advancement essential for motor, sensory and higher order cognitive function. CNS myelin, a multilamellar differentiation of the oligodendrocyte plasma membrane, ensheaths axons to facilitate electrical conduction. Myelination is one of the most pivotal cell-cell interactions for normal brain development, involving extensive information exchange between differentiating oligodendrocytes and axons. The molecular mechanisms of myelination are discussed, along with new perspectives on oligodendrocyte plasticity and myelin remodeling of the developing and adult central nervous system.

Introduction

Neurologic and neurodegenerative diseases of the central nervous system (CNS) are often presented from a “neuron-centric” perspective. Pathological presentation of these diseases is primarily focused on the neuronal deficits and dysfunction that lead to glial cell reactivity and responses. The term glia refers to the historical concept that these cells are the CNS “glue”, but in the past few decades, emerging evidence has proven that glial cells are much more than the “support cells” of the CNS. Glial cells may well constitute 50–90% of the cells in the human and rodent CNS (Allen and Barres, 2009; Doetsch, 2003; Nishiyama et al., 2005; Noctor et al., 2007; Ullian et al., 2001), and understanding their involvement during development and in the adult brain is essential. A recent review by Freeman and Rowitch (2013) highlights the renewed interest in gliogenesis as an integral part of CNS development and function. Glial cells provide valuable support in axonal function, synaptic plasticity and as integral mediators of neuronal connectivity. In addition to development and aging, glial cells play crucial roles in repair and remyelination in CNS disease and disorders (Barres, 2008; Burda and Sofroniew, 2014; Gallo and Deneen, 2014; John Lin and Deneen, 2013; Nave, 2010; Schwartz et al., 2013).

This review focuses particularly on oligodendrocytes, the glial cells that generate CNS myelin, although extensive studies on peripheral nervous system (PNS) myelination by Schwann cells have provided important perspectives that will be noted. White matter deficits, both subtle and pronounced, are a common hallmark of human developmental disorders and neurodegenerative diseases (for review, see Fields, 2008). It has become

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increasingly clear that in order to identify the underlying mechanisms of CNS diseases, both glial cell physiology and neuronal-glial interactions must be considered.

Oligodendrocyte Development and Myelination

Developmental disorders of white matter demonstrate the importance of oligodendrocytes and developmental myelination for CNS function. In rodents, the oligodendrocyte developmental program begins with specification of oligodendrocyte progenitor cells (OPCs) derived from neural stem and progenitor cells during late embryonic gestation. The highly migratory and proliferative OPC is identified by its expression of the NG2 proteoglycan and the platelet-derived growth factor receptor alpha (PDGFRα). OPCs differentiate through a premyelinating stage to become the mature myelinating cell, which generates the myelin internode, and thereby interacts with axons to organize the nodal, paranodal and juxtaparanodal regions of myelinated axons.

Progression through the oligodendrocyte lineage is tightly regulated by a multitude of intrinsic and extrinsic cues, which control myelination both spatially and temporally during development and after demyelination. These signals include growth factors, protein kinases, extracellular matrix molecules, which influence epigenetic modifications, transcriptional and translational regulation, and the actin cytoskeleton in oligodendrocytes (for review see Bauer et al., 2009; Emery, 2010; Kessaris et al., 2008; Miller, 2002; Mitew et al., 2013) (Figure 1). Differences in temporal expression of these factors and signals in the developing CNS result in early lineage progression and myelination in the spinal cord, and later myelination of cortical regions. Increasing evidence indicates that there are regionally diverse OPC populations that may be generated by distinct localized signaling mechanisms (Calver et al., 1998; Clarke et al., 2012; Miller et al., 1994; Richardson et al., 2006; Tsai et al., 2009; Warf et al., 1991). This is an active area of investigation, with much focus on the impact of different signaling molecules in different brain and spinal cord regions. For example, loss of mTOR and mTORC1 have differential impact on oligodendrocyte development in different CNS regions (Bercury et al., 2014; Wahl et al., 2014). Additionally, myelination in heterozygous neuregulin-1 type III mutant mice is reduced in brain while optic nerve and spinal cord myelination are normal (Taveggia et al., 2008). These differences may result from distinct developmental origins of OPC populations, unique neuronal populations to be myelinated or other local environmental signals.

Recent “omics” analyses of the molecular, cellular and biochemical properties of oligodendrocytes and myelin have uncovered many unknown markers of oligodendrocytes and myelin. The myelin proteome includes many more proteins than earlier studies suggested (Ishii et al., 2009; Jahn et al., 2009), and over 700 lipid moieties have now been identified in the myelin lipidome (Gopalakrishnan et al., 2013). The transcriptome of oligodendrocytes at different developmental stages has been established (Cahoy et al., 2008), and there is a searchable data base of RNAs and splice isoforms (http://web.stanford.edu/group/barres_lab/brain_rnaseq.html) for OPCs, newly formed oligodendrocytes and myelinating oligodendrocytes from P17 mouse cortex, along with comparable data for the variety of other glial and neuronal cells of the developing mouse brain (Zhang et al., 2014). Investigations into the regulation of myelination currently must consider how these RNAs,

proteins and lipids are coordinately regulated to generate CNS myelin and how they are altered in animal models of CNS disease. Additionally, these databases will be a valuable resource to cross reference with deep sequencing studies of the human genome that are identifying new genetic variants and candidate genes that are disrupted in multiple developmental and degenerative diseases.

White Matter Deficits in Human Disorders and Disease

In addition to the well-known demyelinating and dysmyelinating diseases such as multiple sclerosis (MS), neuromyelitis optica and the leukodystrophies, myelin deficits resulting from altered glial structure/function and or glial/neuronal interactions are seen in human psychiatric disorders (for review, see Haroutunian et al., 2014; Nave and Ehrenreich, 2014) and developmental disorders including autism spectral disorder (ASD), sensory processing delay disorder (Owen et al., 2013), attention deficit hyperactivity disorder (ADHD) (Li et al., 2010; Wu et al., 2014) and Rett syndrome (Mahmood et al., 2010). Adult onset neurodegenerative diseases including Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS) (Cho, 2013; Defrancesco et al., 2014; Defrancesco et al., 2013; Kang et al., 2013; Kim et al., 2013; Lillo et al., 2012; Pettit et al., 2013; Philips et al., 2013) also show myelin pathology.

