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Review article

Neuronal activity and NIBS in developmental myelination and remyelination – Current state of knowledge

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ABSTRACT

Oligodendrocytes are responsible for myelinating central nervous system (CNS) axons and rapid electrical transmission through saltatory conduction of action potentials. Myelination and myelin repair rely partially on oligodendrogenesis, which comprises oligodendrocyte precursor cell (OPC) migration, maturation, and differentiation into oligodendrocytes (OL). In multiple sclerosis (MS), demyelination occurs due to an inflammatory cascade with auto-reactive T-cells. When oligodendrogenesis fails, remyelination becomes aberrant and conduction impairments are no longer restored. Although current disease modifying therapies have achieved results in modulating the faulty immune response, disease progression continues because of chronic inflammation, neurodegeneration, and failure of remyelination. Therapies have been tried to promote remyelination. Modulation of neuronal activity seems to be a very promising strategy in preclinical studies. Additionally, studies in people with MS (pwMS) have shown symptom improvement following non-invasive brain stimulation. (NIBS) techniques. The aforementioned mechanisms are yet unknown and probably involve both the activation of neurons and glial cells. Noting neuronal activity contributes to myelin plasticity and that NIBS modulates neuronal activity; we argue that NIBS is a promising research horizon for demyelinating diseases. We review the hypothesized pathways through which NIBS may affect both neuronal activity in the CNS and how the resulting activity can affect oligodendrogenesis and myelination.

1. Introduction

Multiple sclerosis (MS) is a neuroinflammatory disease that causes demyelinating lesions in the central nervous system. Depending on the localization of these lesions, various symptoms can occur such as sensory loss, motor dysfunction, bladder dysfunction and vision loss (Dobson and Giovannoni, 2019). Remyelination can occur spontaneously, but in people with MS (pwMS) myelin repair is often aberrant (Patrikios et al., 2006). In demyelinated axons the exchange of information occurs at a significantly slower rate and even conduction blocks can occur (Jeffery and Blakemore, 1997; Matthews et al., 2016). Remyelination is therefore necessary to ensure the continuity of the energy-efficient saltatory propagation of action potentials (Cunniffe and Coles, 2021). In addition to this function, myelin gives trophic support to the axon and contributes to the energy supply of the axon through neuronal activity-dependent release of glutamate and subsequent activation of NMDA receptors on the oligodendrocytes (Saab et al., 2016). Thus, myelin repair is an essential process that prevents mitochondrial stress and subsequent axonal injury that leads to progressive neurodegeneration (Franklin and ffrench-Constant, 2017).

Myelin repair can occur through two different pathways. Most commonly myelin is generated from new mature oligodendrocytes (OL) that differentiate from oligodendrocyte precursor cells (OPCs) (Franklin and Ffrench-Constant, 2008). These OL contain processes that form myelin by wrapping around the axons (Baumann and Pham-Dinh, 2001). Nevertheless, recent insights show that surviving mature

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oligodendrocytes are also able to assist in the remyelination process (Duncan et al., 2018). Following a demyelinating insult, OPCs can be recruited either from the parenchyma or from the subventricular zone (SVZ) (Armada-Moreira et al., 2015). A study using genetic fate mapping in a mouse model of demyelination, in which lysophosphatidylcholine (LPC) was injected in the corpus callosum, revealed that parenchymal OPCs could proliferate as early as seven days after the injury and differentiate into myelinating OLs within two weeks. In contrast, OPCs originating from the subventricular zone generated less OLs and appear in the lesion only four weeks after the demyelinating insult and contribute to the repopulation of the local OPCs that have differentiated in OL (Serwanski et al., 2018).

In contrast to some murine models of remyelination such as the cuprizone or LPC model, where complete remyelination can occur, remyelination in pwMS is incomplete, leading to shadow plaques (i.e., zones where remyelination occurs, albeit with myelin sheets that are thinner than in healthy tissue). The exact mechanism of this failure to complete remyelination is to this date still unknown and probably multifactorial. One hypothesis is provided by a ^{14}C post-mortem study that demonstrated an absence of new OL in these shadow plaques. Remyelination may thus be primarily provided by surviving oligodendrocytes due to a failed OPC differentiation and maturation in MS lesions (Yeung et al., 2019).

Current MS research is increasingly focused on the unmet need for remyelinating therapies that prevent further damage and disability progression and, more crucially, can reverse the existing damage. One way to develop remyelination therapies is by looking at what factors shape myelination in a healthy brain. As we argue in this narrative review, neuronal activity might be an important factor. Different studies found a link between neuronal activity and OPC proliferation, migration, differentiation into OL and myelin production in vitro (Barres and Raff, 1993; Demerens et al., 1996; Stevens et al., 2002) and in vivo (Gibson et al., 2014; Mitew et al., 2018). For instance, activating a subtype of neurons through optogenetic or pharmacogenetic stimulation increased the myelination of these axons in healthy mice (Gibson et al., 2014; Mitew et al., 2018). This led to the hypothesis that neuronal-activity dependent myelination, also called adaptive myelination, can fine-tune conduction velocity, and thereby modulate neural circuits (Fields, 2015; Monje, 2018). This can explain the enhanced myelin production in specific white matter regions seen on functional MRI scans of professional pianists, jugglers and people learning a new language (Bengtsson et al., 2005; Schlegel et al., 2012; Scholz et al., 2009). In preclinical models of MS, modulators of neuronal activity were shown to have promising effects on oligodendrogenesis and subsequent remyelination (Olmstead et al., 2018; Ortiz et al., 2019; Wang et al., 2021c). Additionally, different non-invasive brain stimulation (NIBS) techniques have been able to improve some of the symptoms associated with MS such as spasticity, cognitive deficits, and bladder dysfunction (Centonze et al., 2007a; Centonze et al., 2007b; Mattioli et al., 2016). Whether remyelination plays a role in these findings is yet to be clarified as remyelination was not assessed in these studies.

In this narrative review, we will first discuss the potential mechanisms of neuronal-activity dependent myelination before discussing neuronal-activity dependent remyelination pathways. Finally, we will discuss how these known mechanisms may lead to new treatments and therapies to slow down disease progression in multiple sclerosis.

2. Evidence for neuronal activity-dependent myelination

2.1. Data from animal models

The link between neuronal activity and myelination has been suspected since the 1960s. Gyllensten and Malmfors proposed this link after showing decreased myelination in mice that were reared in the dark (Gyllensten and Malmfors, 1963). Similarly, premature artificial eye opening resulted in hypermyelination of the optic nerve in rabbits (Tauber et al., 1980). More recent studies reveal the importance of exercise in oligodendrogenesis and myelination. For instance, training mice on a complex running wheel accelerates the formation of new oligodendrocytes (McKenzie et al., 2014). Conversely, blocking oligodendrogenesis through the genetic knockdown of myelin regulatory factor (Myrf) resulted in worse performance on the complex wheel, indicating that de novo myelination is required for motor learning (McKenzie et al., 2014; Xiao et al., 2016). Motor training in adult rats also revealed increased myelin staining in the white matter adjacent to the contralateral motor cortex (Sampaio-Baptista et al., 2013).

