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REVIEW

Activity-dependent central nervous system myelination throughout life

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Abstract

Myelin, the multilayered membrane surrounding many axons in the nervous system, increases the speed by which electrical signals travel along axons and facilitates neuronal communication between distant regions of the nervous system. However, how neuronal signals influence the myelinating process in the CNS is still largely unclear. Recent studies have significantly advanced this understanding, identifying important roles for neuronal activity in controlling oligodendrocyte development and their capacity of producing myelin in both developing and mature CNS. Here, we review these recent advances, and discuss potential mechanisms underpinning activity-dependent myelination and how remyelination may be stimulated via manipulating axonal activity, raising new questions for future research.

Keywords: CNS, myelination, neuronal activity, neurotransmission, oligodendrocyte, OPC.

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The evolutionary importance of myelin is that it provides the structural basis for saltatory action potential propagation by restricting action potentials to short unmyelinated axonal segments (the nodes of Ranvier), thus allowing nerve conduction 20–100 faster than nonmyelinated axons of the same diameter—without occupying much space (Nave and Werner 2014). This has effectively enhanced the nervous system compactness, permitting the fast and efficient processing of complex information. It is also increasingly apparent that myelin confers trophic and metabolic support to the axons that it ensheaths (Lappe-Siefke *et al.* 2003; Simons and Nave 2015; Yin *et al.* 2006). The CNS myelination comprises a series of complex cellular events including proliferation and migration of oligodendrocyte precursor cells (OPCs), differentiation of OPCs into mature myelinating oligodendrocytes, axonal ensheathment and node formation (Fig. 1). This programme is tightly controlled by a number of intrinsic factors (Barres and Raff 1999; Baumann and Pham-Dinh 2001; Emery 2010; Mitew *et al.* 2014; Nave and Werner 2014) that are responsive to a range of extracellular cues, including signalling molecules released by neurons or glial cells such as growth factors and neurotransmitters and molecules expressed on the surface of these cells and axons (Mitew *et al.* 2014; Nave and Werner 2014) (Fig. 1).

A potential explanation for the long-lasting controversy over whether neuronal activity regulates myelination (Barres and Raff 1993; Barres *et al.* 1992; Demerens *et al.* 1996; Gautier *et al.* 2015; Gibson *et al.* 2014; Hines *et al.* 2015; Hughes *et al.* 2018; Liu *et al.* 2012, 2016; Makinodan *et al.* 2012; Mensch *et al.* 2015; Mitew *et al.* 2018) or not (Barres and Raff 1999; Bechler *et al.* 2015; Lee *et al.* 2012, 2013; Li *et al.* 2014), is that two distinct modes of myelination both exist: one that is independent of axonal activity and one that depends. Although there is no clear definition of the two

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Abbreviations used: AMPAR, AMPA receptors; BDNF, brain-derived neurotrophic fator; CCP, caudal cerebellar peduncle; CNS, central nervous system; EdU, ethynyl-2′-deoxyuridine; FA, fractional anisotropy; K_{KDR}, delayed outward-rectifying potassium channels; NMDAR, NMDA receptors; NRGs, neuregulin; OL, oligodendrocytes; OPCs, oligodendrocyte precursor cells; P35, postnatal day 35; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PNS, peripheral nervous system; TTX, tetrodotoxin.

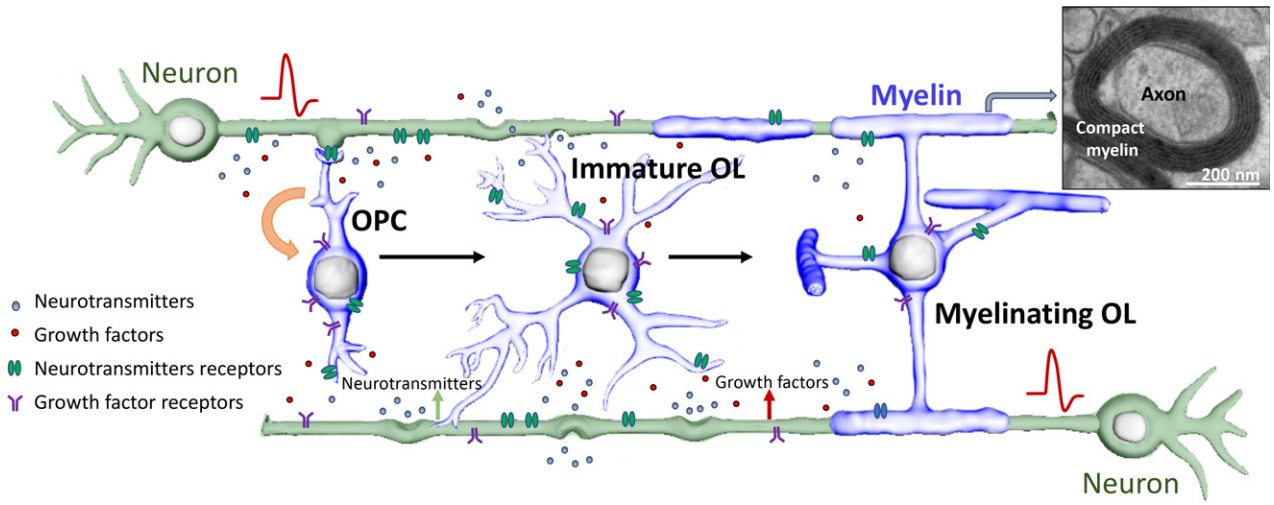

Fig. 1 Schematic showing oligodendroglial lineage development and *de novo* myelination. During development, subventricular cells in the CNS (brain and spinal cord) give rise to committed oligodendrocyte precursor cells (OPCs), which can proliferate and/or then terminally differentiate into post-mitotic immature oligodendrocytes (OL). In response to the appropriate extracellular cues, these immature OL can further mature and become myelinating oligodendrocytes, ensheathing receptive axons and forming compact myelin. Action potential firing by active neurons results in the release of neurotransmitters (such as glutamate, GABA, ATP or acetylcholine) and/or growth factors (such as platelet-derived growth factor, brain-derived neurotrophic factor or neuregulin) via synaptic and non-synaptic mechanisms, and exert multifaceted influence upon both oligodendroglial lineage development and axonal ensheathment. This process is regulated not only at the level of oligodendroglial proliferation and differentiation but also at the level of individual axons.