Genome wide association studies, fMRI imaging and molecular analyses have shown dysregulation in oligodendrocyte gene expression (Cannon et al., 2012; Haroutunian et al., 2007; Haroutunian et al., 2014; Kerns et al., 2010), reductions in white matter volume (Bakhtiari et al., 2012; Cooper et al., 2014; Frazier et al., 2012; Hong et al., 2011; Lewis et al., 2013; Prigge et al., 2013) and changes in myelin proteins (Honer et al., 1999) in these various CNS disorders and diseases. In most of these human conditions, there are significant neuronal pathologies accompanying these myelin changes that may well underlie the disease. In patients with the neurodegenerative disease multiple system atrophy (MSA), cytoplasmic inclusions that contain α-synuclein and other intracellular proteins are predominantly found in oligodendrocyte cell bodies rather than neurons (see Wong et al., 2014 for review). Thus, in neurodegenerative and psychiatric diseases involving neuron and/or oligodendrocyte pathologies, the impact of oligodendrocyte and myelin dysfunction is coming under increasing investigation. However, it has generally been unclear whether the disease and/or therapies induce changes in white matter and myelin or changes in white matter/myelin drive aspects of the disease. In order to understand the consequences of such dysfunction, an in depth understanding of myelination *per se* and of the function of myelin in the adult brain is necessary.

Current questions and approaches

The rapid propagation of electrical activity along an axon is physiologically essential to facilitate efficient and integrated sensory, motor and higher order cognitive function. The historical concept of myelin was as an axonal insulator that allowed faster conduction of axon potentials via saltatory conduction, which then enabled complex nervous systems to evolve within reasonable space constraints. Prevailing perspectives would suggest that its role is more multifaceted than that of a simple electrical insulator, and that it is the bidirectional communication between the myelinating cell and the axon that is essential for

normal nervous system development and function. Bidirectional signaling mechanisms include direct cell-cell interactions, electrical activity, and trophic and metabolic support throughout development and adulthood.

Two crucial questions on the regulation of myelination have been addressed for decades without a definite conclusion. 1) What is the actual mechanism by which the oligodendrocyte extends its plasma membrane to wrap axons and eventually generate the multilayered compact myelin sheath around axons; and 2) How does the oligodendrocyte determine exactly how much myelin to generate for an axon of a specific diameter? Recent technological advancements in high resolution imaging, 3D electron microscopy and genetic approaches have led to new insights into the dynamics of myelination during development and provide valuable experimental evidence relevant to these questions.

Advances in Understanding Myelin Function

Elucidation of the Cellular Mechanism and Process of Active Myelination

Numerous concepts of what myelin is, whether it is needed, and how it is generated have been proposed over several decades (reviewed by Rosenbluth, 1999). These working hypotheses were developed to address the fundamental question underlying the process of active myelination. Dating back to the 1950s, the advent of electron microscopy (EM) in the field of CNS and PNS myelination became a standard tool to evaluate myelin ultrastructure (Bunge et al., 1962; Bunge et al., 1967; Bunge et al., 1965). These EM analyses led to two myelination models that are particularly relevant to current studies (reviewed in Bauer et al., 2009). These include a proposed “jelly roll” structure with the Schwann cell of the PNS migrating around axons or sending an inner tongue repeatedly around the axon to generate the wraps (Geren and Schmitt, 1954) (Figure 2A). Additionally, membranous structures were seen within the oligodendrocyte in the CNS, and the EM images suggested that they eventually fused to generate myelin (De Robertis et al., 1958) The consensus from these early EM studies was that active myelination resulted from the inner turn of the oligodendrocyte membranous sheath extending in a concentric and lateral movement down the axon. In this paradigm, the polarized membranous sheath was spirally wrapping an axon as it concurrently compacted (Figure 2B). These models were of interest, but until recently, static imaging techniques were insufficient to generate conclusive experimental evidence. Live imaging of CNS myelination in EGFP-expressing mice generated the “liquid croissant” model which supports this myelination model (Sobottka et al., 2011). In these studies, oligodendrocyte processes could be imaged opening into a triangular shape in the myelin sheath, which moves in coiled turns around the axon, as the membrane spreads sideward on the axon.

Elegant studies using a combination of high resolution *in vivo* imaging coupled with 3D reconstructions of optic nerve fixed with high pressure freezing/freeze substitution provide additional evidence (Snaidero et al., 2014). High pressure freezing facilitates microsecond fixation, prevents the nucleation of ice crystals to preserve macromolecular structures immobilized in their native state and permits vitrification of thicker samples. This enhanced methodology makes it more feasible to study the dynamic process of myelin biogenesis, even in static images. These studies show that myelination occurs through extension of the

plasma membrane as an inner tongue, expanding laterally down an axon to form the paranodal loops, which is consistent with the original model proposed by Geren (Geren and Schmitt, 1954). Interestingly, cytoplasmic channels in the nascent membranes are present during development, with as much as 25% of the myelin sheath in optic nerve containing these channels during early myelination; there is rapid reduction of these channels from P10 to P14. In this same time frame, some myelin sheath outfoldings are seen, which also are resolved rapidly to generate compact myelin. The cytoplasmic channels provide communication from the outside to the inside of the developing sheath, and membranous vesicles are present within them, reminiscent of the membrane vesicles seen by deRobertis et al. (1957). These cytoplasmic channels appear to fuse into the developing membrane, as compact myelin and paranodal loops form. Figure 2C highlights elements of this current model of active myelination in the CNS. The availability of new EM approaches, such as the high pressure freezing has made it possible to image the details of myelin biogenesis in far greater depth, making a more comprehensive model of active myelination possible.

Snaidero et al. (2014) further examine the molecular mechanism underlying the myelinating process. Through manipulation of the Akt/mTOR pathways, known to increase myelination in the developing CNS (Flores et al., 2008; Goebbels et al., 2010; Narayanan et al., 2009), the substructure of the myelin was altered. When Akt/mTOR signaling was increased by genetically deleting its inhibitor PTEN, the cytoplasmic channels that would normally assemble into paranodes in control tissue were retained as channels, allowing increased production of myelin. Importantly, in adults, in which normal myelin had been generated, these cytoplasmic channels could be re-induced by deletion of PTEN, and over time the reappearance of these cytoplasmic channels was followed by increased thickness of the preexisting myelin sheath. Thus, this study proposes that myelination occurs through communication from cytoplasmic channels out to the expanding myelin membrane, and as myelination completes, these cytoplasmic channels resolve (see Figure 2d). Signaling through the Akt/mTOR pathway regulates the presence of these channels, and thereby myelination.

