Periods of synchronised myelin changes shape brain function and plasticity

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Abstract

Myelin, a lipid membrane that wraps axons, enabling fast neurotransmission and metabolic support to axons, is conventionally thought of as a static structure that is set early in development. However, recent evidence indicates that in the central nervous system (CNS) myelination is a protracted and plastic process, ongoing throughout adulthood. Importantly, myelin is emerging as a potential modulator of neuronal networks, and evidence from human studies has highlighted myelin as a major player in shaping human behaviour and learning. Here we review how myelin changes throughout life and with learning. We discuss potential mechanisms of myelination at different life stages, explore whether myelin plasticity provides the regenerative potential of the CNS white matter, and question whether changes in myelin may underlie neurological disorders.

Introduction

CNS myelin, produced by oligodendrocytes, enables metabolic support to axons[1] and is essential for rapid information transmission[2] and synchronisation[3,4] of axonal inputs between billions of neurons (Box 1). It is becoming clear that myelination is an ongoing process throughout our lives and myelin is increasingly invoked as a fundamental mechanism for learning. Recent advances in magnetic resonance imaging (MRI), e.g. T1 weighted imaging[5,6] and diffusion tensor imaging (DTI)[7,8], now sensitive enough to detect human myelin changes, have identified important features of myelination. These observations are largely supported by incredibly detailed and insightful histological observations on human myelin formation conducted in the late 1800s[9,10] and early 1900s[11-14] and recent single-cell transcriptomic studies on human oligodendrocyte lineage cells[15]. Moreover, recent animal studies have highlighted similarities in life-long myelination to humans, and shown that, throughout life, unmyelinated axons become myelinated[16,17] and that myelin on already-myelinated axons can change, e.g. in internode number and length[16-19], myelin thickness[20-22] or geometry of the node of Ranvier[19,23,24]. Sharp changes in myelin, loss of myelin due to disease, or dysmyelination at critical periods through life, can impact on brain function and lead to serious disability, to varying degrees depending on the extent of damage and the white matter tracts that are affected. Recent MRI[25,26], transcriptome and genome-wide association studies[27-32] have revealed myelin involvement in many diseases that were previously considered to be 'neuronal', such as dementia, schizophrenia, autism, and depression. This highlights the importance of myelin for normal brain function and raises the question of how myelin contributes to learning and neurological disorders. Thus myelin - previously considered static - might in fact be plastic and responsive to changes in neuronal activity. In this review, we evaluate and interpret the evidence, both old and new, for lifelong myelination and myelin plasticity, consider whether myelin plasticity is the mechanism that

promotes myelin repair and how it might be regulated by neuronal activity, and discuss how disruption of myelin plasticity could underlie common neurological disorders.

1. Myelin changes across the lifespan

The last decade has revolutionised our understanding of human myelination. Recent MRI[5-7] and single-cell RNAseq studies[15] combined with early post-mortem studies performed on prenatal to ageing humans[9-14] describe complex myelin dynamics in the human brain. Although these studies are descriptive and much remains to be elucidated, they collectively reveal important characteristics of human myelination (Fig. 1).

First, human myelination is a protracted process that generally proceeds from the posterior to anterior parts of the brain[14,33], into the sixth decade[6,12,14]. Similarly, recent findings in mice have shown myelination of axons in the cortex continues into the second year of life[16,17], comparable to the sixth decade of human life[34].

Second, myelination does not occur simultaneously, rather different brain areas myelinate in a distinct temporal order[5,6,11-14,35], which seems to be conserved between species[36]. More than a century ago, Paul Flechsig noted that different but functionally related brain areas or axonal tracts myelinate concurrently[11,13,37]. Drawing from these studies, and inspired by Flechsig, Yakovlev and Lecours, we propose dividing the temporal sequence of myelin changes into five different stages over the course of human life (Fig. 1A): (1) early childhood, (2) childhood, (3) adolescent, (4) adult myelination, (5) age-related decline in myelin. Projection fibres are the first to be myelinated, followed by the commissural fibres and lastly the association fibres, which continue to myelinate far into adulthood[12,14,37,14] . However, myelin levels do not seem to change linearly with time or at the same rate within each stage, but in a succession of waves[6,13,14], discrete periods of seemingly synchronised and

100 rapid myelin changes. These waves of myelin changes can therefore be denoted as the third
101 characteristic of human myelination. Three distinct waves of rapid myelin changes in the
102 brain are identifiable across the life span (Fig. 1A). The first wave starts around birth and
103 lasts for the first few years of life, followed by a second wave during adolescence. Whether
104 the second wave is indicative of a change towards myelination of anterior regions and upper
105 cortical areas rather than of white matter tracts, prominent in the first wave, remains to be
106 fully determined. The third wave is the onset of a rapid decline in myelin, observed after 60-
107 70 years (depending on the individual)[6], proposed to occur in reverse order to acquisition,
108 from anterior to posterior areas of the brain[38]. Comparably, myelin disappears in cortex of old
109 mice, presumably as myelin maintenance is disrupted with age, only a few months after it has
110 reached steady state[16]. Though these characteristic waves delineate the periods of most rapid
111 myelin changes, myelination of individual axonal tracts, or brain areas, is not strictly
112 confined to these myelin waves.
113
114 The fourth characteristic of myelin changes, defined by early human myelin studies, is that
115 different brain areas can be categorised into different myelination cycles, defined as the
116 length of time from onset of myelination of a tract/area to its full completion, i.e. (1)
117 monophasic (fast clear onset to completion of myelination), (2) multi-phasic (onset followed
118 by a pause prior to a separate myelination round), or (3) slow continuous protracted
119 myelination cycle (Fig. 1B)[14]. From these studies, it is apparent that the monophasic cycle
120 governs early and childhood stages of myelination, and is predominant during the first wave,
121 whereas the multi-phasic and protracted cycles tend to be more frequently detected in brain
122 regions that myelinate later in the course of human development, during adolescence and
123 adulthood[12,14,35,39]. Notably, during the second wave, it appears that some axonal tracts begin
124 their second cycle of myelination, e.g. the parahippocampal gyrus, the cingulum and the

uncinate fasciculus[14,35,39,40], whereas others initiate myelination at that time point and myelinate throughout adulthood (or well into stage 4), e.g. commissural and association fibres[12,14]. Distinguishing a multiphasic myelination cycle with more than two rounds of myelination from a protracted, continuous myelination cycle for a particular tract, can be challenging with only cross-sectional studies. Nonetheless, tracts showing a monophasic myelination cycle display less overall variability than tracts with protracted cycles, such as association fibres[41]. For example, the uncinate fasciculus, which connects parts of the limbic system and is affected in several psychiatric conditions, begins a myelination cycle at the end of the second wave, and shows remarkable variability between subjects[40]. In contrast, the corticospinal tract, a motor pathway important for voluntary movements, myelinates monophasically, early in development during the first wave, and shows little variability[41]. Further to these human observations, studies using model animals, and serial sectioning electron microscopy methods, have indicated that myelination does not occur homogenously along an axonal tract[42] or individual axon[43] and that large diameter axons myelinate before smaller diameter axons[44]. Whether these observations indicate that multiphasic cycles reflect heterogeneity of axons within the tracts remains to be fully determined. Moreover, it is still unclear how observations in model animals align with human myelination and the reported different cycles of myelination.

These studies highlight that myelination dynamics may be more complex than previously thought; spanning foetal life to old age, and with axonal tract specificity. The aforementioned observations are descriptive and from cross-sectional studies, thus any correlation still needs to be fully explored. In contrast to these observations, a study using carbon dating to determine oligodendrocyte age, indicated that nearly all human oligodendrogenesis[45] occurs in the first five years of life (or during the first wave), although

myelin volume in the corpus callosum increases into adulthood[45]. How to reconcile this finding with the observations from MRI, histology and transcriptional studies is unclear. It could indicate that, at later myelin stages, myelination is carried out by direct differentiation[46] of specific non-cycling primed OPCs[47] or by pre-differentiated[47,48] oligodendrocytes poised to myelinate upon receiving the right signal (Box 1), or that myelin changes detected during the later second wave are much smaller than predicted from the preceding studies discussed in this section. These unanswered questions highlight the fundamental need to determine whether similar myelin changes as observed in humans also occur in model animals. However, some aspects of the observed characteristics of human myelination may prove challenging to study in animal models, particularly with regards to multiphasic cycles, due to the narrower temporal window in which development and myelination occurs. Ultimately, the functional implications of the different mechanisms regulating myelination[49], which may be specific to each stage, cycle, and wave, should be investigated from the perspective of lifelong changes in myelin, as the observations made thus far underscore the complexity of myelin dynamics throughout life.

2. Myelin plasticity - Experience dependent myelination

The conventional view of myelin as inert and immutable has been reformed in recent years with the discovery that myelin changes occur with experience[17,50] or the acquisition of new skills[51,52]. These changes are especially remarkable considering that the surface area of myelin produced and maintained by a single oligodendrocyte is up to $2x10^6$ μm^2 [53]. Yet, strong emerging evidence indicates that new myelin internodes appear[16-19,54], existing myelin internodes elongate[16,17,54,55], retract[16,17,55] and even disappear[19], and that these changes are sensitive to experience[17,19] and learning[54] (Box 2).

This dramatic shift in our understanding was sparked by new advances in myelin imaging, permitting surveillance of myelin over time and in the intact brain, in humans and model animals. Initially, MRI studies, e.g. DTI, identified substantial changes in white-matter volume and microstructure developing as individuals master complex cognitive or visuomotor skills, such as reading[56], playing the piano[57] or juggling[51]. Addressing the extent to which these alterations reflect changes in myelin, animal studies employing two-photon microscopy and/or genetic labelling of myelin and oligodendrocytes revealed that sensory enrichment results in increased numbers of oligodendrocytes in the sensory cortex[17] and that motor[52,58], spatial[59] or contextual fear associative[60] learning activates *de novo* myelination, increases myelin-associated gene activity and myelin protein expression. Conversely, social isolation or sensory deprivation during the critical period of myelination decreases myelin thickness, internode length or the number of myelinated axons in the medial pre-frontal cortex (mPFC)[50,61,62], somatosensory cortex[63], auditory cortex[21] and optic nerve[64]. Although not all sensory deprivation studies report a decrease in myelin formation, they consistently show altered myelination[19,65], which presumably depends on the degree of change in patterns of axonal firing rate[66]. Collectively, these aforementioned findings suggest that myelin changes in response to experience. More importantly, recent studies also show that preventing adult *de novo* myelination impairs motor/spatial learning and working memory (further reviewed elsewhere[3]). Thus, myelin changes throughout life seem to enable individuals to learn to respond to an ever-changing environment.