modes of myelination, the *activity-dependent myelination* is considered as a myelinating process dependent on and/or regulated by electrical activity and molecular cues such as growth factors, neurotransmitters or other molecules whose expression or release is regulated by axonal electrical activity (Barres and Raff 1993; Barres *et al.* 1992; Demerens *et al.* 1996; Gautier *et al.* 2015; Gibson *et al.* 2014; Hines *et al.* 2015; Hughes *et al.* 2018; Liu *et al.* 2012, 2016; Makinodan *et al.* 2012; Mensch *et al.* 2015; Mitew *et al.* 2018), while the *activity-independent myelination* is an oligodendrocyte-driven process independent of axonal electrical activity (Barres and Raff 1999; Bechler *et al.* 2015; Lee *et al.* 2012, 2013; Li *et al.* 2014). Cultured oligodendrocytes can survive, proliferate and differentiate in the absence of axons (Barres *et al.* 1993b; Chan *et al.* 2004; Watkins *et al.* 2008; Xiao *et al.* 2010), and produce myelin membrane around 'electrically silent' nanofibres (Bechler *et al.* 2015; Lee *et al.* 2012, 2013; Li *et al.* 2014), suggesting a neuronal activity-independent programme that drives oligodendroglial lineage progression and the initiation of myelination. On the other hand, increasing studies have revealed important roles for activity-dependent myelination, demonstrating that oligodendrocyte development and their capacity of producing myelin is a dynamic process driven by neural activity and experience (Barres and Raff 1993; Barres *et al.* 1992; Demerens *et al.* 1996; Gautier *et al.* 2015; Gibson *et al.* 2014; Hines *et al.* 2015; Hughes *et al.* 2018; Liu *et al.* 2012, 2016; Makinodan *et al.* 2012; Mensch *et al.* 2015; Mitew *et al.* 2018; Wake *et al.* 2011, 2015). CNS myelination is a lifelong process that peaks during development and continues into adulthood (Baumann and Pham-Dinh 2001; Hill *et al.* 2018; Hughes *et al.* 2018; Young *et al.* 2013). There is clear evidence for ongoing addition of oligodendrocytes throughout life, at least in rodents (Hill *et al.* 2018; Hughes *et al.* 2018; Young *et al.* 2013). Thus, a more complete understanding of activity-dependent myelination will provide new insights into the mechanisms that govern nervous system plasticity and aid the development of new therapies that directly target myelin repair after a demyelinating insult. Below, we will perform a systematic review on recent research focusing on activity-dependent myelination during development and adulthood as well as after injury.

Activity-dependent myelination during development

While Río-Hortega initially descried oligodendrocyte morphologies, in 1901, Flechsig put forward a fundamental law of myelogenesis – before the identification of oligodendrocytes, which states 'that the myelinization of nerve fibers in the developing brain follows a definite chronologic sequence such that those fibers belonging to particular functional systems mature at the same time' (Flechsig 1901). But this did not go unchallenged, and a contemporary scholar argued that myelination depended on the size of nerve calibre (Vogt and Vogt 1908). However, it was not until 1960s when

Gyllensten and Malmfors (1963) first introduced the intriguing idea that neuronal activity could influence the behaviour of oligodendroglial lineage cells, that a biological evidence was provided. This study demonstrated that dark rearing could inhibit developmental myelination in the optic nerve (Gyllensten and Malmfors 1963), which was later supported by a similar study showing premature eye-opening could accelerate it (Tauber *et al.* 1980). These studies were also challenged by number of similar studies arguing that axonal electrical activity did not regulate CNS myelination (Colello and Pott 1997; Colello *et al.* 1995; Shrager and Novakovic 1995). This debate is still ongoing, but evidence for this exciting notion, that axonal electrical activity can regulate myelination has now been significantly advanced by a number of recent works investigating multiple aspects of the myelinating process using sophisticated genetic and powerful imaging tools. Here we discuss some key aspects of the activity-dependent myelinating process during development, particularly on OPC proliferation, survival, differentiation and myelin ensheathment.

Neuronal activity regulates oligodendrocyte proliferation

Under normal homeostatic conditions, new myelinating oligodendrocytes can be generated from OPC proliferation (Young *et al.* 2013), or from a pool of constantly differentiating pre-myelinating oligodendrocytes (Xiao *et al.* 2016). In the 1990s, the optic nerve was used as a model to study activity-dependent effects on OPC proliferation and the number of oligodendroglial lineage cells (Barres and Raff 1993). When the developing optic nerves was transected just behind the eyeball, the number of mitotic OPCs dropped by 90% in 4 days, suggesting OPC division was largely regulated by the axons (Barres and Raff 1993). Concordant with this finding, silencing the axonal electrical activity via an intraocular injection of tetrodotoxin (TTX), a toxin that blocks voltage-gated sodium channels and action potentials, also reduced the number of dividing OPCs by 80% (Barres and Raff 1993). This early study provided the compelling experimental evidence that axonal electrical activity stimulates OPC proliferation in the optic nerve during development, indicating a mechanism by which electrical activity in neighbouring axons could control local OPC proliferation.

More recent studies using a range of techniques have confirmed that manipulating neuronal activity alters oligodendrogenesis in multiple CNS regions during development (Gibson *et al.* 2014; Mangin *et al.* 2012; Mitew *et al.* 2018; Venkatesh *et al.* 2015). By far the most common way to identify the OPC proliferation in response to altered neural activity has been the use of thymidine analogues such as 5-ethynyl-2′-deoxyuridine (EdU). Thymidine analogues are incorporated during DNA synthesis and have the advantage of permanently marking dividing cells and their progeny (Nowakowski *et al.* 1989). Gibson *et al.* (2014) adopted an optogenetic approach to stimulate neuronal electrical activity in the premotor cortex of postnatal day 35 mice, OPCs in both the premotor cortex and the subcortical white matter tracts displayed a marked proliferative response. In this experiment, EdU was given at the beginning of the 30-min stimulation period to label dividing OPCs in these mice which were subsequently sacrificed 3 h after stimulation and displayed an approximately fourfold increase EdU+ OPCs, indicating a rapid proliferative response (Gibson *et al.* 2014). This hyperproliferative response to increased neuronal activity was specific to OPCs as other glial cells such as the microglial number (predominantly localized to the superficial cortex) remained intact (Gibson *et al.* 2014). Consistent with these findings, another recent study employed a pharmacogenetic approach and found that 1-week simulation of a subset of somatosensory cortex neurons during early postnatal weeks significantly increased the number of proliferating OPCs in the corpus callosum of both juvenile and adult mice (Mitew *et al.* 2018). These studies not only provide further evidence supporting activity-dependent OPC proliferation but indicate that enhancing synchronized neural activity even in a relatively small number of axons can lead to significant OPC production and/or survival. Interestingly, the same laboratory also found that attenuating neuronal activity of a subset of callosal axons exerted no effect upon OPC proliferation although it was sufficient to suppress the extent of myelination of the silenced axons (Mitew *et al.* 2018).

It is difficult to determine whether neuronal activity directly drives OPC proliferation *in vivo* or whether an altered proliferation is partially secondary to increased differentiation. It has recently been shown that providing mice with a complex motor learning task (running on a complex wheel with variably spaced rungs) has led to a rapid increase in oligodendrocyte production (McKenzie *et al.* 2014; Xiao *et al.* 2016). This increased oligodendrogenesis could be partially because of accelerated cell differentiation. It has long been known that OPC proliferation involves growth factors such as platelet-derived growth factor (PDGF) AA, which increases OPC proliferation *in vitro* and *in vivo*. Exogenous PDGF AA was able to rescue the reduced OPC proliferation as a result of blocked neuronal activity (Barres and Raff 1993), supporting activity-dependent proliferation. PDGF AA signalling has been shown to up-regulate the expression of delayed outward-rectifying potassium channels (K_{KDR}) that are exclusively expressed in OPCs (Barres *et al.* 1990; Chittajallu *et al.* 2005; Larson *et al.* 2016) and these potassium channels are closed linked to cell cycle regulation and OPC proliferation (Barres *et al.* 1990; Chittajallu *et al.* 2002, 2005), whereas glutamate released from active neurons, acting on α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate receptors, inhibits K_{KDR} channels, thus reducing proliferation (Borges *et al.* 1994; Chittajallu *et al.* 2005). It is possible that active axons somehow release signals that stimulate OPC proliferation and then

these newly generated OPCs are to differentiate and specifically myelinate the active axons that have simulated their production.