Visualization and Kinetics of Active Myelination

Current findings suggest that active myelination is a highly ordered and rapid process. Recently, rapid genetic manipulation to over- or under-express proteins in zebrafish along with important live imaging capability have significantly enhanced our understanding of the kinetics of myelination. In the zebrafish, there is a short five hour window during which individual oligodendrocytes produce their first and their final myelin sheaths (Czopka et al., 2013). This temporally regulated process of developmental myelination is constant among oligodendrocytes, irrespective of where in the zebrafish spinal cord they are located or when they begin myelinating. Thus, cells in different parts of the spinal cord myelinate at different times, but they all myelinate within this temporal limit of approximately 5 hours. If this short time frame for oligodendrocyte differentiation is consistent in mammalian systems, local cues that change rapidly during development could impact individual oligodendrocytes development. Single cells could be exposed to unique positive or negative cues impacting local myelination, potentially generating some of the differential regional myelination.

With the ability to visualize oligodendrocyte dynamics and active myelination, a crucial question remains: how does the oligodendrocyte determine how much myelin each axon receives? Across species, oligodendrocytes produce more wraps of myelin around larger caliber axons, and there is a relatively consistent g-ratio (the ratio of the axon diameter: myelinated fiber diameter) for axons of different diameters (Friede and Bischhausen, 1982; Hildebrand and Hahn, 1978). In the rodent PNS, axonal signaling by neuregulin III type I activates ErbB receptors on the surface of Schwann cells to regulate myelin sheath thickness (Michailov et al., 2004). In the CNS, no single factor or mechanism has been identified that regulates myelination, likely because of the complexity of myelination by oligodendrocytes, which have been estimated to generate as many as 40 internodes per oligodendrocyte in optic nerve (Peters A. and Vaughn, 1970). Recent studies in zebrafish demonstrate that oligodendrocytes are quite adaptable in generating appropriate amounts of myelin. The Mauthner axons in the zebrafish are two large diameter ventral projection axons that are myelinated by ventral oligodendrocytes. Dorsally, the spinal cord axons have far smaller diameters. Ectopic production of Mauthner axons in the dorsal spinal cord results in proper myelination of these large caliber axons by local oligodendrocytes that also appropriately myelinate the surrounding smaller caliber axons (Almeida et al., 2011). Thus, localized cues from axons can modify oligodendrocyte function, and individual oligodendrocytes respond to axons of different caliber with different amounts of myelin. These studies emphasize the synergistic relationships between the neuronal circuitry and oligodendrocytes that modify myelin plasticity in the CNS. However, while local axons clearly regulate oligodendrocyte differentiation, the actual signaling pathways regulating this in the CNS remain elusive.

Adult Myelination

Current studies have established that in the uninjured, healthy adult brain, new myelin is continually generated (Yeung et al., 2014; Young et al., 2013). This occurs in multiple CNS areas, and even the fully myelinated adult rodent optic nerve, which contains only about 1% unmyelinated axons (Dangata et al., 1996; Honjin et al., 1977), continues to generate new oligodendrocytes and new myelin in the adult. Interestingly, in the human brain, recent evidence using carbon dating has shown mature oligodendrocyte stability with only a 0.3% turnover rate after 5 years of age. Yet there persists dramatic remodeling of myelin in the adult human brain (Yeung et al., 2014). This is consistent with studies demonstrating that white matter volume can increase significantly in humans after a few weeks practicing a new skill (Bengtsson et al., 2005; Scholz et al., 2009) or can be altered upon cognitive processing such as learning a language (Schlegel et al., 2012). Thus, rapid changes in myelin occur in adults, either from genesis of new cells or new membrane production by existing cells, undoubtedly impacting the plasticity seen in the adult brain.

The relationship of myelin thickness, axonal diameter and internode length is important. Internode length would be expected to regulate axonal conduction velocity, and when Schwann cell internodes are relatively short, changes in their length impact conduction velocity (Court et al., 2004). However, in a PNS model of limb lengthening, changes in internode length occur in the adult, while the axon diameter and g-ratio remain relatively constant. Somewhat unexpectedly, axonal conduction velocity is unchanged, despite

increased internodal length, but it is possible that long internodes have less impact on velocity than short internodes (Simpson et al., 2013).

While extensive data indicate that, after demyelination, remyelinated internodes are thinner and shorter than normal (Blakemore and Murray, 1981; Gledhill and McDonald, 1977), a recent study suggests that at late time points of recovery, as much as 6 months recovery, newly remyelinated fibers have comparable internode length and thickness to developmentally myelinated axons (Powers et al., 2013). This significant difference among studies may result from the extended period of remyelination used by Powers et al., (2013), from the different methodologies of analysis or from different models of demyelination/remyelination, but understanding the underlying mechanisms of myelination and remyelination in the adult brain is extremely important for our understanding of myelin repair in disease.

Discontinuous Myelination

As noted above, fundamental questions about the process of myelination itself are being answered and new studies have provided experimental evidence supporting claims made decades ago. In the past, the familiar concept that myelin internodes were uniformly dispersed down an axon became accepted in the field, but this hypothesis is now being challenged. Classically, it was thought that unmyelinated axon segments along myelinated axons resulted from damage or disruption of myelin. The general consensus was that after active myelination, the mature oligodendrocyte is in a myelin maintenance state, with subtle remodeling of localized areas of myelin, and, when necessary, remyelination by newly differentiating OPCs in demyelinated areas.

