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Dynamics of mature myelin

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Abstract

Myelin, produced by oligodendrocytes, insulates axons to facilitate rapid and efficient action potential propagation in the central nervous system. Traditionally viewed as a stable structure, myelin is now understood to undergo dynamic modulation throughout life. This review examines these dynamics, focusing on two key aspects: (1) the turnover of myelin, involving not only the renewal of constituents but the continuous wholesale replacement of myelin membranes, and (2) the structural remodeling of pre-existing, mature myelin, a newly discovered form of neural plasticity that can be stimulated by external factors, including neuronal activity, behavioral experience, and injury. We explore the mechanisms regulating these dynamics and speculate that myelin remodeling could be driven by an asymmetry in myelin turnover or reactivation of pathways involved in myelin formation. Finally, we outline how myelin remodeling could have profound impacts on neural function, serving as an integral component of behavioral adaptation.

Introduction

Myelin consists of tightly compacted, insulating membranes concentrically wrapped around axons in discrete sheaths called internodes. Between internodes are nodes of Ranvier, specialized axonal sites enriched with voltage-sensitive channels (Fig. 1a,c). This arrangement enables saltatory conduction, wherein action potentials regenerate exclusively at nodes to dramatically increase propagation speed and reduce neuronal energy expenditure. Central nervous system (CNS) myelin is produced by oligodendrocytes, generated via terminal differentiation of oligodendrocyte precursor cells throughout life. Upon formation, new oligodendrocytes extend processes and rapidly elaborate and arrange membrane to form internodes around numerous axonal segments (Box 1).

Following this dynamic period, oligodendrocytes and their internodes stabilize, mostly persisting across the lifespan[1–5]. Mature myelin was long considered static, with changes to CNS myelin architecture only occurring through new myelin-generating oligodendrocytes or pathological demyelination. However, recent evidence indicates mature myelin is

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remarkably dynamic, undergoing both continual renewal of its membrane as well as remodeling of its structure.

This review delves into these dynamics. First, we discuss the turnover of myelin, involving not only the exchange of myelin constituents but the continuous wholesale replacement of myelin membranes. Second, we review the structural remodeling of mature oligodendrocytes and internodes and its modulation by external factors. Third, we explore mechanisms regulating myelin turnover and remodeling. We propose that myelin remodeling could be driven by asymmetrical myelin turnover or reactivation of pathways involved in myelin formation. Finally, we consider the function of myelin remodeling, highlighting how this novel form of plasticity may impact neural adaptation and behavior.

Dynamics of Myelin Turnover

To produce its structure and functionality, myelin contains a unique configuration of lipids and proteins, many of which are situated within its compact structure (Fig. 1b,c). As lipid and protein turnover is typically rapid (hours-days)[6–8] and is essential for cell function and viability, the turnover of seemingly inaccessible myelin components are of longstanding interest. Furthermore, the possibility that plastic changes in myelin turnover could be utilized to alter myelin structure and neural function highlights the importance of understanding these mechanisms.

Lipids

Myelin's unique constitution of lipids (Fig. 1b) facilitates intermembrane adhesion (galactocerebroside, sphingomyelin), myelin-axon adhesion (sulfatide), and membrane rigidity (cholesterol) (reviewed in Poitelon et al., 2020[9]). Pulse-chase dating in adult mice shows that distinct myelin lipid subclasses have radically different longevities. The half-lives of phosphatidylcholine and phosphatidylethanolamine are approximately 20 and 25 days, respectively[10]. By contrast, cholesterol and cerebrosides (including galactocerebroside) are long-lived, with half-lives of approximately 300 and 100 days, respectively[10]. Sulfatide (sulfated galactocerebroside) is similarly long-lived: inducible genetic removal of its synthesizing enzyme in mouse pre-existing oligodendrocytes reduced sulfatide levels only after three-six months[11]. Importantly, the half-replacement times for these lipids mirror their half-lives[10]; thus, there is constant turnover of lipids in mature myelin.

Lipids are presumably exchanged in uncompacted areas of mature myelin, where vesicles are observable[12]. Differential access to or recycling at these regions may explain the disparity in turnover rates between lipid subclasses. Interestingly, long-lived lipids like cholesterol, galactocerebroside, and sulfatide localize to membrane rafts[13], structures with slowed lateral diffusion that sequester lipids[14]. Likely, these lipids are primarily recycled in concert with entire myelin membranes, a possibility supported by similar turnover rates (see Membranes). A recent study found lipid turnover may be modulated by learning, which induced sequential increases in sphingomyelin and galactocerebroside in subcortical white matter of young adult mice[15]. Whether these changes were independent of broader synthesis or removal of myelin membranes is unclear, but these findings advance the possibility that lipid turnover and composition may be a variable feature of mature myelin.

What are the consequences of perturbing myelin lipid turnover? Preventing new sulfatide formation in pre-existing oligodendrocytes in ten-week-old mice caused myelin thinning and abnormalities, mislocalization of nodal/paranodal/juxtaparanodal proteins, axonal degeneration, and motor deficits progressing over eleven months[11]. Broader disruption of myelin lipid synthesis through inducible deletion of quaking (*Qk*) from mature oligodendrocytes in eight-week-old mice caused myelin thinning within one week, followed by outright demyelination without oligodendrocyte loss, slowed axonal conduction, severe motor deficits, and death by seven weeks[16]. Partial rescue occurred with a high fat diet or activators of lipid metabolism[16]. Given the rapid deterioration, this phenotype was likely caused by deficits in production of high turnover lipids, though the responsible subtypes were not determined. These findings indicate that ongoing lipid synthesis is essential for maintaining mature myelin and present the possibility that myelin remodeling could involve modulation of this process.

Proteins

The protein makeup of myelin is unique and complex, facilitating its structure and function (reviewed in Stadelmann et al., 2019[17]) (Fig. 1c). Pulse-chase dating of proteins found in compact myelin (MBP, PLP, Claudin-11) shows they are among the longest lived in the mouse brain, with half-lives of approximately 100 days[6,7,18,19]. These findings are corroborated by inducible gene deletions in mice, which estimated the half-lives of PLP and MBP through measuring residual protein to be 180 days[20] and 77 days[21], respectively. Alignment between these metrics is important as lifetime estimates are complicated by new protein synthesis from ongoing oligodendrogenesis, pulse-chased isotype recycling, and possible disruptions to myelin turnover with gene deletions. Myelin proteins localized to non-compact regions, like CNP (half-life 55 days), are still relatively very long-lived[7,18], while proteins at myelin-axon junctions, like MAG, turn over moderately slower than typical brain proteins[7]. Similar to long-lived lipids, long-lived proteins in compact myelin have comparable turnover rates to myelin membrane, suggesting these proteins may turn over with the entire membrane (see Membranes).