Neurons form structural and functional synaptic connections with OPCs (Fig. 2a). OPCs can receive synaptic input mediated by neurotransmitters such as glutamate and GABA (Bergles *et al.* 2000; Clarke *et al.* 2012; Ge *et al.* 2009; Karadottir *et al.* 2005, 2008; Kolodziejczyk *et al.* 2010; Kukley *et al.* 2007; Lin and Bergles 2004; Osterstock *et al.* 2018; Ziskin *et al.* 2007; Zonouzi *et al.* 2015), suggesting that these neurotransmitters may also control oligodendrocyte development and myelination. Both glutamate and GABA receptors are present throughout the oligodendroglial cell lineage (Hamilton *et al.* 2017; Spitzer *et al.* 2016), suggesting that these cells are well equipped to sense neuronal activity. Glutamate is the most common excitatory neurotransmitter in the CNS and can be released from axons via synaptic and non-synaptic, vesicular and non-vesicular based mechanisms (Spitzer *et al.* 2016; Wake *et al.* 2015). Analysis of cultured OPCs has shown that activating glutamatergic signalling via AMPA/kainate receptors inhibits OPC proliferation (Gallo *et al.* 1996). Concordant with this *in vitro* finding, *ex vivo* studies using cultured brain slices found similar results (Fannon *et al.* 2015; Yuan *et al.* 1998). Similarly, early sensory deprivation via removing whiskers in mice at birth (possibly resulting in a loss of sensory input to the barrel cortex) increased the proliferation of $NG2^+$ OPCs at P6, suggesting that glutamatergic signalling from thalamocortical axons acted to inhibit proliferation *in vivo* (Mangin *et al.* 2012). On the other hand, the role of GABA, the most common inhibitory neurotransmitter in the CNS, on OPC proliferation is less clear. GABA is excitatory in OPCs (as OPCs have high intracellular chloride concentration) but has been shown to exert little effect on OPC development *in vitro* (Gallo *et al.* 1996; Yuan *et al.* 1998). However, a reduction in GABAA receptor-mediated signalling to OPCs increased their proliferation during hypoxia (Zonouzi *et al.* 2015). Furthermore, a myelination assay using organotypic cortical slices has shown that endogenous GABA release decreased OPC proliferation (Hamilton *et al.* 2017), indicating an inhibitory effect. The contradicting influence that glutamate and GABA exert upon OPCs is interesting and may relate to the neuronal firing pattern that governs the release of neurotransmitters. The fact that OPCs have synapses and express an array of neurotransmitter receptors makes them equipped to interpret and differentially respond to distinct activity patterns, as both the firing rate of the neuron and the kinetics of receptors activated will determine different downstream signalling and potential outcome (Karadottir and Kuo 2018).

Neuronal activity enhances oligodendrocyte survival

A few studies have demonstrated that the axon is vital to oligodendrocyte survival during development *in vitro* and *in vivo* (Barres *et al.* 1992, 1993a, 1994). It is possible that the aforementioned activity-dependent proliferative effect

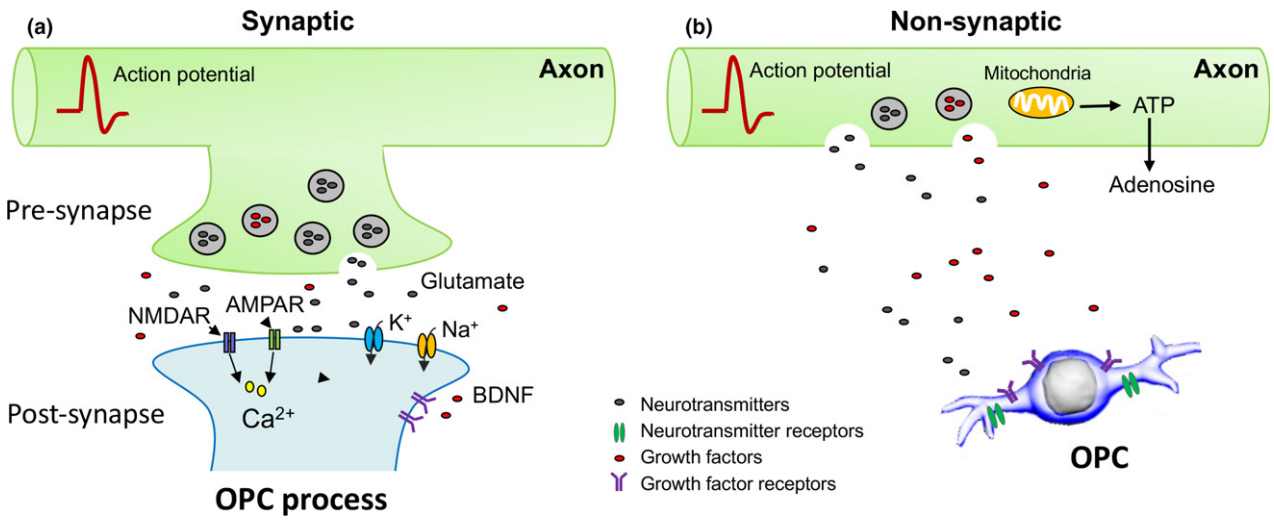

Fig. 2 Neuronal depolarization traverses action potentials along axons, resulting in an activity-dependent vesicular release and activity-dependent non-vesicular release. (a) This enhances the release of neurotransmitters such as glutamate and the fusion of synaptic vesicles into the periaxonal space, which subsequently activates neurotransmitter receptors such as glutamate receptors [α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors (AMPARs) and NMDA receptors (NMDARs)] expressed on the processes of oligodendrocyte precursor cells (OPCs) or oligodendrocytes, promoting influx of Ca^{2+} into the cytoplasm. (b) Alternatively, active axons can also signal OPCs via non-synaptic vascular release of growth factors [e.g. platelet-derived growth factor (PDGF) AA and neurotrophins] and neurotransmitters (e.g. glutamate, GABA or ATP). OPCs express not only ion channels including glutamate-activated ion channels, the sodium and potassium channels, but also receptors of growth factors. These cellular properties make OPCs equipped to respond to neuronal activity.

results from increased cell survival. Indeed, axonal electrical activity controls the production and/or release of trophic factors such as PDGF AA, which ultimately controls the number of oligodendroglial lineage cells that are produced locally (Barres and Raff 1993; Barres *et al.* 1992, 1993a). This activity-dependent survival effect is further supported by another *in vitro* study in which electrical stimulation to mixed cortical cultures promoted oligodendroglial survival, an effect blocked by TTX (Gary *et al.* 2012). Interestingly, electrical stimulation failed to alter cell survival in the absence of neurons *in vitro* (Gary *et al.* 2012), suggesting that a neuron–OPC interaction is critical to this activity-dependent survival effect. Oligodendroglial lineage cells including OPCs and differentiated post-mitotic oligodendrocytes can survival *in vitro* in the absence of neurons through experimentally providing exogenous growth factors such as PDGF AA, neurotrophins (e.g. Neurotrophin-3), insulin-like growth factors or ciliary neurotrophic factor (Barres *et al.* 1993b), and these factors are readily produced by axons as well as other cellular sources. Neuronal activity can regulate oligodendroglial survival via vesicular (Fig. 2) and non-vesicular release of growth factors.