Standard transmission electron microscopy has provided high image resolution, but given the complex tissue organization of the brain, this technique could not visualize the full length of individual myelinated axons in CNS tissue without serial reconstructions of detailed electron micrographs in large tissue volumes. With high throughput automation of 3D electron microscopy and software programs that accelerate processing of high resolution reconstruction maps of these images, it is now possible to study the longitudinal distribution of myelin along individual axons in the rodent cortex. Projection neuron axonal segments have distinct myelination profiles in different cortical layers. There is a myelin gradient, with greater myelin in layers V and VI than in layers II/III. The axons of the deeper cortical layers are more uniformly myelinated, but unexpectedly, there are intermittent unmyelinated axonal segments in superficial layers of the cortex interspersed with myelinated internodes (Tomassy et al., 2014). This distinction of myelination patterns is independent of axonal caliber, i.e., neuronal soma size and axonal diameter are indistinguishable in the deep or superficial cortical layers. The availability of oligodendrocyte progenitors is also not a viable explanation, since the oligodendrocyte progenitor population is evenly dispersed throughout the brain (Tomassy et al., 2014). Furthermore, genetic manipulation of the laminar position of neurons within these cortical layers alters the distribution of mature oligodendrocytes and myelin. These studies suggest that unique features of different classes of cortical neurons regulate the differences in cortical myelination. Since myelin is critical in facilitating conduction velocity, do these unmyelinated segments have an evolutionary basis in

regulating communication speed within different neuronal networks in the brain? These data would suggest that heterogeneous neuronal populations may have differential signaling patterns modulating localized oligodendrocyte myelination, and that the interaction of these neurons and oligodendrocytes may regulate some elements of plasticity in the adult brain. As noted above, new myelin is being generated in the healthy adult brain (Young et al., 2013), and adding new myelin internodes in areas of discontinuous myelination may be a mechanism for local plasticity. Altered or inadequate myelination in the adult could also be a component in some of the psychiatric or neurodegenerative disorders that involve white matter.

Synergism in Oligodendrocyte-Neuronal Interactions Regulate Axon Function and Myelination

Numerous studies have demonstrated an interdependent relationship of oligodendrocytes and the axons they myelinate (for review, see Nave, 2010; Nave and Trapp, 2008). Exciting new studies using cutting edge methodologies underscore the relevance of investigating neuronal-oligodendrocyte interactions.

Metabolic Support

While we have focused on axonal signals modulating oligodendrocyte plasticity, axons are similarly dependent on oligodendrocytes and myelin to provide support to maintain their integrity. Loss of myelin results in major axonal pathology. However, it has been known for many years that myelin can be generated in the absence of major myelin proteins such as PLP or CNP but this myelin is not normal, and myelin perturbation over time leads to axon degeneration (Edgar et al., 2009; Griffiths et al., 1998; Rasband et al., 2005). More recent work indicates that a major element of the oligodendrocyte support of axons may well be metabolic (Funfschilling et al., 2012; Lee et al., 2012; Morrison et al., 2013). Surrounded by myelin, the axon is relatively isolated from the extracellular milieu. There is ample evidence that oligodendrocytes provide essential trophic support to axons (Fruhbeis et al., 2013; Kramer-Albers et al., 2007; Lappe-Siefke et al., 2003; Rasband et al., 2005; Wilkins et al., 2003), and now studies suggest their ability also to provide metabolic support.

Mature oligodendrocytes that are incapable of electron transport use aerobic glycolysis, which generates lactate and pyruvate (Funfschilling et al., 2012). The lactate produced by these cells is rapidly utilized by the axons, except when neuronal function is reduced as under anesthesia, at which point lactate accumulates in the tissue. Aerobic glycolysis in oligodendrocytes is sufficient to maintain the myelin itself, as well as the structure and function of the myelinated axons. These studies generated a model for the metabolic support of myelinated axons, in which myelin delivers lactate to axons. Lactate is then metabolized in the axons, where access to other sources of energy is limited. This initial observation was supported by studies demonstrating that monocarboxylate transporter 1 (MCT1) is highly localized to oligodendrocytes and it was proposed that MCT1 transport of lactate from myelin to the underlying axons is a major source of metabolic support (Lee et al., 2012) (Figure 3).

Extensive studies have established a major role for astrocytes in metabolic support of neurons (see Bouzier-Sore and Pellerin, 2013 for review), and it is likely that the metabolic support provided by oligodendrocytes and myelin is only part of the story (Amaral et al., 2013). Nevertheless, these studies on lactate transport from myelin to axons could substantially impact our understanding of the role of oligodendrocytes and myelin in CNS diseases. If axons are dependent on oligodendrocytes for lactate/pyruvate and there are myelin deficits, axonal degeneration, such as is seen in ALS and other neurodegenerative diseases, may occur. Recent studies suggest an active role for oligodendrocytes in ALS, which is primarily considered a neurodegenerative motor neuron disease (Kang et al., 2013; Yamanaka et al., 2008). Chimeric mice were generated in which the brains had cells that expressed mutant superoxide dismutase I (SOD1[G37R]), which induces an ALS-like disease, as well as cells that expressed wild type SOD1. The predominantly motor neuron degeneration was delayed dramatically by expression of wild type SOD1 in oligodendrocytes, despite high expression of mutant SOD1 in motor neurons (Yamanaka et al., 2008). In other studies, impaired oligodendrocyte function in gray matter oligodendrocytes in the SOD1 (G93A) mutant mouse enhances the vulnerability of motor neurons to ALS-linked genetic insults, speeding the progression of the disease (Kang et al., 2013). Enhanced glial reactivity, proliferation of NG2-positive oligodendrocyte progenitor cells and a dramatic increase in the number of oligodendrocytes occurs in this late stage SOD1 (G93A) rodent model (Kang et al., 2010). Other studies on the SOD1(G93A) mouse demonstrate dysmorphic oligodendrocytes with increased turnover of differentiating oligodendrocytes and reduced myelin basic protein (MBP), relative to wild type mice. As noted above, Lee et al. (2012) propose that MCT1 regulates lactate transport from oligodendrocytes to axons, and a significant loss of MCT1 was seen in spinal cord gray matter in these mice (Philips et al., 2013). Importantly, changes in the metabolic support of axons provided by oligodendrocytes appear likely in ALS patients as well, since (Lee et al., 2012) noted that MCT1 is downregulated by 50% in motor cortex of a cohort of ALS patients. These studies demonstrate the metabolic support by oligodendrocytes is essential for axons in animal models and suggest that the loss of oligodendrocyte metabolic support of axons may result in neurodegeneration in humans.