It was not until the early 1990s that the ability of neurons to impact the behavior of oligodendrocytes was demonstrated by showing a decrease in OPC proliferation in mice that had one optic nerve transected and in mice that had the sodium channel blocker tetrodotoxin (TTX) injected into one eye (Barres and Raff, 1993). A comparable study found that intraocular injection of TTX reduced the number of myelinating oligodendrocytes and myelination. However, this effect was only observed within the first week of postnatal development, suggesting a narrow time window during which electrical activity can influence oligodendrocytes in the optic nerve (Demerens et al., 1996). While these studies provide evidence for the manipulation of oligodendrogenesis through electrical activity, they do not explain why some axons are myelinated while others remain unmyelinated. For instance, in the rodent corpus callosum it has been demonstrated that up to 70 % of the axons are unmyelinated (Sturrock, 1980). In vitro studies exclude the effect of neuronal activity in the initiation of myelination as artificial nanofibers are also being myelinated by oligodendrocytes in culture. The most important factor seems to be the axonal diameter as only those fibers with a diameter larger than 0.4 μm were myelinated (Lee et al., 2012).

The significance of axonal signaling in initial ensheathment of axons was explored in vivo using the zebrafish model. Zebrafish larvae are an excellent model for monitoring in vivo myelination due to their transparency, simplicity, and similarities of the central nervous system to that of humans. Hines et al. were able to confirm the findings by Lee and colleagues (Lee et al., 2012) by demonstrating that the initial ensheathment of axons is not controlled by neuronal activity, since nascent myelin sheaths were formed on axons silenced by tetanus toxin expression (Hines et al., 2015). In contrast, time-lapse imaging demonstrates that neuronal activity is required for the maintenance of these myelin sheaths, since oligodendrocytes retract their processes much more often in silent axons than in electrically active axons. The authors hypothesize that throughout development there is a myelin excess independent of neuronal activity, and that axonal signaling fine-tunes myelination towards active axons (Hines et al., 2015). Additionally, calcium transients in OLs were discovered to influence the decision of stabilization or retraction of myelin, with large amplitude calcium transients causing more retraction of myelin sheaths and brief low amplitude calcium transients stabilizing myelin. This mechanism of myelin retraction was attributed to the effects of calpain, a calcium-dependent enzyme also involved in cellular degradation (Baraban et al., 2018).

Genetic approaches such as optogenetic and pharmacogenetic stimulation have been used to increase neuronal activity in specific neuronal subtypes and assess its effect on oligodendrogenesis. Gibson et al. (Gibson et al., 2014) were able to promote proliferation, differentiation, and myelination in axons of the prefrontal cortex and deep subcortical white matter of both juvenile and adult mice through optogenetic stimulation of neurons. These results also imply that the time-window for myelination of the brain is far larger than what was shown to be the case for the optic nerve in earlier research (Demerens et al., 1996).

Moreover, improvements in gait parameters were reported in the stimulation group (Gibson et al., 2014). Additionally, Mitew et al. (2018) were able to specifically activate somatosensory axons using designer receptors exclusively activated by designer drugs (DREADDS) and provided more evidence for neuronal activity-dependent regulation

of oligodendrogenesis. Intriguingly, they also discovered a bystander effect in neighboring axons that were not activated (Mitew et al., 2018).

Taken together, there is substantial evidence supporting the effect of neuronal activity on both oligodendrogenesis and myelination in healthy rodents. This paves the path for non-invasive manipulation of neuronal activity to enhance myelin formation in humans. However, several questions remain unanswered including those regarding the mechanisms affecting the crosstalk between neurons and glial cells in adaptive myelination. Several studies demonstrated that OPCs express a variety of neurotransmitter receptors including those for glutamate, GABA, purines, and acetylcholine (Butt et al., 2019). Additionally, different in vitro and in situ studies have provided evidence for the release of neurotransmitters following neuronal activity which, in turn, were shown to modulate oligodendrogenesis (Gautier et al., 2015; Hamilton et al., 2017; Stevens et al., 2002; Wake et al., 2011; Zonouzi et al., 2015). Interestingly, human trials using magnetic resonance spectrometry (MRS), MRI or positron emission tomography (PET) also found changes in the release of neurotransmitters following NIBS (Cember et al., 2022; Heimrath et al., 2020; Lengu et al., 2021; Stagg et al., 2009). However, whether the release of neurotransmitters through NIBS leads to enhanced oligodendrogenesis is not known. Furthermore, it remains unclear whether this neurotransmitter release influences oligodendrogenesis directly through the activation of neurotransmitter receptors on OPCs or indirectly through neurogenesis. Evaluating the effects of NIBS and subsequential neurotransmitter release on the distinct steps of oligodendrogenesis in vivo will be crucial to implement a standardized stimulation protocol for myelin enhancement in humans.

2.2. Data from human trials

To this date, no studies have investigated the effects of NIBS on myelination in healthy subjects. Therefore, we will discuss another way of enhancing neuronal activity in humans, namely through exercise-dependent plasticity of white matter (Chen et al., 2019). One difficulty in humans is that it is difficult to quantify myelin since there is to date no accessible radiological marker that assesses myelin specifically. A recent study using ^{11}C MeDAS PET was able to quantify myelin density within MS lesions. However, this method requires arterial blood sampling, which is an invasive procedure reducing its clinical applicability (van der Weijden et al., 2022).

Several other non-invasive, albeit imprecise methods are being used in research to measure myelin; each with their own benefits and drawbacks. Most studies investigating the effects of training on white matter structure have used diffusion tensor imaging (DTI)-based measurements such as fractional anisotropy (FA), radial diffusivity (RD) and mean diffusivity (MD) as reflected in Table 1. FA is a measure of diffusion of water molecules parallel to the axon and ranges from 0 to 1. The greater the FA is, the more restricted the diffusion of water molecule is, reflecting myelination or axon integrity. However, FA is also impacted by axonal diameter, fiber density and fiber orientation (ie. crossing versus uncrossing fibers), therefore lacking specificity for myelin evaluation (Parker et al., 2002). For example, demyelination has been shown to be associated with decreased FA in MS plaques and black holes, which represent T1 hypointensities, reflecting permanent demyelination and axonal damage (Bammer et al., 2000; Filippi et al., 2001; Werring et al., 1999). RD and MD are additional DTI-parameter that can indicate white matter changes. RD represents the direction of water diffusion perpendicular to the axon, while MD represents the average of molecular motion along all axes. Increased RD and MD indicate impairment to the integrity of the white matter as this means molecules move unrestricted (Cercignani et al., 2000; Freund et al., 2010; Song et al., 2002).

