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Clinical Applications of Myelin Plasticity for Remyelinating Therapies in Multiple Sclerosis

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Abstract

Central nervous system demyelination in multiple sclerosis (MS) and subsequent axonal degeneration represents a major cause of clinical morbidity. Learning, salient experiences, and stimulation of neuronal activity induce new myelin formation in rodents and in animal models of demyelination, remyelination can be enhanced by via experience- and activity-dependent mechanisms. Furthermore, preliminary studies in MS patients supports the use of neuromodulation and rehabilitation exercises for symptomatic improvement, suggesting that these interventions may represent non-pharmacological strategies for promoting remyelination. Here, we review the literature on myelin plasticity processes and assess the potential to leverage these mechanisms to develop remyelinating therapies.

Introduction

Disorders of central nervous system demyelination such as multiple sclerosis (MS) represent a major cause of neurological disability worldwide[1,2]. Over two million people worldwide are affected by MS, typically presenting as a relapsing-remitting entity with transient neurological deficits such as visual abnormalities, focal weakness and sensory loss, or ataxia lasting days or weeks accompanied by inflammatory demyelinating lesions in the brain and spinal cord. A subset of patients develop an insidious, progressive disease course approximately 10 – 20 years from onset that is characterized by persistent clinical morbidity in the setting of permanent axonal loss. Although immunomodulatory agents have been successful in limiting the number of white matter lesions on magnetic resonance imaging (MRI) in relapsing-remitting patients, effective disease-modifying therapies for progressive MS have remained elusive, in part due to our incomplete understanding of the cell biology underlying neuron-glial interactions[1,2]. Therefore, discovering and translating fundamental neurobiology knowledge to develop therapies that promote remyelination and prevent progression to progressive MS represents an important research effort going forward.

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Author Contributions

SP and JRC contributed to study conception and design of the review; SP and JRC contributed to the interpretation of studies included in the review; SP contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Dr. Pan reports no potential conflicts of interest. Dr. Chan reports personal fees as a Scientific Advisor to Inception Sciences and Pipeline Therapeutics Inc, which have a commercial interest in remyelinating therapies such as clemastine fumarate, a drug that is mentioned in this review.

Myelin in the central nervous system is formed through the differentiation and subsequent maturation of oligodendrocyte precursor cells (OPCs) into myelinating oligodendrocytes (OLs), a process that persists into adult life[3,4]. Consequently, myelin is one of the only structures in the brain capable of regeneration following injury. In recent years, it has been increasingly appreciated that physiological generation of new myelin is influenced by salient experiences and neuronal activity as a mechanism of structural plasticity to form new memories and adapt to novel situations[5,6,7,8,9,10,11,12,13,14,15,16] (Figure 1, Table 1). Whether this experience- and activity-dependent myelin plasticity occurs in the setting of disease is a matter of significant clinical interest, as it could advocate for the use of rehabilitative exercises or non-invasive neuromodulation as complementary, non-pharmacological approaches to promote remyelination (Figure 2). Indeed, post-mortem examination of chronically demyelinated MS plaques demonstrate limited remyelination despite an abundance of available OPCs, signifying a need to explicitly target mechanisms that promote their differentiation and maturation[17]. In this review, we synthesize the current evidence for myelin plasticity mechanisms in animal models and human imaging studies and discuss their therapeutic potential for myelin repair in demyelinating diseases.

Search Strategy & Selection Criteria

References for this review were identified by searches of PubMed and references from relevant articles. The following search terms were used: myelin plasticity, adaptive myelination, multiple sclerosis, remyelination, demyelination, tDCS, rTMS, physical therapy, white matter plasticity. Only English language articles were included, and the final reference list was generated on the basis of their impact on the field and relevance to this specific review topic.