Neuronal Activity and Adaptive Myelination

Adaptive myelination is an evolving concept that has been investigated in the field for over a decade. This concept implies that neuronal electrical excitability modifies myelin plasticity and that myelin plasticity in turn feeds back to modulate neural activity and behavior. First demonstrated in *in vitro* cultures of PNS Schwann cells and dorsal root ganglion neurons, different frequencies of neural-induced firing influenced *in vitro* myelination through differential expression of a cell adhesion molecule L1 (Stevens et al., 1998). Studies of oligodendrocyte lineage cell/dorsal root ganglion neuron co-cultures suggested that electrical activity stimulated the localized release of neurotransmitters (ATP and vesicular glutamate) at the axo-glial synapse to influence oligodendrocyte calcium levels and modify signaling cascades that feed into local MBP protein translation (Wake et al., 2011). Recent studies demonstrate that some of the glutamate response of oligodendrocytes in myelinating cultures can be altered by signaling molecules, such as neuregulins. In studies on oligodendrocyte/dorsal root ganglion neuron co-cultures, myelination occurs independent of

neuronal activity (Lundgaard et al., 2013). However, after exposure to neuregulin, myelination regulation changes, and it becomes partially dependent on neuronal excitability. Blocking NMDA channels, which initially has no impact on myelination, now reduces myelination by over 80% (Lundgaard et al., 2013).

These *in vitro* studies set the groundwork to investigate *in vivo* models in which modification of neuronal function induced changes in oligodendrocyte lineage progression and myelination. *In vivo* studies establish that myelination can be reduced or increased by neuronal function. Some studies suggest a critical period in which neuronal function impacts myelination, either during early or late development. Neural activity either in the medial prefrontal cortex or the barrel cortex of the somatosensory cortex impacts myelination (Barrera et al., 2013; Makinodan et al., 2012). Social isolation for as little as 2 weeks in the early post-weaning period has a dramatic effect reducing myelination in the prefrontal cortex, although motor activity is unaffected. Oligodendrocyte morphology is far simpler in these mice and myelin thickness is reduced. Reintroduction of mice to a social environment at the end of the two weeks does not improve myelination. In these studies, 30 days social isolation in the adult has little impact on myelin content (Makinodan et al., 2012). Sensory deprivation was induced by whisker trimming starting at P1 and myelination in the barrel cortex was reduced, with dramatic reduction in the density of myelinated axons. Here, however, the critical window was much later in development, consistent with the fact that active myelination of this cortical region occurs later, increasing significantly between P45 and P60 in normal animals. Nevertheless, as with social isolation, sensory deprivation in adult mice had little impact reducing myelinated axons (Barrera et al., 2013). Interestingly, in both cases, it is myelination *per se* that is reduced, since the number of oligodendrocytes themselves are normal in these tissues.

These investigations into the impact of neuronal function on myelination suggested the existence of a critical window of sensitivity, but other studies using social isolation in the adult indicate adults are also susceptible. Long term social isolation (8 weeks) results in significantly thinner myelin in prefrontal cortex, but not corpus callosum (Liu et al., 2012), as has also been seen in other studies on rodents maintained in isolation (Markham et al., 2009). Consistent with studies in younger animals, this again appears to be primarily an effect on myelination, since the number of oligodendrocytes in prefrontal cortex in these socially isolated mice is normal (Liu et al., 2012). As noted above, the impact of neuronal activity is also seen in humans, where extensive long term training, such as piano practice (Bengtsson et al., 2005) or learning to juggle (Scholz et al., 2009) correlates with increased white matter, in a region-specific manner depending on age (Bengtsson et al., 2005). Interestingly, white matter regions that mature in adulthood, e.g., long association fiber systems of the forebrain, are most impacted in adults by piano practicing.

The impact of neuronal activity on myelination in adult brain may result from the ubiquitous presence of OPCs throughout the adult mouse brain (Dimou et al., 2008; Kang et al., 2010; Rivers et al., 2008; Young et al., 2013). In rodent brain, adult NG2-positive OPCs are constantly migrating through the local environment, retracting and extending their branched processes (Hughes et al., 2013). Adult mouse OPCs define limited territories within which individual cells move, avoiding other adult OPCs, just as is seen for zebrafish OPCs during

development (Czopka et al., 2013; Czopka and Lyons, 2011; Kirby et al., 2006; Takada and Appel, 2010), but they retain the ability to migrate to areas of damage and to effectively generate new myelin (Hughes et al., 2013).

The Richardson laboratory has shown that over 30% of mature oligodendrocytes are newly formed in the adult rodent brain (Rivers et al., 2008), which would be a remarkable source of myelin plasticity throughout life. This group investigated the hypothesis that production of new myelin from these newly formed oligodendrocytes, i.e., myelin plasticity, could enhance learning in motor circuits of the brain. Myelin regulatory factor, a transcription factor essential for oligodendrocyte maturation (Emery et al., 2009), was conditionally ablated in adult mice. This blocked new myelin production, but did not impact the existing oligodendrocyte population or result in demyelination (McKenzie et al., 2014). However, the inability to generate new myelin prevented these mice from learning new motor skills on a complex running wheel (McKenzie et al., 2014) (Figure 4). This is a key observation, since this completes a feed back/feed forward mechanism: new motor skills normally increase myelin in the motor cortex but the inability of generate new myelin prevents mice from learning the new motor skills.

Optogenetic studies have provided a more direct *in vivo* demonstration of the impact of neuronal electrical excitation in the premotor cortex on oligodendrocyte lineage cells and myelination (Gibson et al., 2014) (Figure 4). Growing in popularity, novel optogenetic techniques were developed that utilize light-reactive bacterial opsins to change the membrane voltage of cells, resulting in their excitability (Arenkiel et al., 2007; Boyden et al., 2005). The advantage of this technique is the precise and rapid excitation of distinct subpopulations of cells in a non-invasive manner in awake animals with little disruption to the native state of the tissue. In animals expressing the neuron-specific Thy1 promoter driving channelrhodopsin, light induces electrical stimulation of motor cortex layer V neurons. This protocol activated no apparent inflammation but increased OPC proliferation and survival, resulting in increased oligodendrogenesis. Mature oligodendrocyte number increased along with increased MBP protein expression and myelin sheath thickness (Gibson et al., 2014). The functional consequences of these changes in oligodendrocytes and myelin were determined by gait analysis on a Catwalk apparatus. This optogenetic manipulation and increased myelination resulted in increased swing speed of the forelimb associated with the cortical hemisphere that had received optical excitation. Subsequent studies into the mechanism regulating these changes demonstrated that neural activity directly modified oligodendrocyte differentiation and myelination.