Although several studies (Bengtsson et al., 2005; Ekerdt et al., 2020; Engvig et al., 2012; Gebauer et al., 2012; Han et al., 2009; Hofstetter et al., 2017; Hu et al., 2011; Lee et al., 2010; Lövdén et al., 2010; Madler et al., 2008; Mamiya et al., 2016; Moore et al., 2017; Schlegel et al.,

Table 1
training-dependent changes in human myelination on MRI.

Study	Brain imaging	Intervention	Results
(Schmithorst and Wilke, 2002)	DTI	Comparison of five adults with musical training since early childhood and seven adult controls	Increase of FA in genu of corpus callosum and decrease in FA in corona radiata and internal capsule bilaterally.
(Bengtsson et al., 2005)	DTI	Comparison of childhood, adolescence, and adulthood piano practicing versus non-musicians	FA increase in the bilateral posterior internal capsule in childhood practicing. Practicing during adolescence was associated with increased FA in the splenium and the body of the corpus callosum. Adult practicing was associated with increase in FA in the left anterior limb of the internal capsule and in the right temporoparietal junction
(Han et al., 2009)	DTI	Pianist vs non-musicians	Higher FA in the right posterior limb of the internal capsule in the pianist group
(Imfeld et al., 2009)	DTI	Professional musicians versus control	Lower FA in the left and right corticospinal tract in the musician group
(Scholz et al., 2009)	DTI	Juggle training for six weeks	Increase in the FA of right posterior intraparietal sulcus
(Lee et al., 2010)	DTI	Baduk players versus inexperienced players	FA increase in right frontal, cingulum, striato-thalamic and left inferior temporal regions and FA decrease in bilateral dorsolateral premotor and right parietal areas in the group of Baduk experts
(Lövdén et al., 2010)	DTI	Cognitive tasks in young and older adults for 180 days	Increase in FA and decrease in MD in anterior corpus callosum for both young and older adults
(Takeuchi et al., 2010)	DTI	2 months of working memory training	Increased FA in the inferior parietal sulcus and in the border between the frontal and parietal lobe
(Taubert et al., 2010)	DTI	6 weeks of training on a complex whole-body balancing task (one training day per week)	Decrease in FA in bilateral prefrontal white matter and increase in MD in the right inferior parietal and right cerebellar white matter.
(Hu et al., 2011)	DTI	3-year training of abacus-based mental training	Increased FA in corpus callosum, left occipitotemporal junction and right premotor projection

(continued on next page)

Table 1 (*continued*)

Study	Brain imaging	Intervention	Results
			in children with abacaus-based mental training
(Engvig et al., 2012)	DTI	8 weeks intensive memory training	Increase in FA in left anterior hemisphere
(Gebauer et al., 2012)	DTI	5-week spelling training in spelling impaired children	Increase in FA and decrease in radial diffusivity in the left temporal, parahippocampal and hippocampal regions
(Schlegel et al., 2012)	DTI	9-month training of a second language	Increases in FA in the genu of the corpus callosum, the left hemisphere and in the right temporal region
(Hofstetter et al., 2013)	DTI	2-hour spatial learning task	Decrease in MD in the body of the fornix. No changes in FA
(Steele et al., 2013)	DTI	Comparison of early and late trained musicians	Increased FA in the posterior midbody and anterior portion of the isthmus of the corpus callosum in early-trained musicians versus late-trained musicians
(Wang et al., 2014)	DTI	Visuo-spatial motor traning tasks over 9 sessions (2–3 sessions per week)	Increase in FA in the right hemisphere including the posterior and anterior limbs of the internal capsule, corona radiata and the body of the corpus callosum
(Jolles et al., 2016)	DTI	Intense 2-month math tutoring program in third grade children	No significant FA changes in the any of the tracts
(Mamiya et al., 2016)	DTI	Intensive short-term English immersion program in Chinese adults	Increase in FA in the right superior longitudinal fasciculus as a function of the amount of time spent in the immersion program
(Hofstetter et al., 2017)	DTI	Under 1 h training of new word learning	Increase in FA in relation to learning rate in superior longitudinal fasciculus. Reduction in different diffusivity measures in the left inferior frontal gyrus, middle temporal gyrus, and inferior parietal lobule after intervention
(Moore et al., 2017)	DTI	4-week music-cued left-handed motor training	Increase of FA in right arcuate fasciculus in the music group
(Ekerdt et al., 2020)	DTI	3 weeks of word learning in pre-school children	Increased FA in the left precentral white matter
(Tremblay et al., 2021)	DTI	Training of complex visuomotor	Decrease in FA in the left corticospinal tract in the intervention group

Table 1 (*continued*)

Study	Brain imaging	Intervention	Results
		sequence for five consecutive days.	
(Lakhani et al., 2016)	MWF	Ten sessions of visuomotor skill training with the right arm	Increase of MWF in the left intraparietal sulcus and left parieto-occipital sulcus
(Metzler-Baddeley et al., 2017)	MWF, longitudinal relaxation rate R1, restricted volume fraction, DTI	Computerized exercises of verbal and spatial span tasks in healthy adults	Increases in R1, restricted volume fraction, fractional anisotropy and reduced radial diffusivity in the right dorsolateral superior longitudinal fasciculus and the left parahippocampal cingulum. No changes in myelin water fraction
(Beaulieu et al., 2020)	MWF	Poor readers versus good readers between 10 and 18 years	Lower MWF in the left and right thalamus, splenium of corpus callosum, left posterior and anterior limb of the internal capsule and left centrum semiovale in the poor reading group
(Economou et al., 2022)	MWF and DTI	Reading ability in 10-year-old children	Lower MWF in left inferior fronto-occipital fasciculus and anterior segment of the arcuate fasciculus in children with better reading scores. No association between reading abilities and FA
(Biel et al., 2020)	MTR	4 weeks of cognitive training of two-back working memory task	No changes in MTR after intervention in subcortical brain regions.
(Huber et al., 2021)	DKI; WMTI; T1 relaxation	intensive reading intervention for 8 weeks in children with reading difficulties between 7 and 12 years versus age-matched non-intervention controls	Extra-axonal diffusivity was inversely related to the intervention time. (Possibly due to an increase in size or distribution of non-neuronal cells such as glia). No changes in axonal water fraction, overall diffusion kurtosis, and T1 relaxation time

DKI = diffusion kurtosis imaging; DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = mean diffusivity; MTR = magnetization transfer ratio; MWF = myelin water fraction; R1 = longitudinal relaxation rate; WMTI = white matter tract integrity

2012; Schmithorst and Wilke, 2002; Scholz et al., 2009; Steele et al., 2013; Takeuchi et al., 2010; Taubert et al., 2010; Wang et al., 2014) have reported experience dependent plasticity of the white matter using these measurements, discrepancies have been reported as well (Hofstetter et al., 2013; Imfeld et al., 2009; Jolles et al., 2016; Taubert et al., 2010; Tremblay et al., 2021). For one, the methodology of the studies might differ but more importantly the non-specific nature of DTI-imaging to measure myelin make it a suboptimal technique to

visualize myelin and can account for these differences (Winston, 2012). These inconsistencies demonstrate the need for more specific and reliable markers for myelin.