Furthermore, synaptic transmission from neurons to OPCs is another potential mechanism that regulates OPC survival. Inhibiting AMPA receptors via deleting GluA2 and GluA3 in early lineage-stage oligodendroglial cells over the course of early postnatal development *in vivo* exerted no influence upon OPC proliferation as oligodendroglial cells number were unchanged, but led to reduced survival of pre-myelinating oligodendrocytes in the subcortical white matter (Kougioumtzidou *et al.* 2017). In triple knockouts in which all three subunits GluA2/3/4 were knocked out in OPCs, this shortfall persisted into adulthood, which has ultimately resulted in ~ 20% fewer myelin (Kougioumtzidou *et al.* 2017), suggesting a pro-survival role of glutamatergic signalling towards OPCs without altering proliferation and subsequent differentiation, and that activity-dependent oligodendroglial survival and proliferation are mediated by different mechanisms. On the other hand, GABAergic signalling has been reported to increase oligodendroglial death (Hamilton *et al.* 2017). These studies raise a few interesting questions as to how neuronal activity control oligodendrocyte survival via axoglial synapses and homeostatic regulation of neurotransmission, and whether this is a stage specific influence during CNS development.

Perhaps unsurprisingly, oligodendrocyte survival rates are regionally different. Genetically labelling oligodendrocytes and tracking their subsequent survival has shown that the half-life (t1/2) of myelinating oligodendrocytes in the optic nerve is likely to be approximately 2 years which contrast with being over 10 years in the corpus callosum (Tripathi *et al.* 2017). Although this study labelled oligodendrocytes in the young adult mice, it raises an interesting question as to whether axons in these white matter tracts differentially influence oligodendrocyte survival and whether axonal activity of different neural circuits exerts regionally dependent survival effects. In the optic nerve (mouse), most of the axons are myelinated by 4 months of age (Dangata and Kaufman 1997), whereas, in the corpus callosum, there are approximately 30% of axons being myelinated by 6 months of age (Robain and Mandel 1974; Sturrock 1980). Thus, the degree of oligodendrocyte survival may be dependent upon the developmental stage of axons available for myelination and the trophic factors released from these axons in response to altered neural activity. The number of unmyelinated axons (axons available for myelination) may provide a positive feedback signal to enhance the survival of local oligodendroglial cells, whereas the number of myelinated axons may send a negative feedback signal to inhibit the survival (Ueda *et al.* 1999). Neuron-OPC synaptic contacts (at least the glutamatergic synapses) appear to be present predominantly on unmyelinated axons or unmyelinated axonal segments (Kukley *et al.* 2007; Tomassy *et al.* 2014; Ziskin *et al.* 2007), providing structural evidence to support the hypothesis that the number of myelinated axons somehow dictates the production/survival of oligodendroglial cells.

Neuronal activity potentiates oligodendrocyte differentiation

During early postnatal development, the brain is particularly responsive to activity-dependent stimulation. It would be logical to speculate that oligodendrocyte adjusts its differentiation according to neuronal development, and in turn axon-derived signals play important roles in potentiating the transformation of OPCs into post-mitotic mature oligodendrocytes ready to produce myelin. However, unlike in the peripheral nervous system, in which neuregulin-1 on the axonal membrane determines the myelinating fate of Schwann cells (Birchmeier and Nave 2008; Nave and Salzer 2006; Taveggia *et al.* 2005), an equivalent instructive axonal signal that triggers oligodendrocyte differentiation towards myelination has yet been identified in the CNS. Indeed, in the developing CNS, there appears to be a series of neuronal signals that are inhibitory to the differentiation of OPCs towards mature myelinating cells (Emery 2010). Therefore, the question remains whether the neuron plays an active role in promoting oligodendrocyte differentiation.

Recent studies have demonstrated that enhanced neuronal activity increases not only normal oligodendrocyte production but also differentiation during development (Gibson *et al.* 2014; Mitew *et al.* 2018). Optogenetic stimulation of the premotor cortex enhances oligodendrogenesis in both deep cortical layers and subcortical white matter regions. A rapid response of oligodendroglial proliferation was observed within 3 h of stimulation, and 4 weeks after a 7-day stimulation paradigm a subset of oligodendrocytes (equating to approximately 20% of the total initial spike) integrated into mature cells (Gibson *et al.* 2014). Concordant with this

finding, a 7-day pharmacogenomic activation of a subset of cortical somatosensory neurons almost doubled the production of differentiated oligodendrocytes in the underlying white matter tract corpus callosum, resulting in a 20% increase in the total density of mature oligodendrocytes (Mitew *et al.* 2018). While neuronal activity-induced oligodendrocyte differentiation could be secondary to a proliferative response of OPCs, it is plausible that neuronal activity promotes OPCs (newly generated and/or residential) to directly differentiate into post-mitotic oligodendrocyte without prior cell division. This is supported by two recent studies in which providing mice with a complex motor learning task (complex wheel running) rapidly increased the generation of pre-myelinating ($Enpp6^+$) oligodendrocytes (McKenzie *et al.* 2014; Xiao *et al.* 2016) and only a small proportion of OPC differentiation is directly preceded by proliferation (Xiao *et al.* 2016). Through genetically tracing newly differentiated oligodendrocyte, Mitew *et al.* (2018) have shown that enhanced neuronal activity resulted in an approximately twofold increase in the rate of oligodendrocyte differentiation, an effect possibly incorporating the contribution of both OPC proliferation as well as direct differentiation of these cells into mature myelinating oligodendrocyte. Thus, these findings collectively indicate that stimulating neuronal activity could directly potentiate the differentiation of newly generated OPCs without prior cell proliferation to mature myelinating oligodendrocytes.

