Title: Myelin: a gatekeeper of activity-dependent circuit plasticity?

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One sentence summary: Long thought to be bystanders, the cells that drive myelination in the central nervous system help refine brain circuit function

Abstract

The brain is responsive to an ever-changing environment, enabling the organism to learn and change behaviour accordingly. Efforts to understand the underpinnings of this plasticity have almost exclusively focussed on the functional and underlying structural changes that neurons undergo at neurochemical synapses. What has received comparatively little attention is the involvement of activity-dependent myelination in such plasticity and the functional output of circuits controlling behaviour. The traditionally held view of myelin as a passive insulator of axons is changing to one of lifelong changes in myelin, modulated by neuronal activity and experience. Here we review the nascent evidence of the functional role of myelin plasticity in strengthening circuit functions that underlie learning and behaviour.

Introduction

Over half of the human brain is white matter, which supports rapid and synchronized transfer of information across the many grey matter areas of the central nervous system (CNS). The function of white matter depends on oligodendrocytes. These specialised glial cells wrap a lipid-rich membrane, myelin, around axons in the CNS, increasing the speed of the action potential and providing axons with energy for impulse propagation (*1*) required for maintaining high impulse frequency (*2*). Changes in myelin within a tract or brain region can impact the function of neural circuits, such as those involved in emotion, cognition, motivation and associated behaviour, by fine-tuning and reducing failure rate of information transfer between different areas in the brain's grey matter.

While the essential function of myelin has long been recognized in white matter diseases such as multiple sclerosis, where myelin loss leads to both motor and cognitive dysfunction (*1, 3*), it remains widely viewed as a passive insulator. However, evidence indicates that myelination in mammals is a protracted dynamic process involved in CNS function and development (*4, 5*). Myelination in humans begins during the last trimester and extends into late adulthood (*4*) and varies between individuals, potentially affecting personality traits (*6*).

Human post-mortem histological observations suggest that myelination of axonal tracts linking brain regions is synchronized with the functional maturation of the neural circuits they form (*4*). Likewise, magnetic resonance imaging (MRI) studies have revealed that the maturation of sensorimotor or language-related white matter tracts in humans is associated with the development of these basic skills in childhood, whereas the maturation of frontoparietal (*7, 8*) and frontostriatal (*9*) white matter pathways coincides with protracted development of executive functions and behavioural control during adolescence and early adulthood.

Evidence is accumulating that myelination is not confined to the developmental period, but that myelin turns over and its patterns change throughout the lifespan, which may relate to experience-

dependent changes in the function of neural circuits. Here we focus on the functional implications of myelin changes, capitalising on previous reviews of mechanisms of myelin plasticity (*4, 5*) to assess how these might be linked to circuit function underlying learning and memory.

Myelin: from conduction to circuit function

Myelin increases the speed of propagation and the temporal resolution of the action potential, by effectively decreasing the capacitance of the axonal membrane and increasing its resistance by reducing current leak across the membrane. Myelin, therefore, extends the membrane electrical length constant and reduces action potential propagation failure rate. Between myelin segments, axons have exposed patches of membrane rich in voltage-gated sodium channels, nodes of Ranvier (Fig. 1A), that allow the action potential to propagate from node to node (*10, 11*). Myelin also enhances the fidelity of information transmission, due to its biophysical properties (*10, 12*) and by facilitating metabolic support from oligodendrocytes to axons (*2*).

Six biophysical variables can affect the speed and/or fidelity of action potential propagation: axon diameter (*13*), myelin thickness (*12, 14*), internode length (*15*), peri-axonal space (*12*), paranodal tightness (*12*), and the nodal geometry (*16*) (Fig. 1A). In the mammalian CNS, these biophysical parameters differ along and between axons, even in the same tract or area. For instance, conduction velocity varies along the length of retinal ganglion cell axons, with a difference between the optic nerve and optic tract (*17*). Moreover, axons within the same circuit, tract and area can be unmyelinated, partially myelinated or fully myelinated along their length (Fig. 1B). For example, up to 70% of axons in the corpus callosum, one of the main white matter tracts connecting the two brain hemispheres, remain unmyelinated (*18*), and some myelinated axons in the cortex can exhibit a partial myelin pattern (*19*). Some axons in the auditory circuit have progressively shorter myelin internodes, particularly at the point they enter the grey matter (Fig. 1B; *20*). This heterogeneity implies that the velocity and fidelity of conduction can vary within and between neural circuits, suggesting a role for myelin in the temporal precision of computations in functional circuits (Fig 1C).

Oligodendrocytes, via myelin, also provide ion homeostasis and metabolic support to the axon (*21*). This support can be adapted according to demand, e.g., increased neuronal firing rate increases siphoning of potassium (*22, 23*) and lactate release (*24*). This can affect conduction fidelity and help to maintain high frequency firing rates (*2, 22, 24*). Dysregulation of oligodendrocyte metabolic support (*2*), or ion homeostasis (*22, 25*), can alter circuit synchronisation and function.