In that context, multicomponent relaxometry metrics such as myelin water fraction (MWF) have shown more specificity for myelin than DTI-based measures (Madler et al., 2008). Recently, MWF has been used more extensively in studies to observe differences in white matter following training. Depending on the T2 relaxation rate water content of different brain structures can be measured (Whittall et al., 1997). MWF reflects the proportion of water trapped in myelin and is defined by the proportion of the (short) T2 relaxation rate (specific for myelin) to the whole T2 region (MacKay and Laule, 2016). MWF demonstrates a strong correlation with histopathological measures making it a good candidate for myelin assessment (Laule et al., 2006). During a training of visuo-motor skills in the right arm, an increase in MWF in areas of the brain engaged in the particular task was observed (Lakhani et al., 2016). Other research compared reading abilities in children with MWF and found conflicting outcomes. While Beaulieu et al. discovered a positive link between myelination of several brain regions including the left hemisphere and reading abilities, Economou et al. reported a negative correlation between left hemisphere myelination and reading ability (Beaulieu et al., 2020; Economou et al., 2022). The authors explained these inconsistencies by identifying distinct methodologies, including sample size, region of interest, and demographic characteristics.

Using diffusion kurtosis imaging, one group (Huber et al., 2021) investigated the impact of an 8-week intense reading challenge on children with reading problems and looked for structural white matter alterations. This technique takes into consideration barriers like cell membranes and organelles and takes advantage of the non-Gaussian distribution of water diffusivity (Jensen et al., 2005). Using this method, one can quantify the white matter tract integrity (WMTI) by measuring diffusion in two non-exchanging compartments such as the intra-axonal and extra-axonal compartments (Fieremans et al., 2011). In their study, a change was only observed in the extra-axonal diffusivity after the reading intervention, and it was negatively linked with intervention duration. It is possible that this indicates a modification in non-neuronal cells, such as glial cell density. This might confirm previous preclinical work that neuronal activity is able to enhance the proliferation of OPCs (Huber et al., 2021).

These studies underline that white matter structure can be altered through experience well beyond the developmental time window. However, further studies with more specific radiological biomarkers for myelin are warranted before firm conclusions can be drawn regarding the short- and long-term effects of training and by extension neuronal activity on myelination. Table. 2.

3. Evidence for neuronal activity-dependent remyelination

3.1. Data from animal models

Remyelination is an essential process for restoring conduction velocities after a demyelinating insult. In multiple sclerosis, for unknown reasons, the regeneration process is faulty, therefore not all injuries heal. In normal conditions, the regeneration process usually requires proliferation, differentiation, and maturation of OPCs that ultimately make contact with the demyelinated axon and, through reciprocal communication, receive the signal to myelinate (Gautier et al., 2015). In multiple sclerosis, the failure to remyelinate seems to arise mainly at the differentiation and maturation stages (Franklin and ffrench-Constant, 2017).

Given that under normal conditions myelination can be altered with neuronal activity (ie. adaptive myelination) through optogenetics (Gibson et al., 2014) or whisker trimming (Mangin et al., 2012) for instance, the question rises whether neuronal activity can also impact remyelination. Gautier et al. demonstrated in a toxin-induced model of demyelination and subsequent remyelination that demyelinated axons from the corpus callosum form de novo synapses with OPCs, comparable to the synapses in developing unmyelinated axons. In addition, the group revealed that glutamate release and neuronal activity are required for appropriate remyelination, and that blocking both leads to an increased pool of OPCs and a decreased number of differentiated oligodendrocytes (Gautier et al., 2015).

The observation that OPCs are present in certain MS lesions, yet remyelination fails within these lesions, led to the hypothesis that the micro-environment in which these precursor cells reside might not favor maturation (Chang et al., 2002). One possible explanation for the failure of remyelination could lie in the glial scar formation triggered by the activation of astrocytes following a demyelinating insult (Miller and Mi, 2007). In this light, Ortiz et al. (2019) explored whether optogenetic activation of neurons may promote oligodendrogenesis in a context of demyelination. They used a model of focal demyelination caused by LPC injection in the corpus callosum at the level of the motor cortex and discovered that repetitive photostimulation of demyelinated callosal fibers was able to promote OPC differentiation and remyelination. However, the proliferation of neither microglia nor astrocytes was affected by neuronal activity (Ortiz et al., 2019). Although astrocytes and microglia release factors that can promote or impede remyelination (Domingues et al., 2016), Ortiz and colleagues (Ortiz et al., 2019) did not explore the impact of optogenetics on the release of these factors. As a result, the influence of neuronal activity on creating a microenvironment that is favorable to remyelination remains unexplored. In another model of demyelination, a chemogenetic strategy to stimulate neurons in the primary motor cortex improved remyelination and thus confirmed that neuronal activity is able to enhance myelin repair in a context of demyelination (Luo et al., 2021).

While chemogenetic and optogenetic approaches are very useful methods to activate or suppress specific subtypes of neurons, it cannot be translated in clinical studies, hence alternative ways are required to modulate neuronal activity (White et al., 2020). Transcranial magnetic stimulation, transcranial direct current stimulation, and transcranial alternating current stimulation are among the most used NIBS and have been investigated in several neuropsychiatric diseases. Conversely to chemogenetic and optogenetic stimulation, NIBS activates also a wide array of cells including microglia and astrocytes (Luo et al., 2022; Medina-Fernandez et al., 2017). The exact cellular mechanisms and the impact of different stimulation protocols on these glial cells are not yet elucidated, and further preclinical research is warranted in order to be able to translate preclinical findings to humans.

3.2. Transcranial magnetic stimulation in preclinical models of demyelination

Transcranial magnetic stimulation (TMS) is a non-invasive technique that uses a copper wire coil to generate electrical currents in a plane perpendicular to the magnetic field (Janssen et al., 2015). A conventional coil produces electrical currents that are adequate to depolarize superficial axons in the gray matter but not those in the deeper white matter or deep nuclei of the brain (Lefaucheur et al., 2014). Therefore, newer coils have recently been developed that are able to target deeper brain locations including the hippocampus, nucleus accumbens, and cerebellum (Samoudi et al., 2018). Moreover, TMS used repeatedly induces long-lasting effects that endure beyond the duration of the stimulation (Klomjai et al., 2015). TMS has been used sparingly in research regarding remyelination, yet existing data suggest that it may be an effective tool for enhancing remyelination. Notably, repetitive TMS (rTMS) demonstrated an improvement in myelin repair in a rat model of demyelination. Additionally, rTMS was found to stimulate the proliferation and migration of neural stem cells from the SVZ to the lesion site. Whether these neural stem cells differentiated into remyelinating OL was not investigated (Sherafat et al., 2012). Nevertheless, the potential of NIBS to accelerate differentiation of neural stem cells into myelinating OL was demonstrated in a rat model of stroke. This finding identifies a potential source of myelinating OL following NIBS (Zhang et al., 2020).