Conclusion

The emergence and accessibility of high throughput electron microscopy and the surge in unique genetic models and optogenetic tools to study the dynamic process of CNS myelination modulating neural circuitry begin a new era investigating the complex networking in the brain. The evidence that humans undergo minimal oligodendrogenesis after early childhood but rapidly undergo myelin turnover throughout adulthood suggests that adaptive myelination may be a major element of the fine tuning of heterogeneous neural cell populations in various regions in the brain (Yeung et al., 2014). New experimental

evidence about the fundamental processes of active myelination and the oligodendrocyte-neuron relationship suggest that metabolic pathways, extracellular signaling mediators and electrical activity all facilitate changes in CNS plasticity via heightened oligodendrogenesis to strengthen motor learning and function. Studies demonstrating that constant changes in white matter contribute to life-long cognitive and motor processing provide promising insight into the potential role of oligodendrocyte dysfunction as a primary contributor in CNS disorders and disease (Scholz et al., 2009; Yeung et al., 2014). The recent study demonstrating altered metabolic monocarboxylate transporter expression in human ALS cortex (Lee et al., 2012) may be just one example of the importance of oligodendrocyte metabolic and trophic support on axonal integrity.

In diseases such as multiple sclerosis, while the most obvious pathological presentation is plaques that have little myelin, there may also be elements of the disease that result in myelin dysfunction undetectable by standard approaches. For example, normal appearing white matter in multiple sclerosis tissue often has reduced axonal density, which is generally attributed to inflammation (Frischer et al., 2009). This normal appearing white matter may well have dysfunctional myelin that cannot provide the necessary trophic and metabolic support for axons. The extensive studies showing reduced white matter in disease (Bakhtiari et al., 2012; Defrancesco et al., 2014; Haroutunian et al., 2014), as well as in normal aging in humans (Haroutunian et al., 2014) suggest that altered myelin and oligodendrocyte function in human brain are major factors in neurodegeneration. The concept that myelin dysfunction could be just as important as myelin loss with respect to neurodegeneration is extremely important and may have great significance for future research directions.

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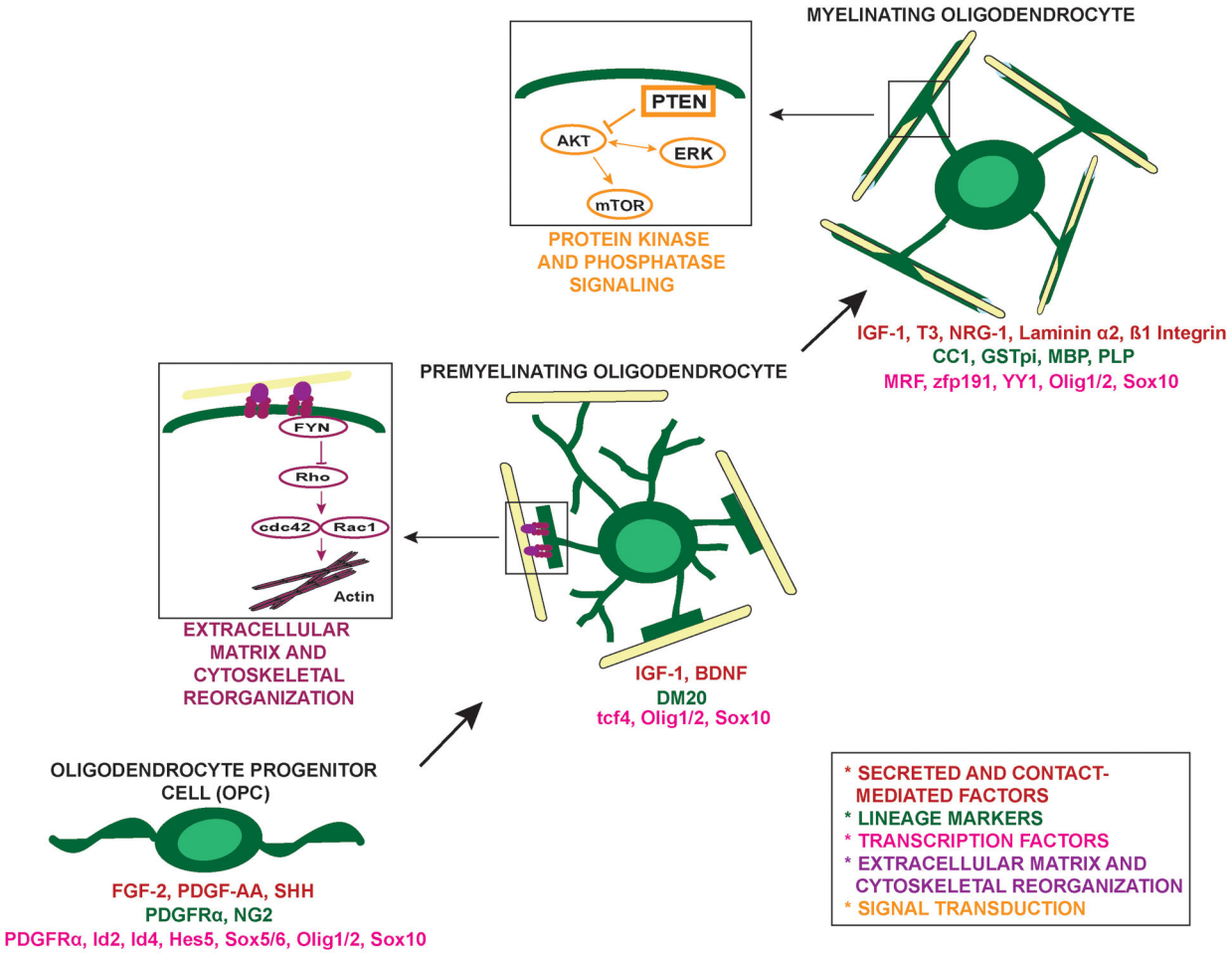

Figure 1. Extrinsic and intrinsic cues regulate the oligodendrocyte program.

Progression through the oligodendrocyte lineage is mediated by numerous factors. As highlighted, signaling from the extracellular matrix (sub-figure adapted from Bauer et al., 2009) is critical in modulating the dynamic cytoskeletal reorganization of the premyelinating-myelinating oligodendrocyte transition. Additionally, signal transduction through the Akt/mTOR pathway, modified by PTEN, has been shown to be a regulator of myelin biogenesis. It should be noted that the ERK1/2 signaling pathway is also involved in regulating CNS myelination (Ishii et al., 2012), but this figure focuses on the Akt/mTOR pathway investigated in Snaidero et al. (2014).

