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Myelin plasticity in adulthood and aging

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Abstract

The central nervous system maintains the potential for molecular and cellular plasticity throughout life. This flexibility underlies fundamental features of neural circuitry including the brain's ability to sense, store, and properly adapt to everchanging external stimuli on time scales from seconds to years. Evidence for most forms of plasticity are centered around changes in neuronal structure and synaptic strength, however recent data suggests that myelinating oligodendrocytes exhibit certain forms of plasticity in the adult. This plasticity ranges from the generation of entirely new myelinating cells to more subtle changes in myelin sheath length, thickness, and distribution along axons. The extent to which these changes dynamically modify axonal function and neural circuitry and whether they are directly related to mechanisms of learning and memory remains an open question. Here we describe different forms of myelin plasticity, highlight some recent evidence for changes in myelination throughout life, and discuss how defects in these forms of plasticity could be associated with cognitive decline in aging.

Introduction

A principal regulator of axonal conduction in the central nervous system is myelination, a multi-layered extension of compacted cell membrane formed by glial cells called oligodendrocytes. The tight wrapping of oligodendrocyte cell membrane around neuronal axons forms a structure that decreases axonal membrane capacitance and allows for saltatory conduction of action potentials. Myelin sheath generation, stability, length and thickness are all tightly regulated through molecular and biophysical cues arising from the axon and the local microenvironment [1-3]. Changes to any of these elements has the potential to modulate conduction velocity, an often overlooked but critical feature that can be used to precisely modify the timing and synchrony of signal arrival at distinct postsynaptic targets [4-6]. Differential conduction velocity accounts for a range of emergent neural circuit functions including, coincidence detection for sound localization in the auditory brainstem [7,8], electric organ discharge in electric fish [9], olivocerebellar processing in the cerebellum [10], thalamocortical processing in the somatosensory cortex [11], and timing of retinal ganglion cell inputs to the brain [12]. These examples likely reflect a widespread feature exploited by neural circuits to accomplish particular tasks by tuning conduction

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velocity to match circuit demands. Importantly, even with these examples, evidence for functional plasticity at the level of conduction velocity and how these types of signals are disrupted in disease is largely lacking. Understanding how fixed or flexible these structures are is critical to fully appreciate the mechanisms of neural network plasticity.

Oligodendrocytes are generated from a population of resident progenitor cells called NG2 glia (also commonly referred to as oligodendrocyte progenitor cells or OPCs) [13-15]. NG2 glia are resident in the adult brain and maintain the capacity to differentiate into mature myelinating oligodendrocytes. Oligodendrocyte differentiation is tightly regulated in different brain regions and at different developmental stages via a number of mechanisms, including differences in local axonal subtypes, neuronal activity, and phenotypic differences between local NG2 glia populations [2,16,17]. It is likely that these factors directly contribute to differences in the plasticity of myelin between gray and white matter regions.

Here we discuss and define the different types of plasticity exhibited by myelinating oligodendrocytes (summarized in Figure 1). We outline what is currently known and yet to be discovered about these different forms of plasticity and we discuss how defects in myelination and mechanisms of plasticity could be involved in age-related cognitive decline.

Oligodendrocyte generation

The predominant form of myelin plasticity stems from the ability of oligodendrocytes to continuously be generated via terminal differentiation of NG2 glia (Figure 1). Because of this, oligodendrocyte production and subsequent formation of new myelin internodes is not limited to a specific developmental window, potentially allowing for the myelination of previously unmyelinated or partially myelinated axons. Pulse chase fate-mapping experiments using thymidine analogue labeling of dividing cells and transgenic labeling of NG2 glia using the cre/lox technique have provided the most direct evidence for the continued differentiation of oligodendrocytes in vivo [18-23]. Overall, these studies have found that in the postnatal brain NG2 glia differentiate exclusively into myelinating oligodendrocytes and patterns of differentiation vary between different white matter tracts (i.e. optic nerve and corpus callosum) and between white and gray matter regions. Differentiation sustains throughout development but declines somewhat in adulthood. It is thought that the differences between brain region and across various ages are due to differences in ion channel expression, epigenetic signatures, resident glial phenotypes and axonal populations, and sensitivity to various growth factors [24-28].