Disruption to protein turnover in young adult mice perturbs myelin structure, although over a slower timescale than lipid turnover. Reducing protein synthesis by 25% in mature oligodendrocytes had minimal effect over three weeks[22]. However, over six months, halving expression of several myelin proteins via inducible *Erk1/2* deletion from mature oligodendrocytes resulted in progressively thinner myelin, myelin loss, axonal degeneration, and motor deficits[23]. Dramatic myelin thinning and loss progressing over months without oligodendrocyte loss also resulted from inducible deletion of *Mbp* (MBP) in mature oligodendrocytes[21]. A more subtle decrease in the number of myelinated axons was observed ten months post-deletion of *Plp1* (PLP) from mature oligodendrocytes; however, the remaining myelin presented with numerous ultrastructural abnormalities[20]. Likewise, impairing the removal of myelin proteins has structural impacts. Two recent studies found that myelin proteins are degraded via (macro)autophagy[24,25]. Blocking autophagy in oligodendrocytes caused myelin protein accumulation[24,25]. Over months, mice experienced progressive myelin thickening and other ultrastructural disruptions, resulting in motor deficits and precocious death[24,25]. These studies indicate that myelin protein turnover

occurs over months and maintaining balance in this process is essential for the long-term maintenance of intact myelin. Intriguingly, altering the balance of protein turnover may be a means by which myelin structure could be remodeled to adapt myelin function.

Membranes

Myelin lipids and proteins are regularly replaced, but whether this occurs through the turnover of the entire myelin membrane structure or simply through the exchange of its constituents is unresolved. However, recent studies suggest there is indeed turnover of myelin membranes, and this is how at least some myelin constituents are renewed. Removing *Mbp* from mature oligodendrocytes in mice resulted in large, uncompacted membrane tubules originating in the inner tongue and paranodes[21]. These tubules were devoid of MBP but expressed PLP and were relatively newer than compact myelin[21], consistent with the possibility that new myelin membranes, containing lipids and proteins, are constantly incorporated at the inner tongue and paranodal regions of mature sheaths (Fig. 1d), reminiscent of growth during sheath formation[12]. Without MBP, essential for wrapping and compaction[26], these membranes could not incorporate to replace compact myelin that otherwise progressively thinned over six months until it was eventually lost[21]. Remarkably, even six months post-tamoxifen, the abundance of MBP in the remaining compact myelin was unchanged[21], suggesting recycling of MBP – and likely other long-lived myelin proteins and lipids – occurs in concert with removal of compact membranes.

How, then, are compact membranes removed? First, myelinoid bodies – large, rounded, multi-lamellated structures present in cytoplasmic regions of myelin – are long considered to be a site of myelin recycling (Fig. 1e) (reviewed in Hildebrand et al., 1993[27]). They are thought to bud from compact myelin and contain myelin degradation products[27]. Consistent with a source-product relationship, these structures incorporated pulsed stable isotope-labeled precursor to the same extent as compact myelin[21]. Future studies manipulating the formation of myelinoid bodies will provide further insights into their role in myelin membrane removal. Second, removal of lipids and proteins that constitute compact myelin can occur through autophagy and endocytosis (Fig. 1e). In blocking autophagy, concomitant with myelin thickening, both cytosolic (MBP) and integral membrane proteins (PLP, MOG) accumulated and, under normal conditions, these proteins could be found within autophagosomes[24,25]. Given that autophagy per se digests only cytoplasmic material, the presence of integral membrane proteins suggests the formation of amphisomes, the fusion of endosomes with autophagosomes prior to lysosomal degradation, which was indeed visualized in the cytoplasm of cultured oligodendrocyte myelin[24]. Internalization and lysosomal digestion of myelin membranes by oligodendrocytes is also observed in zebrafish, where new oligodendrocytes remove some of their nascent sheaths[28]. Though, lysosomal digestion may not be the only endpoint: oligodendrocyte release of myelin protein-containing exosomes, caused by the fusion of late endosomes or amphisomes with the plasma membrane, has been observed *in vitro*[29]. Lastly, membrane removal could be executed by microglia and astrocytes (Fig. 1e). These cells actively phagocytose aberrant myelin from sheaths during development and following myelin structural remodeling during metamorphosis[28,30]. Additionally, microglia are implicated in phagocytosing entire nascent sheaths in developing zebrafish[31], though not all studies agree[28]. Whether glia remove

myelin membranes in the healthy adult CNS is unknown but is interesting grounds for future study.

These data indicate that mature myelin undergoes continual renewal of not only its constituents but of entire membranes. Amazingly, myelin turnover is well-balanced to maintain intact internodes throughout life despite the range in turnover frequency between myelin components, different translation sites for myelin proteins, and the apparent mechanistic separation between myelin synthesis and removal. Intriguingly, asymmetry in myelin turnover may underlie structural changes in aging[32] or, on the other hand, may be harnessed to plastically modulate myelin structure to fine tune its function.

Dynamics of Myelin Remodeling

Myelin turnover could proceed without any net gain or loss, resulting in a stable myelin structure throughout life. However, recent work shows several features of mature myelin, including myelin thickness, periaxonal space width, and the length of internodes and nodes, can undergo structural modification in the adult CNS (Fig. 2). Furthermore, entire internodes of mature oligodendrocytes may be generated or lost (Fig. 2). Myelin remodeling is an exciting new facet of neuroplasticity, providing a means by which pre-existing myelin could modify neural function and behavior.

Myelin Thickness

Across the lifespan, a prolonged, marginal increase in the average number of myelin wraps enlarges the thickness of sheaths (Box 2) in several mouse and primate CNS regions[1,33–38] (Fig. 2). This ongoing myelin thickening typically occurs independent of changes in axonal diameter[33–37], but in mouse optic nerve the radial growth of myelin and axons occurs in concert[1]. This prolonged radial growth of myelin implies that, on average, there exists an asymmetric addition and removal of myelin membranes. However, the temporal and spatial dynamics of this growth are unknown. Do wraps accumulate within a sheath unidirectionally and linearly? Do all mature sheaths undergo the same changes or do different oligodendrocytes or axons adjust their myelin differently?

Additionally, myelin thickness in young adult rodents can be altered by neuronal activity or behavioral experience. Prolonged optogenetic or chemogenetic activation of cortical projection neurons induced thicker myelin in corpus callosum[39,40]. Amazingly, after chemogenetic activation, this thicker myelin was found specifically around those axons with elevated activity[40]. In a genetic model of absence seizures, myelin was thicker in corpus callosum following seizure onset[41]. Social isolation or chronic social defeat stress reduced myelin thickness in medial prefrontal cortex[42–44], while environmental enrichment or partial hearing deprivation increased myelin thickness in corpus callosum and trapezoid body fibers, respectively[45,46].