The importance of neuronal activity in ensuring normal oligodendrocyte maturation has also been demonstrated by situations of neuronal inhibition. Socially isolating mice upon weening resulted in irreversible deficits to late-stage oligodendroglial generation and subsequent myelination of the prefrontal cortex (Liu *et al.* 2012, 2016; Makinodan *et al.* 2012). In this study, oligodendrocytes proliferate normally, however failed to develop morphological complexity and made approximately half the normal number of processes and internodes. A similar deficit was induced in the somatosensory cortex upon sensory deprivation via whisker removal (Hill *et al.* 2014), which resulted in a reduced density of mature cells and an increased density of apoptotic progenitors. Somewhat in contrast to this, or a demonstration of differential white matter versus grey matter oligodendroglial regulation, blocking visual input to the optic nerve upon eye-opening resulted in excessive oligodendrocyte maturation (Etxeberria *et al.* 2016) and abnormal myelination pattern as evident by increased density of paranodes with shorter internodes (Etxeberria *et al.* 2016), in line with the hypothesis that activity fine-tunes myelination for precise neurotransmission or may reflect that OPCs differentiation depends on certain frequency of firing or firing rate, as Schwann cells differentiation and myelination in culture can either be reduced or enhanced with different stimulation frequencies (Stevens *et al.* 1998).

A few recent studies have attempted to elucidate potential mechanisms underpinning the activity-dependent effects on oligodendroglial differentiation. It is known that OPCs respond to glutamate through AMPA/Kainate and NMDA receptors, with receptor density being down-regulated during oligodendrocyte differentiation (Kukley *et al.* 2010). The neuronal action potential-stimulated release of vesicular glutamate onto OPCs has been shown to induce glial excitatory post-synaptic currents mediated via AMPA/Kainate receptors (Nagy *et al.* 2017). This study also suggests that the specific pattern of neuronal activity could differentially regulate glutamate release, which in turn could differentially influence the post-synaptic current within OPCs, further supporting the hypothesis that neuronal activity fine-tunes myelination for precise neurotransmission. Furthermore, new evidences have revealed that neuron–OPC interactions are more complex than expected, and there exit non-synaptic mechanisms of communication between the two cell types. The activation of non-synaptic receptors by ambient neurotransmitters or local spillover and the ability of OPCs to sense neuronal activity through a potassium channel suggest that distinct modes of communication mediate different functions of OPCs (Goebbels *et al.* 2017; Karadottir and Kuo 2018; Maldonado and Angulo 2015; Spitzer *et al.* 2016). Alternatively, axons can release factors to instruct OPC to exit the cell cycle (Stevens *et al.* 2002). Increasing axonal activity leads to the release of ATP, which is then converted to adenosine that inhibits OPC proliferation and promotes oligodendrocyte differentiation (Stevens *et al.* 2002). In culture, ATP released by axons can indirectly signal to oligodendrocytes via stimulating adjacent astrocytes to release the promyelination cytokine such as LIF (Ishibashi *et al.* 2006). In addition, contact-mediated replacement may be another indirect mechanism that explains increased proliferation to replace cells from those in an existing pool that differentiate into new oligodendrocytes to meet acute demand (Hughes *et al.* 2013; Xiao *et al.* 2016). Importantly, a contact-mediated mechanism may also explain why increased OPC proliferation may occur to maintain density in conditions where sensory deprivation (presumably decreased activity) leads to excessive death of immature oligodendrocytes (Hill *et al.* 2014).

Neuronal activity drives the extent of myelin formation

One oligodendrocyte is able to generate approximately 50 myelinating processes with intermodal lengths ranging between 20 and 200 μm (Hildebrand *et al.* 1993; Matthews and Duncan 1971). The roles of neuronal activity in driving the late stages of myelination such as the initiation of myelination and axonal ensheathment by myelin membranes have been demonstrated both *in vitro* and *in vivo*. One study in the late 1990s has shown that blocking axonal activity in the myelinating co-cultures via TTX significantly reduced the formation of myelinated axonal segments, demonstrating that

diminishing neural activity reduces the myelinating capacity of oligodendrocytes *in vitro* (Demerens *et al.* 1996). This is also supported *in vivo*, where intraocular injections of TTX in the developing optic nerve prior to the onset of myelination significantly reduced the number of myelinating, but not pre-myelinating, MBP^+ mature oligodendrocytes (Demerens *et al.* 1996). This is further supported by Bruce Trapp and colleagues, who found oligodendrocytes can still survive following axotomy of the neonatal optic nerve, however they only produce fewer and shorter processes, and ultimately fail to form myelin in the transected nerves (Ueda *et al.* 1999). Results of these studies together suggest that the presence of viable axonal signals not only initiates but enhances the myelinating capacity of oligodendrocytes without influencing the total number of cells, indicating a powerful role of neuronally derived signals in determining the extent of myelin formation by oligodendrocytes ensheathing the axon.

Recently a few elegant studies have made powerful use of the real-time imaging in the developing zebrafish model to further interrogate the effects of axonal activity on the myelinating capacity of oligodendrocytes (Czopka *et al.* 2013; Hines *et al.* 2015; Mensch *et al.* 2015), in particular the number and length of myelin sheaths surrounding the axon (Baraban *et al.* 2018; Hines *et al.* 2015; Koudelka *et al.* 2016; Mensch *et al.* 2015). The study by David Lyons's laboratory (Mensch *et al.* 2015) has found that synaptic vesicle release significantly influenced the number of myelin sheaths formed by individual oligodendrocytes within a short period of formation (only a few hours in the zebrafish; Czopka *et al.* 2013). Furthermore, Bruce Appel's laboratory has demonstrated when single axons were silenced oligodendrocytes preferentially ensheathed neighbouring axons (Hines *et al.* 2015), suggesting an axonal selection in oligodendrocyte myelination. Concordant with these findings, analysis of the mammalian brain has demonstrated that electrically stimulated axons were 'favourably' myelinated by the newly generated oligodendrocytes *in vivo* (Mitew *et al.* 2018) and *in vitro* (Wake *et al.* 2015). Furthermore, nascent myelin sheaths formed on electrically silenced axons were shorter in length than controls, suggesting that axonal activity regulates the longitudinal growth of myelin sheath (Hines *et al.* 2015). What is more interesting, however, is that axonal 'competition' may exits in surrounding axons as silencing a single axon, but not all axons, impedes nascent myelin formation (Hines *et al.* 2015). Together, these studies indicate that neuronal activity is likely to not only influence axon selection for myelination but also powerfully control the extent of myelination by individual oligodendrocytes ensheathing the axon.

The above animal-based work is also supported by human studies that early life experience can affect myelin microstructure and associated functions. Using diffusion tensor neuroimaging (a measure of water diffusivity in diffusion-weighted imaging that correlates with myelination, fiber density, and axonal diameter), it has been shown that the extent of piano practice during development (childhood and adolescence) exert positive influence upon myelinating tracts of multiple brain regions such as subcortical fibres in the frontal lobe and the corpus callosum (Bengtsson *et al.* 2005). In addition, myelination of the pyramidal tract was found to be more structured in pianists than in non-musicians (Bengtsson *et al.* 2005). Conversely, a longitudinal study of over 260 families suggests that early childhood traumatic experience such as abuse or neglect may exert detrimental influence upon cognitive function later in life (Egeland *et al.* 1983). Similarly, children aged between 8 and 10 years who were poor readers display hypomyelination of cerebral white matter (left anterior centrum semiovale) compared to good readers, however, this white matter structure difference can be partially rescued after remediation in reading skills (Keller and Just 2009). Thus, these findings suggest that experience associated with critical developmental periods may exert dramatic influence upon the plasticity of human myelinating tracts and associated functions, and that myelination is a dynamic process driven by experience.