Table 2
NIBS in preclinical models of MS.

Study	Preclinical model	Location of injury	Intervention	Readout	Result
(Sherafat et al., 2012)	LPC in adult female SD rats	Corpus callosum	rTMS (60 Hz; 0.7 mT) for 2 h twice a day for 7,14, or 28 days postlesion	LFB staining to detect demyelination. IHC (BrdU as a marker of cell proliferation, Nestin as a marker of neural stem cells, MBP as a marker of myelin)	Attenuation of demyelination at all time points and increased levels of MBP in lesion area on days 14 and 28 postlesion after TMS compared to sham. Increase in BrdU and Nestin-positive cells between the SVZ and lesion on days 7 and 14 postlesion after TMS compared to sham.
(Medina-Fernandez et al., 2017)	MOG-EAE in DA rats	Spinal cord	TMS (60 Hz, 0.7 mT) for 2 h once a day for three weeks	Motor score assessment. Griess method for nitric oxide. ELISA for LBP. Chromogenic endotoxin quantification for LPS. Nissl staining for pyknosis (measurement of apoptosis). IHC (GFAP as a marker for astrocytes)	Improvement of motor skills at day 35 after TMS compared to sham. Decreased pyknotic nuclei after TMS compared to sham. Reduction of astrocytosis and metabolites of neuroinflammation (nitric oxide, LBP and LPS) after TMS compared to sham.
(Duarte et al., 2018)	CPZ 0.2% for 4 weeks in male C57BL/6 J mice aged 7 weeks	Corpus callosum	Six sessions of LLLT (808 nm wavelength in a single point equidistant between the eyes and ears of the animals for 20 s) for 3 consecutive days during the fourth week of cuprizone treatment	LFB. IHC for MBP, GFAP, IBA-1 (marker for microglia), PDGF-beta receptor and Ki67 (markers for OPC proliferation), Olig-2 (marker for oligodendrocyte lineage cells)	Increased myelin staining after LLLT compared to sham. Increase in oligodendrocyte lineage cells and proliferative OPCs compared to sham. Decrease in astrogliosis and microgliosis compared to sham
(Olmstead et al., 2018)	C57BL/6 J mice fed with CPZ 0.2% for either five (to look for slowdown of demyelination) or 15 weeks (to look for increase in remyelination)	Corpus callosum	TFUS at 3 distinct frequencies (0.625, 1.09 and 2.0 MHz), 20 stimulations per second lasting for 30 s followed by a rest period of 90 s, repeated for a total of 30 min per day for five consecutive days during the fourth week or 13th week.	T2-weighted 14-T MRI, LFB	MRI images showed no decrease in demyelination after TFUS in the 5-week group compared to sham but showed increased remyelination after TFUS in the 15-week group compared to sham. LFB showed an increase in myelin staining only for the 1.09 MHz frequency in the 15-week group compared to sham.
(Li et al., 2019)	SCI in SD rats	Spinal cord	LFPEMF (0.25 A, 250 V, pulse width of 1 ms, 50 Hz, 1mT) for 4 h a day for 8 weeks post-surgery	BBB score to assess for motor recovery. HE and LFB staining of spinal cord tissue to assess for severity of SCI. IHC and WB to assess for differentiation of OPCs into OLs. TB staining of the spinal cord to assess for remyelination. WB to detect BDNF and NGF levels and ELISA to analyze the expression of TNF-α and IL-6	LFPEMF resulted in better motor scores 3–8 weeks post-SCI compared to sham. LFPEMF attenuated demyelination 14 days post-SCI compared to sham. LFPEMF increased the pool of mature OLs 4,7 and 14 days after SCI compared to sham. LFPEMF increased remyelination 1,2 and 3 weeks after SCI compared to sham. LFPEMF increased the levels of neurotrophic factors BDNF and NGF post-SCI while the levels of the anti-inflammatory cytokines TNF-α and IL-6 were decreased compared to sham.
(Stevanovic et al., 2019)	EAE in DA rats aged 10–14 weeks	Spinal cord	rTMS (iTBS or cTBS) for 10 days starting 14 days after EAE induction	IHC for BDNF, GFAP, Iba-1 ant ki-67	Increased levels of BDNF after both iTBS and cTBS compared to sham. Both cTBS and iTBS reduced the number of proliferative astroglia and microglia compared to sham.
(Dragic et al., 2020)	EAE in DA rats aged 10–14 weeks	Spinal cord	rTMS above the frontal cranial bone starting from 14 days after induction of EAE for 10 consecutive days. iTBS consisted of 20 trains of ten bursts (3 pulses at a frequency of 50 Hz) repeated at 5 Hz (lasting 192 s with 10 s intervals between trains. cTBS consisted of a single 40 s train burst of 600 pulses repeated at 5 Hz	IHC for GFAP, Iba-1, and MBP.	Both iTBS and cTBS diminished the duration of the paralysis after EAE-induction compared to sham. Both iTBS and cTBS attenuated the loss of MBP after EAE-induction compared to sham. Both iTBS and cTBS attenuated the microglial and astrocytic activation after EAE-induction compared to sham.

(*continued on next page*)

Table 2 (*continued*)