However, it remains unclear whether these changes were mediated by pre-existing, mature sheaths adding additional wraps and/or by newly-generated oligodendrocytes augmenting wrapping during sheath formation. These manipulations were performed in young adults, which have abundant ongoing myelin formation, and analogous manipulations

at earlier developmental timepoints show similar – and often greater – impacts on myelin thickness[40,41,46–50], suggesting the radial growth of newly-generated sheaths is sensitive to these factors. Furthermore, in several studies, changes to myelin thickness were abated with manipulations that influence new oligodendrocyte formation[39,41,42,47]. In contrast, enhancing radial growth of only new myelin formed after two months of age was not sufficient to alter overall myelin thickness measurements[51]. Tracking myelin thickness in bone fide mature sheaths will resolve whether mature myelin thickness is in fact sensitive to neuronal activity or behavioral experience. Similarly, ongoing myelin thickening over the lifespan could be accounted for by adult-born oligodendrocytes forming thicker myelin than those born during development. However, the initial myelin formed by adult-born oligodendrocytes is actually thinner than that formed by developmentally-born oligodendrocytes[1] or than surrounding mature myelin[52], strongly supporting the concept of ongoing radial growth of mature sheaths.

Which pathways regulate myelin thickness in mature sheaths? Similar to myelin formation, the MAPK-ERK and PI3K-Akt-mTOR pathways are essential for ongoing thickening of mature sheaths. Genetic removal of pathway components from pre-existing oligodendrocytes in young adult mice resulted in thinner myelin six-twelve months later[23,53], while pathway hyperactivation in pre-existing oligodendrocytes increased myelin thickness as early as three weeks later[12,51,54,55]. Upstream of ERK1/2, signaling through oligodendrocyte FGFR2 appears to drive this ongoing myelin thickening[36,56]. These pathways promote expression of oligodendrocyte transcription factors, myelin proteins, and lipid synthesis enzymes[51], and increase the presence of cytoplasmic channels[12] and the size of the inner tongue[54], indicating a role in myelin growth rather than removal. Recently, signaling between microglia and oligodendrocytes via TGFβ/TGFβR1 was implicated in mediating myelin thickness in early adulthood in mice[34]. Blocking this pathway resulted in thicker myelin and an enlarged inner tongue[34], indicative of elevated myelin growth[12], suggesting that microglial TGFβ normally suppresses radial myelin growth.

Is myelin removal also subject to exogenous regulation to affect myelin thickness? A recent study in mice found that reducing oligodendrocyte glucose uptake induced myelin thinning (Fig. 2) and elevated oligodendrocyte autophagosome formation[57], suggesting that autophagy-dependent removal of myelin membranes can be modulated. Whether changing rates of autophagy underlie dynamics of myelin thickness under more physiological conditions is an interesting future question.

Periaxonal Space Width

The approximately 12 nm space between the myelin inner tongue and the axon membrane, known as the periaxonal space (Box 2; Fig. 1a), serves as a longitudinal conducting pathway during saltatory conduction[58] and may facilitate depolarization-dependent signaling between myelin and the internodal axon[58,59]. Recently, changes to the width of the periaxonal space in young adult mice have been observed[60]. Low intensity repetitive transcranial magnetic stimulation induced periaxonal space widening in corpus callosum, while spatial learning induced periaxonal space shrinking in hippocampal fimbria[60] (Fig. 2). Changes in width averaged a few nanometers and were predicted to impact conduction velocity

by five percent or more[60], though individual internodes may undergo larger modulation. Importantly, whether these findings represent remodeling of mature sheaths or alterations in wrapping by newly-generated oligodendrocytes is still unknown.

Relatively little is known about the mechanisms that determine or modulate periaxonal space width. Myelin-associated glycoprotein (MAG), an oligodendrocyte transmembrane protein that spans the periaxonal space, is implicated in ensuring normal periaxonal space width[61,62], although not all studies agree[63]. Structural analyses of MAG led to the intriguing hypothesis that periaxonal space width could be determined by MAG's conformation and binding partners[64]. Another possibility is that maintaining ion and fluid homeostasis alters periaxonal space width. Potassium channels, transporters, and connexins redistribute potassium released into the periaxonal space during neuronal firing[65–69]. Without some of these molecules, neuronal firing causes severe swelling of this compartment[66,69], provoking the compelling possibility that subtler changes to periaxonal space width could occur from neuronal firing under physiological conditions. With much more to uncover, we anticipate an exciting future for this emerging topic.

Internode Length

Compared to radial myelin structures, the ability to visualize changes in internode length using fluorescent longitudinal *in vivo* imaging has accelerated our understanding of mature internode length dynamics over the lifetime and in response to exogenous manipulation (Fig. 2).

Following rapid extension to establish their positions, internodes in the embryonic zebrafish spinal cord continue to increase in length, while maintaining their relative positions, to compensate for ongoing axonal growth[70]. The inverse phenomenon occurs during xenopus metamorphosis: as optic nerve axons decrease in length, so too do myelin internodes[30]. After brain size is established, 15-20% of pre-existing cortical internodes in young adult mice exhibited changes in length over about a month[3,71–73]. Extension (increasing length) or retraction (decreasing length) both occurred, even in internodes made by the same oligodendrocyte[3], though their relative proportions differed between regions[3,71–73] and myelinated axonal subtype[72]. Changes in length were typically small (5-10 microns), but some internodes changed more than 20 microns[3,71,72]. Intriguingly, isolated internodes lacking neighboring internodes were responsible for the overwhelming majority of dynamics[3,73]. By inducibly fluorescently-labeling oligodendrocytes, these dynamics were confirmed in sheaths at least a month old[3].

As mice reach middle age, internode length dynamics precipitously decrease, with only 1% of pre-existing cortical internodes exhibiting changes over 50 days[74]. The vast majority were retractions averaging approximately 15 microns and, unlike in younger mice, dynamics were not biased to isolated internodes[74]. By old age, retractions are substantially elevated again: almost 20% of pre-existing cortical internodes underwent retraction over 60 days in two-year-old mice[32]. Many internodes at this timepoint also exhibited abnormal morphologies and sometimes were entirely removed, perhaps implicating these age-dependent retractions in a broader myelin pathology[32]. Bias towards retraction with aging may explain why

average internode length is shorter in older animals[75] and why fully myelinated tracts continue to have naked axonal regions for myelination by new oligodendrocytes[1].

Mature internode lengths are sensitive to behavioral experience. Forelimb reach training induced pre-existing internodes in young adult mouse motor cortex to retract approximately 25 microns over a few weeks[71,73]. The increased retractions were biased to internodes in more continuously myelinated regions and often of sequential internodes along the same axon[73], suggesting the involvement of specific neurons in this plasticity. Indeed, the axons experiencing internode retraction were those active during motor learning[73]. Axon-specific changes to internode length were also observed with monocular deprivation in young adult mice: sequential periods of elevated extension and retraction occurred in internodes on layer 2/3 visual cortical parvalbumin interneurons but not on cortical projection neurons[72]. This axon-specificity of internode length remodeling raises the intriguing possibility of axonal bias in remodeling of other myelin features.