Whether these experience-driven changes in myelin are necessary for learning or simply reflect adjustments to new circuit requirements[67], is still unclear. These studies focussed on areas that were actively myelinating at the time of the study, suggesting that during a myelination cycle, myelination is sensitive to the environment and, presumably, to changes in

200 neuronal activity. Indeed, this link between sensory input changes and myelination puzzled
201 Flechsig and others, when they noticed that myelination in prematurely born babies matched
202 that of full-term babies shortly after birth, instead of age-matched unborn foetuses[9,10,13].
203 Hence, myelin plasticity is not confined to post-childhood myelination, but rather to the
204 myelination cycle of each tract. Based on the aforementioned observations, it is tempting to
205 conclude that areas that start myelination during the second wave (adolescence), and have a
206 protracted cycle of myelination show the longest period of plasticity and correspond to areas
207 adaptable to the ever-changing environment. Indeed, areas related to the learning paradigms
208 tested in most human studies to date, such as the mPFC, hippocampus, thalamus, and
209 intracortical connections, actively enter a prolonged myelination cycle at the time of the
210 second wave[6,14,39,68]. Emerging mouse studies also detect *de novo* myelination following
211 learning in the same brain regions as in humans[54,59,60]. However, not all myelin changes are
212 fully confined to the normal myelination cycle of a tract, as evidenced by the birth of new
213 oligodendrocytes in the optic nerve long after myelination is completed, albeit in small
214 numbers[18,69], or the observation that myelin becomes thinner when auditory sensory
215 deprivation is induced after myelination of the trapezoid body axonal tract is completed[21].
216 Oligodendrogenesis in the optic nerve has been argued to reflect myelin maintenance rather
217 than plasticity, as there is no net increase in myelin and the optic nerve has higher myelin
218 turnover compared to other areas[69]. Therefore, while myelin plasticity in the form of *de novo*
219 myelination might be confined to a myelination cycle, the pre-existing myelin may have the
220 capacity to change throughout life, even after a myelination cycle is completed (Box 2).
221
222 These findings further indicate that there are different forms of myelin plasticity (Box 2): one
223 governed by oligodendrogenesis and *de novo* myelination, another by alterations in the
224 existing myelin and a third by changes in the geometry of the node of Ranvier, all leading to

changes in the myelin pattern within a circuit (Box 3). How these different forms of plasticity map onto the different periods of myelination remains to be discovered, alongside whether some brain regions are more plastic than others, reminiscent of synaptic plasticity mechanisms which only continue in specific areas of the adult CNS, such as the hippocampus. Hence these observations provoke multiple questions for the future, perhaps the most prominent being, 'what are the potential mechanisms that drive different forms of myelin plasticity?'

3. Mechanisms of myelin plasticity

A plethora of signals are known to regulate myelination (as reviewed in[49,70,71]), but the fact that myelination correlates with learning, and learning is driven by alterations in neuronal activity, makes it conceivable that neuronal activity-dependent mechanisms may drive myelin plasticity, much as neuronal activity drives other forms of plasticity in the brain. However, whether and how activity regulates myelination has been a topic of debate for over a century, with evidence both opposing and supporting activity-dependent myelination (as reviewed by[70,72,73]). This is akin to the debate on activity-dependent or independent mechanisms of synapse formation during development[74]. Likewise, a potential explanation for these apparent contradictions is that myelin formation can be regulated by both neuronal activity dependent and independent mechanisms, but as with synaptic plasticity, refinement and maintenance are mainly driven by neuronal activity.

Mechanisms of de-novo myelination - myelin plasticity driven by OPCs

Oligodendrocyte precursor cells (OPCs), which differentiate into myelinating oligodendrocytes throughout life, are evenly distributed throughout the adult brain[75,76] and comprise around 5% of all cells in the adult CNS[76]. OPCs receive synaptic inputs[77,78] from

unmyelinated axons[79,80] (or from unmyelinated segments of partially myelinated axons[43]) and express neurotransmitter receptors, such as ionotropic glutamate[77-80] and GABA receptors[81-83]. Consequently, OPCs are able to monitor and respond to changes in neuronal activity much like neurons. Disrupting synaptic communication in unmyelinated axons alters myelination in the fish spinal cord[84,85], mouse optic nerve[65] and on parvalbumin neurons in mouse cortex[83], and OPC differentiation[86], presumably acting via the axon-OPC synapse. Furthermore, OPC differentiation is reduced when AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors)[86] are altered, and NMDAR (N-methyl-D-aspartate receptor) activation induces myelin basic protein (MBP) translation[87] and myelination[88]. Moreover, OPC proliferation, cell cycle exit and differentiation seem to be regulated by physical activity[89], experience[90] and learning[48,52]. Surprisingly, following motor skill training, OPC differentiation[48,52] occurs within a similar time frame to changes in dendritic spines during synaptic plasticity[91]. Thus, synaptic communication between unmyelinated axons and OPCs provides an attractive potential mechanism for learning-dependent *de-novo* myelination - a form of myelin plasticity that depends on OPC differentiation.

Yet, when cultured in the absence of neurons, OPCs still proliferate and differentiate into myelinating oligodendrocytes, extend myelin-like sheets, and can ensheath polystyrene nanofibres[92,93] and paraformaldehyde fixed axons[94]. Moreover, blocking neuronal activity in the optic nerve with tetrodotoxin (TTX) at birth, does not affect myelination[95] and, similarly, deleting NMDAR[96,97] and AMPAR[98] in OPCs has little or no effect on myelination. These observations provide strong evidence that myelination can occur in the absence of neuronal activity and glutamate signalling – or neuronal signalling at all. Conversely, blocking neuronal activity in a tract with TTX injection at the start of its myelination cycle, decreases OPC proliferation[99] and oligodendrogenesis[100] in the mouse optic nerve and zebrafish spinal

cord[101], postnatal functional alteration in AMPAR kinetic properties alters proliferation and reduces OPCs differentiation[86], and postnatal electric[102], opto-[20] or chemogenetic[22] stimulation of cortical neurons increases OPC proliferation, oligodendrocyte formation and myelination of the subcortical white matter. These findings provide compelling evidence that neuronal activity can drive myelination.

The link between changes in neuronal activity and myelination has often been observed, but has proven elusive and contradictory and thus has fuelled debate from the start. More than a century ago, based on his sensory enrichment and deprivation experiments, Hans Held explained these contradictions by proposing that two modes of myelination must exist, independent and dependent on neuronal 'activity'[103]. Indirect evidence is now accumulating in support of this hypothesis. When synaptic vesicle release from axons is impaired, myelination of the reticulospinal, but not the commissural primary ascending neurons of the developing spinal cord is disrupted[104]. Similarly, augmenting firing rates of corticofugal projection neurons does not enhance myelination, whereas increasing firing rate of cortico-callosal projection neurons does[20]. These observations may indicate that in some tracts, myelination is not driven by sensory input or activity, or that the timing of intervention is important. Accordingly, blocking neuronal activity in the optic nerve with TTX either at postnatal day P0[95] or P4[100] triggers either no effect[95] or an effect[100] on myelination, and knocking out AMPAR embryonically has little effect on myelination[98], whereas altering AMPAR postnatally affects OPC differentiation[86]. Indeed, *in vitro* work shows that the same axonal type can undergo both activity-independent and dependent myelination[105]. The switch between these modes of myelination occurs when the concentration of growth factors neuregulin-1 (NRG1) or brain-derived neurotropic factor (BDNF) increases simultaneously with active axons releasing glutamate that activates OPCs' glutamate receptors - these three

300 factors occurring together switch OPCs towards the activity-dependent mode of myelination.
301 This mode is faster than activity independent myelination[105], presumably as NMDAR
302 activation increases the energy supply to developing oligodendrocytes[106]. Following the
303 switch, OPCs have an altered NMDAR subunit expression and increased surface density of
304 NMDARs (Fig. 2A)[105]. This change would therefore alter how OPCs detect glutamate and
305 subsequently decipher neuronal activity[105], which is an attractive potential mechanism
306 explaining how OPCs could become biased towards active axons[85]. The notion of a switch to
307 activity-dependent myelination has been clearly shown *in vitro*, indicating that a switch can
308 happen when these conditions are met, but further experiments are warranted to directly
309 address this concept *in vivo*. Intriguingly, though, *in vivo* OPCs are heterogeneous in their
310 response to neuronal activity[101], neurotransmitter and ion-channel expression, between age
311 and brain areas[101,107]. These differences, presumed to reflect different OPC states[47,107], may
312 explain the varied myelination cycles (Fig. 1B), and determine which areas are primed for
313 activity-dependent myelination.
314

315 The extent to which the notion of two modes of myelination maps onto different tracts and
316 regions[20,104], or whether one mechanism is prevalent during different myelin waves, is
317 unknown. NMDAR[96,97,106] and NRG1-dependent[108,109] mechanisms appear largely
318 dispensable for early developmental myelination when deleted in oligodendrocyte lineage
319 cells, although myelination is slowed[106], indicative of the slower activity-independent mode
320 of myelination[105]. Similarly, developmental myelination is largely unaffected when the
321 NRG1 receptor ErbB3 is knocked out in OPCs[108]. One interpretation of these findings is that
322 when activity is blocked[95] or receptors important for activity-dependent myelination are
323 deleted[96,97,106,108,109] early in embryonic development (before the switch towards activity-
324 dependent myelination has occurred), myelination occurs by the slower activity-independent

mode (Fig. 2B). It seems clear that myelination during the first wave is relatively unaffected when activity-dependent mechanisms are disrupted, much like how synapses can form early in development in the absence of glutamate signalling or neuronal activity[74]. However, in areas which myelinate predominantly in the second wave, such as the mPFC, myelination is disrupted when proteins involved in activity-dependent myelination are deleted, e.g. when ErbB3 is knocked out in OPCs[50]. Likewise, learning-dependent myelination during the second wave is disrupted when BDNF TRKB receptors are knocked out[110]. It is thus conceivable that areas like the mPFC, where myelination is notably protracted and starts during the second wave, rely on an activity-dependent program, subject to modulation by experience.

Mechanisms of alterations of existing myelin - myelin plasticity driven by oligodendrocytes

In addition to OPCs driving *de novo* myelination, mature myelinating oligodendrocytes also show capacity for plasticity, such as elongating[16,17,54,55] or retracting[16,17,55] existing myelin internodes. In some cases myelinating oligodendrocytes can completely retract a myelin internode or extend new processes to form new myelin internodes (Box 2)[19]. Despite many outstanding longitudinal *in vivo* imaging studies following myelination in the cortex[16,17,54] during normal homeostasis, it is only after monocular deprivation that a few oligodendrocytes have been shown to extend new myelin sheaths, indicating the rarity of this phenomenon. It is definitely much less frequent than the modest changes in existing myelin internodes driven by myelinating oligodendrocytes and the robust *de-novo* myelination driven by OPCs[16,17,54]. Although existing myelin shows evidence of being plastic it is in general very stable in the adult brain[16,17]. Further evidence is needed to fully appreciate the extent of this form of myelin plasticity. Collectively though, these changes seem to be modified with learning[54] or sensory experience[17,19] (Box 2), and when neuronal firing rate is increased or decreased, the

length[65] and thickness[20,22] of existing internodes is altered. The underlying mechanisms are less well characterised, but mature myelin sheaths also express ionotropic glutamate receptors[78,111,112], which face the periaxonal space. Remarkably, neuronal activity induces internodal specific calcium changes in the myelin sheath[113,114], which are NMDAR-dependent and sensitive to blocking of glutamate vesicular release[112]. These findings suggest that direct communications between axons and the myelin sheath might underlie activity-dependent, glutamate-mediated changes in myelin, primarily in sheath thickness and internode length, particularly as the frequency and size of the calcium changes predicts the length or elongation of the internode[113,114] (Box 2). In addition to direct mechanisms, emerging evidence supports a role for microglia[115] and astrocytes[116] in the regulation of myelin plasticity, in particular where microglia phagocytose myelin internodes, during development, according to neuronal activity levels[115].