Myelin may, therefore, have a more sophisticated role in circuit function. For instance, differential myelination of olivocerebellar and thalamocortical axons regulates the conduction velocity of individual axons within these tracts and contributes to the synchronized activity of populations of cerebellar Purkinje cells and cortical neurons onto which these fibres synapse (*26, 27*). Moreover, the number and length of myelin internodes have been shown to underlie coincidence detection in the auditory system, in which distinct patterns of myelination in cochlear neuron collateral branches correlate with differential conduction velocity, tuned to allow for temporal summation of inputs arising from both ears (*28*). Failure to provide energy to axons by oligodendrocytes results in impairment of auditory input synchrony and temporal summation in the auditory cortex (*2*). Dysregulations in myelination, ion homeostasis or energy provision alter neuronal firing rate and synchronisation, and the associated function of the related circuits (*2, 23, 29*). Emerging from these studies is a potential functional role for oligodendrocytes in modulating the velocity and fidelity of conduction along and between axons, to regulate synchronization of inputs in neuronal circuits involving several brain regions by facilitating coincidence of activity onto specific post-synaptic neurons (Fig. 1C). This may impact activity-/timing-dependent synaptic plasticity (*30*), a mechanism suggested to be needed for memory formation (*31*). Thus, mechanisms influencing timing should be considered when designing models of neural networks. Such attempts with models that factor-in active modulation of conduction velocity have demonstrated that spike-time arrival, phase differences of oscillatory brain activity and neural phase synchronization are all sensitive to small changes in myelin parameters (Fig 1; *32, 33*). While computational models for the role of oligodendrocyte metabolic support and ion homeostasis for activity-dependent circuit

plasticity are lacking, existing models indicate that neuronal activity-dependent alterations in myelination alone can promote neural phase synchronization (*33*) relevant for memory formation.

Myelin plasticity may, therefore, provide mechanisms through which experience and associated learning may modify brain connections, presumably by shaping the computation of neural circuits via alterations in the timing of neuronal signal transmission.

Oligodendrocyte lineage structural and functional cellular plasticity

Oligodendrocyte lineage cells display two forms of plasticity: short-term functional and long-term structural plasticity. This, in addition to the heterogeneity in the extent to which axons in the CNS are myelinated (Fig. 1B), offers diverse scope for dynamic myelin changes to fine-tune neural circuits.

The strongest experimental evidence is for structural plasticity in the form of myelin plasticity, involving both oligodendrocytes and the oligodendrocyte precursor cells (OPCs) from which they differentiate, in a multistep process (Fig. 2). OPCs are the main proliferative cells in the adult CNS (*34*) and are evenly distributed throughout it (*34, 35*), but their function has not been fully elucidated. Throughout life, OPCs differentiate into new myelinating oligodendrocytes in a mechanism that can be bidirectionally modulated by changes in neuronal activity. When neuronal activity is enhanced *in vivo* pharmacologically in the optic nerve (*36*), or with optogenetic (*37*) or chemogenetic stimulation (*38*) of cortical neurons in the adult motor or somatosensory cortex, OPC proliferation, differentiation and myelination increases in the stimulated area. Conversely, decreasing neuronal activity using pharmacological manipulations (*36*) or directly with chemogenetics (*38*), decreases OPC differentiation and myelination in mice. Although identifying the exact mechanisms underlying these activity-dependent changes warrants further work *in vivo*, evidence from *in vitro* experiments implicates mechanisms similar to those involved in synaptic plasticity, including the reliance on growth factors, like brain-derived neurotrophic factor (BDNF)

or neuregulin, and concurrent activation of glutamate receptors on OPCs (*39*). In addition to myelin plasticity, OPCs also phagocytose axons/pre-synapses (*40*), indicating OPCs may have more versatile structural plasticity than previously anticipated.

It is unclear whether intermediary oligodendrocytes can affect neuronal function (Fig. 2), although results from behavioural studies indicate that this may be a possibility (*45, 46*). This could be mediated by secreted factors that induce nodal clustering on unmyelinated axons, leading to accelerated conduction velocity (*47*).

Myelin plasticity is not restricted to activity-dependent differentiation of OPCs into new myelinating oligodendrocytes (Fig. 2B). Longitudinal *in vivo* imaging of myelin, in mice, has revealed that established myelin undergoes turnover and quantifiable structural plasticity, where oligodendrocytes modify internodal length (*41, 42*), the length of the nodes of Ranvier (*43*), and remove or add new myelin internodes (*43*). These changes, as well as alterations in the thickness of the myelin sheath (shown by g-ratio measurements from electron micrograph images (Fig. 2A; *37, 38*)), can all be influenced by changes in neuronal activity and experience. Thus, myelin structural plasticity continuously alters myelin patterns in neural circuits throughout life.