Injury can also induce internode length remodeling. In developing zebrafish spinal cord, internodes can reinitiate rapid lengthening in response to ablation of an adjacent internode[70]. In most cases, lengthening internodes were “pushed back” by new sheaths forming in the vacated space, but in a few cases, new sheaths did not form, and the neighboring internodes extended to fully close the gap[70]. By contrast, in young adult mouse cortex, internode loss did not induce remodeling of adjacent uninjured internodes[76]. Nevertheless, injured oligodendrocytes themselves can alter the length of their pre-existing internodes. Internodes surviving inflammatory injury in young adult mouse cortex retracted, shrinking approximately 30 microns[76]. A subset then reinitiated extension, growing to partially restore their lost length, though some extended into new regions[76]. Similarly, in *ex vivo* rodent spinal cord, excessive neuronal activity or excitotoxic glutamate induced a subtle, reversible retraction of internodes[77,78]. Whether internode length remodeling can be targeted to prevent or repair damage in injury and disease is an important topic for future investigations.

Which mechanisms regulate remodeling of mature internode length? In developing sheaths, internode length is influenced by myelin-axon adhesion molecules[79–81], mTOR signaling[82], microtubule nucleation[83], ion channels[84], neuronal activity and vesicular release[85–91], and calcium signaling[89,92,93]. Might these mechanisms be involved in remodeling mature internode lengths? While observable sheath calcium transients precipitously decrease as internodes mature[94], the specificity of internode remodeling to activated axons following motor learning raises the intriguing possibility that activity-dependent calcium signaling could reinitiate in sheaths along specific axons to direct their remodeling. Consistent with this possibility, blocking calcium signaling prevented internode retraction following high frequency stimulation and glutamate application in *ex vivo* rodent spinal cord[77,78]. Exploring whether this mechanism applies in more physiological conditions and with cell-type specific manipulations will be of great interest.

How myelin-axon adhesion complexes and myelin membranes are modified to facilitate internode length remodeling remains unclear. Paranodal loops, normally adhered in place to the axon, would need to reinitiate movement along the axon as during sheath formation. Furthermore, myelin membranes would need to adjust, by either (1) rapidly adding or

removing membrane (see Membranes) or (2) redistributing membrane into outfoldings or more or fewer wraps. In metamorphosizing xenopus optic nerve, retracting internodes remain compact but undergo dramatic outfolding and detachment from axons, which is resolved by astrocyte phagocytosis[30]. Dynamic internodes in adult mouse brain are also thought to remain compact[3] but sheath dysmorphia is difficult to assess using fluorescence microscopy. Future correlated ultrastructural analyses will provide invaluable insights into the changes in myelin-axon adhesion and membrane remodeling that facilitate adjustments in internode length.

Internode Formation and Loss

Following the highly dynamic period of nascent sheath formation and removal by newly-generated oligodendrocytes[95–97], mature oligodendrocytes appear to maintain these internodes across the lifespan[3]. So far, the formation or loss of an internode by mature oligodendrocytes has not been observed under baseline conditions but can occur in injury, aging, and in response to behavioral experience (Fig. 2).

Oligodendrocytes that survive a demyelinating injury involving pathological internode removal have been observed via longitudinal *in vivo* imaging to generate new internodes[71,76,98]. Only a few new internodes were formed per oligodendrocyte[71,76,98] but this prevalence increased with forelimb reach training[71]. Some internodes grew from pre-existing processes, while others utilized de novo process growth from the oligodendrocyte soma[98]. Similar to internodes from newly-generated oligodendrocytes, these internodes extended over a few days and established typical internode lengths[98], but other ultrastructural parameters are yet to be determined. In mouse cortex, new internodes from surviving oligodendrocytes were primarily observed in the same positions as lost internodes[71,76], while in developing zebrafish spinal cord, surviving oligodendrocytes frequently mistargeted their new internodes to wrap neuronal cell bodies[98]. Other approaches in larger mammals, including humans, have found results consistent with new internode formation by surviving oligodendrocytes[99,100], a start to validating these findings with parallel techniques.

Can new internode formation and loss occur without injury? While motor learning did not induce new internode formation in mature oligodendrocytes in the intact mouse[71], visual deprivation was observed to induce both formation of new internodes and loss of pre-existing internodes from mature oligodendrocytes in young adult mouse visual cortex[72]. In aged mouse cortex, internode loss was common, with approximately 10% of pre-existing internodes being lost over two months[32]. Oligodendrocyte cell loss also occurred at this stage[3,32]; thus, future studies should determine whether internode loss during aging is restricted to these degenerating oligodendrocytes or is more widespread. In fact, whether internode loss from mature oligodendrocytes in any condition is a novel form of myelin plasticity or simply a pathological response to damage to or loss of axons or oligodendrocytes/myelin remains to be determined.

Which mechanisms regulate internode formation and loss in mature oligodendrocytes? One study in mice found that surviving oligodendrocytes with constitutive ERK1/2 activation had myelin within a demyelinating lesion following remyelination, perhaps indicative of

new internode formation in this region[51]. Possibly, signaling that governs nascent sheath formation and removal in newly-formed oligodendrocytes becomes reactivated to initiate these processes in mature oligodendrocytes. This may include molecular factors, such as endothelin receptor B-PKC epsilon[101], NRG1[96], ErbB receptors[48,96,102], Fyn[95], Rab5[97], laminin[103], beta1 integrin[104], Nogo A[105], and Ephrin A1-EphA4-RhoA-ROCK[98,106], and cellular mechanisms of sheath removal (see Membranes). Understanding these mechanisms may have important implications for preventing and repairing damage in aging and disease.

Node Length

The nodal/paranodal/juxtaparanodal region contains a unique array of anchoring and adhesion proteins and ion channels that facilitate myelin-axon adhesion and action potential regeneration (reviewed in Rasband and Peles, 2021[107]). Nodes highly resemble the axon initial segment, the site of action potential initiation, which is capable of adjusting its length and positioning in response to changes in neuronal activity[108,109], supporting the possibility that nodes are equipped with similar capabilities. Indeed, node lengths can undergo modulation in adults, including in response to changes in neuronal activity or experience (Fig 2).

Nodal dynamics often occur along with modulation of other myelin features. In continuously myelinated regions, internode retraction is intrinsically tied to the lengthening of nodes and can induce this micron-sized structure to expand dramatically[73,77,78]. Subtler changes in node length accompanied periaxonal space width remodeling, but whether these structures remodeled jointly or independently remains to be determined. Node length decreased and periaxonal space width increased in corpus callosum following low intensity repetitive transcranial magnetic stimulation while node length increased and periaxonal space width decreased in hippocampal fimbria following spatial learning in young adult mice[60]. Node length changes in both directions were small, averaging around 0.15 microns[60]. Crucially, by fluorescently pre-labeling mature oligodendrocytes or preventing the formation of new oligodendrocytes, these nodal changes were attributable to pre-existing rather than newly-formed nodes[60]. Node remodeling also accompanied changes in sheath thickness and paranode length, decreasing in length concomitantly with increases the other parameters following environmental enrichment[45] or constitutive activation of ERK1/2 in pre-existing oligodendrocytes[51] in adult mice. Myelin thickness and paranode length might be expected to grow in concordance, given that additional wraps form additional paranodal loops and myelin thickness and paranode length are positively, though loosely, correlated[38]. However, how myelin thickening would reduce node length and whether these effects occur independently is unknown.