Learning-induced myelin plasticity in animal models

Although the majority of central nervous system myelin is established during postnatal development, a pool of proliferating OPCs are maintained in adulthood to continually generate OLs for maintenance and repair of myelinated circuits in physiological and diseased brain states[3,4] (Figure 1). This capacity for new myelin formation has raised the possibility that myelin along axons can be actively modulated in a manner akin to Hebbian synaptic plasticity wherein activation of a specific neural circuit induces adaptive changes in myelination of that circuit to support learning and memory processes. As there is a growing body of evidence that OLs provide metabolic support to the underlying axon via transfer of short-carbon chain metabolites such as pyruvate and lactate through monocarboxylate transporters, myelination may also help to maintain neuronal energy homeostasis and prevent degeneration in the setting of demyelination[18,19]. OPCs are also thought to serve multiple functions aside from oligodendrogenesis such as neurotransmitter homeostasis, modulation of synaptic efficacy, and innate immunity[20]. Notably, OPCs exhibit excitatory potentials in response to neurotransmitter release and, in adult mice, repetitive optogenetic or chemogenetic stimulation of cortical neurons is sufficient to induce the proliferation and differentiation of neighboring OPCs into OLs, suggesting that myelin plasticity can be directly instructed by neuronal activity[5,6,21,22].

Naturalistic learning experiences are similarly able to regulate OPC proliferation and new myelin production. Mice that learned to run on a complex wheel with missing rungs were found to have increased post-training $EdU^+/CC1^+$ and *Enpp6*$^+$ cells, representing differentiated OLs, in the primary motor cortex[7,8]. This increase was not detected in the optic nerve, demonstrating task-based specificity of the effect and the potential for targeting myelin formation to specific brain regions in a clinical setting. Likewise, an increased number of differentiated OLs were detected in the sensorimotor cortex of rats weeks after participating in a forelimb reaching task, indicating that this phenomenon generalizes to other forms of motor learning[23]. A recent study was able to directly image this process in living animals using two-photon microscopy, observing a two-fold increase in oligodendrogenesis in the motor cortex of trained mice in the weeks following a forelimb reaching task[16]. Furthermore, pre-existing myelin sheaths, which are generally inert under baseline conditions, exhibited increased rates of dynamic length changes, suggesting a remarkable capacity for learning-dependent plasticity.

Myelin plasticity is also a feature of other learning modalities such as spatial or episodic memory formation. Mice that trained to escape to a hidden water maze platform exhibited increased proliferation and differentiation of OPCs in the prefrontal cortex, anterior cingulate cortex, and corpus callosum relative to untrained controls[7]. Importantly, they were also able to confirm long-term increases in the density of myelinated axons in the corpus callosum and cingulum on electron microscopy. In a parallel study, contextual fear learning, in which a neutral context is associated with an aversive shock stimulus, also induced immediate post-training proliferation of OPCs with long-term increases in mature OLs and myelinated axon density on electron microscopy in the prefrontal gray matter[8]. Both studies did not detect increased oligodendrogenesis in brain areas associated with initial memory encoding such as the dorsal hippocampus nor in non-memory associated regions such as the somatosensory cortex, again suggesting a high degree of task-based regional specificity.

Experience-induced myelin plasticity in animal models

In addition to explicit learning paradigms, salient experiences or deprivation of those experiences have bidirectional influences on oligodendrogenesis and myelin formation, illustrating the potential interaction of positive or negative psychosocial factors with remyelination in MS patients. Mice that were reared in an enriched environment, a multisensory experience with an expanded cohort of social companions, exhibited increased proliferation and differentiation of OPCs in the sensorimotor cortex compared to animals housed in standard caging[23]. In another study, two-photon longitudinal imaging revealed that, under baseline conditions, many OPCs differentiate into pre-myelinating OLs but do not stably integrate into the circuit as mature OLs but instead undergo programmed cell death. Remarkably, animals reared in an enriched environment exhibited a five-fold increase in successful maturation into myelinating OLs in the primary somatosensory cortex[11]. The presence of pre-myelinating OLs in the absence of mature OLs in chronically demyelinated MS lesions suggest a similar barrier to integration and maturation that can possibly be overcome with multimodal enrichment and sensory experience[17].

Conversely, social isolation causes profound decreases in myelin thickness in the prefrontal cortex of both in juvenile and adult mice with corresponding decreases in myelin-associated transcripts such as *Mog*, *Mag*, and *Mbp*[12,13]. Stress has a variable effect on myelination that appears to depend on the duration and nature of the stressor, with chronic stressors such as repeated social defeat stress having a negative effect on myelination appreciated both on histological and gene expression analysis[24,25,26]. A number of studies examining developmental myelination also demonstrate decreased OL differentiation and myelination in response to deprivation of various sensory modalities, in diametric opposition to the effects of an enriched environment[14,15,16]. Collectively, these studies highlight the sensitivity of myelination to various environmental stimuli and suggests that consideration of these regulatory factors in clinical practice may facilitate optimal remyelination following injury.