A major question remaining from these studies is whether the generation of new cells is for the replacement of dying oligodendrocytes or results in long-term accumulation of new myelination in the adult. One way to test this is to analyze the generation of oligodendrocytes in the adult optic nerve, a white matter tract that is almost completely myelinated during development [29]. Tracking the fate of NG2 glia in adult mice revealed that approximately 6% of all oligodendrocytes were generated between 4 and 5.5 months [21] despite evidence that 99% of all axons would already be myelinated at 4 months [29]. Is this indicative of replacement of dying oligodendrocytes or de-novo myelination of the small population of unmyelinated axons? A subsequent study analyzed the long-term stability of

oligodendrocytes generated in the optic nerve starting at 2 months and found a significant loss of oligodendrocytes over the next 4 months [30]. Taken together these studies provide evidence for oligodendrocyte replacement in the adult in a region that is almost completely myelinated. Interestingly the oligodendrocytes generated after 4 months of age produced more myelin sheaths that were shorter on average compared to those generated at 2 months [21]. Similar differences in internode length have been found in aging [31] as discussed below. Thus, in order to remyelinate or replace the myelin originally made by the dying cell, multiple internodes (from multiple oligodendrocytes?) may be required. As internode length and distribution are critically important for conduction velocity these changes could theoretically result in altered axonal conduction after remyelination has occurred.

In contrast to the optic nerve, fate mapping analyses of oligodendrocyte generation and death in the corpus callosum and cortex, regions which are incompletely myelinated, have shown continued production of new oligodendrocytes at least extending to 1 year of age [32] coincident with the long-term stability of the cells generated in early adulthood [18,20,23,30]. Consistent with this, recent work in human tissue has demonstrated continued generation of new oligodendrocyte in the cerebral cortex [33]. These data suggest that oligodendrocyte generation persists and potentially results in myelination of previously unmyelinated axons. Intravital time-lapse imaging of oligodendrocytes, myelin, and axons in the adult mouse cortex has now directly shown the long-term stability of mature oligodendrocytes in addition to the continued generation of new oligodendrocytes and myelin on previously unmyelinated axons [34,35]. These live imaging experiments did not reveal any evidence for oligodendrocyte or internode replacement, however they were limited to the upper layers of the cerebral cortex and extended for shorter time periods compared to the transgenic fate mapping experiments conducted in fixed tissue. It has been suggested that mature oligodendrocytes can produce new myelinating internodes however direct evidence of this is currently lacking and might occur only in disease contexts [36,37].

Signals directly inducing the formation of new oligodendrocytes in the adult brain are not well defined however there is growing evidence to suggest that new cells are not produced stochastically but rather in a targeted manner based on environmental cues. Neuronal activity [38-43], social isolation [44,45], and sensory stimulation [46,35,19,47,48] have all been shown to influence NG2 glia proliferation and oligodendrogenesis. The precise molecular cues and signaling pathways involved in these changes are not clear and future studies will likely reveal how neuronal activity precisely modulates the differentiation of NG2 glia and formation of new myelinating oligodendrocytes and what consequence the formation of new myelin has on the neural circuitry.