Exploration of mechanisms underlying node length remodeling is just beginning. A recent study suggested a role for thrombin in detaching node-adjacent paranodal loops from the axon to increase node length in young adult mouse optic nerve[117]. However, such an effect of thrombin was only observable when astrocyte exocytosis (including of thrombin inhibitor nexin1) was blocked[110], suggesting additional mechanisms are likely at play. Paranodal loops need not even detach to modify node length: instead, individual paranodal loops could alter their lengths or translocate along the axon. Another outstanding question is how axonal

protein complexes reorganize following nodal remodeling given myelin's role in assembling the nodal/paranodal/juxtaparanodal region (reviewed in Rasband and Peles, 2021[107]), the redistribution of axonal components following demyelination[111–113], and the "pushing" of axonal nodal components by dynamic internodes during myelin formation[114]. Lengthened nodes following motor learning sometimes lacked sodium channels entirely while others had redistributed sodium channels along their enlarged length[73]. After node lengthening from high frequency stimulation or glutamate application, normally juxtaparanodal potassium channels encroached into the paranodal and nodal regions[77,78], suggesting breakdown of the axonal paranodal cytoskeletal "barrier" that typically prevents reorganization. How other components adjust to node length remodeling, whether components adjust in response to submicron-level length remodeling, and the temporal dynamics of component reorganization will be fruitful grounds for further investigation and may provide insights into the functional implications of these structural modifications. Finally, given the various ion channel subtypes present across the lifespan and in disease, an intriguing possibility is that nodes may dynamically adjust their ion channel composition independent of changes in length[107].

Overall, these data provide compelling evidence that mature oligodendrocytes and myelin undergo a diversity of structural modifications throughout life and in response to external stimuli (Fig. 2). Which mechanisms underlie myelin remodeling is the subject of ongoing investigation, but asymmetries in myelin turnover and reactivation of pathways involved in myelin formation are likely major players. In future work, it will be important to determine how remodeling is managed at the level of the oligodendrocyte, whether remodeling of sheaths impacts others from the same cell, and if not, how oligodendrocytes target remodeling to subsets of sheaths.

Function of Myelin Remodeling

Neuroplasticity is considered to form the basis of neural adaptation, allowing the brain to alter (learning), maintain (homeostasis), or restore (recovery from injury) its function in response to changing circumstances. Traditionally considered to involve changes to neuronal connectivity, neural adaptation is increasingly understood to also depend on non-neuronal cells, including oligodendrocytes.

Myelin remodeling could influence neuronal adaptation through modulating action potential conduction (Fig. 3a,b). Myelin dramatically increases action potential propagation speed, but the specific structural parameters of myelin determine its precise impact. Myelin thickness positively correlates with conduction velocity[46,58,102,115,116], with the greatest marginal impact from the first few wraps[58,115], while periaxonal space width is negatively correlated[58,60,115]. The relationship between node length and conduction speed is concave when nodal ion channel density remains stable, whereas when ion channel number remains stable, node length and conduction speed are negatively correlated[117]. In both cases, lengthening nodes are predicted to slow conduction and even cause conduction failure[73,117]. For internode length, in fully myelinated regions, there exists an optimal length for conduction velocity[85,117,118]. However, myelination along axons is not always continuous: large unmyelinated regions exist intermittently in regions like cerebral cortex in adult mice[3,119]. In such regions, myelin coverage, which may be modulated

bidirectionally through internode extension, formation, retraction, or removal, positively correlates with conduction velocity[73,120], with the largest marginal effect through creating or eliminating continuous stretches of myelin[73]. Experimentally-observed myelin remodeling was predicted to change conduction velocity by 20% or more, including causing the outright failure of conduction[60,73]. Intriguingly, this modulation was bidirectional[60,73], suggesting myelin remodeling may serve to fine tune – rather than merely enhance – conduction velocity.

Altering conduction shifts the postsynaptic arrival time of action potentials (Fig. 3a,b). This, in turn, impacts spike timing-dependent plasticity and neuronal synchrony. Previous work has implicated oligodendrocytes and myelin, though not specifically their remodeling, in establishing neuronal synchrony, while direct evidence of an impact on spike timing-dependent plasticity is still outstanding. Using dysmyelinated rodent models, researchers showed that normal myelin is required for establishing a uniform conduction time between regions[116,121,122]. In the cerebellar cortex, this myelin-induced spike timing uniformity was essential for establishing synchronous spontaneous firing of Purkinje cells[121]. Several studies have also established a role for adaptive myelination in promoting synchrony. Following contextual fear conditioning in mice, the coupling of sharp wave ripple and spindle oscillations between hippocampal regions, thought to contribute to memory consolidation, was prevented by a gene deletion in oligodendrocyte precursor cells that disrupted experience-dependent oligodendrogenesis[123]. Likewise, during epilepsy development in rodents, seizure-induced myelination contributed to inter-regional synchrony and epilepsy progression[41]. Computational modeling also supports a role for myelin in promoting synchrony. Modulating myelin in an activity-dependent manner caused network synchronization and increased firing rates[124]. Another computational model specifically modulated pre-existing myelin coverage in response to oligodendrocyte integration of conduction timing along an axon bundle and found that this synchronized correlated spikes[125]. Importantly, myelin-induced synchrony is implicated in enhancing motor and spatial learning[122,123]. These data evoke the exciting possibility that remodeling of *mature* myelin could serve a similar role of fine-tuning conduction to facilitate neuronal synchrony and enable learning. Consistent with this idea, learning success was highly correlated with the extent of internode retraction and consequent node lengthening during learning[73], though future studies should determine the causality of this relationship.

Modulating conduction via myelin remodeling could serve additional roles. Structural plasticity of axon initial segments, which highly resemble nodes, tempers neuronal excitability following sustained changes in neuronal activity[108,109]. Perhaps nodal plasticity serves a similar purpose. Modeling suggests node lengthening could cause conduction delay and failure[73], potentially providing a means to counteract sustained changes in neuronal activity from learning- or injury-induced plasticity. Additionally, myelin remodeling may restore conduction following injury. Internode formation and extension following demyelination likely aides in recovering conduction in demyelinated axons by restoring myelin coverage – a role primarily achieved by newly-formed oligodendrocytes[126]. Future work correlating longitudinal *in vivo* measurements of conduction velocity and myelin remodeling will aid in determining the links between these parameters in individual axons and across neural circuits.