White matter plasticity in human imaging studies

Putative changes in myelination and other white matter adaptations following complex motor or cognitive training have also been observed in human subjects (Table 2). These observations are typically based on the measurement of fractional anisotropy (FA) on diffusion tensor imaging, which is often interpreted in human imaging studies as a proxy for myelination but can be confounded by other structural changes in the white matter such as increased vascularity, cerebrospinal fluid volume, axonal diameter, or presence of OPCs and other glial cells[27,28,29,30]. Interpretation of DTI parameters are further complicated when fiber organization is not highly coherent, such as in the gray matter where myelin plasticity effects have been reported in animal models[9,10,11,16]. Despite these significant shortcomings, these measures allow for non-invasive within-subject imaging in humans and have been historically important in bridging the divide between basic myelin biology and clinical translation. In a study of complex motor learning, participants scanned before and after six weeks of juggling training exhibited significantly increased FA in the sub-adjacent white matter to the intraparietal sulcus that persisted four weeks after the conclusion of training[31]. In a cross-sectional comparison of concert pianists with age-matched non-musicians, concert pianists exhibited increased FA in the internal capsule with inter-individual variation in FA correlating with the degree of childhood piano practicing[32]. Cognitive tasks such as working memory training are able to induce increased FA in parietal fibers while visual perception learning was shown to increase FA in the white matter tracts sub-adjacent to the visual cortex in older adults[33,34]. Notably, even relatively brief experiences such as two hours of training in a car racing video game were able to induce white matter plasticity in the fornix[35]. Post-training neuroimaging changes have also been observed using other MRI modalities that are purported to have greater specificity for myelination. Subjects that underwent ten sessions of visuomotor skill training over four weeks demonstrated a significant increase in myelin water fraction of the left intraparietal and parieto-occipital sulci[36]. In another study, subjects that participated in two months of adaptive memory training did not demonstrate a change in the myelin water fraction but did exhibit a significant increase in the intrinsic longitudinal relaxation rate, an MR metric thought to be sensitive to changes in myelination, within the frontoparietal network[37].

Collectively, these data indicate a potential for experience-dependent white matter adaptation in humans that, as in animal models, appears to be highly specific to task-associated brain regions. The relative contribution of new myelin formation in these studies is tenuous given the inability for DTI and other MRI imaging modalities to measure myelination in isolation, particularly in cases where post-training effects are observed on a much more rapid timescale than would be expected for myelin formation[10]. Nevertheless, histological correlations with DTI signal in animal studies support some degree of myelin involvement[29,38,39]. Newer diffusion MRI modalities such as neurite orientation dispersion and density imaging (NODDI) are capable of resolving intracellular and extracellular water fractions, partially eliminating some of the confounding sources of contributions to white matter microstructure in DTI and abetting the assessment of myelin content in gray matter[40]. NODDI has seen preliminary use for tracking microstructural changes in MS patients and can be utilized for further investigating white matter plasticity mechanisms in healthy and diseased human subjects[41,42]. Sequences such as myelin water imaging (MWI), magnetization transfer imaging (MT), and direct ultrashort echo time (UTE) are also potential modalities that are theorized to capture myelin more specifically on the basis of their interaction with its unique biophysical properties[,44,45,46]. However, empirical validation of these techniques, such as through correlating signal changes with demyelinating lesions in MS patients in which there is extensive axonal damage, edema, inflammatory infiltration, and gliocytosis, demonstrate only partial histological associations and are profoundly subject to the same confounders as DTI[43,45,46]. Positron emission tomography (PET) utilizes radiotracers, such as stilbene derivatives, that can targeted towards myelin with molecular specificity and has been deployed to track disease progression in MS, but PET technology is costly and not widely available[47]. Nevertheless, validation of MRI modalities using PET and post-mortem histology as a gold standard will be necessary future efforts to definitively demonstrate that post-training white matter changes can be attributed, at least in part, to myelin plasticity.