Myelin distribution

Different locations of the CNS display differing degrees of myelination, depending on the timing and extent of oligodendrocyte generation. Axons in some white matter regions, such as the optic nerve, are rapidly and almost completely myelinated early in development while axons in other regions, like the cerebral cortex, display a greater degree of coverage heterogeneity with myelination proceeding into adulthood [29,49,50]. Fully myelinated axons can be in close proximity to other partially or fully unmyelinated axons and these

differences can reflect distinct subtypes of both excitatory and inhibitory neurons. For example, significant diversity exists between pyramidal excitatory neurons within different cortical layers with upper layer neurons generally having patchier myelination compared to deeper layer neurons [50]. Moreover, distinct interneuron populations display variable myelination with fast-spiking parvalbumin expressing interneurons being the most heavily myelinated [51]. Recent data also suggests that single oligodendrocytes can exhibit preferential myelination of axons from either inhibitory or excitatory neurons [52]. This raises the possibility that there could be specific signals arising from subsets of neurons which signal to subpopulations of oligodendrocytes to initiate their myelination. The universality of these observations to multiple brain regions and in larger data sets must be determined. Furthermore, whether or not these data represent oligodendrocyte heterogeneity and how dynamic these myelin profiles are throughout life is yet to be resolved.

Intravital imaging of individual partially myelinated excitatory axons in layer I of the cortex has revealed that new internodes are continuously generated throughout development and into late adulthood, potentially signifying an ever-changing pattern of myelination across some axons [34,53]. Importantly, even at peak myelination in late adulthood some axons maintain their partial myelination patterns. This suggests that in some cases the action potential conduction down partially myelinated axons changes and in others it remains constant. It may also point to alternative functions of intermittent myelination, such as inhibiting axonal branch or synapse formation. Signals inducing these differential myelination patterns and how an oligodendrocyte decides to myelinate one portion of an axon and not another are unknown.

Axon diameter is one mechanism that is used to instruct myelination of some axons and not others. Experimentally increasing axon diameter via neuronal genetic deletion of *Pten* can induce myelination of axons that would not normally ever become myelinated [54]. In addition to increasing axon diameter, this manipulation also increased secretion of promyelinating factors such as brain derived neurotrophic factor. Thus, while there is clearly a diameter threshold and correlation between axonal diameter and propensity for myelination [55,56], direct evidence for diameter alone influencing myelin plasticity and distribution along axons is lacking. Likewise, there is no evidence that partially myelinated axons exhibit differential diameter at myelinated vs nonmyelinated regions.

Neuronal activity and local vesicular release from the axon could also potentially be used to construct a specific myelin distribution pattern. Consistent with this, chemogenetic modulation of activity in a subset of parvalbumin interneurons resulted in changes in myelin patterning specifically along the activated axons [57]. Importantly, however, these manipulations also resulted in changes in axonal arborization. Thus, at least in this study, it is not clear if the change in myelination was simply a secondary effect of greater axonal arborization that was permissive to myelination or specific activity-dependent signaling directly to oligodendrocytes initiating the formation of new myelin sheaths. This provides an important example showing that axonal structural plasticity must be considered when performing and interpreting experiments correlating changes in neuronal activity with myelin plasticity. While secondary changes in myelination would have an effect, a primary change in axonal structure is likely more significant for influencing neural circuitry.

Incomplete myelination along stretches of single axons could play several functional roles. One possibility is that it may permit overall circuit flexibility by balancing plasticity potential while utilizing the speed and efficiency benefits of myelination at distinct locations. A fully myelinated axon would have insufficient capacity for the generation of new axonal branches, synapses, and myelin internodes and thus a decreased ability to respond to environmental stimuli via structural modifications and remodeling. Another possibility is that the deposition of new myelin sheaths on previously unmyelinated axons offsets changes in axonal metabolic demands. Myelination has been shown to provide metabolic substrates to axons [58]. This support has been shown to be modulated, at least in part, by changes in neuronal activity and neurotransmitter release. Oligodendrocytes are able to sense glutamate and traffic GLUT-1 transporters to the plasma membrane, increasing intracellular glucose and lactate production which can then be shuttled to ensheathed axons (Figure 1) [59]. It is possible that over time the demands or intrinsic capability of the axon to generate its own substrates declines and deposition of new myelin can compensate and maintain proper axonal function.