The aforementioned observations convey that myelin is plastic, and responsive to experience and neuronal activity. Myelin plasticity manifests in multiple forms (Box 2), the clearest example being changes mediated by augmented OPC differentiation into new myelinating oligodendrocytes, but also changes in existing myelin orchestrated by mature oligodendrocytes, which has been less extensively studied. The notion that myelin is plastic is still in its infancy, but changes our understanding of circuit function and plasticity[4,117]. Thus, future work will need to determine the rules of plasticity and the impact of myelin changes on brain circuits.

4. Myelin regeneration and plasticity – two sides of the same coin?

Myelin plasticity likely underlies the extraordinary capacity for myelin regeneration following damage in humans and animals alike, particularly in the young[118] (Fig. 3). Despite

this strong regenerative potential, myelin regeneration or remyelination often fails in diseases like multiple sclerosis (MS), leading to sustained clinical deficiency[118]. Failure of myelin regeneration appears age-dependent[118], in line with when myelin levels decline with age during the third wave[6] (Fig. 1A), presumably as maintenance is reduced and OPCs enter quiescent state[47,107,119]. Nonetheless, in young adults, myelin regeneration is efficient, particularly when occurring during myelin stages 3 (adolescence) and 4 (adult; Fig. 1A), potentially because OPCs are in a state[47,107,119] primed for differentiation and capable of responding to myelin damage as the forebrain is still undergoing myelination (Fig. 1A). Since myelin plasticity can be driven by OPC differentiation and existing myelinating oligodendrocytes, a role for the surviving myelinating oligodendrocytes is now being proposed.

Myelin regeneration driven by OPCs - akin to the de-novo myelination mode of myelin plasticity

Accumulating evidence implicates neuronal activity as an important regulator of myelin regeneration [54,120-122]. Like adult myelin plasticity, remyelination is increased following motor skill learning[54] and physically active MS patients tend to display increased white-matter integrity[123], assumed to be a sign of increased remyelination. This indicates that OPC differentiation is promoted by activity; indeed, like unmyelinated axons in development, demyelinated axons reform synaptic inputs with OPCs[120,124,125]. Furthermore, blocking neuronal activity, vesicular release or glutamate receptors (both AMPAR and NMDAR) impairs remyelination, indicating that remyelination is driven by neuronal activity and axoglial glutamate synaptic signalling[120]. Conversely, optogenetic or epidural stimulation of motor cortex neurons promotes remyelination following lysolecithin injections in the corpus callosum[122] or traumatic spinal cord injury[121] respectively. These activity-dependent changes

in remyelination efficiency likely result from changes in the rate of OPC differentiation, as following demyelination, increases in neuronal activity led to enhanced oligodendrogenesis[121,122] and blockage of activity resulted in the accumulation of undifferentiated oligodendrocyte progenitors[120], reminiscent of chronic demyelinating MS lesions containing OPCs that have failed to differentiate[126,127]. Remarkably, presynaptic markers localise close to OPC processes in focal demyelination lesions generated in rodents, and are both upregulated in demyelinated lesions in MS patients and localised close to OPC processes in MS lesions undergoing repair[120,125]. These findings strongly suggest that axon-OPC synaptic signalling is a relevant mechanism for remyelination in MS.

That neuronal activity and experience regulate remyelination, much as myelin plasticity is regulated, suggests that myelin repair and plasticity are variations of the same phenomena. In this context, it is intriguing to note that, similarly to remyelination, myelin plasticity decreases with age[6,16,17] and that loss of myelination efficiency correlates with changes in ion channel and glutamate receptor surface expression in OPCs[107]. Therefore, failure of remyelination with age may result in part from changes in the way adult OPCs sense neuronal activity, in addition to environmental differences[128] and clearance of myelin debris[16,129]. Studies aiming to rejuvenate the environment or the OPCs have shown increased myelin regeneration[128,]. Consequently, determining the OPC state that is important for myelin regeneration, then modifying the balance of OPC states towards those that are primed for differentiation, might constitute a promising novel avenue for remyelination-promoting therapies.

Myelin regeneration by oligodendrocytes - akin to the mode of myelin plasticity relating to the modulation of existing myelin

Myelin plasticity driven by mature myelinating oligodendrocytes corresponds mainly to alterations of existing myelin internodes, although one study reported that mature oligodendrocytes can retract myelin internodes and extend new processes to form new myelin internodes (Box 2)[19] following monocular deprivation. Similarly, following a demyelinating insult surviving myelinating oligodendrocytes seem to be able to extend new myelin sheaths to remyelinate demyelinated axons[54,130], and the formation of these new remyelinating sheaths is enhanced with motor skill learning[54]. Thus, myelin plasticity driven by existing oligodendrocytes seem to be evoked in remyelination. However, when a single oligodendrocyte is depleted, generation of a new internode, or replacement, by pre-existing oligodendrocytes is not detected[131]. This perhaps indicates that survival of an oligodendrocyte that has lost all or part of its myelin sheath, is needed to initiate pre-existing oligodendrocytes to extend new myelin internodes and it may therefore be more representative of myelin maintenance. These observations follow few post-mortem human studies on MS that claim an extensive contribution of pre-existing myelinating oligodendrocytes to remyelination[132,133]. These findings are definitely thought provoking, and invite re-examination of the evidence (as reviewed in detail elsewhere[134,135]). However, there are difficulties with determining remyelination in post-mortem tissue, and relying on proliferation markers to distinguish *de-novo* remyelination from remyelination generated by pre-existing myelinating oligodendrocytes is problematic as OPCs can directly differentiate into myelinating oligodendrocytes without proliferating first[46]. The evidence for remyelination by pre-existing myelinating oligodendrocytes shows that this occurrence is still rare, and their contribution is small in comparison to OPC differentiation[54,130].

It may be more important to establish how the pattern of myelin is regenerated. Emerging data provide evidence for patterns of myelin being important, and show that remyelination

450 can re-establish the pattern of myelin on axons[54,130,131,136] (Box 3). Circuit function can be
451 altered in cases where remyelinated myelin internodes do not fully overlay the previous
452 pattern[54,130,131,136]. The success of re-establishing the right pattern is partly dependent on
453 surface molecules on the axon[136], in particular the remaining protein at the node of
454 Ranvier[136], and zebrafish data indicate that OPC driven remyelination seems better able to re-
455 establish myelin patterns than remyelination by pre-existing oligodendrocytes[130]. The
456 relative importance of pre-existing oligodendrocyte remyelination, and mechanisms
457 underlying this, requires further study[134]. However, current data strongly support enhancing
458 OPC differentiation to increase remyelination and functional recovery after a demyelinating
459 injury. Thus, it still remains a major research focus to find new therapeutic strategies for
460 white matter diseases such as MS.
461
462 **5. Does dysregulation of myelination contribute to common neurological disorders?**
463 Several studies have now demonstrated that suppression of adult oligodendrogenesis impairs
464 some types of learning and memory, suggesting that myelin might have a considerably
465 broader function than anticipated[52,59,60,137]. Likewise, it is increasingly being proposed that
466 deficits in myelin formation and maintenance may underlie multiple CNS disorders,
467 including conditions that have been exclusively associated with deficits in neuronal function.
468 For example, myelin defects – hypomyelination, hypermyelination, white matter damage, etc.
469 - have been reported in autism spectrum disorders, epilepsy, schizophrenia, depression and
470 Alzheimer's disease[25,26,138]. These observations are consistent with recent genome-wide
471 association studies and transcriptome analyses that have linked mutations in myelin-specific
472 genes or dysregulation of oligodendrocyte gene expression to diseases thought to be primarily
473 of neuronal aetiology[27-32]. Indeed, our analysis of published human brain single cell
474 transcriptomic data indicates that, compared to neurons, oligodendrocyte lineage cells express

a proportionally higher number of genes that are linked to neurodevelopmental, psychiatric or neurodegenerative diseases (Fig. 4B; Varga, B.V., Lauzikaite, E., Mohorianu, I, Káradóttir, R.T., unpublished data). Intriguingly, the typical age of onset of neurological disorders coincides surprisingly well with the three waves of myelin changes that we propose in this review (Fig. 4A). Whether deficits in myelin formation and maintenance contribute to the changes underlying some of these disorders is receiving increasing consideration[138,139]. However, these important correlations have not yet been followed by direct evidence showing that dysregulated myelination contributes to the development of neuropsychiatric or neurological disorders on a functional and mechanistic level, thus any causative role remains a hypothesis for now. Nonetheless, these studies, and the fact the onset of various neurological diseases correlates to the periods of greatest changes occurring in myelin in the human brain, underscore the importance of understanding the regulation of myelination throughout life and of determining whether myelin plays a role, as it may be key to establishing novel therapeutic approaches to these complex neurological disorders.

Future perspective

The last decade has seen a revolutionary shift in our understanding of myelin, and it is becoming clear that myelin changes with age and experience. The accelerated pace of discoveries in recent years, combined with now having the experimental tools to directly address the causality of the important observations made more than a century ago, have opened up a series of exciting new questions for the future, far more than it is possible to list.

Going forward it is important to determine the temporal and regional dynamics of myelination throughout life, in line with our knowledge of neuronal plasticity. Similar to neuronal plasticity, is there a specific window for myelin plasticity in some areas whereas

other regions remain plastic throughout life; if so, are the regions that remain plastic the regions with multiphasic and protracted myelination cycles? What regulates the onset of myelination in different brain regions and tracts, and how are different cycles of myelination initiated? Yakovlev and Lecours noted that heterogeneous axonal tracts tend to have a multiphasic myelination cycle. Does this indicate that the axon determines when myelination starts, or is there a switch in the myelination programme that initiates myelination of certain axons? Does variation in the onset of myelination between regions relate to reported oligodendrocyte and OPC heterogeneity? Is myelination governed by the same mechanisms throughout life or are distinct mechanisms, either activity-dependent or independent modes of myelination, predominant during different myelin waves and cycles of myelination? Fundamental to answering these questions is to establish how well human myelination is recaptured by animal models, to delineate the limits of functional interrogations and comparisons.