Neuronal stimulation to promote remyelination

Optogenetic and chemogenetic stimulation of neuronal activity have been indispensable in defining activity-dependent mechanisms of myelin plasticity, but their need for invasive surgical intervention and/or viral gene delivery precludes direct clinical application in patients[5,6]. In animal models of chemical demyelination, blocking AMPA neurotransmission from denuded axons to neighboring OPCs prevented differentiation and remyelination, while repetitive optogenetic stimulation of demyelinated axons enhanced remyelination and restored functional conduction velocity of the lesioned circuit[48,49]. Taken together, these data suggest that stimulation of neuronal activity is an important driver of the remyelination process and that non-invasive neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) may be viable strategies to promote myelin repair.

Repeated sessions of cortical stimulation via rTMS is currently used to treat neuropsychiatric diseases such as medication-refractory major depressive disorder and have minimal adverse effects[50]. Although lasting therapeutic benefits from theta frequency rTMS stimulation are thought to arise from long-term changes in synaptic plasticity, data in animal

models suggest that rTMS can also induce myelin plasticity by promoting the maturation of pre-myelinating OLs and enhancing myelin elaboration from newly myelinating OLs[51]. Accordingly, rTMS has been shown in smaller studies of MS patients to decrease spasticity, with concurrent changes in functional connectivity between the two primary motor cortices consistent with an increase in myelination[52,53]. Similarly, rTMS has been shown to improve autonomic dysfunction, hand dexterity, and cerebellar deficits associated with MS[53,54,55]. Repetitive tDCS also appears to have therapeutic potential - in a cohort of MS patients with impaired attention and executive function, tDCS given in conjunction with cognitive rehabilitation was associated with neuropsychological improvement up to six months later[56]. Collectively, these studies suggest that non-invasive neuromodulation has the potential to alleviate clinical disability in MS, but to what degree these effects are mediated through activity-dependent remyelination remains an important question that will require high fidelity biomarkers of myelin repair to answer. To date, visually evoked potential latency is the only biomarker of remyelination to be validated in a clinical trial, but it is an indirect measure and only applicable in the setting of visual pathway demyelination[57]. As with human white matter plasticity studies, the development and validation of more reliable myelin imaging techniques in MS patients such as NODDI, MWI, MT, UTE, and PET will be critical steps towards this goal, highlighting a need for interdisciplinary collaboration between basic neuroscientists, neurologists, medical physicists, and neuroradiologists[40,41,42,43,44,45,46,47].

Physical rehabilitation to promote remyelination

Although there is an abundance of evidence for experience-dependent myelin plasticity in animal models under healthy physiological conditions, it is less clear whether these mechanisms can promote remyelination following injury. In a longitudinal two-photon imaging study of mice participating in a reward-based forelimb reaching task, chemical demyelination was induced via three weeks of cuprizone ingestion and remyelination dynamics were imaged in the corresponding motor cortex over the course of two months. Mice that underwent training exhibited an accelerated remyelination curve that plateaued higher than untrained controls several weeks following cessation of cuprizone ingestion[16]. By tracking individual oligodendrocytes over time via two-photon imaging, they also definitively observed that existing OLs could contribute to remyelination by elaborating new myelin sheaths without the differentiation of new cells, a possibility previously only indirectly hinted at by radioactive carbon dating of partially remyelinated MS shadow plaques[58]. A greater number of pre-existing OLs were observed to generate new myelin sheaths in trained mice, suggesting that this alternative pathway of myelin repair can be modulated by experience-dependent myelin plasticity mechanisms. Nevertheless, further investigation is warranted here, as the majority of remyelination in clinical and preclinical models stems from differentiation of OPCs into OLs and myelin from surviving OLs appears to be a relatively minor contribution[1,2,59]. It should be noted that these increases did not occur in mice that repeated the task after already learning it, dissociating the effects of physical activity from motor learning[16]. Furthermore, demyelinated axons were preferentially remyelinated over axons that were previously never myelinated, though a recent study demonstrated that this fidelity can vary with the original pattern of

myelination[60]. These data suggest that the overall pattern of myelination can be regenerated to a large extent, which is encouraging for restoration of function.