Myelin thickness

Myelin's ability to reduce the membrane capacitance of an axon is directly related to its thickness. Increased thickness bolsters the ability of the internode to insulate the covered axon and facilitate conduction. Axon caliber has long been thought to directly dictate sheath thickness in order to optimize functionality across morphologically distinct axons [60]. However, evidence has suggested that thickness may not be static and thus is not wholly dictated by axon diameter. Many of the factors shown to increase NG2 glia proliferation and oligodendrocyte formation, such as changes in neuronal activity or social environment, also result in changes in myelin sheath thickness [39,40,45]. Because thickness measurements are generally obtained through electron microscopy, it is unclear whether these factors influence thickness of newly produced internodes, established internodes, or a combination of the two. Even so, all cases could result in modulation of axonal conduction and thus contribute to overall myelin plasticity.

One possible mechanism governing changes in myelin thickness is a change in neuronal activity. Optogenetic and chemogenetic induced neuronal hyperstimulation have both been shown to result in increased myelin thickness [39,40]. Chronic light stimulation of cortical layer V projection neurons expressing the excitatory opsin ChR2 elicited a significant increase in myelin thickness [39]. Likewise, chronic chemogenetic neuronal stimulation via the activating modified g-protein coupled receptor, hM3Dq, also resulted in an increase in myelin thickness, as seen by a decrease in average g-ratio [40]. This effect was observed in both 3-week-old and 10-week-old mice, despite being slightly less pronounced in the older cohort. Furthermore, hM3Dq activated axons were more likely to be myelinated as compared to control in both age groups. Importantly, for both studies it is not clear if preexisting myelin sheaths increased their thickness or if newly generated myelin from recently differentiated NG2 glia accounted for the thicker myelin sheaths. A separate study attempted to investigate this question by examining the effects of upregulated ERK1/2 signaling specifically in mature oligodendrocytes [61]. Conditionally expressing constitutively active MEK1 protein in Proteolipid Protein (PLP) positive cells significantly

increased myelin thickness in the corpus collosum and spinal cord, suggesting that mature oligodendrocytes may be able to regulate pre-existing sheath thickness. In contrast to increases in activity, decreases in neuronal activity in the optic nerve via monocular deprivation did not cause a decrease in myelin thickness [48], while social isolation did result in decreased myelin thickness in the prefrontal cortex [44,45]. Reasons for these discrepancies are not clear, other than the obvious differences in brain region and sensory manipulation. Also, it is not clear if the decrease in thickness in the social isolation experiments reflects a difference in newly formed vs preexisting myelin. Thus, direct physiological evidence for dynamic changes in myelin thickness in a compact myelin sheath is not yet available.

Myelin compaction

In addition to thickness, membrane compaction between individual layers and extrusion of the oligodendrocyte cytoplasm are also critically important for the function of myelin. Direct evidence for this comes from myelin basic protein deficient mice which have a defect in establishing compact myelin and develop a severe shivering phenotype [62]. In the peripheral nervous system, the myelin sheath maintains distinct cytoplasmic channels called Schmidt-Lanterman Incisures within an otherwise compact myelin sheath. These channels are thought to be important for transport of molecules throughout the myelin sheath and potentially also for transport and signaling between the Schwann cell and underlying axon. It was previously believed that such channels did not exist in CNS myelin, however recent studies using electron microscopy of high-pressure frozen tissue in order to maintain cytoarchitecture have provided evidence of these channels throughout the CNS [63-65] and confirm previous studies suggesting the presence of these channels via dye injections in the spinal cord [66]. The precise function of these channels is not clear but their maintenance is critical as transgenic mice with 2,’3’-cyclicnucleotide 3’-phosphodiesterase (CNP) deletions that fail to form and/or maintain these channels exhibit pronounced myelin pathology and axonal degeneration [65,67].