A second area of focus concerns the emerging notion of the pattern of myelination (Box 3), in the form of different myelin internode distributions along axons, and between axons in a tract; as well as the myelin pattern made by individual oligodendrocytes. How is this regulated, and does this pattern have any connection with different myelination cycles or myelin waves? Are axons first myelinated with intermittent myelin internodes[43,] as observed in the optic nerve[42], and then later become fully myelinated along the axon? Are multiphasic cycles related to a change in the type of axons becoming myelinated (as suggested by Yakolev and Lecours[14]) or the addition of myelin internodes on partially myelinated axons, or both? Do the axons determine the myelin pattern by laying out surface molecules, as suggested by Orthmann-Murphy and colleagues[136], and if so, is it possible to pre-identify the myelin pattern before axons are myelinated, and alter it by manipulating surface molecule

525 expression? What are the consequences of misaligned patterns; do they significantly alter
526 neuronal circuit function, as in part suggested by Bacmeister and colleagues[54]?
527
528 Third, and possibly one of the most important questions, is how and to what extent myelin
529 regulates neuronal circuit function. Flechsig noted early the functional relationship between
530 the initiation of tract myelination and the maturation of neuronal circuits. The question
531 remains, how do the different myelin waves and cycles of myelination relate to the function
532 of neuronal circuits? How does myelin regulate circuit function? Presumably the myelin
533 pattern is important for synchronisation of the neuronal circuit, as suggested by many[54,131,136]
534 but direct experiments are needed to determine this, which are beginning to come
535 forth[59,60,117]. Improvements in tools will be vital to allow direct and simultaneous
536 manipulations of myelin and measurements of circuit function. The impact of myelin on
537 circuit function is a nascent field that will undoubtedly grow in importance in the coming
538 years, as it may underscore our understanding of cognition and multiple neurological
539 disorders. Thus, it is important to determine the functional implications of myelin
540 dysregulation in neurological disorders.
541
542 Lastly, the relative importance of pre-existing oligodendrocytes and OPCs for myelin
543 plasticity and remyelination, and the underlying mechanisms, require further study. How
544 pre-existing oligodendrocytes modulate the myelin sheath, and the mechanisms by which
545 they generate new myelin sheaths, remain open questions. Currently, the contribution of pre-
546 existing oligodendrocytes seems small in comparison to that of OPCs, particularly as learning
547 and memory is significantly impaired when OPC differentiation is prevented. However,
548 similar studies have not been conducted for pre-existing oligodendrocytes, and even less is
549 known about whether the OPCs or the intermediate pre-myelinating oligodendrocytes play

other roles in myelin plasticity besides becoming myelinating oligodendrocytes. As experimental tools improve, so will our understanding of myelin plasticity. Of future importance is to determine which, if not all, forms of myelin plasticity to promote and when and how to harness the power of myelin plasticity to promote efficient myelin regeneration.

Conclusion

In 1901, after a lifetime of post-mortem studies, Flechsig put forward a fundamental law of myelogenesis - 'the myelinogenetic law' - 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"*[11,13]. Flechsig and Held postulated a link between neuronal activity and myelination, now mostly forgotten. Only recently have we witnessed a revolution in the way we think about myelin, conventionally perceived as static and impassive, but now recognized to be dynamic and responsive to experience. Myelin plasticity relies on an abundant and widespread population of oligodendrocyte progenitors that sense and respond to neuronal activity by altering their rate of oligodendrogenesis, a mechanism that is arguably the most relevant example of structural remodelling in the adult brain. Decreasing capacity for myelination with age has long been considered to play a major part in the failure to repair in traditional myelin disorders, but new findings indicate that oligodendrogenesis is a requirement for some types of learning and memory and suggest that loss of myelin plasticity may contribute to the aetiology of unexpected CNS disorders, whose temporal onsets align with waves of myelin change in relevant brain areas. To better understand the significance of this contribution, research in the years to come will need to focus on the functional impact that waves of gain and loss of myelin have on neuronal circuits.

Figure legends

Figure 1: Myelin changes across the lifespan. (A) A schematic graph of forebrain myelin changes during the human life span, summarising data interpreted from early histological[9-14,35], modern MRI[5,6] and gene expression[15] studies, with a slight focus on cortical myelin changes. The shaded areas correspond to the myelin waves - periods of rapid synchronised myelin change during early years, adolescence and ageing - and the numbers above indicate the different stages of myelination as defined by Flechsig, Yakovlev & Lecours, and others. **(B)** A schematic representation of the different cycles of myelination defined as the length of time from onset of myelination of a tract/area to its completion, i.e. (1) monophasic (clear fast onset and completion of myelination), e.g. optic nerve or auditory brain stem; (2) multi-phasic (onset followed by a pause prior to a separate myelination round), e.g. cingulum, uncinate fasciculus and parahippocampal gyrus, or (3) slow continuous protracted myelination cycle, e.g. commissural and association fibres. Horizontal bars exemplify rounds of myelination across time that are characteristic for each cycle[14]. The third bar on the multiphasic cycle is presented in a faded colour to convey that the exact number of cycles is specific to each tract/area. It should also be noted that the timing of onset and completion of a myelination cycle can be highly variable and tract dependent.

Figure 2: Two modes of myelination (A) *In vitro* experiments highlight that there are two modes that can drive the formation of myelin. *Left:* default mode that is independent of neuronal activity. In the absence of growth factor or neuronal signalling, OPCs differentiate into oligodendrocytes that myelinate axons - this mode is slower. *Right:* activity-dependent mode of myelination, occurs in the presence of NRG1 or BDNF and active neurons releasing glutamate that activates NMDA-receptors on OPCs, leading to increased and altered NMDAR expression. Switched OPCs differentiate into oligodendrocytes that myelinate

active axons - this mode is faster than the activity-independent (default) mode. **(B)** A model of the two modes of myelination, based on the literature, predicts that the timing of experimental intervention may determine the outcome. Altering mechanisms of activity-dependent myelination **before** the switch takes place has no drastic consequences for myelination. This is in sharp contrast to interventions made **after** the switch has taken place and myelination has become activity-dependent. The prediction would therefore indicate that at this point, altering neuronal activity, glutamate receptor expression or growth factor signaling would greatly impact myelination. As the switch is under tight control by environmental factors, it is possible that only OPCs within a small area are switched to activity-dependent myelination, leading to regional as well as temporal differences in myelination mode.

Figure 3: Mechanisms of remyelination (A) In the healthy tissue, axons are myelinated by oligodendrocytes and OPCs are evenly distributed throughout the tissue. (B) After a demyelinating insult, damaged oligodendrocytes die and myelin disintegrates leaving axons demyelinated. (C) Recruitment phase starts with clearance of the myelin debris by microglia-derived phagocytes followed by OPC recruitment, when OPCs within the area and OPCs that have migrated into the lesion site from the surrounding areas start to proliferate. (D) Differentiation phase, OPCs differentiate into myelinating oligodendrocytes. (E) Remyelination phase, differentiated oligodendrocytes regenerate lost myelin. According to the classical concept of remyelination, new myelin is produced in the demyelinated lesion mostly by the newly-formed oligodendrocytes. New emerging data show that on rare occasions, some of the surviving oligodendrocytes may also produce new myelin sheaths and contribute to remyelination, although the extent of their contribution remains to be determined.

Figure 4: Oligodendrocyte, myelin changes, and onset of neurological and psychiatric conditions (A) Timeline of manifestation of neurological and psychiatric conditions, which map onto the three waves of myelin changes, illustrated by the shaded areas as in Figure 1. **(B)** Gene variants associated with neurodevelopmental (6 different conditions, e.g., autism spectrum disorder, epilepsy, attention deficit hyperactivity disorder (ADHD), cognitive impairment), psychiatric (11 conditions, e.g., bipolar disorder, schizophrenia, anxiety disorder, depression) and neurodegenerative (6 conditions, e.g., Alzheimer's disease, dementia, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease) conditions were cross referenced with genes expressed in major brain cell types in the adult human cerebral cortex. The percentages indicate relative number of genes expressed in a specific cell type associated with a specific pathological condition. **(C)** Pie slices indicate the proportion of gene variants associated with pathological conditions per cell type, normalized to the total number of genes expressed in the cell type ((#gene variants in cell type/#gene variants associated with condition)/(#genes expressed in cell type/#genes expressed in all cell types)). The size of the pies thus shows relative contribution of gene variants expressed by a specific cell type to gene variants associated with pathological states. Bar graphs indicate the number of conditions per cell type where the relative number of gene variants associated with pathological conditions is significantly higher than expected by Hypergeometric distribution. $p<0.001$ except microglia $p<0.01$. Data source: The NHGRI-EBI Catalog of human genome-wide association studies (https://www.ebi.ac.uk/gwas/), Allen Brain Map Human Multiple Cortical Areas SMART-seq (https://portal.brain-map.org/atlases-and-data/rnaseq).

Box 1: Oligodendrocyte lineage cells progression and key myelin parameters

Myelin is formed by glial cells called oligodendrocytes that enwrap neuronal axons with a lipid-rich membrane called myelin[53]. The oligodendrocyte lineage cells arise from diverse embryonic neural progenitors which give rise to oligodendrocyte precursor cells (OPCs)[53]. Early on, OPCs evenly populate the whole CNS and remain throughout life, becoming the main proliferating cell population in the adult brain and spinal cord[76]. Throughout the lifespan, OPCs differentiate into pre-myelinating (immature) and finally into myelinating oligodendrocytes[18,46,53]. Emerging data indicate a new intermediate stage, between a proliferating OPC and pre-myelinating oligodendrocyte, a primed oligodendrocyte lineage cell that is neither PDGFRα positive nor marked with early differentiation marker CC1, but characterized by the expression of *Enpp6* and Olig2[48]. These cells have exited the cell cycle but can rapidly differentiate into myelinating oligodendrocytes given the right signals[48]. The classical view is that the sole role of OPCs and intermediate oligodendrocyte lineage cells is to differentiate into myelinating oligodendrocytes. OPCs often differentiate into immature oligodendrocytes, which do not myelinate axons and undergo apoptosis, presumably because more immature oligodendrocytes are produced upon neuronal signal than are actually needed for myelination[140]. However, evidence is starting to emerge that OPCs and immature pre-myelinating cells might fulfil other functions as well, including synaptic strengthening[141] or altering neuronal function in some way, as blocking OPC differentiation into *Enpp6* expressing cells seems to be enough to affect circuit function[48]. It is known that OPC differentiation and myelination are orchestrated by numerous cellular and molecular signals, such as axonal diameter, growth factors, extracellular signalling molecules, adhesion proteins, neurotransmitters, and neuronal activity (as reviewed extensively in[49,142]). Nevertheless, the relative importance of, and cooperation between, these signalling pathways is not yet fully clear. The oligodendrocyte lineage can be identified by unique common