Oligodendrocyte lineage cells can also display short-term plasticity (Fig. 2B). OPCs can shed the NG2 protein, which can interact with glutamate receptors at neuronal synapses and influence neuronal synaptic plasticity (*44*). Myelinating oligodendrocytes can alter action potential propagation speed by regulating potassium levels in the peri-axonal space (*48*) and changing the expression and distribution of molecules involved in the metabolic support of the axon, potentially relevant in setting its maximum firing rate (*2, 24*). Plasticity displayed by oligodendrocyte lineage cells seems to be affected by neuronal activity (*24, 37, 38, 44*), consistent with neuronal activity playing a regulatory function in myelin modulation, particularly in adulthood (*36-39, 49*). However, the role of myelin plasticity in brain functions, such as learning and memory, is only now being investigated.

Myelin plasticity in learning and memory

Our understanding of myelin function is changing from the concept of providing inert structural support to it being a plastic and dynamic actor of adaptive (and maladaptive) behaviour, especially through its role in memory, defined here as a change in circuit function caused by an experience leading to a behavioural change and learning, the process by which memory is acquired (*50*)

MRI studies have revealed that when humans learn new motor (e.g., juggling, playing the piano) or cognitive (e.g., learning to read) skills, structural changes occur in the white matter tracts related to the fine-tuning of circuits (*51*). A caveat of these studies is that the nature of white matter changes detected by structural MRI techniques, like fractional anisotropy, is unclear, although it is assumed to be myelin (*52*). Nonetheless, consistent with the human data, rats that undergo motor learning tasks show an increase in fractional anisotropy (an indication of white matter microstructure) on MRI scans, which is associated with increased optical density of the myelin protein MBP in the white matter subjacent to the motor cortex (*53*). Such studies provide some validation of the outcomes of MRI analyses and support the hypothesis that changes in myelin accompany learning and/or memory.

Studies capitalising on the many advantages of transgenic mice have sparked the notion that *de novo* myelin formation may be a form of brain plasticity, similar, but in addition to, synapse formation, which is generally accepted to be a mechanism for learning, even though direct experimental evidence has been difficult to provide (*54*). The evidence that new oligodendrocytes are formed during the acquisition of a new motor skill in mice, and the subsequent demonstration that preventing OPC differentiation into new myelinating oligodendrocytes impairs behavioural performance in a wide array of tasks (Fig 3A; *45, 55-57*), further supports the hypothesis that myelin is causally involved in learning and/or memory.

OPC proliferation in learning and memory

Cross-sectional studies in mice consistently report that OPC proliferation is fast, almost immediate, upon initiation of training in a behavioural task (Fig. 3; *46, 55, 56*). In some studies, the first timepoint tested was days or weeks post-training, making it difficult to draw any firm conclusions about the exact time course of OPC proliferation across tasks/memory systems (Fig 3B). Longitudinal *in vivo* experiments indicate that OPC proliferation may reflect a homeostatic response to a loss of OPCs (*35*). In fact, the overall number of OPCs does not change during motor skill learning (*58*) and proliferation seems to be preceded by OPC differentiation into pre-myelinating oligodendrocytes (*46*) (Fig. 2A & 3B). These pre-myelinating oligodendrocytes are not labelled by the proliferation marker EdU (*46*), and as the majority of OPCs directly differentiate following learning a new motor skill, this indicates the presence of primed OPCs (*59, 60*) equipped to directly differentiate, without proliferating first (Fig. 2A), upon changes in neuronal activity. This structural plasticity occurs at a speed similar to that of structural synaptic plasticity (*61*). However, despite evidence for fast OPC proliferation and early differentiation, detectable changes in oligodendrogenesis (identified as $CC1^{+}$/ EdU^{+} cells; Fig 2A) do not appear until days or weeks later (Fig 3B; *45, 46*), even though myelination can be a rapid process (at least in the developing zebrafish (*62*)). Hence oligodendrogenesis detected using this method may indicate a second round of OPC differentiation.

Oligodendrogenesis dynamics in learning and memory

Overall, the systematic assessment of oligodendrogenesis dynamics over the course of learning behavioural tasks reveals differences that are suggestive of some circuit specificity. These tasks test different types of memory (Fig. 3) underpinned by partly overlapping but dissociable neural circuits on which the task-related memory relies, including prefrontal cortex (PFC)-dependent short term/working memory, hippocampus-dependent spatial memory, dorsal striatum-dependent procedural memory (*63*) or amygdala/hippocampus-dependent Pavlovian and emotional memory (*64*). Oligodendrogenesis dynamics differ in brain regions and timing, depending on the task (Fig. 3B; *46, 55, 56, 58*). While further research is warranted to understand the reasons for these

differences, oligodendrogenesis dynamics can be useful in deciphering the potential role of specific activity-dependent myelin plasticity in task-relevant circuits.