Whether or not the cytoplasmic channels in CNS myelin are sites of plasticity is not known, although there is some evidence for age-dependent changes in their density and prevalence [64,65]. It is likely that newly formed myelin contains more non-compacted regions as the sheath is lengthening but it is also possible that a mature myelin sheath could maintain these channels and utilize them for communication with the axon or sheath remodeling as described in the next section. Development of methodologies for dynamic visualization and manipulation of these noncompact cytoplasmic channels is necessary in order to directly address these questions.

Myelin internode length

New myelin sheath formation occurs during a defined period, lasting several hours, during which time pre-myelinating oligodendrocytes sample surrounding axons and begin sheath extension [41,43,68,69]. A proportion of oligodendrocyte cell processes which initiate extension subsequently mature into a stable myelin sheath while the rest retract shortly after formation and are lost. This suggests the existence of multiple checkpoints regulating myelin

production from initial axon selection through maturation and elongation. Physical characteristics of axons, such as axon diameter (as discussed above), have been implicated as larger diameter axons tend to be myelinated more quickly and to a greater extent than smaller axons. There is also some evidence to suggest that axon derived molecular cues, in the form of pro-/inhibitory cell surfaces markers and/or secreted molecules, may also play a role [70].

Activity-dependent vesicular release is one mode thought to be involved in the formation and stability of newly forming myelin segments [71]. Work in zebrafish has demonstrated that blocking vesicular release in spinal cord axons decreases the stability and length of newly forming myelin sheaths [41,43]. Interestingly, this appears to be important for some axonal populations and not others [72]. Subsequent work has identified calcium signaling as one important mechanism involved nascent sheath elongation. Two concurrent zebrafish studies, using the genetically encoded fluorescent calcium indicator GCaMP6, described high frequency calcium transients within newly formed sheaths promoted elongation, while long lasting, low frequency transients led to sheath retraction [73,74]. Regulation of such calcium fluctuations may be related to neuronal activity. Increasing activity via electrical stimulation was able to induce calcium fluctuations within oligodendrocytes and increased sheath extension by 60% while tetrodotoxin induced neuronal silencing decreased calcium fluctuations and sheath extension by 43% [74].

Once formed, some internodes retain the ability to extend or retract along the axon, changing the total length of the sheath. One study done in embryonic and larval zebrafish found that, while the majority of internode growth was completed within the 3 days of formation, sheaths were able to continue extending in a comparatively slow fashion after initial production. This slow growth was correlated with an increase in size of the developing fish, suggesting that internode extension could be compensating for increases in total axonal length [75]. Two separate studies, done in mice, have both described long-term evidence for myelin remodeling in layer I cortex via intravital fluorescence optical imaging [34,35]. By monitoring individual internodes over days to months a recent study revealed that some sheaths in mice between 2 and 3 months old exhibited length plasticity well after their initial formation While 81% of the sheaths monitored remained stable, 15% lengthened, extending outwards along unmyelinated sections of each axon and 4% retracted from an established position, decreasing their total length. Partially myelinated axons, where many internodes are not directly adjacent to each other, were more likely to exhibit this behavior, as 25% extended and 7% retracted [34]. Individual oligodendrocytes also displayed heterogeneous internode remodeling, with some extending, retracting or remaining stable, indicating that such plasticity is modulated locally, not across the whole cell. A parallel study characterized similar properties of myelin remodeling in 1-year old mice with differing results. In the aged animals, less than 1% of observed internodes underwent extension or retraction [35]. This difference in remodeling frequency described by the two studies may be explained by the age difference in the mice used. The cortex of a 2-month old mouse has a greater percentage of partially myelinated axons compared to 1-year old mouse [34] which likely has an effect on the dynamics of myelin plasticity. The precise mechanisms that govern these changes are unclear, however it seems likely that they would have a direct impact on axon membrane capacitance and conduction.