Then, the questions remain how neuronal activity controls the dynamic process of myelinogenesis. Several recent studies have suggested vesicular release as one key mechanism through which neuronal activity regulates the extent of myelination (Fig. 2) (Hines *et al.* 2015; Koudelka *et al.* 2016; Mensch *et al.* 2015; Wake *et al.* 2011, 2015). Action potential firing by electrically active axons in culture could result in glutamate release from synaptic vesicles, promoting early events that regulate myelin formation such as local myelin protein synthesis (Wake *et al.* 2011), proposing a scenario that neuronal activation traverses action potentials along axons, resulting in an activity-dependent vesicular (synaptic or non-synaptic) release of neurotransmitters such as glutamate which subsequently activates their receptors such as AMPA receptors and NMDARs expressed on the processes of OPCs, promoting influx of Ca^{2+} into the cytoplasm and initiating intracellular pathways of myelinogenesis (Fig. 2). Indeed, the intracellular Ca^{2+} has recently been shown to mediate the dynamics of myelin formation such as elongation in response to neuronal activity (Baraban *et al.* 2018; Krasnow *et al.* 2018). Electrical stimulation of axons rapidly increases Ca^{2+} in OPCs processes in culture, which is inhibited by blocking vesicular release using botulinum A (Wake *et al.* 2015). *In vivo* live imaging in zebrafish has shown that local Ca^{2+} signalling within oligodendrocytes influences their capacity of myelin elongation, and that higher frequency Ca^{2+} transient activity in myelin sheaths precedes faster elongation (Baraban *et al.* 2018). Complementary to this finding, a study has demonstrated that neuronal activity evokes Ca^{2+} transients within the developing oligodendrocytes and myelin, and that Ca^{2+} transients correlates with myelin sheath lengthening (Krasnow *et al.* 2018). Myelin sheath elongation occurs rapidly

(around 1 h) after Ca^{2+} elevation within myelinating oligodendrocytes, and likewise its shortening is associated with a low frequency of Ca^{2+} transients (Krasnow *et al.* 2018). Thus, the aforementioned studies together indicate a neurotransmission pathway from axons to OPCs to induce local Ca^{2+} signalling, underpinning the activity-dependent myelinogenesis. In the context of ischaemia, NMDA glutamate receptors has been shown to drive Ca^{2+} increase in myelin (Micu *et al.* 2006), suggesting axo-myelinic neurotransmission could be another potential new mode of cell signalling that regulates activity-induced myelination in the CNS (Micu *et al.* 2018).

Myelin plasticity in the adult CNS

The early intriguing idea that neuronal activity could influence the behaviour of oligodendroglial lineage cells during early development (Barres and Raff 1993; Gyllensten and Malmfors 1963; Tauber *et al.* 1980) was further stoked by fascinating studies associating changes myelin microstructure with experience in the adult. For example, social isolation of young adult mice resulted in myelin thinning in the prefrontal cortex, a region important for social function (Liu *et al.* 2012; Makinodan *et al.* 2012). Humans who learn a new complex motor tasks exhibited alterations to MRI-based measures of myelin microstructure in regions involved in hand-eye coordination (Scholz *et al.* 2009). Furthermore, after repeated training in a complex body balance task for several weeks, adult human participants exhibited increased myelin microstructure in the frontal subcortical white matter, assessed by fractional anisotropy (Taubert *et al.* 2010). It is noteworthy that this complex training also led to a volume increase in multiple grey matter regions such as the prefrontal cortex (Taubert *et al.* 2010), and there is a continuous increase in these white and grey matter changes during a 6-week training period, indicating a dose-responsive plasticity effect (Taubert *et al.* 2010). Thus, both rodent and human studies suggest that environmental alterations and experience influences myelin plasticity in white and grey matters of the adult CNS.

The experimental tools of modern neuroscience have enabled the generation of direct evidence for neuronal activity regulation of oligodendroglial lineage cell function in adult CNS. Optogenetic stimulation of excitatory projection neurons in the premotor cortex demonstrates that neuronal activity elicits rapid, robust and circuit-specific OPC proliferation, promotes oligodendrogenesis and increases myelin sheath thickness within the projections of the premotor circuit. Neuronal activity was found in this study to regulate oligodendrogenesis similarly in juvenile and in adult mice (Gibson *et al.* 2014). Neuronal activity-regulated oligodendrogenesis was associated with improved motor function, and oligodendrogenesis was necessary for the observed functional improvement (Gibson *et al.* 2014). Similarly, chemogenetic stimulation or inhibition of somatosensory cortex activity regulates somatosensory projection neuron myelination (Mitew *et al.* 2018). Chemogenetic strategies for regulating parvalbumin-positive interneuron activity in the medial prefrontal cortex similarly demonstrated that inhibitory interneuron myelination is regulated by activity in adulthood (Stedehouder *et al.* 2018). Topographical analysis revealed that myelination of axons after stimulation is accompanied by higher branch orders paralleled by an increase in axonal arborization (Stedehouder *et al.* 2018), suggesting axonal structure may also underpin activity-dependent myelin plasticity. Nevertheless, finding of this study adds a layer of complexity to that ways that myelin alterations could influence neural circuit function. The proliferative response of OPCs to neuronal stimulation appears to be more protracted in the adult mice than in juvenile mice, suggesting that there is an additional homeostatic regulation of OPC behaviour in response to neuronal activity in the adult CNS (Mitew *et al.* 2018).

To what extent myelin plasticity contributes to forms of learning in the adult CNS is largely unknown. An important set of experiments by the Richardson lab has provided the first evidence that adaptive oligodendrogenesis contributes to cognitive function (McKenzie *et al.* 2014). Training mice to perform a complex motor task was found to elicit OPC proliferation and oligodendrogenesis (McKenzie *et al.* 2014) similar to that observed with the abovementioned optogenetic stimulation of premotor cortex (Gibson *et al.* 2014), a region involved in motor planning. New oligodendrocyte production proved to be necessary for acquisition of the complex motor task (Gibson *et al.* 2014; Xiao *et al.* 2016). These experiments illustrate a role for activity-regulated oligodendrogenesis in motor learning and underscore the possible role that activity-regulated changes in myelin-forming cells could play in other forms of learning, indicating that ongoing myelination regulates aspects of learning in the adult CNS. We still have limited knowledge of how new oligodendrocytes integrate into the pre-existing myelinated circuits, and whether learning complex skills require new circuits brought to play.

How might changes to myelin microstructure, and resultant alterations in conduction velocity, alter neural circuit function and influence behaviour? Much remains to be learned about how myelin plasticity may alter neural circuit dynamics, and different rules may be operant in different circuits. For example, myelin plasticity-regulated changes in spike time arrival could influence spike-time-dependent synaptic plasticity, while in other circuits the first impulses to arrive may be selected to exert dominant influence over downstream neuronal activity. This is a fertile area for further research by computational neurobiologists.