Although oligodendrogenesis (e.g., $CC1^+/EdU^+$ cells) is a useful surrogate, it has some limitations and may wrongly estimate the extent of *de novo* myelination. First, this approach does not detect oligodendrocytes generated from direct differentiation of OPCs, which can occur early in the learning process (Fig. 2; *46*). Secondly, increases in newly formed oligodendrocyte numbers do not necessarily translate into increased myelination, as high numbers of oligodendrocytes can be detected in demyelinating lesions that fail to remyelinate (*65*). Thirdly, newly formed oligodendrocytes often die (*35, 66*), with only about 20% becoming stable myelinating oligodendrocytes (*42*). Nevertheless, quantifying myelinating oligodendrocytes, using either transgenic mice that enable specific labelling of newly-formed myelinating oligodendrocytes (*56*), e.g., using a promoter only expressed in myelinating oligodendrocytes (i.e., *Tau* or *MOG*; Fig. 2A) to drive mGFP expression, or electron microscopic analysis (Fig. 1A; *55, 56*), have corroborated that increased myelination occurs in some regions undergoing oligodendrogenesis, even if only days or weeks after the first OPC differentiation. A longitudinal *in vivo* imaging study in mice, visualizing terminally myelinating oligodendrocytes and not OPC differentiation, revealed a biphasic process taking place in the upper layer of the motor cortex during motor skill learning. The number of new myelinating oligodendrocytes decreased during the learning period, and later increased, eventually exceeding the number of cells displayed by non-trained controls two weeks following learning (*58*). The percentage increase in new myelinating oligodendrocytes detected post-training was comparable to that of the change in the number of synapses in the same brain region after learning the same skill (*61*). The delayed appearance of myelinating oligodendrocytes indicates a pause in the constitutive myelination programme during learning, before myelinating oligodendrocytes appear.

Conceivably, in the first hours of learning, OPCs proliferate and either enter a primed state or start differentiation, as identified with *Enpp6* expression (Fig 2A; *46*), but pause (*58*) until they have integrated the activity-dependent instructions that determine which axons should undergo

myelination, e.g. those within the circuit underlying learning. This could indicate a switch from a constitutive to an activity-dependent targeted myelination programme (*39*). Indeed, knocking out BDNF receptors in OPCs, needed for activity-dependent myelination, results in memory impairment in an object recognition task (*67*). Alternatively, the pause in myelination may indicate a switch from myelination of excitatory neurons to interneurons (*43*). Thus, while the proliferation of oligodendrocytes seems non-specific to the function and underlying neural substrate that is being recruited in tasks, the pattern of myelination is, indeed, task- and memory system-dependent.

Grey and white matter myelin plasticity

The heterogeneity in oligodendrogenesis timing (Fig. 3B) across brain regions involved in behavioural tasks may reflect differences in myelination between grey and white matter. For example, in mice learning the Morris water maze (*55*), oligodendrogenesis is first detected in specific grey matter regions before being detected in white matter, whereas myelination is detected at the same time in white and grey matter in mice learning to run on a complex wheel (Fig 3; *46*). White matter myelination predominantly affects long-distance connections between brain regions, likely involved in macro-circuit function which depends on cooperation between different brain regions. Grey matter myelination, predominantly of interneurons and excitatory connections within a restricted brain region, is potentially involved in micro-circuit function. Myelination of short-range axons in the grey matter is considered unlikely to have a meaningful effect on conduction velocity. However, electrophysiological recordings indicate that myelination of short-range interneurons induces physiologically relevant changes in conduction velocity (*68*). Moreover, the dispersed myelin pattern in the grey matter may be optimized for spatiotemporal integration of impulses (*69*), and the pattern of myelin in the grey matter seems to have functional relevance (*58*). Modelling of biophysical properties of myelin indicates that these changes could modulate input synchronisation within the micro-circuit (*20, 32, 33*). Alternatively, grey matter myelin may predominantly serve to provide metabolic support to the axon to fuel increased neuronal activity, facilitating repetitive fast firing rates (*2, 24*). The exact role of grey matter myelination remains to be determined, but it seems to affect micro-circuit function.

The differences in timing of oligodendrogenesis between regions may also reflect differences in the type of neurons becoming myelinated. Myelination of neuronal subtypes is differently regulated by neuronal activity (*37, 70*). Oligodendrocytes can be biased towards certain neuronal subtypes (*71*), although with a change in circuit function they are capable of switching between them (*43*). Hence the differences in the region and timing of oligodendrogenesis may reflect, and allow the interrogation of, a hierarchy of functional involvement in local and systems level circuit plasticity underlying behaviour.

Functional implications of oligodendrogenesis for memory

Causal interrogation of the functional role of OPC differentiation into newly formed oligodendrocytes can be achieved by preventing it at any time in transgenic mouse models that use inducible OPC-specific Cre lines to genetically delete one of the transcription factors *Myrf* or *Olig2* (*57, 72*). This prevents ongoing differentiation into new oligodendrocytes and *de novo* myelination without influencing pre-existing myelin (*45, 57, 72*). Despite lacking control over localisation (all oligodendrocyte formation is prevented throughout the CNS after tamoxifen administration), this approach offers an opportunity to causally establish the role of myelin plasticity in brain function. For example, it is possible to interrogate the involvement of *de novo* myelination in either learning or memory consolidation (in carefully designed behavioural experiments), by altering the timing of tamoxifen administration to occur before, during, or following training. Preventing OPC differentiation into new myelinating oligodendrocytes consistently impairs memory across a wide array of behavioural tasks (*45, 55-57*), although differences between study designs make direct comparisons difficult. Nevertheless, the varying times at which the deficits emerge (Fig. 3B) seem to coincide with the requirements for systems level consolidation of memory (i.e., the functional coordination of multiple brain regions mediating the long term storage of a memory) (*73*).