Node of Ranvier length

While myelin length, thickness, and compaction all play roles in facilitating axon conduction, structural changes at nodes of Ranvier may also play a role in tuning action potential velocity. A key characteristic of myelinated axons is the localization of voltage gated sodium channels to nodes of Ranvier [76]. In contrast, the same sodium channels are evenly distributed throughout the plasma membrane of unmyelinated axons. As the channels are confined to the nodes in myelinated axons, the number and density of channels at each node modulate the ability of the membrane to depolarize. Moreover, different node lengths, i.e. different sized gaps between adjacent internodes, would allow for differential densities of local sodium channels.

Experimental evidence has shown that there is heterogeneity in node length across different axons. Simulations modeling the effect of node length on AP propagation suggest that increasing node length from the shortest observed (0.5μm in the optic nerve and 0.43μm in the cortex) to the longest (1.7μm in both the optic nerve and cortex) can alter conduction speeds by up to 20% in the optic nerve or as much as 24% in cortical axons [77]. Interestingly, there is less length heterogeneity amongst nodes found on the same axon, suggesting a mechanism for regulation along individual axons. Because changes in node length can have substantial effects on conduction speeds, node remodeling in response to external stimuli would be a ready-made way of tuning neuronal circuitry. In fact, it has also been suggested that remodeling in this way could offer a more metabolically efficient means of tuning conduction, as retracting or extending two paranodes would require orders of magnitude less membrane flux than modifying internode length or thickness [77]. While direct evidence for such remodeling is not available, several studies have found significant alterations in nodal length after adverse stimuli including chronic stress [78], high frequency neuronal activity [79], acoustic over exposure [80], and cerebral vascular hypoperfusion [81]. Thus, future work, likely using live imaging, will reveal the extent to which nodes of Ranvier can remodel and if this influences action potential conduction in vivo.

Myelin plasticity in aging

Evidence for myelin defects can be found in disorders that present during development and adolescence such as schizophrenia, bipolar disorder, and autism [82,83] in addition to diseases associated with adulthood and aging such as Alzheimer’s disease [84,85] and amyotrophic lateral sclerosis [86,87]. However, even in normal aging there is significant evidence that myelin defects are an early pathological hallmark that occurs in oligodendrocytes before other cells in the brain exhibit signs of degeneration [31,88-90]. Age-related disruptions in white matter tracts have been reported using low-resolution magnetic resonance imaging (MRI) based approaches in humans [91,92] and specific myelin defects have been found in postmortem tissue from aged humans and other primates [93-96] in addition to rodents [31,97].

If myelin plasticity, as defined in the previous sections, is necessary for neural network homeostasis than any interruption in these processes would result in a degenerative cascade ultimately resulting in severe cognitive decline [98]. Reasons for specific oligodendrocyte

vulnerability in aging are not clear however several possibilities have been proposed including decreased remyelination capacity from reduced NG2 glia differentiation [99], unique metabolic demands specific to myelinating oligodendrocytes [100,101], and differential vulnerability of oligodendrocytes to oxidative damage [102] among other potential mechanisms [103].

Aged NG2 glia exhibit decreased oligodendrocyte differentiation in several contexts. First, baseline homeostatic oligodendrocyte generation declines with age in a region-dependent manner [18,21,22]. If myelin maintenance relies on oligodendrocyte replacement, as suggested by some studies in the optic nerve [21], then decreased oligodendrocyte production in advanced aging would result in net myelin loss. On top of this, there is evidence that oligodendrocytes generated in older animals produce shorter and fewer myelin sheaths [31]. This means that the loss of a single oligodendrocyte in the aged brain might require the production of multiple oligodendrocytes to reestablish the myelin pattern. This effect would be compounded in situations where myelin is damaged. If the regenerative capacity of oligodendrocytes is compromised in aging, then incomplete myelin repair could occur in both acute brain injury and in chronic myelin diseases. Chronic stages of multiple sclerosis are characterized by incomplete remyelination [104] presumably due to the inability of NG2 glia to differentiate [99]. Direct age effects on oligodendrocyte differentiation capacity in animal models have been demonstrated via parabiosis [105] and cell transplant [27] experiments suggesting that the brain microenvironment and current state of the cell influence the age-dependent changes in NG2 glia behavior. Cellular state mechanisms may include alteration in the epigenetic status of NG2 glia [28,106,107] while microenvironmental factors could include both changes in growth factor signaling, inflammatory state of other glia [108], tissue stiffness [109], and accumulation of myelin debris [34,97,110]. There is evidence that each of these signals can influence oligodendrocyte generation. Identification of the molecular mechanisms involved in the effects of age on NG2 glia differentiation will likely provide useful therapeutic targets in the future.