674 transcription factors, like Olig1 & 2 and Sox10, and different stages of the lineage can be
675 identified by a number of distinct surface and intracellular protein markers[53]. OPCs are
676 identified by the surface proteoglycan neuron-glial antigen 2 (NG2), platelet-derived growth
677 factor α receptor (PDGFαR) and/or the transcription factor NKX2.2. Differentiating
678 oligodendrocytes start to express BCAS1[71], O4, galactocerebroside (GalC), the enzyme 2',3'
679 - cyclic-nucleotide 3'-phosphodiesterase (CNPase)[53]. Mature oligodendrocytes can be
680 identified by the expression of myelin basic protein (MBP), myelin-associated glycoprotein
681 (MAG), myelin oligodendrocyte glycoprotein (MOG), CNPase and proteolipid protein (PLP),
682 enriched in their ensheathing myelin processes[53]. Both OPCs and oligodendrocytes show
683 substantial heterogeneity within their respective populations depending on age and brain
684 region, presumably reflecting their distinct functional properties, susceptibility to neuronal
685 signaling and differentiation and/or myelination potential, as such may be in line with the
686 different myelination cycles[47,107,119]. Currently, it is unclear whether these multiple
687 heterogeneous populations have clearly defined, distinct functions[47,101,107,119], or whether their
688 functional heterogeneity reflects different states of the same population[47].
689
690 Myelin effectively decreases the cross-membrane capacitance and resistance of axons, and
691 thus increases the temporal resolution of depolarisation and reduces the current leak across
692 the membrane[2,143]. These biophysical properties of myelin reduce the failure rate of action
693 potential propagation and enable the action potential to depolarise an increased distance along
694 the axonal membrane[2]. Oligodendrocytes generate one myelin sheath per axon, but along
695 axons there are multiple myelin sheaths made by different oligodendrocytes, with intermittent
696 gaps between them[43]. These exposed patches of axonal membrane have a high density of
697 voltage-gated sodium channels and are named nodes of Ranvier. The action potential in
698 essence travels from node to node. Myelin is particularly important for rapidly conducting

699 axons as it enhances the speed and fidelity of information transmission, via these classical
700 biophysical properties[2,143] and siphoning potassium released during the action potential[71],
701 and by enabling metabolic support from oligodendrocytes to axons via lactate release[144]. The
702 key parameters of myelin that have been shown to alter conduction velocity are internodal
703 length and myelin thickness, usually expressed as a g-ratio (quantified as the ratio between
704 the axonal diameter and the myelinated fibre diameter).
705
706 The classical static view of myelin and its functions has been challenged in recent years by
707 showing that OPC differentiation and myelination is far more flexible and context-dependent
708 than previously thought, which opens up the possibility of myelin having broader roles in the
709 context of neuronal circuit function.
710
711

Box 2: Multiple forms of myelin plasticity.

Myelin can in principle change in three different ways. (1) addition of new myelin internode, mainly driven by OPC differentiation (marked in green), onto previously unmyelinated axons or unmyelinated areas of intermittently myelinated axons; (2) altering existing individual myelin internodes such as the thickness or the length (elongation (marked in green) or retraction (marked in red): note that a mature oligodendrocyte can alter different internodes independently); or (3) changing the architecture of the nodes of Ranvier and increasing ion channel density at the node (marked with purple ovals across membrane).

(1) Addition of new myelin internodes *(green internodes) - mainly driven by OPC differentiation*

Many white matter tracts retain a substantial proportion of unmyelinated or partially myelinated axons, which can potentially become myelinated during life[145]. Myelination of this population of axons and axonal segments thus offers a large dynamic range in plasticity in the adult CNS, whereby newly generated oligodendrocytes contact and ensheath these axons or add new internodes in response to neuronal activity[16,17,20,22,54]. In areas where tracts are rather extensively myelinated but oligodendrocyte turnover is high, e.g. optic nerve and corticospinal tract, the addition of new internodes represents an important mechanism for myelin maintenance[18,69]. Evidence highlighting this type of remodelling has been provided by studies in which ablation of an individual oligodendrocyte or a single internode triggered oligodendrogenesis and replacement of the ablated sheath with a new internode[55,131]. In some circumstances pre-existing oligodendrocytes can extend new myelin sheaths on axons[19], although this remains a rare occurrence[19,54,136]. These changes in myelin profiles along an axon may serve to fine-tune the conduction delays of individual fibres to optimise circuit activity.

737

738 **(2)** ***Modulation of existing myelin (blue internodes) - plasticity driven by the mature***
739 ***oligodendrocyte***

740 The relationship between axonal diameter, myelin thickness and internode length is largely
741 variable in the adult CNS, possibly reflecting another form of myelin plasticity driven by
742 mature oligodendrocytes. They can change the thickness of existing myelin[21] and elongate
743 (green changes) or retract (red changes) myelin internodes depending on neuronal
744 activity[20,113,114] and neurotransmitter signaling[65,146]. Thicker myelin is generated in response
745 to increased activity[20,22] and thinner myelin results when activity is attenuated or
746 social/sensory input is reduced[21,50,61].

747

748 **(3)** ***Modulation of nodal properties***

749 Changes in the properties of nodes of Ranvier may represent yet another form of myelin
750 plasticity. Nodal length in the optic nerve and cerebral cortex show a high degree of
751 variability[147]. Axons might be able to modify the nodal length, both in health and in disease,
752 to regulate speed of conduction, as computational models indicate that nodal geometry can
753 impact on conduction velocity similar to the range of speed variation resulting from changes
754 in internode length and myelin thickness[147]. Remarkably, neuronal activity and experience
755 modulate nodal properties, as spatial learning[24] and chronic stress[23] alter the nodal length, and
756 monocular deprivation results in displacement of the node along myelinated fibres[19].

757

758 Collectively these data suggest that adding new internodes or changing existing internodes,
759 myelin thickness and node properties may occur in response to neuronal activity and
760 experience. These changes in myelin profiles along an axon may serve to fine-tune the
761 conduction delays of individual fibres to optimise circuit activity.

Box 3: Myelin patterns

Axons in the CNS are either unmyelinated[148], partially myelinated[43], fully myelinated or fully myelinated with different patterns of progressively shorter myelin internodal length along the axon and larger nodal distances[149]. Thus, along a single axon and between axons there is a different pattern of myelination, providing differences in myelin patterns within and between neuronal circuits (see diagram A).

Additionally, a new concept is emerging from longitudinal remyelination studies[54,131,136], moving away from focussing on single internodes or placements of internodes along an axon, to considering the pattern of internodes formed by an oligodendrocyte (see diagram B). Oligodendrocytes can myelinate up to 50 axons[53], but it is unclear how they choose how many and which axons to myelinate. It seems they are biased towards active axons[85]. The pattern of internodes formed by an oligodendrocyte seems to be stable, as when one oligodendrocyte is depleted there is a remarkable reestablishment of the same pattern[131]. However, the pattern becomes disrupted with extensive oligodendrocyte damage, as can occur in white matter disease studies[54,136], with very few oligodendrocytes reforming previous patterns[136]. The restoration to previous myelin pattern appears to depend on whether nodal proteins on the axon remain in place[136]. Disruption of the pattern seems to have an impact on the performance of learnt motor skills[54]. Peculiarly, the normal myelination programme pauses during learning of a new motor task, but then post-learning, myelinating oligodendrocyte numbers exceed compared to controls, indicating perhaps a change in the mechanism of myelination to establish a new myelin pattern organisation[54]. The myelin pattern is likely to change with age or experience as internodes are eliminated, shortened or enlarged. To what extent and how this pattern changes with time, and its impact on neuronal circuits, remains uncertain.

Drawing from the findings mentioned in Box 2 on myelin plasticity, it is possible that these myelin changes serve to align myelin patterns along axons in a given neuronal circuit, but how this may be adjusted and regulated is completely uncertain. It is possible to hypothesize that individual oligodendrocytes myelinate axons that belong to the same circuit and are adjusting the pattern of myelin within circuits. Within the corpus callosum it seems that oligodendrocytes tend to myelinate either somatosensory or motor neuronal axons, with a minority myelinating both types of axons[150], although in areas such as the somatosensory cortex, oligodendrocytes myelinate both inhibitory and excitatory neurons[43]. How this translates to other regions is unclear, but future experiments will elucidate whether the pattern of myelin is an important determinant of circuit function.

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Competing interests statement

The authors declare no competing interests.

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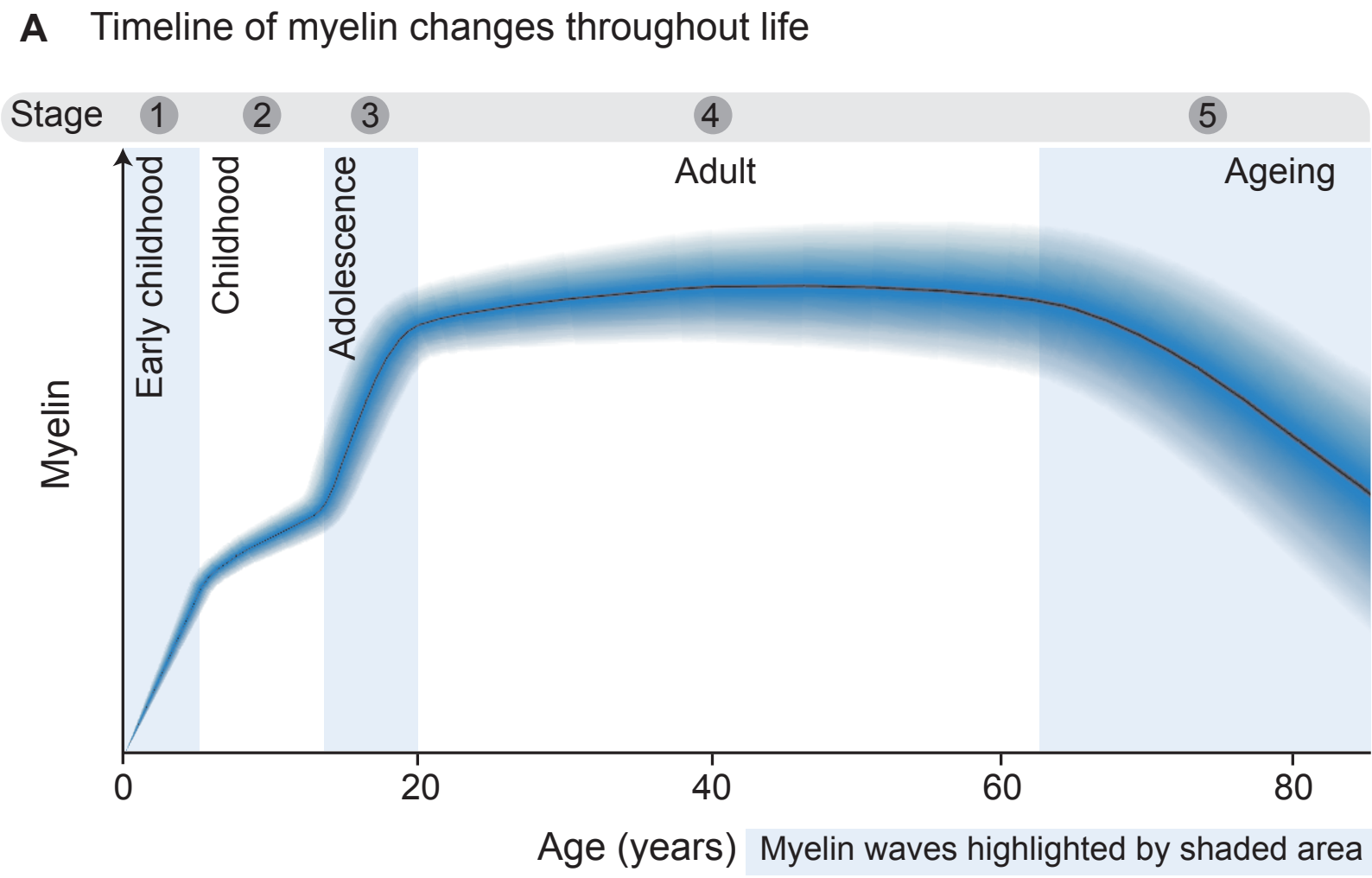