Oligodendrogenesis in motor circuit plasticity

The link between myelin and motor function is well established. Motor defects are one of the main phenotypes of dysfunctional myelination, and conversely, transgenic animals in which myelin or myelination has been enhanced show enhanced behavioural outcomes in a range of motor skill tasks (*74, 75*). Mice in which oligodendrogenesis is blocked do not appear to exhibit non-specific motor deficits in running ability, but begin to show behavioural impairments in learning to run on the complex wheel within 2.5 hours (*45*), which aligns with early OPC differentiation in white matter (Fig. 3B; *46*). However, early differentiation in the motor cortex occurs a few hours later and oligodendrogenesis ($CC1^+$/ EdU^+) only appears in both white and cortical grey matter 4 days after introduction to the task (Fig. 3B). In another motor task, the single-pellet reaching task, oligodendrogenesis in the upper layer of the cortex occurs comparatively later (Fig. 3B; *58*).

How behavioural impairments can precede oligodendrogenesis is unclear. This may indicate a previously unknown role for primed OPCs or pre-myelinating oligodendrocytes in circuit function (Fig. 2), or instead that direct differentiation to newly myelinating oligodendrocytes occurred elsewhere in the underlying neural circuit extrinsic to the brain regions investigated. These studies have focused on the motor cortex and the underlying white matter, presumably because when motor cortex (*76*), or the corpus callosum (*77*), are removed, motor skill learning and/or memory are impaired. However, motor skill learning is not confined to these regions; other regions of the motor circuit are also involved e.g., striatum, thalamus, and/or cerebellum (*78*). Some evidence suggests that the cerebellum is needed for early skill training whereas the motor cortex is needed for long-term retention of a motor skill (*79, 80*). It is possible that oligodendrogenesis, and presumably myelination, may occur at different times elsewhere in this distributed neural circuit, aiding mice to develop a strategy to run efficiently on a complex wheel. Once mice have developed a strategy, it is transferrable to other complex wheels without alteration in oligodendrogenesis, so that impairing OPC differentiation then no longer impairs running speed (*45, 46*). Hence, the capacity for OPCs to differentiate is necessary for developing a locomotor skill, although it remains to be elucidated where in the underlying distributed brain regions these changes need to occur, and whether pre-myelinating oligodendrocytes are involved in learning (Fig. 2B).

Oligodendrogenesis in memory consolidation

The synchronised timing of grey and white matter oligodendrogenesis in motor skill learning is in contrast to the differential trajectories of oligodendrogenesis observed in hippocampus-dependent spatial memory (*81*), as measured in the Morris water maze (*55*). In spatial memory, oligodendrogenesis is first detected during learning in cortical and subcortical areas, at the first probe test that ensures navigation relies on spatial memory and not on an egocentric wayfinding strategy (Fig. 3A; *82*). In the white matter connecting these brain regions, oligodendrogenesis is, in contrast, only detected 4 weeks after learning.

Oligodendrogenesis has been reported to take place with a delay of 4 weeks from the probe test (Fig. 3; *56*), in another form of hippocampus-dependent memory; contextual Pavlovian fear memory (*83*). Mice that cannot produce new oligodendrocytes display deficits in remote, but not recent, recall of contextual fear memory, in line with the delayed engagement of oligodendrogenesis (*56*). However, newly formed myelinating oligodendrocytes (detected by genetic fate mapping OPC differentiation into $mGFP^+$ myelinating oligodendrocytes) are observed in the total absence of any EdU^+ oligodendrocytes in the dorsal hippocampus one week after initiation of conditioning in this task (Fig. 3B). This suggests early direct OPC differentiation to myelinating oligodendrocytes that is not followed by later oligodendrogenesis in the hippocampus during early consolidation of the fear memory. This observation needs further investigation but highlights the potential for temporal differences in oligodendrogenesis dynamics between brain regions and indicates that fast direct differentiation of OPCs into newly myelinating oligodendrocytes may occur in some task-dependent regions.

The varied temporal distribution of oligodendrogenesis (Fig. 3B) may indicate a general difference in myelin plasticity in encoding and systems-dependent consolidation of a memory (*84, 85*). Indeed, in spatial and contextual fear memory, the memory initially encoded in the hippocampus requires functional coupling with cortical regions (*86*) to be consolidated, a process mediated by

the interplay between cortical oscillations and hippocampal sharp wave ripples (*87*). In mice that cannot produce new oligodendrocytes, deficits in recall of a contextual fear memory are preceded by alterations in systems level coupling between cortical oscillations and hippocampal sharp wave ripples (*55*), although in control mice oligodendrogenesis is not detected until weeks later. Potentially, the early direct differentiation to myelinating oligodendrocytes detected in the hippocampus (*56*), or oligodendrocyte-mediated axonal nodal clustering (Fig 2; *47*), may be sufficient to support early consolidation of learning and initiate systems-level changes necessary for long term changes in behavioural responses, although not needed for recent recall. Blocking oligodendrogenesis impairs task-evoked changes in neuronal calcium spikes in the medial PFC and reduces expression of the immediate early gene *cFos*, a marker of cellular activity (*88*), in brain regions involved in Pavlovian fear memory (*56*), such as the hippocampus and amygdala (*89*), at the time of remote recall. This is in line with the temporal nature of the behavioural deficits in recall observed in mice in which new oligodendrogenesis is blocked. Together these data suggest an involvement of myelin plasticity in the systems level consolidation mechanisms underlying long-term contextual fear memory.