Study	Preclinical model	Location of injury	Intervention	Readout	Result
(Yang et al., 2020)	Male C57BL/6 J mice fed with CPZ 0.2 % for five weeks	Corpus callosum, caudate putamen, frontal cortex and hippocampus	Deep rTMS (30–40 Hz for 2 s with a resting interval of 8 s. Each 2 s stimulation was composed of six pulses at 1000 Hz) once a day during weeks 2–5 of the CPZ-feeding period	Behavioral tests (Y-maze, open-field test, social interaction test). IHC for MBP, GST-π (marker for mature OL) and Iba-1	Deep rTMS reduced anxiety-like behavior, increased social interaction and spatial memory compared to sham Deep rTMS attenuated the myelin breakdown in frontal cortex and hippocampus compared to sham. Deep rTMS alleviated the loss of OL in the corpus callosum and frontal cortex but not in the caudate putamen compared to sham. Deep rTMS alleviated the increase in microgliosis in the corpus callosum and frontal cortex and in the caudate putamen compared to sham. Deep rTMS decreased the levels of the pro-inflammatory cytokine IL-1β in the corpus callosum and frontal cortex and in the caudate putamen compared to sham. Deep rTMS decreased the levels of the pro-inflammatory cytokine IL-6 in frontal cortex and in the caudate putamen compared to sham. Deep rTMS increased the levels of the anti-inflammatory cytokine IL-10 in the hippocampus compared to sham
(Mojaverrostami et al., 2022)	Male C57 BL/6 mice, 8 weeks old CPZ 0.2 % fed for 12 weeks	Corpus callosum	Anodal tDCS (10 min, 0.1 mA) daily from week 12 to week 16. Anode was placed above the corpus callsoum. Cathode was connected to the skin of the thorax. MSC from the bone marrow of 6–8weeks old C57BL/6 were harvested and injected in the right ventricle at week 14	Rotarod test. LFB staining. qRT-PCR for p53, BDNF, SOX2, GADPH. TUNEL assay. IHC for Olig-2.	tDCS and tDCS + MSC increased the running time on the rotarod test compared to the CPZ-group. Both the tDCS and tDCS + MSC groups were able to enhance remyelination compared to the CPZ-group. tDCS + MSC was more efficient than tDCS alone. tDCS and tDCS + MSC were able to increase the levels of BDNF and SOX2 compared to the CPZ-group. There was no difference in the levels of P53 after tDCS compared to the CPZ-group. But the combination of tDCS and MSC was able to decrease the levels of P53 compared to the CPZ-group. tDCS and tDCS + MSC were able to decrease the number of apoptotic cells compared to the CPZ-group
(Marenna et al., 2022)	EAE-MOG in female C57BL/6 mice aged 6–8 weeks	Optic nerve	tDCS with one electrode above the somatomotor cortex and the other electrode on the ventral thorax (325 μA for 10 min) from day 3 to day 7 after EAE-induction	VEP. LFB staining. IHC for Iba-1, SMI 312 (marker for axons), Caspr, and MBP	EAE-cathodal decreased VEP latency compared to EAE-anodal and EAE-sham. EAE-cathodal decreased microgliosis compared to EAE-anodal and EAE-sham. EAE-cathodal decreased the axonal loss compared to EAE-anodal and EAE-sham. All EAE groups (cathodal, anodal and sham) exhibited more demyelination than the healthy group. EAE-cathodal had a higher number of non-damaged nodes of Ranvier than EAE-sham and EAE-anodal.

BBB= Basso-Beattie-Bresnahan; CPZ = cuprizone; DA = Dark Agouti; EAE = experimental autoimmune encephalomyelitis; HE= hematoxylin and eosin; IHC= immunohistochemistry; LBP= Lipopolysaccharide-Binding Protein; LFB = Luxol Fast Blue; LFPEMF = Low Frequency Pulsed Electromagnetic Field; LLLT = low-level laser therapy; LPC = lysophosphatidylcholine; LPS = lipopolysaccharide; MOG= myelin oligodendrocyte glycoprotein; MBP = myelin basic protein; MSC = mesenchymal stem cells; MTR= magnetization transfer ratio; OL = oligodendrocyte; qRT-PCR = quantitative real-time polymerase chain reaction; SCI= spinal cord injury; SD = Sprague-Dawley; SVZ = subventricular zone; TB= Toluidine Blue; TBS= Theta Burst Stimulation; iTBS = intermittent Theta Burst Stimulation; cTBS = continuous Theta Burst Stimulation; TFUS = transcranial focused ultrasound; VEP = visual evoked potentials; WB = Western Blot

Similarly, in a rat model of spinal cord demyelination, transcranial low frequency pulsed electromagnetic fields also demonstrated enhanced remyelination through increased oligodendrogenesis and attenuation of inflammation (Li et al., 2019). Mechanistically, it seems that neuronal activity increases the expression of neurotrophins such as BDNF and NGF in the spinal cord while reducing the expression of pro-inflammatory cytokines such as TNF- α and IL-6 (Li et al., 2019; Luo et al., 2021).

3.3. Transcranial direct current stimulation in preclinical models of demyelination

Transcranial direct current stimulation (tDCS) is another intriguing noninvasive technique that modulates cortical excitability. The effects on cortical excitability are opposite depending on the polarity of the stimulation (anodal or cathodal). Anodal stimulation lowers the action potential threshold, while cathodal stimulation hyperpolarizes the neuronal membrane and makes neuronal firing less probable (Nitsche et al., 2008); However, this does not occur uniformly, since certain neurons in deeper cortical layers may be activated by cathodal stimulation and inhibited by anodal stimulation, suggesting that the orientation of the neurons in relation to the electrical field is important (Stagg and Nitsche, 2011). Additionally, repetitive anodal stimulation seems to facilitate long-term potentiation through BDNF release and TrkB activation (Fritsch et al., 2010); Only one study has explored the potential of tDCS to promote remyelination. In the cuprizone mouse model, researchers found that tDCS treatment resulted in a greater level of remyelination than in the control group. Moreover, the remyelination was enhanced when tDCS was combined with mesenchymal stem cell transplantation (Mojaverrostami et al., 2022). Since it is a non-invasive, inexpensive, and simple-to-use at home device, tDCS might be an interesting tool to investigate in pwMS to enhance remyelination.

3.4. Transcranial alternating current stimulation in preclinical models of demyelination

Endogenous brain oscillations are required for cognitive function and have been demonstrated to be disturbed in a variety of neurodegenerative disorders (Chan et al., 2021). Electrophysiological instruments such as EEG and MEG may record these oscillations (Vosskuhl et al., 2018). Injecting alternating currents into an intact scalp is one way to manipulate these oscillations. If electrical fields are strong enough, transcranial alternating current stimulation (tACS) may force endogenous brain oscillations to a pre-defined oscillatory pattern (Liu et al., 2018). Other factors that might alter tACS effects include phase and frequency (Antal and Paulus, 2013). It was discovered that when doing a cognitive task, in-phase stimulation improved cognition whereas out-of-phase stimulation lowered the individuals' cognitive abilities (Polania et al., 2012). The ultimate goal of tACS is to increase cognitive performance by strengthening connections between distant brain regions. The precise mechanisms of this entrainment remain unknown, although it has been shown that, unlike tDCS, tACS influences the timing of action potentials rather than the firing rate of action potentials (Krause et al., 2019). Despite being a promising technique, it remains unclear what the effects of tACS are in remyelination as no studies using this technology have been conducted to date.