A Timeline of myelin changes throughout life
Stage 1 2 3 4 5
Early childhood
Childhood
Adolescence
Adult
Ageing
Myelin
0 20 40 60 80
Age (years)
Myelin waves highlighted by shaded area

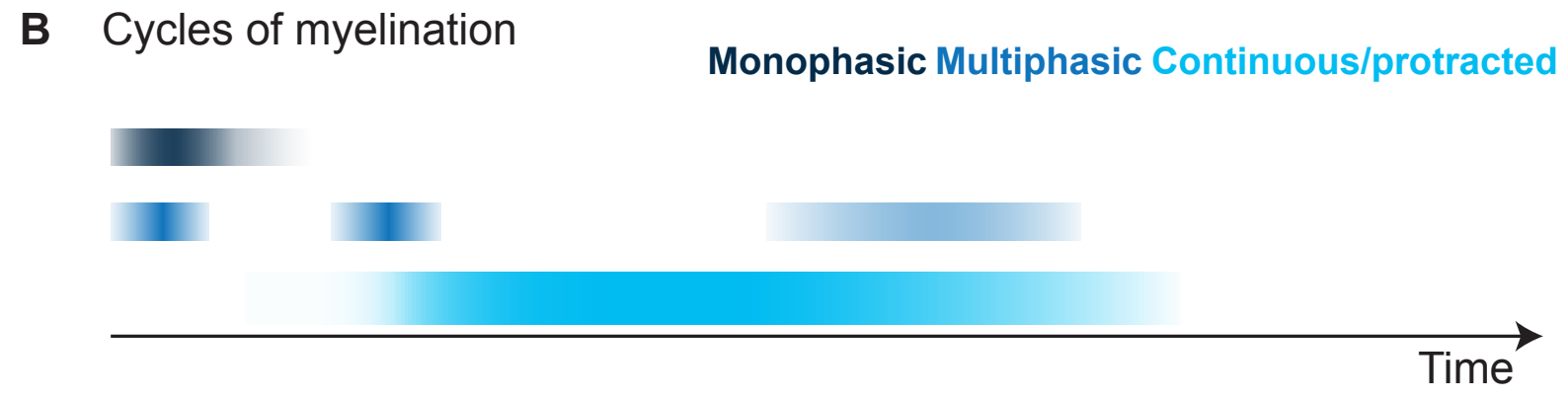
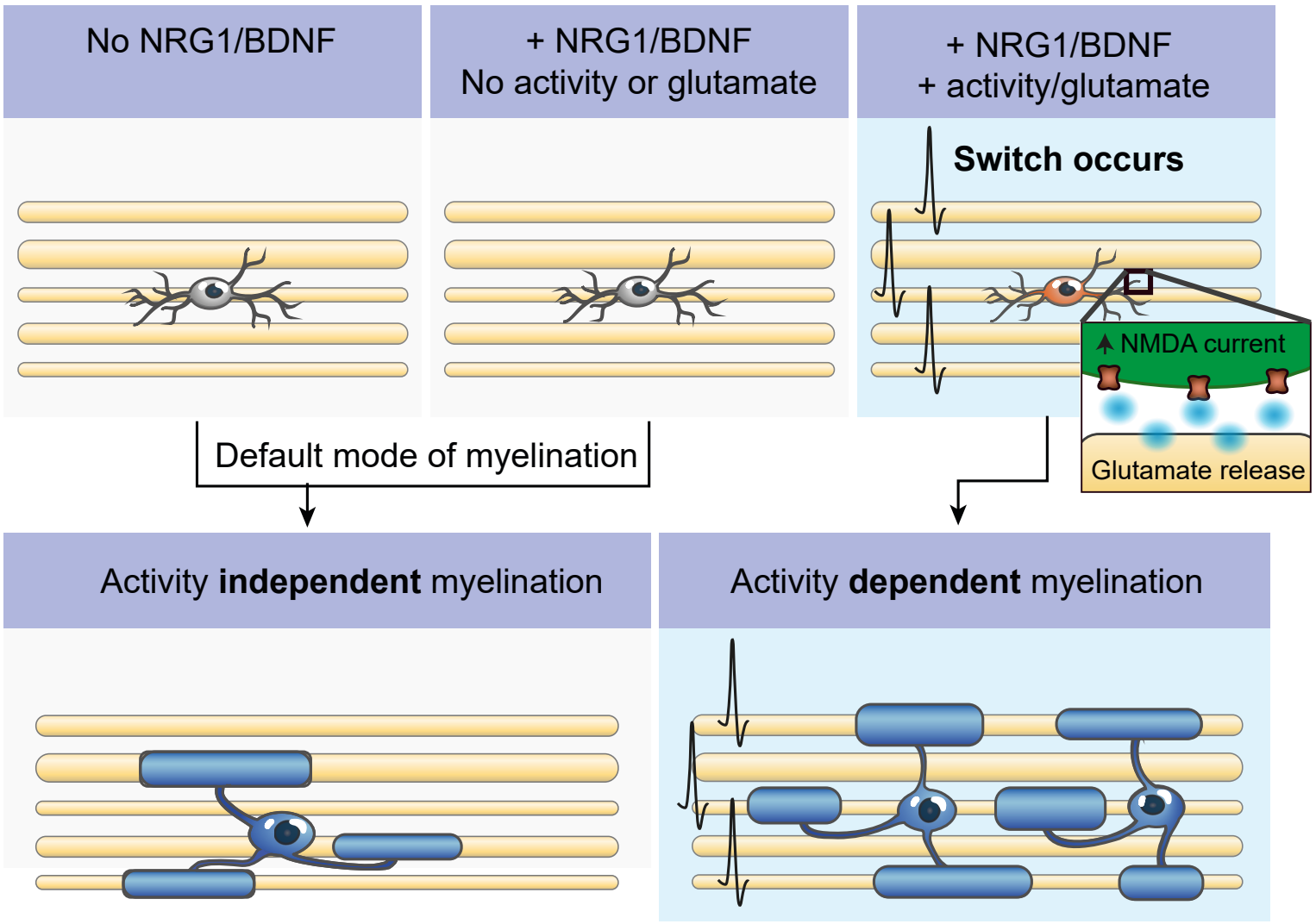
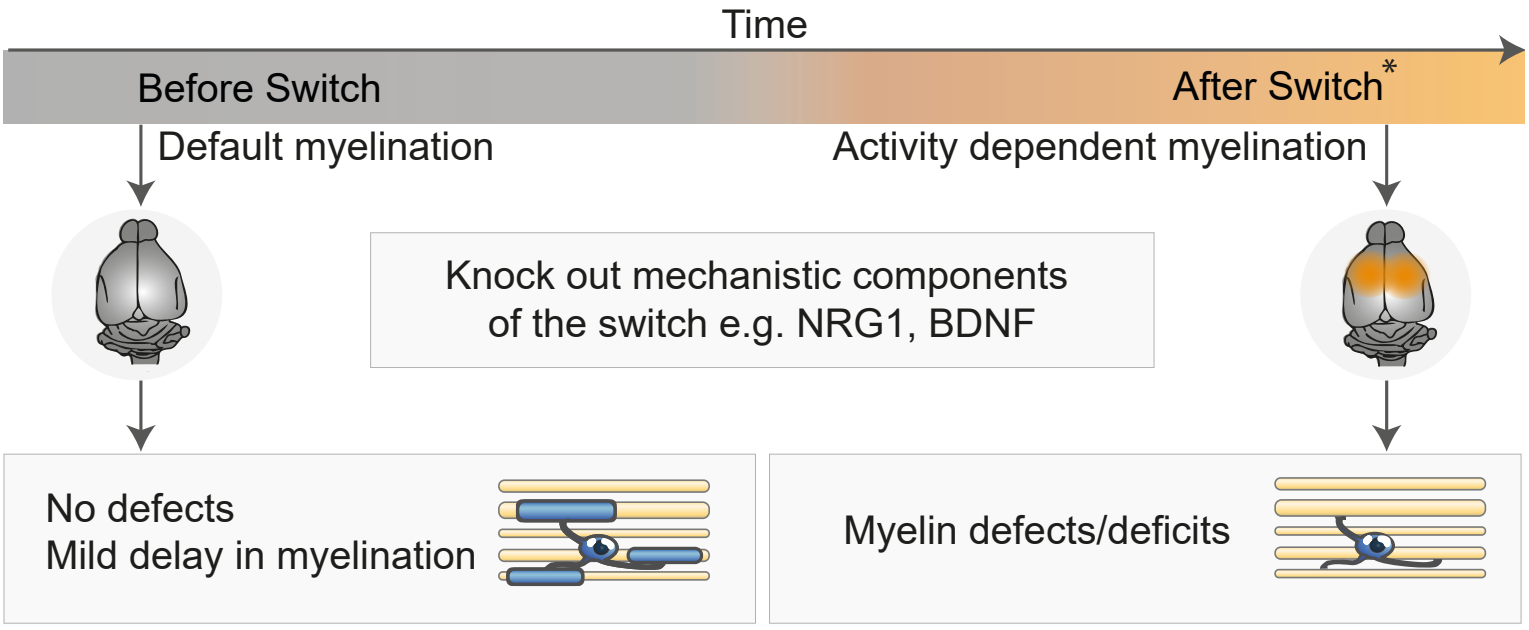

B Cycles of myelination
Monophasic Multiphasic Continuous/protracted
Time

Figure 1

A Two modes of myelination model



B Outcomes dependent on timing of intervention



* As the switch is triggered by activity and growth factors, different regions will switch at different timepoints