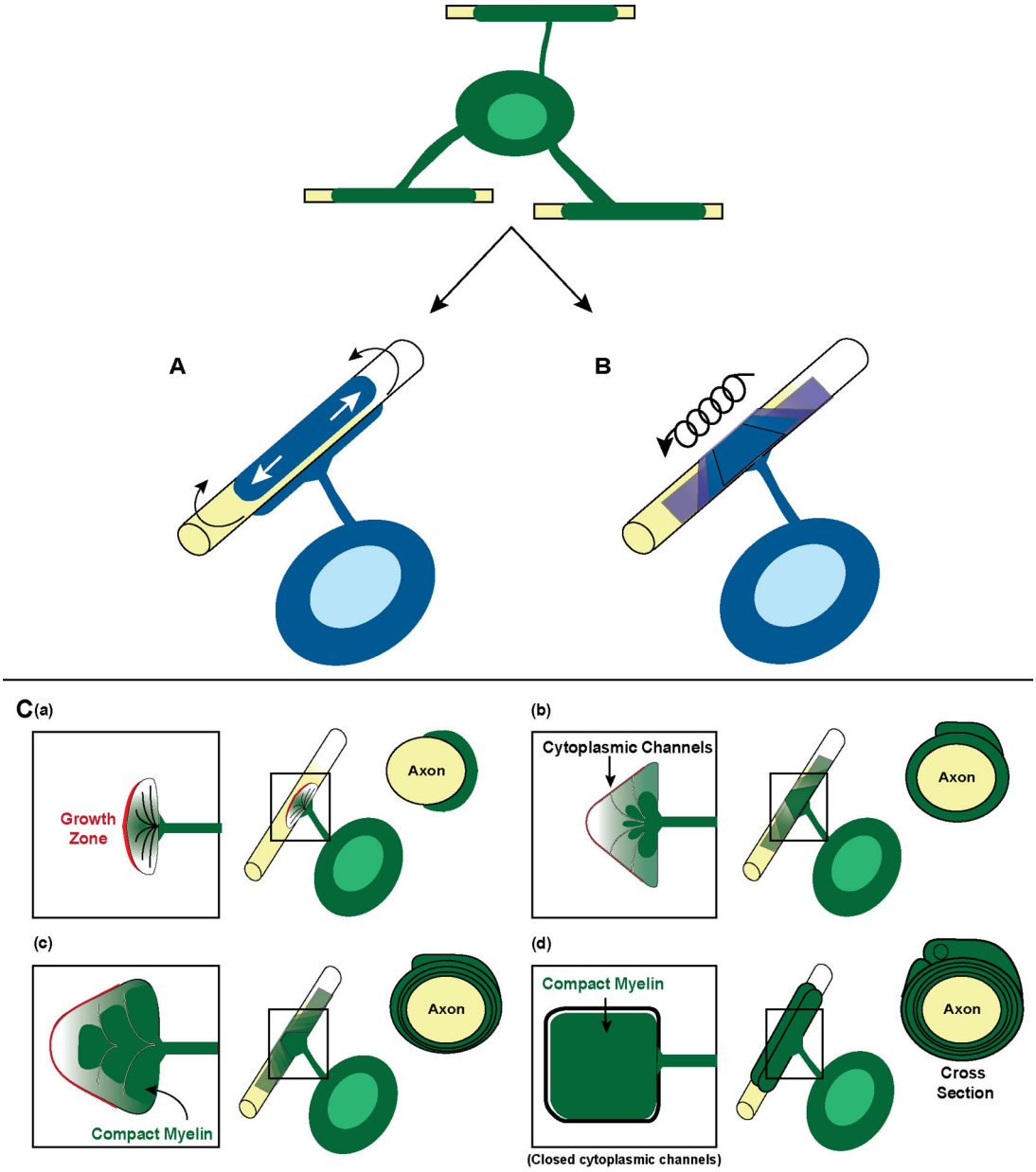

Figure 2. Past and present models of myelination.

In the past, two models of myelination (blue) have been proposed to ensheath an axon. (A) Schematic of the proposed "jelly roll" model of myelination in which myelin concentrically wraps around the axon repeatedly overlapping the same internode. (B) Lateral spiral movements of an oligodendrocyte process around an axon with eventual compaction. (C) Current model of myelination adapted from (Snaidero et al., 2014). (a) The grown zone (red) of an individual oligodendrocyte process contacts the axon which it will ensheath. (b) The inner tongue of the oligodendrocyte process pushes under the outer tongue to generate the compact myelin (dark green). Cytoplasmic channels (white) allow communication between the inner and outer tongue. (c) More compact myelin is generated. (d) Cytoplasmic channels

close once the appropriate number of myelin wraps per axon is generated and myelination is complete.