Likewise, no differences in oligodendrogenesis were detected in the hippocampus at the time of probe test following spatial navigation training in the Morris water maze, supporting the view that myelin plasticity in this circuit is more relevant for systems level consolidation of spatial memory than for learning. In fact, inhibiting new myelinating oligodendrogenesis, by knocking out the transcription factors *Myrf* or *Olig2* in adult OPCs before (*57*), during or immediately after (*55*) training, did not affect learning but impaired the consolidation of recent and remote spatial memory. Moreover, spatial memory (*57*) and neuronal *cFos* (*56*) activity can be enhanced by promoting OPC differentiation into myelinating oligodendrocytes. However, *Myrf* deletion from OPCs after a memory has been consolidated does not result in behavioural deficits, demonstrating that knocking out *Myrf* does not inherently prevent spatial memory retrieval (*45, 55*) and that further production of myelin is unnecessary to maintain a memory that has already been consolidated.

Our understanding of the role of myelin plasticity in learning and memory, and where myelin changes occur in circuits underlying memory, is underexplored. Nonetheless, these studies collectively support the conclusion that myelin plasticity could be a mechanism for systems level memory consolidation, aiding retrieval.

Beyond task-related circuit plasticity

The studies summarised above suggest that suppression of adult oligodendrogenesis differentially impairs learning and memory across different systems, and that myelin might have a broader function than previously thought (*45, 55, 56, 58*). A series of studies indicate that myelin dysfunction substantially affects neuronal firing rate (*29, 90*), jitter (*91*), latency of action potential (*2, 91*), synchrony (*2, 92*), synaptic mechanisms (*29, 90*) and eventually neural circuit function (*2, 29*). Together with the evidence that dysfunctional myelin or altered myelination during development impairs learning and adaptive behaviour (*74, 93-96*), this body of data suggests that even small changes in myelin across the lifespan can impact the circuit- and systems-level mechanisms involved in cognition and behaviour. Deficits in myelin formation and maintenance have been suggested to contribute to multiple CNS disorders that involve alterations of learning and memory, which have hitherto been considered to have a neuronal basis, such as schizophrenia, addiction, depression and dementia (*97, 98*).

Summary and future directions

Here, we have highlighted experimental evidence for myelin plasticity shaping the circuits and systems involved in learning and memory. This nascent field introduces alternative mechanisms of brain plasticity that may underlie memory. Whether myelin plasticity provides a mechanism for the generation of memory engrams (the specific collection of neurons underlying a specific memory) (*84*) warrants further research.

Seminal work on the basic regulatory mechanisms of myelination (*99*) have led to the emergence of experimental tools that allow manipulation of new myelin formation, and investigation of the role of myelin in learning and memory. However, efforts should be made to bring together the expertise of myelin biology with behavioural neuroscience and experimental psychology, to frame hypotheses about circuit function in well-defined psychological and neural systems.

The timing of some behavioural impairments following *Myrf* deletion in OPCs warrants investigation of the roles of different oligodendrocyte stages on neural circuit function. Additionally, more refined approaches than the global inhibition of ongoing myelination in the CNS are needed to dissect the functional role of *de novo* myelination in different brain regions, or in the white matter tracts connecting them. Most studies to date have utilized fate mapping of EdU^+ OPCs, using $EdU^+/CC1^+$oligodendrocytes as a surrogate marker for new myelination. However, not all OPCs proliferate before differentiation (Fig. 2). Experimental tools such as genetic fate mapping of OPC differentiation into myelinating oligodendrocytes, along with EdU fate mapping, provide an improved approach for identifying fully myelinating oligodendrocytes and thereby establish where, when, and how, learning and memory-related myelination occurs.

The next steps would be to determine the mechanisms of myelination, and, in the grey matter, how the myelin pattern is established and which neurons are becoming myelinated - is it projection neurons, interneurons or both? What determines when and how OPCs proliferate, differentiate and myelinate axons, and how does learning-associated myelination affect ongoing lifelong myelination in the underlying circuits? Do pre-myelinating oligodendrocytes affect neuronal function? Further evaluation of the functional role of myelin in the CNS is needed to disentangle the contributions of metabolism, ion homeostasis and myelin-dependent biophysical properties of the axons to circuit function. Future research will need to combine myelin biology with *in vivo* neurophysiology to establish the causal relationship between myelin and circuit function.