A number of mechanistic and conceptual questions remain, including the molecular mechanisms that mediate activity-

regulated communication between neurons and oligodendroglial lineage cells and the manner in which newly generated oligodendrocytes contribute to myelination. Do the new oligodendrocytes replace older internodes, wrap previously unmyelinated axons or wrap unmyelinated regions on axons exhibiting a variable internode length and pattern (Tomassy *et al.* 2014)? An obvious question is what the cellular source of new myelin is in the adult CNS. In the adult CNS, there is an ongoing OPC differentiation into myelinating oligodendrocytes (Hill *et al.* 2018; Hughes *et al.* 2018; Young *et al.* 2013), indicating that adult myelination/maintenance could be generated by newly differentiated oligodendrocytes from the existing pool. However, it is unknown whether these newly differentiated cells exhibit sufficient plasticity to respond to neuronal activity and generate new myelin segments (myelin remodelling) and/or replace existing ones (myelin turnover). The degree to which this ongoing differentiation and myelin formation is activity dependent is unknown. A recent series of studies indicate that oligodendrocytes are generated throughout life (Young *et al.* 2013) and are very stable in the healthy brain of mice until late adulthood (Hill *et al.* 2018; Hughes *et al.* 2018; Tripathi *et al.* 2017). This stability of oligodendrocytes throughout life argues against a cellular turnover mechanism of new myelin incorporation, although replacement or remodelling of individual internodes remains a possibility concordant with the co-existence of older and newer oligodendrocytes. Two-photon imaging through a chronic cranial window reveals that newly generated oligodendrocytes myelinate previously unmyelinated axonal territory in the superficial somatosensory cortex, and that this increases with sensory stimulation (Hughes *et al.* 2018). Thus, regions of the nervous system that exhibit incomplete myelination well into adulthood, such as the cerebral cortex and intercortical association fibres, accumulate increasing amounts of myelin throughout adulthood, at least in the healthy brain and in the absence of sensory deprivation. Whether adult myelin plasticity similarly exists in regions that are more completely myelinated during development, such as the optic nerve and the spinal cord, remains to be determined.

Activity-dependent remyelination after injury

Myelin regeneration or remyelination is the endogenous regenerative mechanism by which myelin is restored to demyelinated axons, resulting in the alleviation of neurological symptoms that are associated with many neurological disorders, in particular demyelinating diseases such as multiple sclerosis (MS). The degree of myelin repair within MS lesions is variable; generally MS lesions remyelinate relatively efficiently early on in the disease; however, at later stages many lesions remain chronically demyelinated (Irvine and Blakemore 2008). Following a demyelinating insult, endogenous adult OPCs respond to injury and migrate into the lesion where they proliferate to repopulate the lesion and differentiate into myelinating oligodendrocytes (Franklin and Ffrench-Constant 2008). However, this initial remyelinating process ultimately fails, mainly because of 'stalled' OPC differentiation, leaving sustained clinical symptoms (Franklin *et al.* 2012). Indeed, Gautier *et al.* (2015) found an increase in the number of OPCs accompanied by reduced differentiation in the induced rodent myelin lesion (Gautier *et al.* 2015), a scenario that resembles that of chronically demyelinated lesions in MS where there is a differentiation block (Wolswijk 1998, 2000). Persistent demyelination followed by failure of remyelination ultimately results in axonal damage and neuronal loss, leading to progressive clinical disabilities (Irvine and Blakemore 2008). Thus, understanding the regenerative process, and the regulation of OPC differentiation, is of great therapeutic potential, and as currently, no remyelinating therapies are available for demyelinating diseases.

The fact that neuronal activity regulates myelinogenesis in the mature CNS suggests the possibility that remyelination might also be activity dependent. However, that would require that demyelinated axons retain their capacity to conduct action potentials. While the axonal conduction block has been reported after myelin injury (McDonald and Sears 1969; Pender 1988; Smith *et al.* 1979), it is clear that not all demyelinated axons become electrically silent in lesions and that some axons can in fact conduct following demyelination (Felts *et al.* 1997), or become spontaneously active within myelin lesions (Smith and McDonald 1982). Furthermore, it has been argued that, in some demyelinated MS lesions, the demyelinated axons are capable of conducting action potentials (Ghatak *et al.* 1974; Phadke and Best 1983). These findings are supported by the analyses of rodent models of central demyelination in which axon integrity is preserved and demyelinated axons are able to conduct action potentials, albeit at an expected reduced velocity (Etxeberria *et al.* 2010; Gautier *et al.* 2015; Sahel *et al.* 2015). Thus, the human and rodent studies collectively suggest that demyelination itself does not necessarily result in a blockage of nerve conduction and that there may exist a time window when axons are still healthy and electrically active in myelin lesions. Axonal conduction along demyelinated axons is likely made possible by a switch in voltage-gated Na^+ channel subunit expression and distribution, from focal to diffuse, as has been observed in experimental allergic encephalomyelitis and MS (Craner *et al.* 2003, 2004; Moll *et al.* 1991)

Recent evidence has shown that OPCs within the myelin lesions express glutamate receptors and receive synaptic inputs (Etxeberria *et al.* 2010; Gautier *et al.* 2015; Sahel *et al.* 2015). Thus, like in development, OPCs within the myelin lesions are capable of sensing neuronal activity. Whether these inputs are from demyelinated axon or

previously unmyelinated axons that synapse with these OPCs in lesions can only be tested in a white matter tract where all axons are myelinated in the adult. There are a few white matter tracts that fulfil these criteria, as a mixture of myelinated and unmyelinated axons are found in most white matter areas such as the caudal cerebellar peduncle. When inducing demyelination in the caudal cerebellar peduncle, synaptic input is detected in OPCs, indicating that indeed demyelinated axons generate *de novo* synapses with OPCs (Gautier *et al.* 2015). Furthermore, demyelinated axons up-regulate presynaptic proteins in both the animal model of demyelination and human MS lesions (Etxeberria *et al.* 2010; Gautier *et al.* 2015). The OPCs recruited to demyelinating lesions sense glutamate release primarily by AMPA/kainate receptors at the time of highest proliferation and, while at a later stage just prior to differentiation, these cells start to sense glutamate release and also via NMDA receptors (Gautier *et al.* 2015). Neuronal activity, vesicular release of glutamate, AMPA/kainate or NMDA receptors seems to play important roles in promoting remyelination, as when any of these mechanisms are inhibited locally within demyelinating lesions, remyelination is severely perturbed (Gautier *et al.* 2015; Li *et al.* 2013; Lundgaard *et al.* 2013). A functional communication between axons and OPCs is potentially required for a successful remyelination.