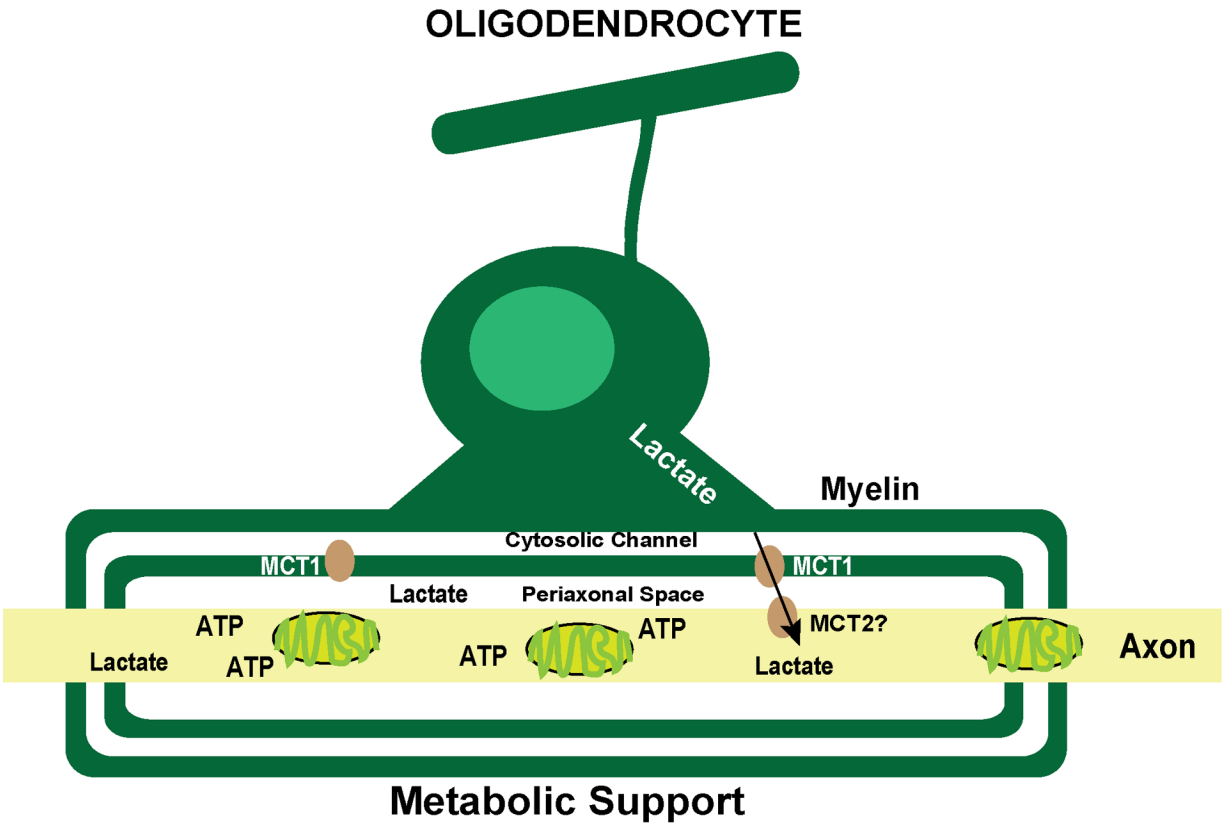

Figure 3. Myelin metabolic support influences axonal integrity.

Model of oligodendrocyte-derived lactate delivered by the MCT1 transporter to the axon where it is metabolized and used as an energy source. Adapted from Funfschilling et al. (2012).

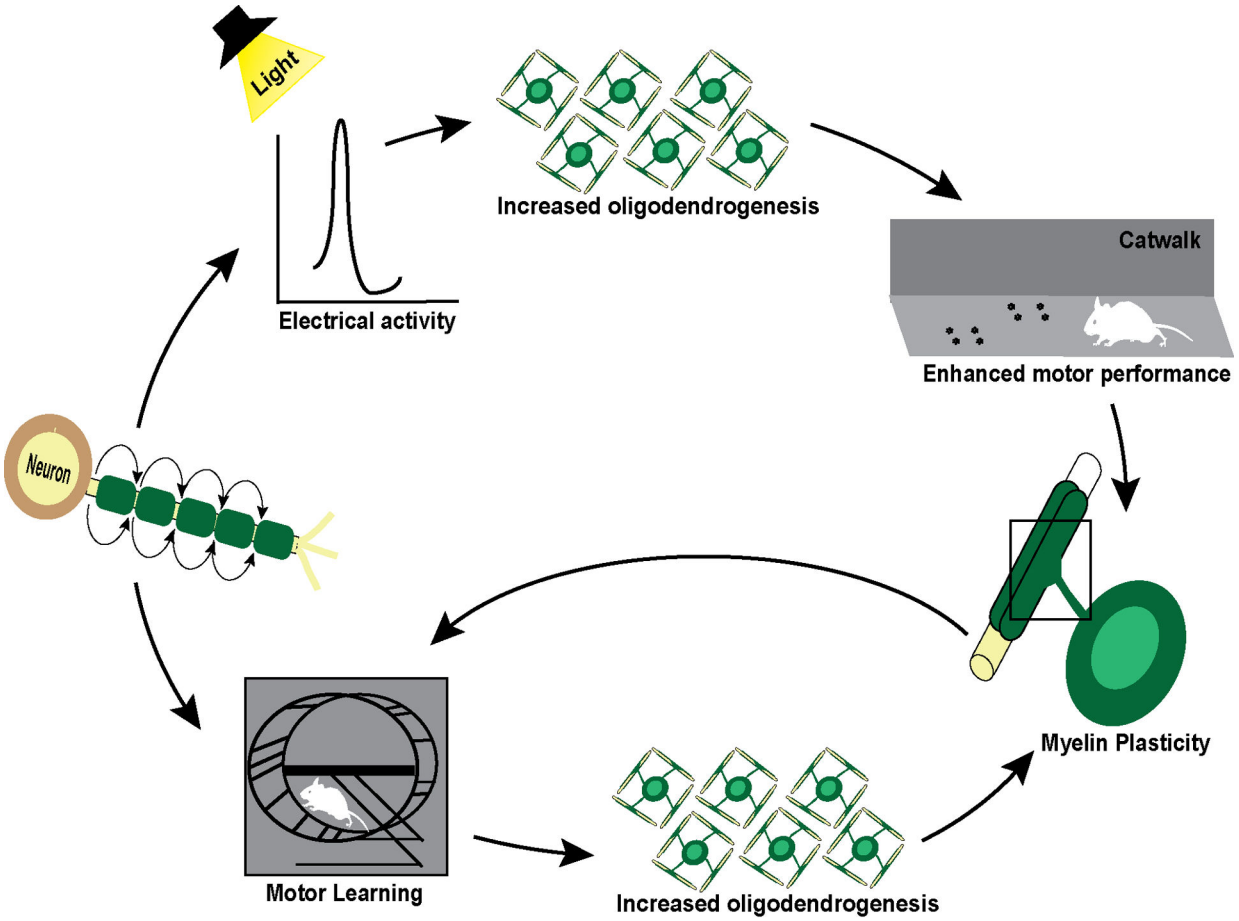

Figure 4. Neural activity influences oligodendrocyte plasticity.

Schematic of the neural induced modification of oligodendrogenesis and the feedback loop from myelin plasticity enhancing neural-mediated behavior. In rodents, optogenetic induced electrical activity results in enhanced oligodendrogenesis resulting in enhanced swing speed on a Catwalk apparatus. Additionally, motor learning on a complex wheel requires new oligodendrogenesis. Mouse illustration provided and used with permission from Dr. Michelle Monje.