Along with myelin remodeling, axons undergo structural plasticity in response to neuronal activity and learning. Elaboration of axonal branches occurred in mouse cortical parvalbumin interneurons following chemogenetic activation[127] and in primate visual cortex following perceptual learning[128]. Furthermore, learning altered the formation and elimination of cortical en passant (efferent) boutons[129,130] while chemogenetic activation induced a greater number of inhibitory axo-axonic (afferent) boutons on activated cortical pyramidal neurons[131]. Intriguingly, myelin may also shape such axonal architecture. Myelinated segments of cortical pyramidal neurons or interneurons lack axonal branch points[132–134], en passant synapses[119,132], and axo-axonic synapses[119] while mice with deficient myelin exhibited encroachment of en passant boutons into normally myelinated regions of parvalbumin interneurons[132]. Furthermore, myelin components are implicated in inhibiting axonal sprouting[135] and limiting neuronal plasticity[136]. Might myelin remodeling affect neural adaptation through covering or exposing axonal regions to influence axonal remodeling (Fig. 3c)? Future work examining myelin and axonal remodeling in concert will shed light on this exciting possibility.

Myelin remodeling could alter the energetic support of neurons (Fig. 3d). Oligodendrocytes support neuronal health, firing, and perhaps information processing by providing metabolites[116,137–139], proposed to be shuttled from internodes to their underlying axons[140]. This metabolic support is thought to be especially important in continuously myelinated axons given that myelin isolates axons from extracellular metabolites[141]. Thus, remodeling myelin coverage may alter the local supply of metabolites from myelin and extracellular sources to modify axonal energetics. Another study found that oligodendrocytes sustain neuronal firing in glucose-deprived mouse optic nerves through beta-oxidation of fatty acids[57]. This was proposed to be through increased autophagy and catabolism of myelin lipids, as reducing glucose uptake by oligodendrocytes increased autophagosome formation and thinned myelin[57]. Though, whether this process involves the increased removal of lipids from compact myelin or the diversion of lipids that would be used for myelin synthesis is uncertain. In either case, by tweaking the balance of myelin turnover to either favor formation or removal, energy could be stored as lipids when resources are abundant and utilized in periods of deprivation, enabling stable neural function across conditions. Perhaps myelin thickening over the lifetime serves to accumulate fatty acids while internode retraction in aging enables the use of these fatty acids for energy. Leveraging emerging technologies for *in vivo* measurement of local metabolites will facilitate further dissection of whether myelin remodeling influences neuronal energetics and the spatial dimensions of these effects.

Another outstanding question is the scale and distribution of myelin remodeling required to impact behavior. Only limited subsets of neurons (<20%) are involved in given task-specific memories (reviewed in Rao-Ruiz et al., 2019[142]) and single cortical “hub” interneurons can influence population activity and synchrony[143]. By focusing myelin remodeling to these axonal populations[72,73], behavioral impacts could be realized with relatively little remodeling (Fig. 3e). As mechanisms regulating myelin remodeling are discovered, manipulation of specific structural changes to myelin will help to elucidate the local impact of remodeling on individual axons. Furthermore, manipulation of remodeling in specific axonal subtypes or circuits will clarify the role of remodeling in broader neural function and

behavior. Population-wide assessments of neuronal responses to myelin remodeling will be an important tool in this endeavor (reviewed in Shenoy and Kao, 2021[144]). We anticipate these studies will provide critical insights into how the CNS adapts across the lifespan and in response to a changing environment.

Conclusion

Research has established the dynamic nature of mature oligodendrocytes and myelin, but there is much more to uncover. The field is just beginning to define the scope of myelin dynamics, and will be greatly propelled by technological progress to enable *in vivo* longitudinal monitoring of more features like myelin thickness or myelin lipids and proteins. These investigations will likely find additional parameters subject to dynamic modulation, such as lipid composition or the composition and distribution of nodal ion channels. But even for established myelin dynamics, many outstanding questions remain. The mechanisms regulating myelin remodeling are almost entirely unknown, though they likely involve the machinery of myelin formation or turnover. Defining these mechanisms will be critical to enable manipulation of remodeling and exploration of its function. Given the scale and specificity of myelin remodeling, this form of plasticity could have profound impacts on neural function, serving as an integral component of behavioral adaptation. We anticipate an exciting future for this nascent field that has continued to redefine the nature and function of myelin.

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Box 1:

Dynamics of Myelin Formation

Myelin internode formation in new oligodendrocytes in zebrafish begins with a highly dynamic period of simultaneous nascent sheath initiation and removal, resulting in the net accumulation of nascent sheaths over several hours[95–97]. Over the next few days, most nascent sheaths are stabilized while some are removed, after which total sheath number is maintained[95–97]. During this period, membranes (lipids and proteins) are trafficked from the secretory pathway to the innermost layer of myelin, the inner tongue, where they incorporate into the growing sheath while other myelin proteins can be translated locally[12,145]. Driven by actin disassembly[146,147], the number of myelin wraps increases in proportion to axonal diameter[148]. Myelin wraps begin to grow laterally, starting with the outermost (earliest) wrap[12], which establishes the internode's position along the axon[70]. Lateral extension continues from the outside-in until the inner tongue abuts against the spiraling row of lateral edges of the other myelin layers, known as the paranodal loops, which adhere to the axon[12] (Fig. 1a). As paranodal adhesion matures, the assembly of the nodal region proceeds, including clustering of voltage-gated ion channels (reviewed in Rasband and Peles, 2021[107]). From the outside-in, the layers of myelin membrane compact, bringing the inner and outer leaflets of consecutive lipid bilayers in extremely close apposition and extruding cytoplasm and extracellular fluid[12]. Membrane compaction and paranodal myelin-axon sealing facilitate an electrical insulation of the axon but prevent intracellular trafficking throughout the internode. To facilitate delivery of myelin components during internode formation, some regions remain uncompacted: the inner and outer tongues and paranodal loops form a contiguous cytoplasmic perimeter around the myelin membrane, while cytoplasmic channels penetrate the center[12]. As myelin formation completes, the inner and outer tongues reduce in size and most cytoplasmic channels disappear[12], presumably reducing – but not eliminating[149] – trafficking from the soma through the internode. Concomitantly, oligodendrocytes assume a distinct, mature gene expression profile[150]. However, mature oligodendrocytes and myelin remain dynamic, with ongoing turnover and remodeling that resemble dynamics present during initial myelin formation and likely involve shared cellular and molecular mechanisms.

Box 2:

Radial Myelin Measurements

Electron microscopy is the gold standard for radial measurements of myelin compartments. Myelin thickness is often measured as a g ratio, calculated as axon diameter / (axon + myelin diameter), to account for the positive correlation between myelin thickness and axon diameter[148]. In contrast to peripheral myelinated axons, this ratio is not constant across axon diameter in the CNS – myelin is proportionally thicker in thinner axons[148]. Therefore, g ratios of CNS axons are frequently evaluated within binned ranges of axon diameter. Changes in g ratio are typically considered to reflect changes in the number of myelin wraps. However, these measurements usually include the uncompacted inner tongue and the periaxonal space between the inner tongue and the axon. Changes to these compartments or in the level of myelin compaction could also alter myelin thickness measurements and should be properly considered.