Beyond the promise of a better understanding of the cellular and neural systems basis of learning and memory, a deeper knowledge of the functional role of myelin plasticity may unlock alternative

421 therapeutic approaches for neurodegenerative diseases and neuropsychiatric disorders. While little
422 is known about the role of oligodendrocytes and myelin in these diseases, the development of new
423 methods (*98, 100*) to determine their contributions could lead to a new understanding of these
424 conditions. The advancement of remyelination strategies promoting OPC differentiation into new
425 myelinating oligodendrocytes may offer avenues to remediate cognitive deficits (including
426 memory), or aberrant functional engagement of brain circuits in psychiatric diseases. Collectively,
427 this calls for further investigation of the functional role of myelin plasticity.

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Fig. 1. Myelin parameters and action potential propagation

A. Axons in the central nervous system (CNS) have multiple myelin sheaths along their lengths, each originating from a different oligodendrocyte. Some key parameters of myelin shown to alter conduction velocity are internodal length, myelin thickness (usually expressed as a g-ratio), and nodal geometry (nodes have a high density of voltage-gated sodium channels, seen as orange ellipses). Electron micrograph image is a cross-section of a myelinated axon (yellow), showing multiple myelin wraps. **B.** Axons in the CNS can be unmyelinated, partially myelinated, fully myelinated or fully myelinated with different patterns of progressively shorter internodal length and larger nodal distances. Along a single axon and between axons there are different patterns of myelination, providing differences in myelin patterns within and between neuronal circuits. **C.** Schematic diagram of a neural circuit, depicting yellow projection neurons (A, B and C), and orange interneurons. In the naive circuit, myelination promotes action potential propagation, but despite neurons A+B simultaneously firing action potentials, inputs arrive asynchronously at post-synaptic neuron C due to different conduction velocities. During learning or experience, myelin changes along the circuit may modulate conduction velocity to allow synchronous spike arrival at neuron C. (EM image by Dr Sebastian Timmler; Illustrations by Ms Kimberley Evans)

Fig. 2. From OPCs to myelinating oligodendrocytes

A. Oligodendrocyte precursor cells (OPCs) differentiate into myelinating oligodendrocytes in a multistep process dependent upon the transcription factor *Myrf.* Cell markers for each lineage stage and their approximate onset/offsets are shown below the lineage progression diagram. Emerging evidence suggests that OPCs can enter a primed state, mostly likely in G1 phase arrest. These cells, and newly differentiated cells, marked by high *Enpp6* expression, are present in the brain ready to rapidly differentiate further into pre-myelinating, and then myelinating, oligodendrocytes. Only proliferating OPCs incorporate EdU (yellow nuclei), which fate maps OPC differentiation into myelinating oligodendrocytes. Cells already past the proliferative stage are not marked by EdU. **B.** Table illustrating the forms of plasticity displayed by oligodendrocyte lineage cells with implications for circuit plasticity: divided into long-term structural and short-term functional plasticity. (Abbreviations: EdU: Ethynyl-2'-deoxyuridine; Myrf: Myelin Regulatory Factor; Sox10: SRY-Box Transcription Factor 10; Olig2: Oligodendrocyte Transcription Factor 2; NG2:

neuron-glial antigen 2; PDGFRa: Platelet Derived Growth Factor Receptor Alpha; *Enpp6*: Ectonucleotide Pyrophosphatase/Phosphodiesterase 6; BCAS1: Brain Enriched Myelin Associated Protein 1; CC1: anti-adenomatous polyposis coli clone CC1; ASPA; aspartoacylase; MBP: Myelin Basic Protein; PLP: Proteolipid Protein 1; MAG: Myelin Associated Glycoprotein; MOG: Myelin Oligodendrocyte Glycoprotein). (Illustrations by Ms Kimberley Evans)

Fig. 3. Oligodendrogenesis dynamics across behavioural paradigms

A. An introduction to the four behavioural paradigms in which oligodendrogenesis and the role of *de novo* myelination have been investigated. **B.** Schematic diagram of the dynamics of OPC proliferation (blue), direct OPC differentiation (green), oligodendrogenesis (orange), myelin modifications (yellow), and the timing of behavioural impairments following the genetic arrest of OPC differentiation into new myelinating oligodendrocytes (pink). Respective method of analysis: neuronal activity (cFos immunolabelling or in vivo calcium imaging); proliferation (EdU labelling); differentiation (CC1, ASPA immunolabelling); longitudinal visualisation of OPC proliferation / differentiation (transgenic mouse model NG2-mGFP); myelination (electron microscopy quantification of myelinated axons, or fractional anisotropy quantification; or tau-mGFP transgenic mouse models to identify myelinating oligodendrocytes by genetically fate mapping OPC differentiation or MOG-mGFP for longitudinal visualisation of the appearance of fully myelinating oligodendrocytes). (Illustrations by Ms Kimberley Evans)