Figure 2

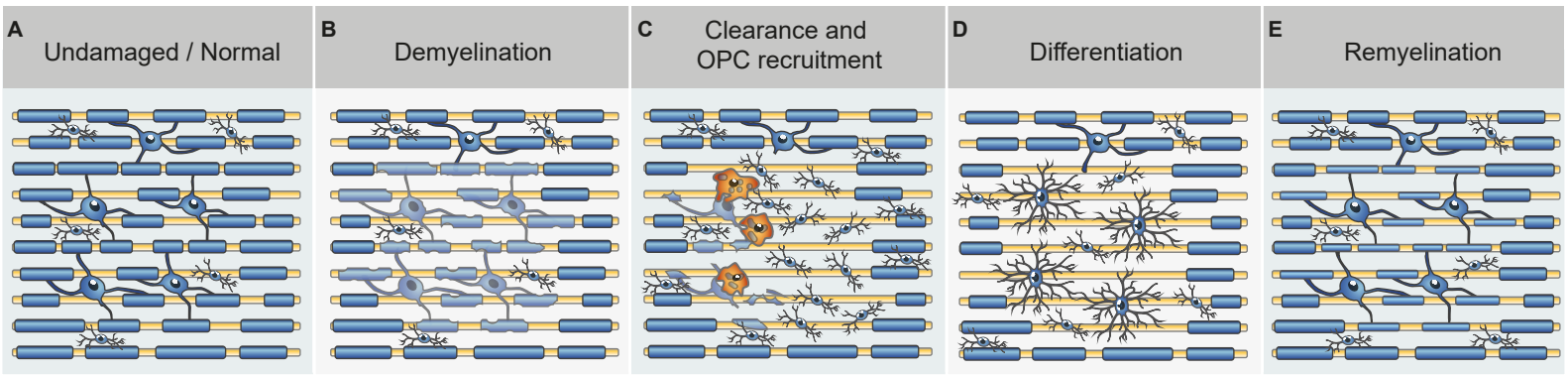
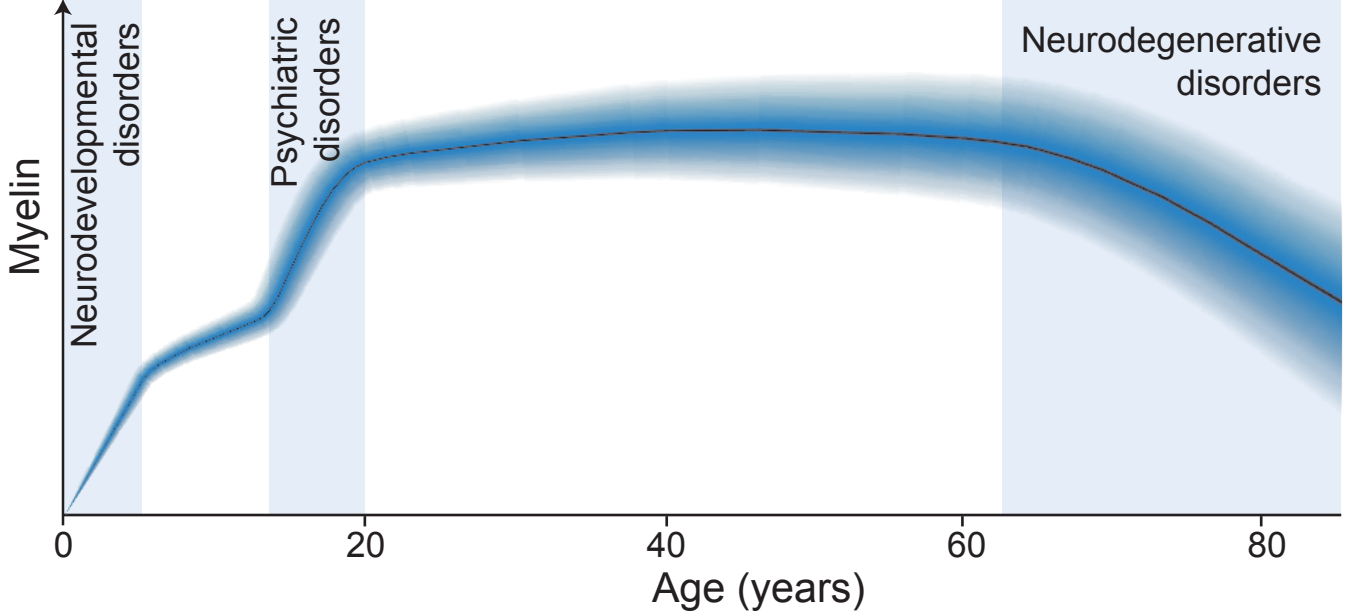
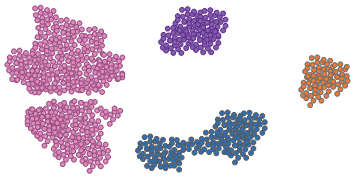

A
Undamaged / Normal
B
Demyelination
C
Clearance and
OPC recruitment
D
Differentiation
E
Remyelination

Figure 3

A



B



	Astrocyte	Neuron	Microglia	Oligodendocyte
All expressed genes (8427 total)	1109 **(13.2%)**	7099 **(84.2%)**	382 **(4.5%)**	1340 **(15.9%)**
Neurodevelopmental (461 total)	86 **(18.7%)**	289 **(62.7%)**	27 **(5.9%)**	125 **(27.1%)**
Psychiatric (2975 total)	545 **(18.3%)**	2016 **(67.8%)**	117 **(3.9%)**	823 **(27.7%)**
Neurodegenerative (687 total)	116 **(16.9%)**	414 **(60.3%)**	46 **(6.7%)**	163 **(23.7%)**

C

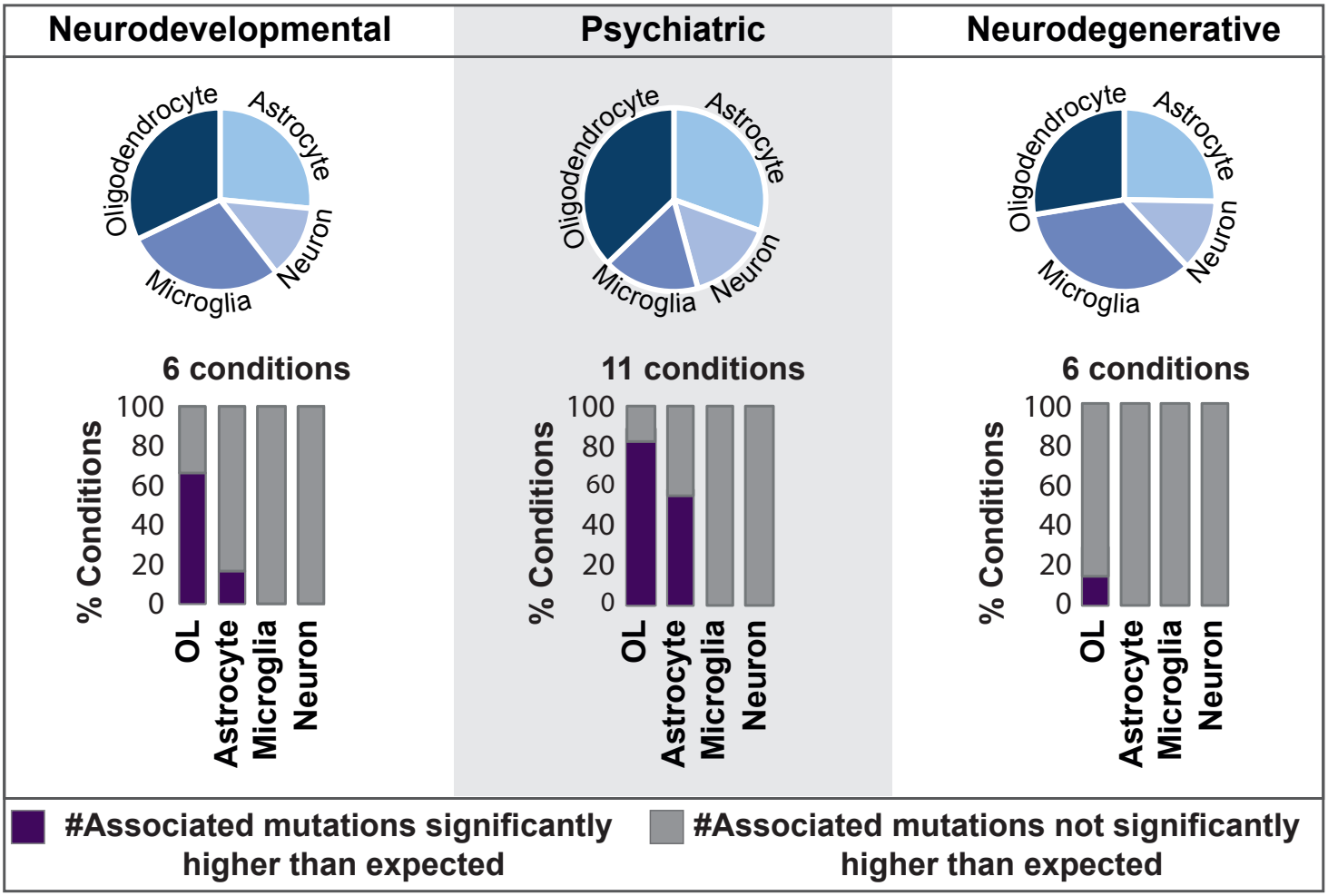
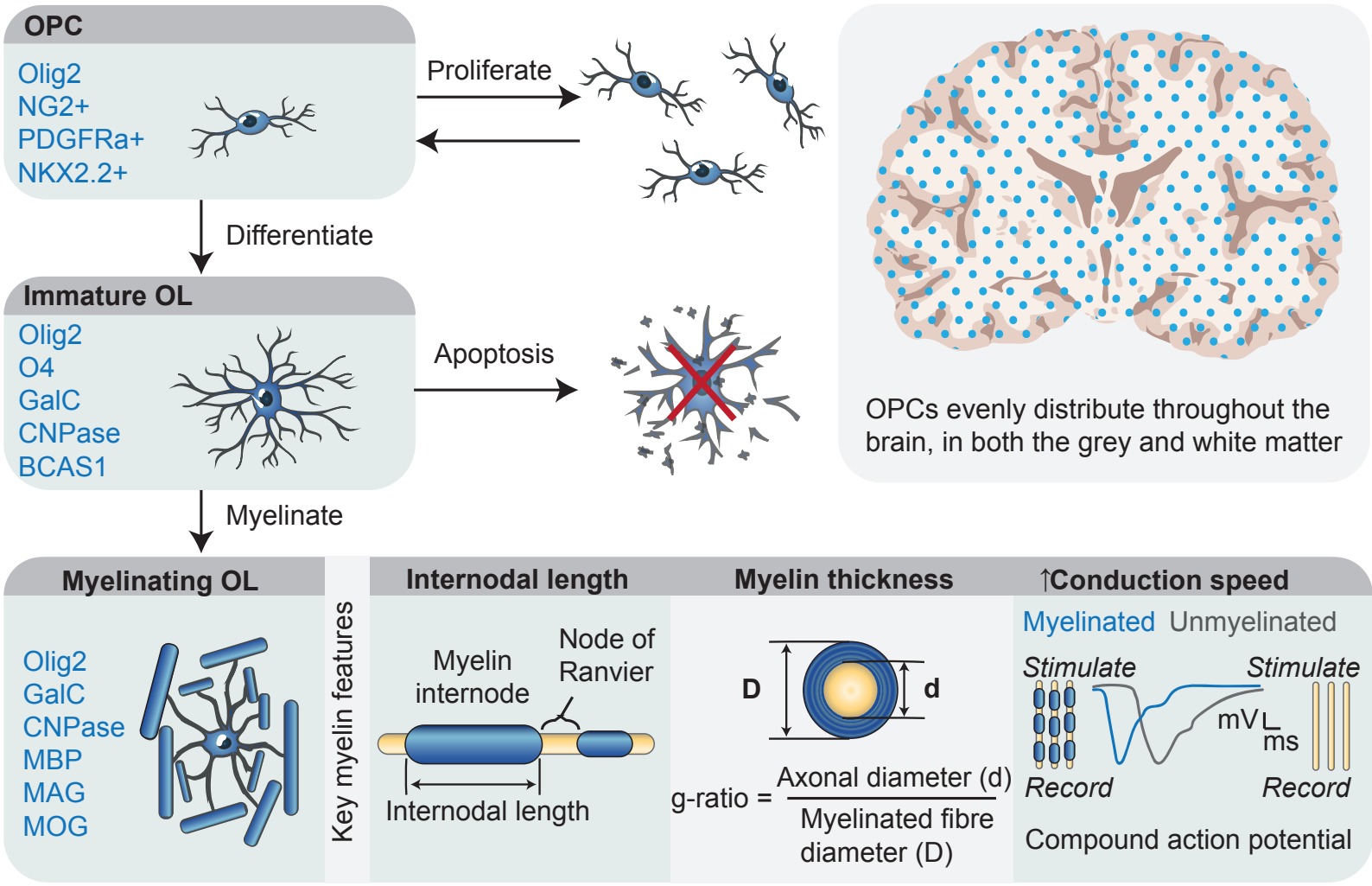
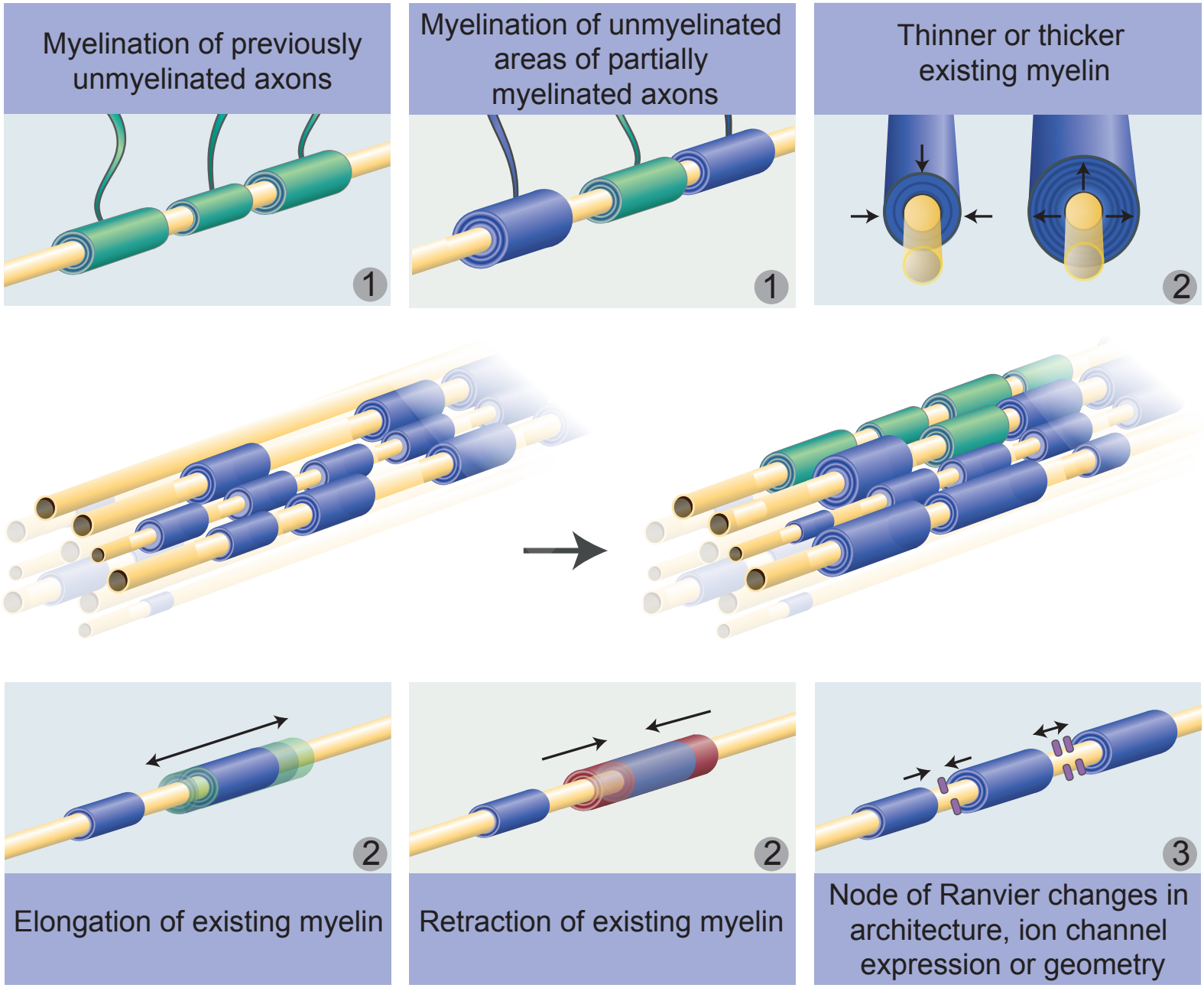