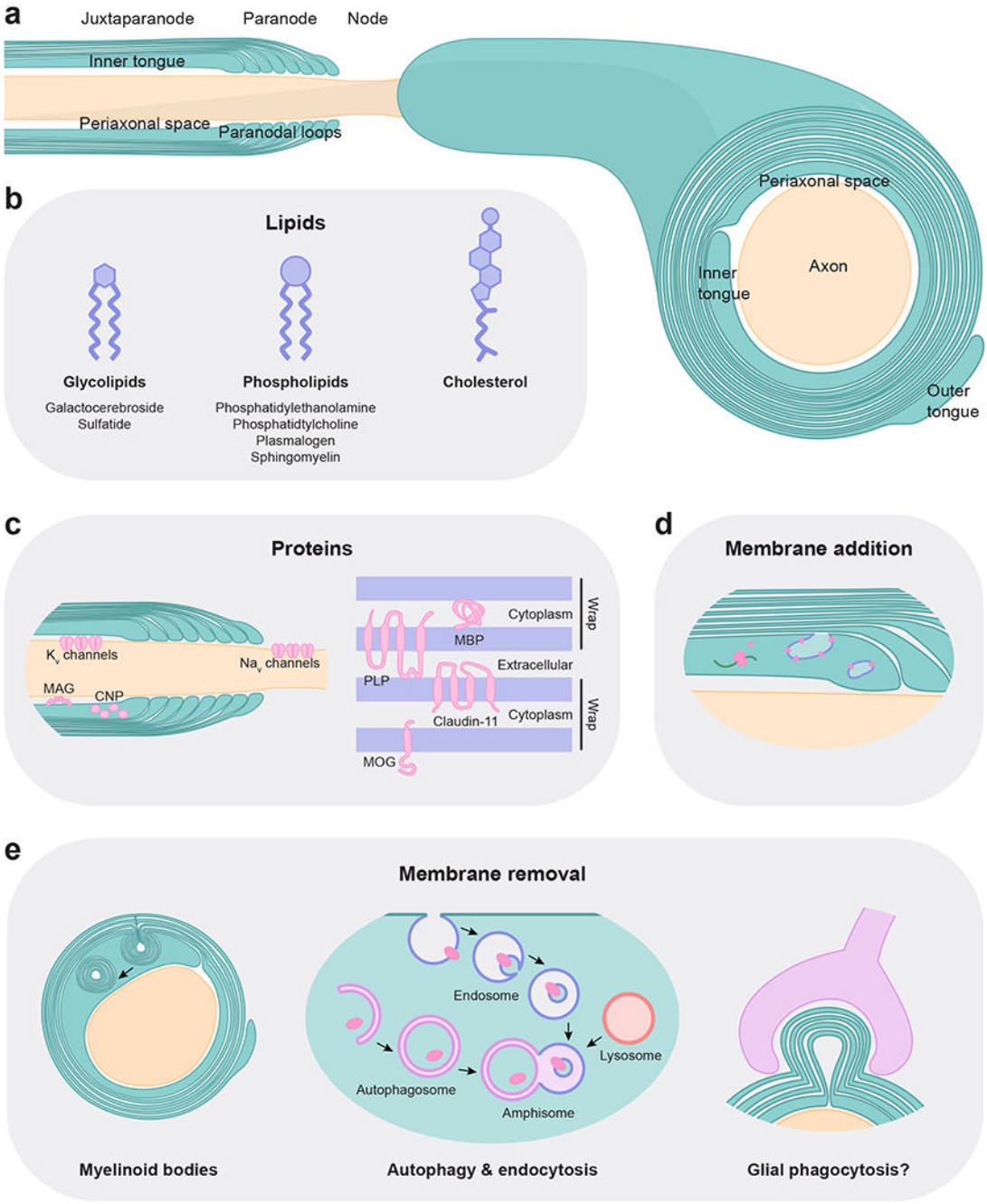

Fig. 1 |. Myelin components and turnover.

a, Schematic of myelin, a highly organized structure with well-defined compartments. **b**, Myelin membranes have aunique constitution of lipidsthatare turned over at different rates. **c**, Myelin proteins localized to compact membranes (right) are turned over more slowly than proteins in non-compact myelin or at the myelin-axon junction (left; e.g. CNP and MAG, respectively). **d**, Lipids and proteins are added to mature myelin at the inner tongue and paranodal loops from trafficked vesicles and local translation. **e**, Membranes are removed from mature myelin via myelinoid bodies and concerted autophagy and endocytosis.

Microglia and astrocytes, which phagocytose myelin in other contexts, could be involved in turnover of mature myelin. How the residual myelin sheath remains structurally organized and intact after multiple layers of myelin are removed is not fully understood.