In contrast, another study demonstrated a therapeutic effect of physical activity on remyelination in the absence of learning[61]. Following focal chemical demyelination of the spinal cord white matter, mice that were allowed unrestricted access to a running wheel exhibited increased OPC proliferation and density of remyelinated axons with thicker myelin sheaths compared to controls with a locked wheel. Remarkably, the effects of exercise on remyelination were equivalent to the effects of administering clemastine fumarate, an anti-muscarinic compound that was recently validated as a remyelinating agent in a clinical trial for MS patients with chronic demyelination[57]. When exercise was administered in conjunction with clemastine, the degree of remyelination enhancement was even higher and accompanied by an increased total density of axons that was not present when exercise or clemastine were prescribed alone, suggesting a neuroprotective effect of the combined regimen[61]. Although the relative contributions of unskilled exercise and motor learning towards promoting remyelination is unclear, one potential explanation for the discrepancy between these two studies is that a forelimb reaching task may not generate the requisite degree of physical activity required for therapeutic benefit. Exercise may also recruit additional mechanisms, such as modulation of angiogenesis, metabolic status, inflammation, and trophic factor release, that also act to promote remyelination and/or confer neuroprotection[62]. Importantly, the authors identify PGC1α as an intracellular mediator of this process that is transiently upregulated in exercising mice, which in turn induces transcriptional activity of myelin-related genes such as *Plp* and *Mbp*. This finding is notable in that very few myelin plasticity studies investigate intermediary signals that mediate the interaction between neuronal activity and myelination. In another study that similarly examined molecular mediators of myelin plasticity, the authors utilized transgenic knockout animals to demonstrate that neuron-derived BDNF binding onto OL TrkB receptors was necessary for activity-dependent myelination in the setting of chemotherapy-induced cognitive impairment[63].

Overall, these data support further research into determining whether a combined clinical approach of pharmacological therapy with a prescribed exercise regimen could be effective for promoting myelin repair, particularly for patients with symptoms of motor weakness or cerebellar dysfunction. As studies of myelin plasticity in both animal models and humans all point to a high degree of task-based regional specificity for new myelin formation, there will likely be a need to develop personalized rehabilitation programs based on neurological symptoms and anatomical localization of lesions on neuroimaging. Whether other cognitive tasks or sensory experiences such as water maze training or enriched environment exposure have positive effects on remyelination following injury remains a salient question and will be an important direction for future research. Abnormalities of MWI in MS patients and decreased myelination in mouse models correlate with cognitive deficits, and there is preliminary evidence that cognitive exercises and rehabilitation alleviate these symptoms in a clinical setting[44,56,63,64,65,66,67]. However, as with physical rehabilitation and non-invasive neuromodulation approaches, the development of neuroimaging biomarkers of remyelination and their application in prospective trials as a primary outcome will be critical in determining the degree to which these clinical benefits are mediated through myelin

repair. Moreover, future studies should be designed with longer follow-up times in order to demonstrate more robust and long-term effects prior to the consideration of clinical trials. Careful selection of the patient population is also warranted, as patients that have already suffered significant axonal loss and progressive disease may not be suitable candidates for remyelinating therapies.

Conclusion

Existing standard of care for MS patients largely revolves around immunomodulatory therapies, which are effective in lowering lesion burden during the relapsing-remitting course of the disease but not in preventing progressive axon degeneration and permanent clinical disability[1]. Pharmacological induction of remyelination in denuded axons has been shown to be neuroprotective in the setting of inflammatory demyelination, and advances in understanding fundamental oligodendrocyte biology have already translated to clinical practice as novel remyelinating agents[57,68]. Moving forward, non-pharmacological strategies to enhance remyelination that leverage our expanding knowledge of myelin plasticity mechanisms such as motor rehabilitation, cognitive training, and non-invasive neuromodulation are a readily actionable area of investigation that could confer similar benefits with minimal adverse side effects (Figure 2). These efforts will also be important for promoting repair in other settings of demyelination such as stroke and traumatic brain injury[69,70]. However, developing reliable methods to longitudinally monitor remyelination and disease progression on neuroimaging studies will be necessary for the success of these efforts. In conjunction with existing medical therapies to suppress the immune system and promote OPC differentiation, these approaches may represent a new clinical paradigm to maximize the potential for myelin repair in patients suffering from demyelinating diseases.