3.5. Transcranial focused ultrasound in preclinical models of demyelination

Transcranial focused ultrasound (TFUS) is an innovative technology that has the potential to control neuronal activity in the brain. It works by using ultrasonic pulses to generate a precise energy field within the brain, which can be used to stimulate or suppress neuron activity. While the exact mechanisms of how this modulation works are still unknown, researchers are working to identify the parameters that can lead to activation or inhibition of neurons (Zhang et al., 2021). An earlier study indicated that TFUS therapy was able to increase myelin regeneration in cuprizone-fed mice (Olmstead et al., 2018). These effects could partially be explained by an increased expression of TGF-β, TGF-βR1, and TGF-βR2 after LFMS, a pathway that was previously shown to facilitate remyelination (Hamaguchi et al., 2019; Wang et al., 2021c).

3.6. NIBS as a neuroprotective tool

Beside remyelinating effects, NIBS such as theta burst transcranial magnetic stimulation, low-level laser therapy, and repeated transcranial ultrasound stimulation can also slow down myelin breakdown in the demyelination phase of the cuprizone mouse model (Duarte et al., 2018; Huang et al., 2022; Yang et al., 2020). The neuroprotective effect of theta burst TMS seem to occur through lowering of pro-inflammatory cytokine production by microglia (Yang et al., 2020). This switch of microglia from a pro-inflammatory to a pro-regenerative state is dependent on both neuronal activity and outward axonal potassium-signaling (Hughes and Appel, 2020; Ronzano et al., 2021). The node of Ranvier has recently been discovered to play a critical role in this transition as it serves as a communication hub between axons and microglia. Through the expression of a potassium channel, THIK-1, microglia sense the release of potassium by the axon. The critical role of THIK-1 was confirmed in the LPC of model of MS as inhibiting this receptor led to an increase in pro-inflammatory cytokines and a decrease of pro-regenerative cytokines, ultimately resulting in reduced remyelination (Ronzano et al., 2021).

In summary, these different studies reveal that modulation of neuronal activity is an interesting way to induce cross-communication between glial cells and neurons. While oligodendrocytes directly impact (re)myelination through wrapping myelin around axons, microglia and astrocytes are indirectly involved in the process and seem to respond to neuronal activity by inducing a favorable microenvironment for myelin repair.

3.7. Human data

No human studies to date have found an increase in remyelination in pwMS after modulation of neuronal activity. However, in another demyelinating disorder, spinal cord injury, it was shown that patients who underwent eccentric rehabilitation in the form of downhill training had an improvement in MWF in brain motor-learning regions and mixed motor- and sensory-tracts in the ventral cervical spinal cord (Faw et al., 2021; Mancini et al., 2020). This seems to corroborate previous studies indicating that training can induce myelin plasticity in healthy humans (see above). Moreover, in a parallel study, the researchers observed an increase in oligodendrogenesis and enhancement of contacts between axons and oligodendrocytes in spinal cord-injured mice that underwent the same intervention (Faw et al., 2021; Mancini et al., 2020).

Given that neuronal activity can be altered with optogenetic, chemogenetic techniques and NIBS (Gibson et al., 2014; Krause et al., 2019), that these techniques produced promising results in preclinical studies of adaptive myelination and myelin repair in mouse models of MS (Cullen et al., 2019; Ortiz et al., 2019; Wang et al., 2021c) and that NIBS has been able to improve some symptoms of MS in a limited number of studies in pwMS (Aloizou et al., 2021; Hiew et al., 2022), we argue that NIBS is a potential technique to improve remyelination in pwMS.

Two problems arise when using NIBS in pwMS. For one, the exact mechanisms of NIBS are not yet elucidated which results in the lack of a uniform protocol to study remyelination. Secondly, as discussed before, due to the lack of specific myelin markers, studies that have used NIBS to investigate symptomatic relief in MS neglected the component remyelination. Despite these limitations, non-invasive brain modulation has already demonstrated encouraging benefits in terms of fatigue, spasticity, and bladder control for instance (Aloizou et al., 2021; Hiew et al.,

2022). Whether this symptomatic relief is due to an increase in conduction rates as a result of improved myelin integrity is thus still a matter of debate. Considering the lack of evidence for remyelination, we will discuss the symptomatic improvements in pwMS seen in different studies after NIBS.

The limited studies that have been conducted with tDCS regarding the effects on the motor function of the upper limb in pwMS have shown conflicting results. Many of the reasons can be found in the methodology. For instance, there are disparities in age, MS type, and disease duration amongst the studies (Hiew et al., 2022). In addition, the stimulation intensity and stimulation timing were not same in these studies and higher stimulation intensities up to 2 mA seem to be more effective (Masoudian et al., 2020). Moreover, while some research examined the effects of tDCS during a manual task (Masoudian et al., 2020; Meesen et al., 2014), others examined the effects of tDCS after a manual task (Rumpf et al., 2018). Lastly, outcome measurements are not always similar throughout the studies, therefore comparisons are not always possible. For instance, serial finger tapping may not be sensitive enough to detect tDCS-induced improvements (Hiew et al., 2022). In the future, it is advisable to work with a standardized protocol in which greater intensities of up to 2 mA are used and stimulation is performed during manual tasks. Since the nine-hole peg test is the universal task for assessing dexterity in the clinical evaluation of pwMS, it seems a reasonable standardized method for evaluating the effects of stimulation on upper limb function.

Similar inconsistencies are seen in the trials using tDCS which evaluated lower limb function (Hiew et al., 2022). Stimulation protocols and outcome measurements were also responsible for these differences. For instance, single sessions of tDCS were shown to be ineffective regarding gait parameters compared to repetitive sessions (Workman et al., 2019). In addition, combining repetitive anodal tDCS (atDCS) and aerobic exercise were beneficial for gait velocity and walking distance. These advantages sustained at four-week follow-up which opens up the possibility for combining tDCS with rehabilitation to treat motor deficits in pwMS (Pilloni et al., 2020). A recent systematic review (Wang et al., 2021a) revealed that combining a training task with tDCS can increase cortical excitability even more. So, if one extrapolates the findings of the preclinical work regarding neuronal activity, one might argue that increased myelin integrity and subsequent better conduction velocities resulting from these interventions might explain the improved gait parameters seen in the study.

tDCS seems also capable of alleviating non-motor symptoms of MS, such as fatigue and cognitive impairment (Hiew et al., 2022). The left dorsolateral prefrontal cortex and the somatosensory area S1 are the favored tDCS target locations for fatigue improvement with tDCS, while only stimulation of the left dorsolateral prefrontal cortex was shown to improve cognitive tasks (Hiew et al., 2022; Mattioli et al., 2016). It is, however, difficult to investigate fatigue improvement due to the subjectivity of most outcome measurements. One possible measurement of fatigue is the P300 wave, an event-related potential that may be assessed during an oddball task in which a rare stimulus is presented within a succession of conventional stimuli. This measurement was previously shown to be lowered in amplitude and to have an increased latency in pwMS compared to healthy controls and has been linked to diminished cognition and increased fatigue (Chinnadurai et al., 2016; Pokryszko-Dragan et al., 2016). In one study with tDCS, the amplitudes of the P300 wave were increased without affecting the latency in pwMS. Moreover, during a simple reaction time task, this increased amplitude was accompanied by a fatigue-related decrease in reaction time (Fiene et al., 2018). These studies give evidence that tDCS is able to ameliorate a variety of MS symptoms including motor and non-motor symptoms.