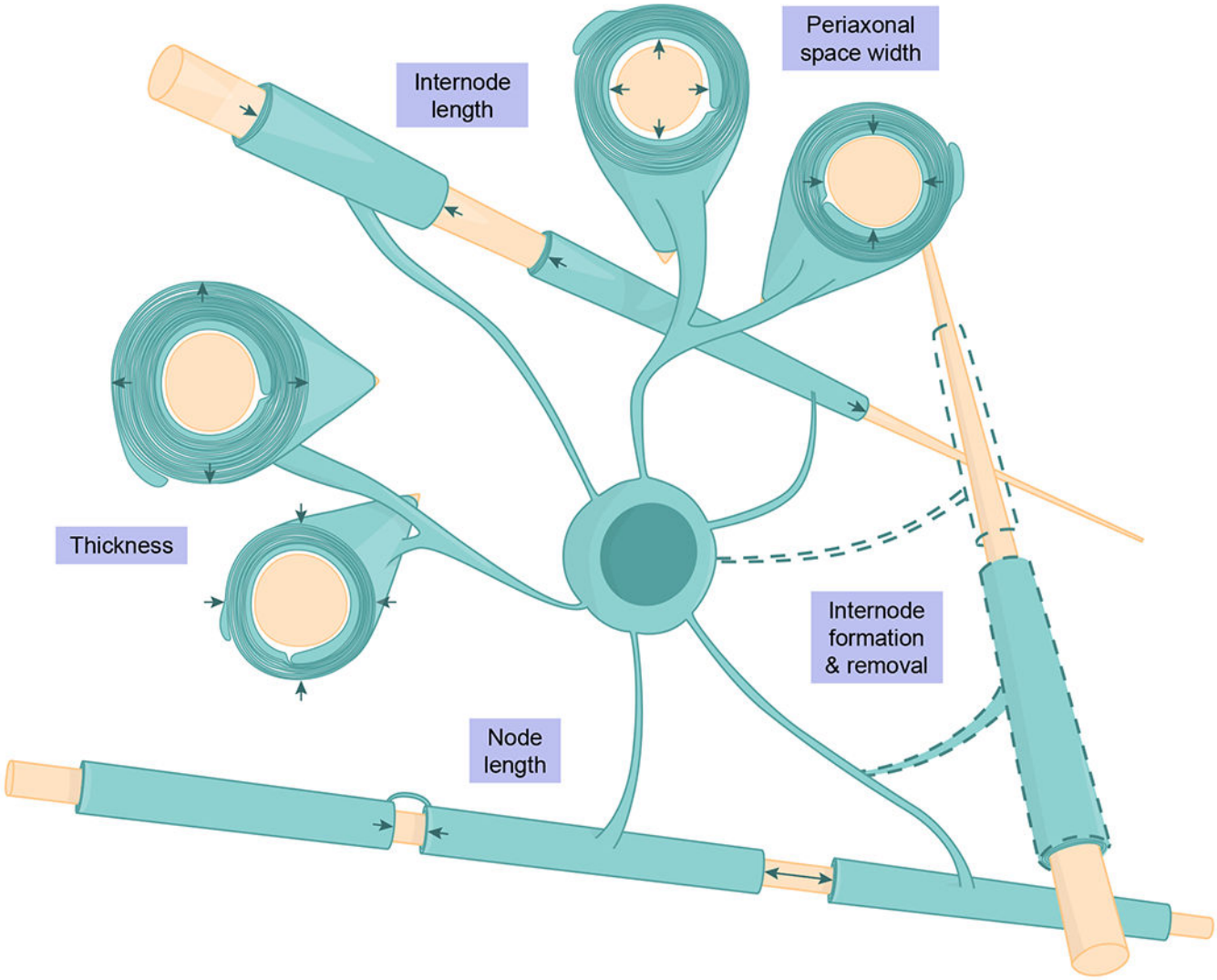

Fig. 2 |. Myelin remodeling.

Numerous structural parameters of mature oligodendrocytes and myelin undergo remodeling over time or in response to neuronal activity, behavioral experience, injury, or genetic manipulation. The dynamics of each parameter are shown in isolation for clarity; however, remodeling of one parameter may impact another (e.g., internode and node length) and an individual sheath may undergo multiple structural changes.

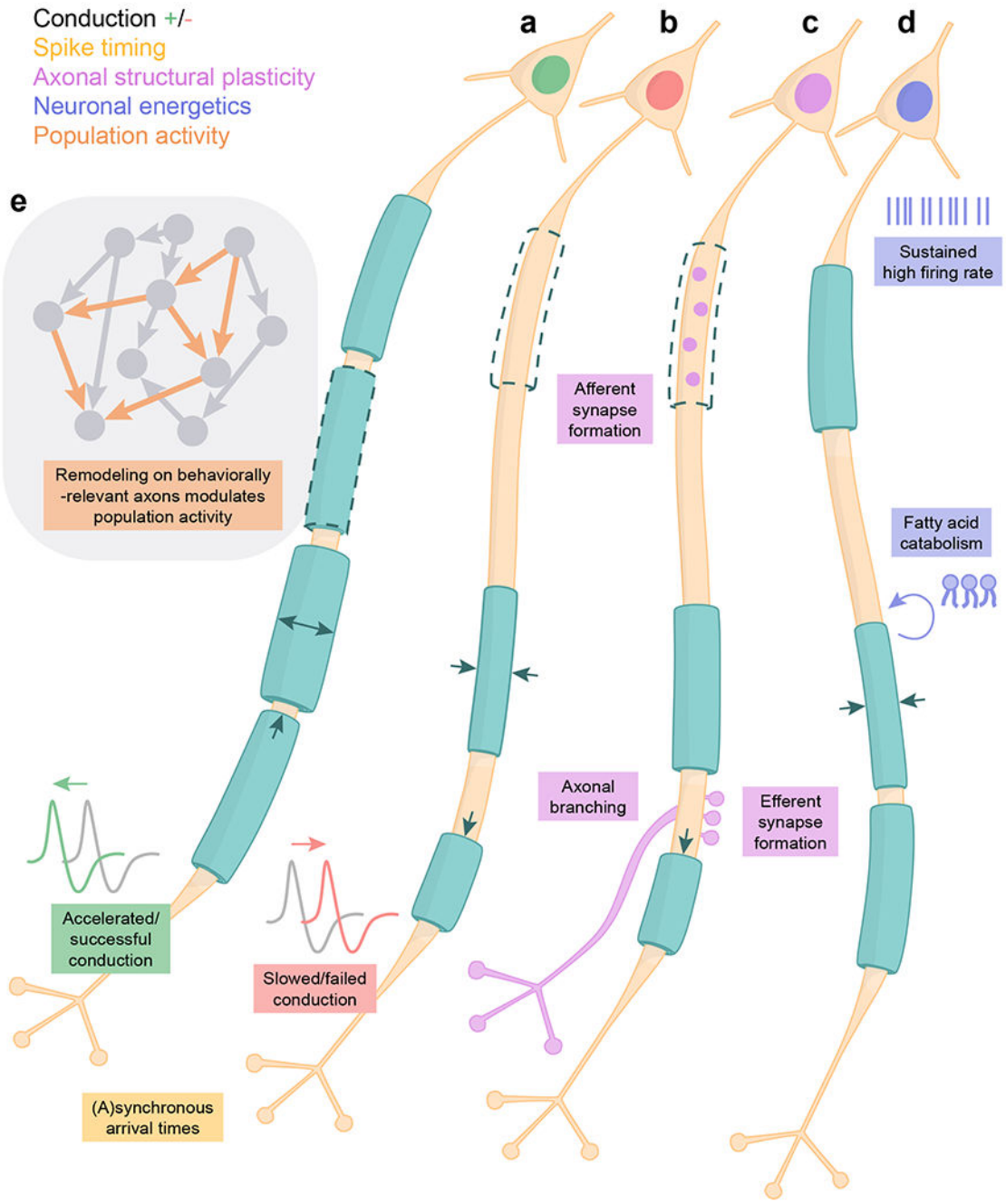

Fig. 3 |. Potential functions of myelin remodeling.

a-d, Potential functional implications of myelin remodeling. **a**, Anaxon experiences internode formation, myelin thickening, and internode extension, causing accelerated or successful action potential conduction. **b**, An axon experiences internode removal, myelin thinning, and internode retraction, causing slowed or failed action potential conduction. Changes in conduction in **a** and **b** alter the synchrony of action potential arrival times. **c**, An axon experiences internode removal and retraction, enabling axonal remodeling. **d**, An axon experiences myelin thinning. Myelin lipidsare used for energy to support neuronal firing. **e**,

Myelin remodeling occurs on axons involved in a specific behavior to modulate neuronal population activity.