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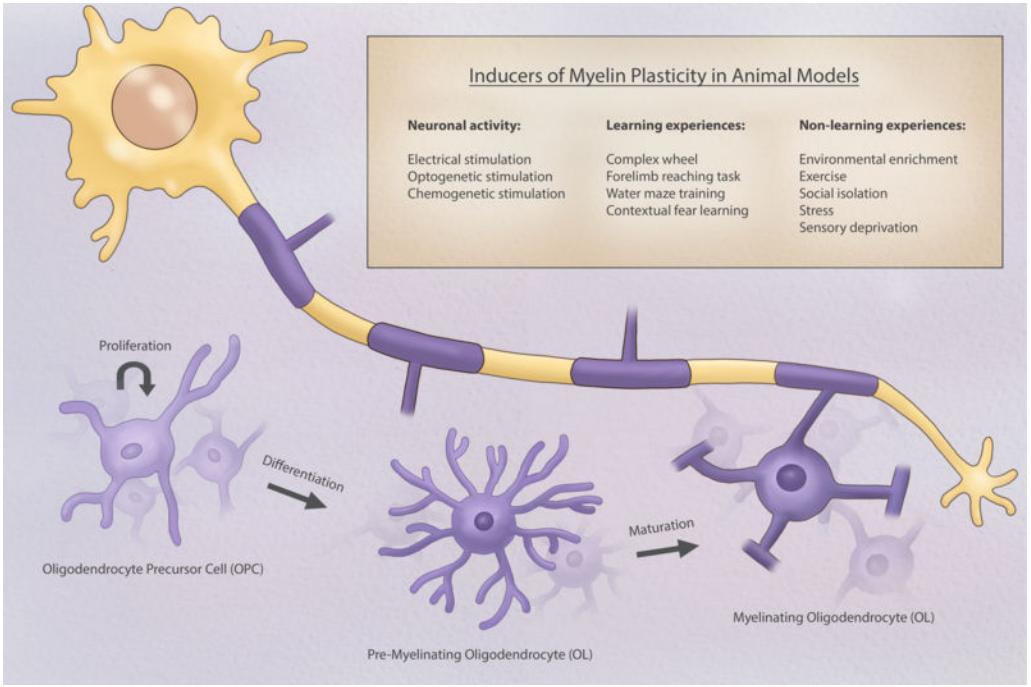

Figure 1. Overview of oligodendroglial lineage and inducers of myelin plasticity in animal models.

Myelinated axon with schematic depiction of the major oligodendroglial cell lineages below: Oligodendrocyte precursor cells proliferate to maintain a pool of progenitor cells throughout life, and differentiate into pre-myelinating oligodendrocytes, which subsequently mature and integrate stably into myelinating oligodendrocytes that form compact myelin sheaths[3,4]. Histological examination of demyelinating lesions in multiple sclerosis suggest that differentiation and maturation processes are impaired in a disease setting[17]. Table inset summarizes mechanisms of myelin plasticity that have supporting evidence in the literature via experimental animal models, ontologically sorted by direct neuronal stimulation, learning experiences, and non-learning experiences. Evidence across studies suggest that myelin plasticity acts broadly on proliferation, differentiation, and maturation.