The time course of glutamate receptors (AMPA and NMDA) expression in OPCs in demyelinated lesions is in line with their roles during developmental myelination: AMPA receptors are seemingly important in the early phase of OPC proliferation, survival and initial differentiation, whilst NMDA receptors are expressed at a late stage of oligodendroglial lineage progression and required for terminal differentiation and axonal ensheathment by myelin membranes (Gautier *et al.* 2015; Li *et al.* 2013; Lundgaard *et al.* 2013). Furthermore, the effects of NMDA receptor activation on remyelination appear to be mediated via the Akt/mTOR pathway (Li *et al.* 2013; Lundgaard *et al.* 2013) and as in development (Mensch *et al.* 2015) it is predominantly the remyelination of small diameter axons that depends on neuronal activity and glutamate. Larger calibre axons still become myelinated when vesicular release of neurotransmitters is blocked (Mensch *et al.* 2015) and are also remyelinated even when activity or synaptic signalling are inhibited (Gautier *et al.* 2015). Therefore, neuronal activity is likely to regulate remyelination by via a glutamate-mediated signalling between axons and OPCs. Targeting of this mechanism may be developed into new remyelinating strategies and, in fact, drug discovery studies have now identified several compounds that promote OPC differentiation and remyelination which modulate neurotransmitter signalling in OPCs (Abiraman *et al.* 2015; Deshmukh *et al.* 2013; Mei *et al.* 2014, 2016; Najm *et al.* 2015).

A switch between activity-independent and activity-dependent myelination?

While neuronal activity clearly influences oligodendroglial lineage progression and their capacity of myelination, myelination can also occur independent of axonal activity, at least *in vitro* (Bechler *et al.* 2015; Lee *et al.* 2012, 2013; Li *et al.* 2014). Oligodendroglial cells can survive, proliferate and differentiate *in vitro* in the absence of neurons (Barres *et al.* 1993b). Recently, oligodendrocyte myelination including oligodendroglial-axon contact, myelin wrapping and compaction have also been achieved *in vitro* using electrically silent artificial nanofibers (Bechler *et al.* 2015; Lee *et al.* 2012, 2013), suggesting that there exit intrinsic oligodendrocyte-driven mechanisms that regulate fibre-glial contact and myelinogenesis. Although there is currently no direct evidence demonstrating that axonal calibre alone dictates the myelinating fate of central neurons, genetically increasing the axonal diameter of the cerebellar parallel fibres, and concomitantly change a number of important signalling molecules, induces myelination on these normally unmyelinated axons (Goebbels *et al.* 2017). Analysis of myelinating cultures using engineered nanofibers have shown the size of fibre diameter exerts a direct impact upon the number of fibres being ensheathed by oligodendrocytes and their subsequent myelinogenesis (Lee *et al.* 2012), suggesting that oligodendrocytes display some level of sensitivity to the biophysical properties of fibres themselves and that this is a myelinating progress dependent upon fibre calibre but not axonal electrical activity. This is further supported by Bechler *et al.* (2015) that, in the absence of axonal molecules, oligodendrocytes that originate from different CNS regions exhibit diverse capacities in myelin sheath elongation with spinal cord oligodendrocytes generating longer myelin sheaths than the cortical ones. Thus, oligodendrocytes have a remarkable intrinsic capacity to initiate and generate myelin independent of axonal electrical activity, although biophysical properties of fibres such as axonal calibre still influence the extent of myelinogenesis.

A prevailing hypothesis is that two modes of myelination (activity-dependent and activity-independent) may exist simultaneously *in vivo* (Koudelka *et al.* 2016) and *in vitro* (Li *et al.* 2013; Lundgaard *et al.* 2013). When levels of the growth factors such as neuregulin (NRGs) or brain-derived neurotrophic factor (BDNF) are elevated, presumably by release from active neurons (Esper and Loeb 2009; Greenberg *et al.* 2009; Matsuda *et al.* 2009), OPCs switch to myelinating mode via an activity-dependent mechanism (Lundgaard *et al.* 2013), probably because NMDAR activation increases the energy supply to developing oligodendrocytes (Krasnow and Attwell 2016; Saab *et al.* 2016). However, the relative importance of each myelination mode is still unclear. Indeed, BDNF itself has long been known to regulate activity-dependent neuronal functions such as

synaptic plasticity (Huang and Reichardt 2001; Lu 2003). Neuronal activity can trigger BDNF release from axons and dendrites (Matsuda *et al.* 2009). BDNF itself plays a critical role in the myelinating process, in particular myelin formation and axonal ensheathment, presumably via signalling to the TrkB/Erk signalling pathway (Ishii *et al.* 2012, 2013, 2014; Nicholson *et al.* 2018; Wong *et al.* 2013; Xiao *et al.* 2010, 2012), suggesting it as a candidate mediating activity-dependent myelin formation. In addition, NRGs are predominantly expressed by neurons during CNS development. Interestingly, blocking NRG1 signalling in oligodendrocyte lineage cells via ablating its receptor ErbB3 exerts litter effect upon myelination during normal development (Brinkmann *et al.* 2008), but significantly disrupts experience-induced myelination (Makinodan *et al.* 2012). That said, forced over-expression of NRG-1 is able to enhance axonal ensheathement (Brinkmann *et al.* 2008), leaving the possibility that NRG signalling plays at least some roles within the CNS. Conceivably activity-independent and -dependent myelination may occur within the same or different neural circuits. The relative roles of the two modes of myelination are still largely unknown. It is possible that an activity-independent intrinsic pathway may pre-establish an initial pattern of oligodendrocyte myelination which is then controlled and modified by activity-dependent cues to meet neural circuit development and functions. The activity-dependent myelination might have evolved in order to accelerate the myelinating process along the 'correctly' firing active axons during periods of learning, and thus may be important to fine-tuned neuronal circuits.

Conclusion and future perspectives

In summary, myelination can proceed via axonal-dependent and -independent mechanisms. Neuronal activity clearly exerts multifaceted influence upon the myelinating process, ranging from oligodendroglial cells proliferation/survival, differentiation through to myelin formation. It is unclear which stage(s) of the myelinating process are most susceptible to neuronal activity or experience. The sequential cellular events of CNS myelination could be regulated via activity-dependent synaptic and non-synaptic vesicular release as well as non-vesicular release. Synaptic contacts between the processes of neurons and oligodendrocytes may regulate vesicle release functions and that such synapses may control the activity-dependent myelinating process including oligodendroglial cells proliferation, the stabilization of axon–oligodendrocyte contacts or their subsequent myelin sheath elongation. It remains unclear whether this functional synapse only occurs between electrically 'active' axons and the processes of oligodendrocytes. Alternatively, activity-regulated axonal release could locally influence individual oligodendrocytes in a non-synaptic manner, regulating their lineage progression and overall myelinating capacity such as myelinate axons that are previously unmyelinated or incompletely myelinated. In the CNS, activity-dependent myelination occurs not only during normal development when myelination is most active but also into late adulthood when the myelinating rate slows down. It is unknown whether similar or differential mechanisms underpins activity-dependent myelination during development, in adult and after injury. The technological advance in neuroscience and the ability to precisely manipulate neuronal activity will allow future studies to address the above questions, which will significantly advance our understanding in the axoglial signals that regulate myelination, providing new insights into neural plasticity and functions in both health and diseases.

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