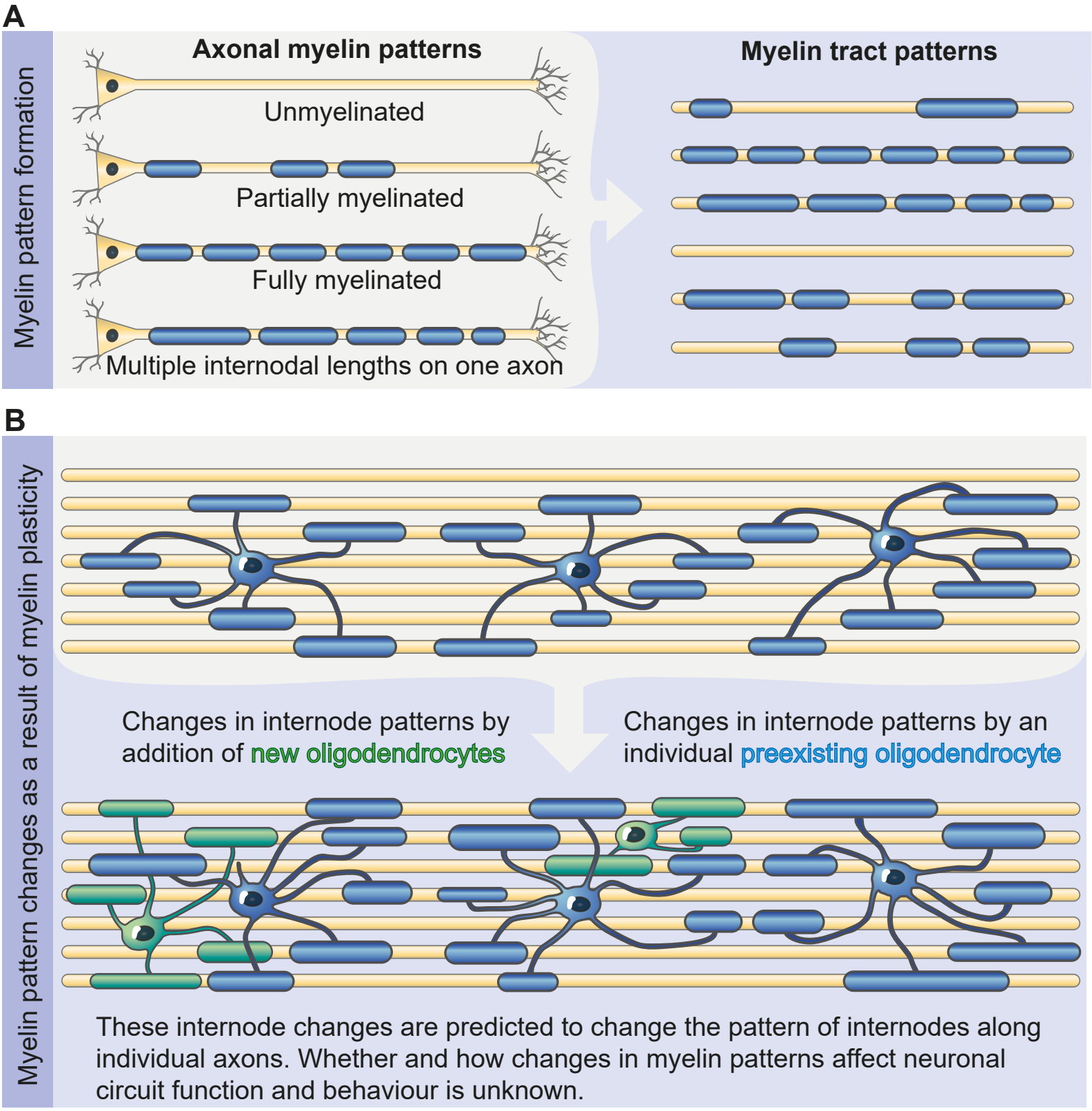
Figure 4


OPC
Olig2
NG2+
PDGFRa+
NKX2.2+
Proliferate
Differentiate
Immature OL
Olig2
O4
GalC
CNPase
BCAS1
Apoptosis
Myelinate
OPCs evenly distribute throughout the brain, in both the grey and white matter
Myelinating OL
Olig2
GalC
CNPase
MBP
MAG
MOG
Key myelin features
Internodal length
Myelin internode
Node of Ranvier
Internodal length
Myelin thickness
D
d
g-ratio = Axonal diameter (d) / Myelinated fibre diameter (D)
↑Conduction speed
Myelinated
Unmyelinated
Stimulate
Stimulate
mV
ms
Record
Record
Compound action potential

Box 1


Myelination of previously unmyelinated axons
1
Myelination of unmyelinated areas of partially myelinated axons
1
Thinner or thicker existing myelin
2
2
Elongation of existing myelin
2
Retraction of existing myelin
3
Node of Ranvier changes in architecture, ion channel expression or geometry

Box 2


A
Myelin pattern formation
Axonal myelin patterns
Unmyelinated
Partially myelinated
Fully myelinated
Multiple internodal lengths on one axon
Myelin tract patterns
B
Myelin pattern changes as a result of myelin plasticity
Changes in internode patterns by addition of new oligodendrocytes
Changes in internode patterns by an individual preexisting oligodendrocyte
These internode changes are predicted to change the pattern of internodes along individual axons. Whether and how changes in myelin patterns affect neuronal circuit function and behaviour is unknown.

Box 3