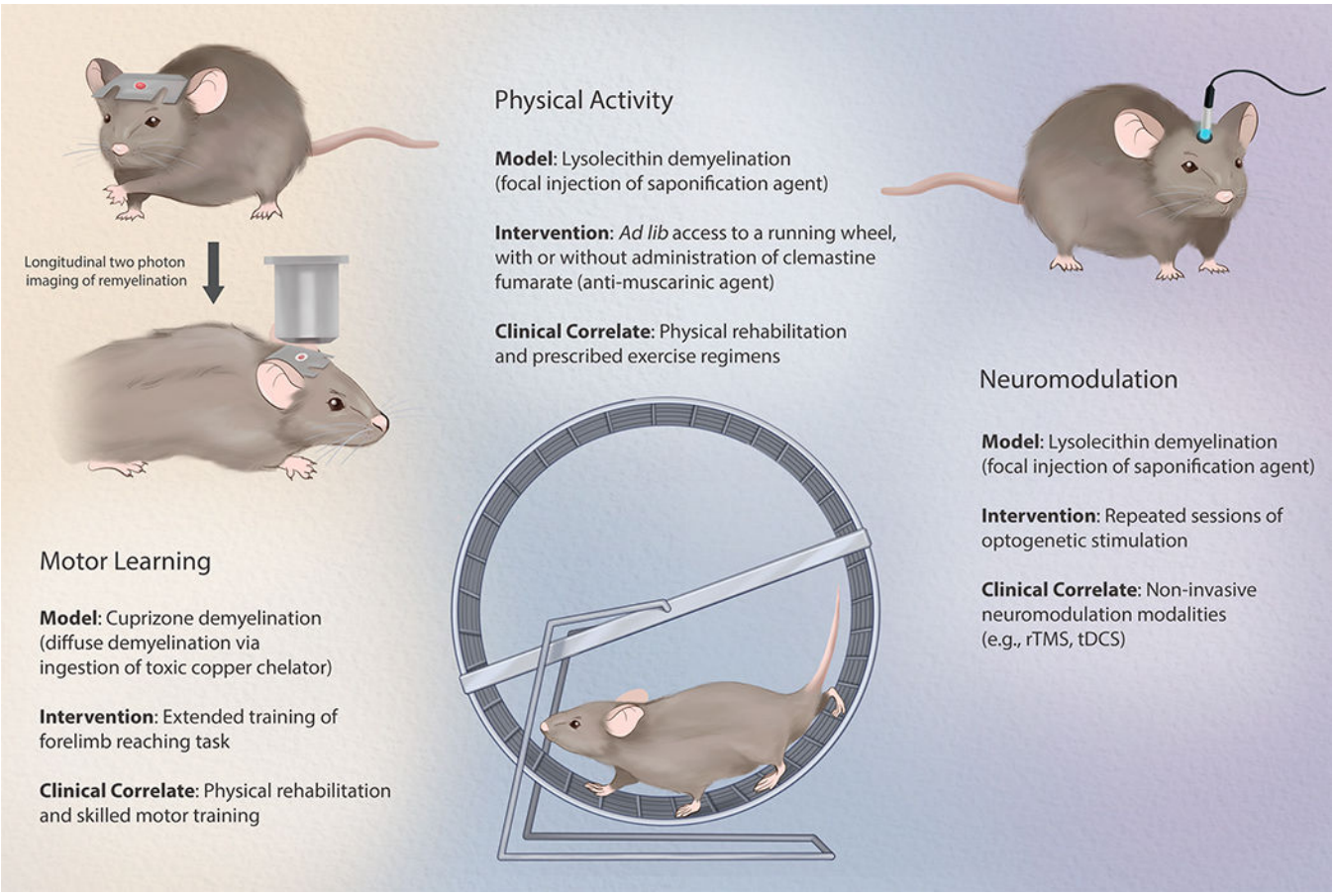

Figure 2. Evidence for myelin plasticity mechanisms in animal models of remyelination and potential clinical applications.

Three examples of studies demonstrating that myelin plasticity mechanisms can promote remyelination in the setting of animal injury models, with corresponding potential clinical translation of each mechanism. Left panel, extended forelimb reach training increases remyelination visualized by *in vivo* longitudinal two-photon microscopy following diffuse toxic demyelination induced by cuprizone diet[16]. Physical rehabilitation and skilled motor learning are potential clinical applications of this mechanism, Middle panel, *ad lib* access to a running wheel following lysolecithin demyelination of spinal cord white matter increases remyelination and remyelinated sheath thickness; concurrent administration of the anti-muscarinic clemastine fumarate, which promotes oligodendrocyte differentiation, appears to have a synergistic effect on remyelination that is additionally neuroprotective[50]. Physical rehabilitation and unskilled physical exercise are potential clinical applications of this mechanism, Right panel, repeated but not single session optogenetic stimulation of the motor cortex enhances remyelination following lysolecithin demyelination of the underlying corpus callosum[36]. Non-invasive neuromodulation techniques such as rTMS and tDCS are potential clinical applications of this mechanism.

Table 1.