Outside oligodendrocyte differentiation not much is known about the effects of age on myelin plasticity. Accumulation of myelin debris in the aging brain has the potential to impact myelin sheath length remodeling, axonal plasticity, and node of Ranvier stability. Moreover, myelin decompaction could occur without immediate oligodendrocyte loss but with similar functional consequences in terms of action potential conduction. Finally, even if structural defects are not present in the myelin sheath there could be age-related dysfunction of oligodendrocyte metabolic support to axons. Increasing evidence suggests that this often-underappreciated myelin function could be disrupted in aging [58,59]. It is possible that the ability of oligodendrocytes to shuttle lactate/pyruvate to axons is disrupted overtime due to changes in GLUT-1/MCT-1 density within myelin sheaths (Figure 1). Much work is needed to precisely dissect how age impacts these other forms of myelin plasticity and whether these cellular and molecular mechanisms can be translated to other neuropathological states.

Conclusions

Myelin plasticity encompasses a range of potential changes in myelin structure, density, and function. These include the generation of new oligodendrocytes from their endogenous progenitors NG2 glia, to changes in myelin length, distribution, thickness, and compaction (summarized in Figure 1). Each feature has the potential to modulate neural network function via alteration in synchronous arrival of signals at postsynaptic targets. The in vivo temporal dynamics and the distinct signals that induce each form of plasticity are just now being revealed. Notably the direct functional consequences of such changes are largely unknown.

Most evidence for myelin plasticity thus far comes from cell culture and transgenic fate mapping in fixed tissue. However, with the development of new label-free optical imaging approaches, such as Coherent Anti-Stokes Raman Scattering (CARS) , Optical Coherence Microscopy (OCM), Third Harmonic Generation (THG) , and Spectral Confocal Reflectance (SCoRe) microscopy, combined with new fluorescent labeling approaches for cellular observation and manipulation in vivo [111-116], we are at the early stages of understanding the extent to which myelin plasticity plays a role in homeostatic maintenance of brain function in addition to its potential mechanisms related to learning and memory. While more work is necessary to directly observe, define, and describe myelin plasticity in vivo, the next exciting challenge is to connect these cellular observations with neural circuit function and ultimately behavior.

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Highlights

- Myelin plasticity occurs throughout development and adulthood
- Myelin plasticity ranges from the generation of new oligodendrocytes to fine structural changes in the myelin sheath over extended periods
- Various environmental cues can induce myelin plasticity
- Defects in myelin maintenance are likely involved in age-related cognitive decline