In addition to tDCS, intriguing findings on MS symptom management were also found with rTMS (Gandiga et al., 2006). Targeting the leg motor cortex area with intermittent theta burst stimulation (TBS), a stimulation protocol consisting of high frequency stimulation (up to 50 Hz) given at theta frequency, has been shown to reduce lower limb spasticity in different studies (Aloizou et al., 2021). This resulted in a recommendation of class B in the most recent recommendations for the therapeutic use of rTMS (Lefaucheur et al., 2020). Interestingly, high frequency rTMS of the motor cortex to target spasticity has also shown improvements in bladder control (Centonze et al., 2007b). Other applications albeit less investigated for rTMS in MS include cerebellar dysfunction, major depression and cognitive dysfunction and fatigue (Aloizou et al., 2021). In conclusion, we may assert that there is some evidence connecting NIBS to the alleviation of MS symptoms. To ensure comparable study and draw conclusions regarding the efficacy of these treatments, however, defined procedures and outcome measurements are required.

3.8. Future perspectives

NIBS is being used in more and more clinical studies due to their therapeutic potential in various neuropsychiatric disorders. However, the precise mechanisms remain unclear, resulting in different protocols being used in research. This makes comparative analyses very challenging and accounts for conflicting results. To get a better understanding of the impact of these varied protocols on (re)myelination, NIBS should be tested in a preclinical setting, since evaluating different stimulation strategies on animal models is simpler and permits the investigation of cellular mechanisms. NIBS affects not only neurons but also astrocytes and microglia and these cells have been shown to be involved in myelin plasticity and repair (Hong et al., 2020; Luo et al., 2022; Ronzano et al., 2020). Understanding the impact of distinct NIBS protocols on neuronal activity and glial cells will enable researchers to adapt these protocols to pwMS in a uniform manner and improve remyelination.

Repeated electrical stimulation of axons was already shown to activate glutamate receptors on oligodendroglial cells both in vitro and in vivo (Nagy et al., 2017). Moreover, the pattern of stimulation has an impact on glutamate release and oligodendroglial cell behavior (Nagy et al., 2017). The pattern of electrical stimulation was also shown to be important in the activation of astrocytes (Wang et al., 2021b). Finally, low current electrical stimulation also influences microglial function, and the waveform of the stimulation seems to regulate their function (Lennikov et al., 2022). A recent in vivo tDCS study also showed dynamic modulation of microglia function after stimulation through neuron-microglia communication (Gellner et al., 2021). These studies demonstrate that electrical stimulation and more importantly, the pattern of stimulation is of essence in the regulation of glial cell function. Therefore, modulating these glial cells through neuronal activity could be an interesting way to achieve enhanced remyelination. Different protocols of electrical stimulation in vitro and in preclinical experiments should be employed to detect changes in the glial cell dynamics in normal circumstances; in situations of demyelination and in situations of remyelination. This would aid researchers in the use of a standardized protocol to enhance remyelination in (pre)-clinical studies.

In order to advance the field of NIBS, one must be aware of the obstacles of these techniques in human investigations. For instance, the human skull is thicker than that of a rodent. Therefore, it is vital to quantify, using computer models, the stimulation strength required to have the same effect on deeper locations in human individuals. Inter-individual variables such as brain anatomy, skull thickness, and genetics also contribute to distinct effects after NIBS (Hunold et al., 2021). This means that individual protocols may be required to achieve the desired effects on remyelination. In addition, researchers are restricted by the low currents to prevent side effects such as scalp irritation or headaches (Russo et al., 2017). This results in densities that are restricted to superficial structures since the skull and soft tissue attenuate most of these currents (Vöröslakos et al., 2018). Newer stimulation protocols that require smaller currents to stimulate deeper structures are on their way. For instance, temporal interference is a novel neuromodulation paradigm that aims at modeling neuronal activity in deeper

lying brain areas by sending in two slightly different oscillating waves at high frequency. The idea is that neuronal populations are 'transparent' (i.e. 'low- pass filters') to high-frequency oscillations and that only the (deeper) brain region's activity where the two waves have a strong interference are entrained on the difference of these frequencies (Grossman et al., 2017).

Finally, further study is required in the realm of myelin biomarkers. Currently, it is not feasible to determine with a high degree of accuracy from human research if a treatment induces remyelination. Immunohistochemistry must thus be used to examine both present and emerging radiographic markers. This may be accomplished via both preclinical research and the comparison of these MRI techniques with immunohistochemical staining of postmortem tissues. Future research examining the effects of NIBS should therefore include existing yet suboptimal radiographic markers of myelin (as reviewed by Mancini et al. (Mancini et al., 2020)) to determine if remyelination might be the cause of the possible alleviation of MS symptoms. In this regard an ongoing trial with repetitive TMS for 4 weeks will assess the safety of the procedure. In addition to assessing symptom improvement and quality of life, the researchers will analyze T2 lesions, atrophy, and myelin content using several MRI measures such as diffusion tensor imaging (DTI), magnetization transfer ratio (MTR) and quantitative T1 mapping (qT1) (Makowiecki et al., 2022). Finally, we also recommend the use of quantitative susceptibility mapping (QSM) or macromolecular proton fraction (MPF) for assessing novel therapies for remyelination, since these MRI approaches seem to correlate reliably with histological markers of myelin both in animal models and in post-mortem tissues (Kisel et al., 2022; Rahmanzadeh et al., 2022).

4. Conclusion

Overall, this review underlines the value of the modulation of neuronal activity in the observed (pre)clinical changes in white matter structure and in oligodendrogenesis after training or brain stimulation. Increased knowledge on the mechanism of action of NIBS is needed to create standardized protocols. Further, to test for enhanced (re)myelination in clinical trials, more accurate and specific radiographic indicators for myelin are required. Current markers, for instance, do not eliminate confounding axonal characteristics such as axonal diameter and therefore are not specific to myelin (Beaulieu, 2002). Due to the absence of these specific techniques for observing remyelination, studies demonstrating symptomatic improvement did not search for remyelination. While meta-analyses indicate that rTMS improves spasticity and repetitive tDCS might improve fatigue and cognition in pwMS, the role of remyelination in these improvements remains unknown (Chen et al., 2022; Kan et al., 2022). Given a good technique for detecting myelin, one may argue that these trials would have shown signs of remyelination, since symptomatic alleviation is likely an indication of the resolution of conduction deficiencies and, therefore, myelin repair.

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Data availability

No data was used for the research described in the article.

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