Evidence for myelin plasticity in selected animal models

Subject	Intervention	Results	Notes
P35 mice (Gibson et al., 2014)	Optogenetic stimulation (20 Hz cycles over motor cortex, 30 minute sessions for 7 days)	Increased proliferation of OPCs in stimulated cortex and subcortical white matter; increased differentiated OLs and myelin thickness 4 weeks post-stimulation	Cellular changes associated with improved motor function of the corresponding limb
P60–66 mice (Mitew et al., 2018)	Chemogenetic stimulation (1 week, somatosensory cortex)	Increased OPC proliferation and differentiation; increased number of myelinated axons with thicker myelin	Activity-dependent myelination was biased towards the stimulated axons
P60–90 mice (McKenzie et al., 2014)	Running on a complex wheel	Increased proliferation of OPCs and differentiated OLs in the corpus callosum and motor cortex days post-training	No effect upon re-exposure to wheel post-training
P60–90 mice (Xiao et al., 2016)	Running on a complex wheel	Rapid increase in differentiated OLs in the corpus callosum and motor cortex hours post-training	This study detected differentiated OLs, but no evidence of myelination. No changes in the optic nerve.
P42–56 mice (Bacmeister et al., 2020)	Forelimb reaching task (20 minute sessions over 3 weeks)	Two-fold increase in oligodendrogenesis in the motor cortex of trained mice	Increased myelin sheath dynamics also observed; effects were seen following chemical demyelination model
P70–84 mice (Steadman et al., 2019)	Morris water maze training	Increased OLs in prefrontal cortex, corpus callosum, and anterior cingulate cortex; increased myelinated axons in corpus callosum and cingulum	No increase in OLs in dorsal CA1 or alveus. Myelin thickness unchanged.
P56 mice (Pan et al., 2020)	Single trial contextual fear conditioning	Increased OPCs 24 hours post-training in prefrontal cortex and amygdala; increased OLs and myelinated axons 30 days post-training in prefrontal cortex	No increase in OLs in somatosensory cortex, dorsal hippocampus, or amygdala. Myelin thickness unchanged.
8–14 month old mice (Hughes et al., 2018)	Enriched environment (20 days)	Fivefold increase of successful integration of newly differentiated OLs	Baseline rate of integration of new OLs is only 22%
P60 mice (Liu et al., 2012)	Social isolation (2 weeks)	Reduced myelin thickness	Number of OLs is unchanged
P21 mice (Makinodan et al., 2012)	Social isolation (2 weeks post-weaning)	Reduced myelin thickness, decreased *Mbp/Mag* transcripts	Post-weaning integration did not rescue myelination, suggesting the presence of a critical period

Abbreviations: P_, postnatal day _; OPCs, oligodendrocyte precursor cells; OLs, oligodendrocytes; *Mbp,* myelin basic protein (gene); *Mag,* myelin-associated glycoprotein (gene); CA1, cornu ammonis 1 (hippocampal subfield).

Table 2.

Evidence for white matter plasticity in selected human imaging studies

Subject	Study Type	Intervention	Results	Notes
48 healthy adults (Scholz et al., 2009)	Longitudinal	Juggling (6 weeks of training)	Increased FA in the posterior intraparietal sulcus and increased density in adjacent occipital/parietal gray matter 0 and 4 weeks post-training	No correlation of structural changes with juggling performance
8 adult concert pianists and 8 non-musicians (Bengtsson et al., 2005)	Cross-sectional	History of piano practicing (retrospective)	Increased FA in the internal capsule, corpus callosum, and frontal lobe fibers	Degree of childhood practicing correlated with degree of FA change
11 healthy adults (Takeuchi et al., 2010)	Longitudinal	Computer-based working memory task (2 months, daily ~25 minute sessions)	Increased post-training FA in intraparietal sulcus white matter and anterior corpus callosum	Amount of working memory training correlated with degree of FA change
18 older adults (aged 65–80) and 21 younger adults (aged 19–32) (Yotsumoto et al., 2014)	Longitudinal	Texture discrimination task (3 daily sessions)	Increased post-training FA in the white matter underlying visual association cortex	Effect only present in older subjects
70 healthy adults (Hofstetter et al., 2013)	Longitudinal	Car racing video game (2 hours)	Immediate post-training decrease in MD in the fornix	Rats that underwent 1 day of water maze training also exhibited decreased MD in the fornix
40 healthy adults (Caeyenberghs et al., 2016)	Longitudinal	Adaptive working memory training (40 45 minute sessions over 2 months)	Increase in the intrinsic longitudinal relaxation rate within the frontoparietal network	No change in myelin water fraction or other MR metrics
17 right-handed healthy adults (Lakhani et al., 2016)	Longitudinal	Visuomotor training (10 sessions over 4 weeks)	Increased post-training MWF signal in the left intraparietal and parieto-occipital sulci.	Negative correlation between the rate of motor skill acquisition and change in MWF.

Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; MWF, myelin water fraction.