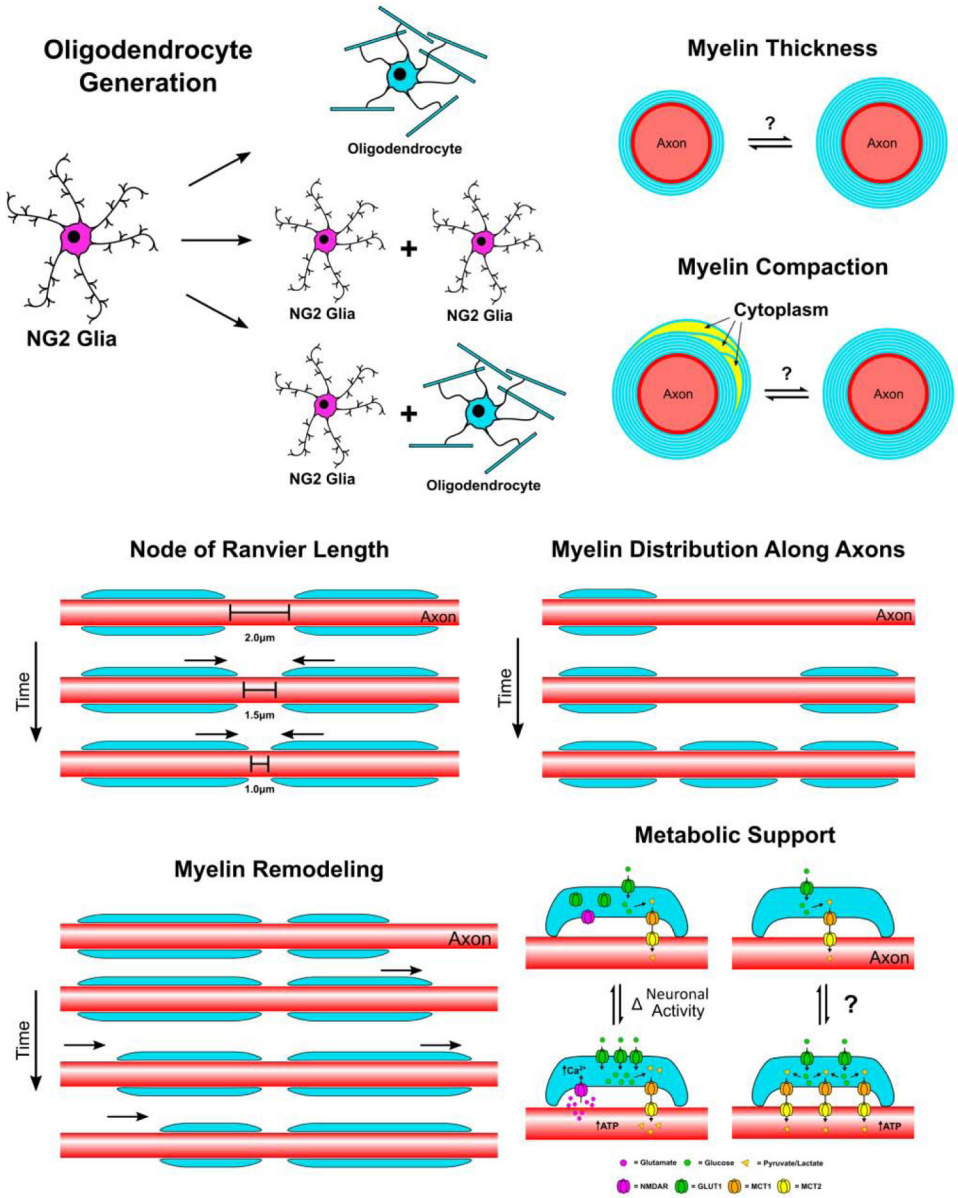

Figure 1: Forms of myelin plasticity

Myelinating oligodendrocytes maintain the capacity for multiple forms of plasticity in the adult central nervous system. First NG2 glia act as an endogenous source of new oligodendrocytes while maintaining a resident population via self-renewal. This allows for population homeostasis as NG2 glia would otherwise be depleted over time through direct differentiation into mature oligodendrocytes. In addition to direct differentiation, recently divided NG2 glia receive signals to differentiate or remain at the progenitor stage. After terminal differentiation, the myelin sheath is potentially capable of additional forms of structural and molecular plasticity including changes in myelin thickness, degrees of myelin compaction, length and positioning of the myelin sheath, and length of individual nodes of Ranvier. In addition to myelin structural changes, expression and distribution of molecules and transporters involved in providing metabolic support to myelinated axons have the

potential to change in response to neuronal activity and throughout life. Each of these forms of plasticity, ranging from the generation of new oligodendrocytes do more subtle changes in node length, have the potential to modulate conduction velocity, neural circuitry, and axonal health.