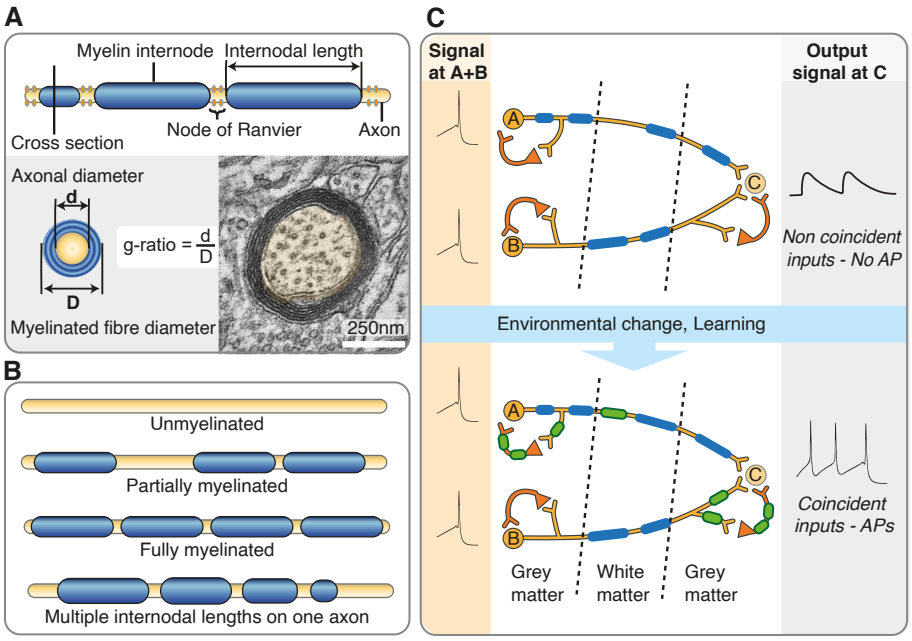
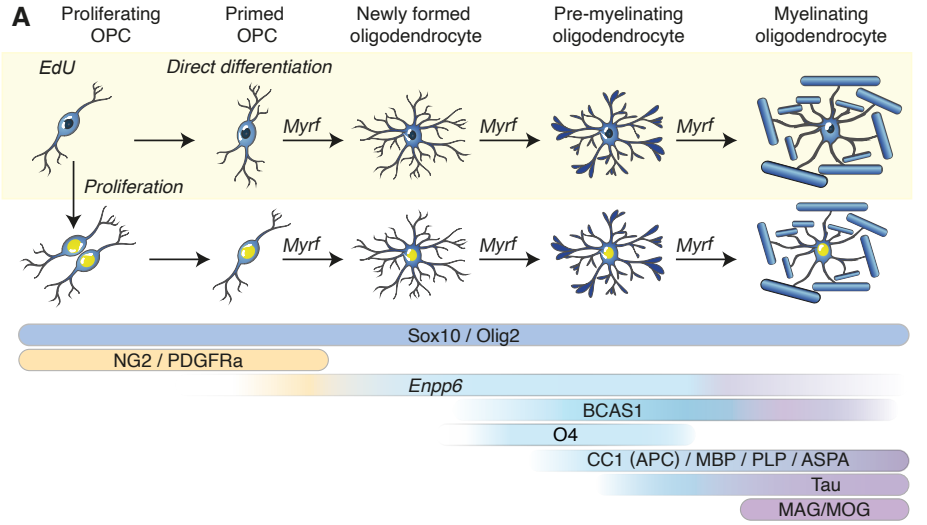

A
Myelin internode
Internodal length
Cross section
Node of Ranvier
Axon
Axonal diameter
d
D
g-ratio = d/D
Myelinated fibre diameter
250nm
B
Unmyelinated
Partially myelinated
Fully myelinated
Multiple internodal lengths on one axon
C
Signal at A+B
Output signal at C
A
B
C
Non coincident inputs - No AP
Environmental change, Learning
Coincident inputs - APs
Grey matter
White matter
Grey matter

Figure 1

A

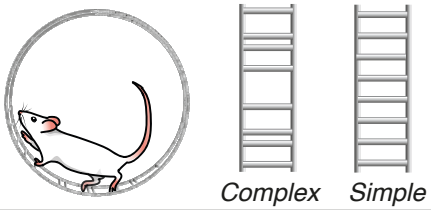
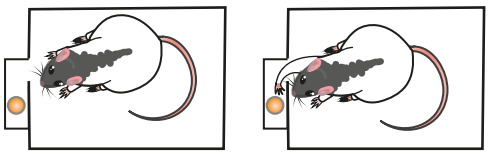
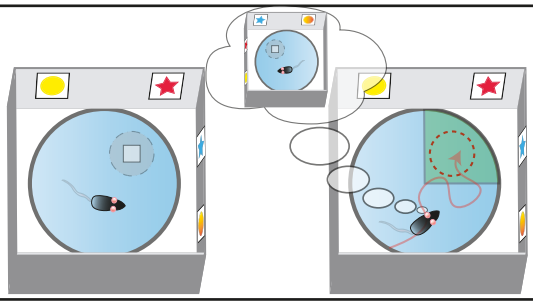
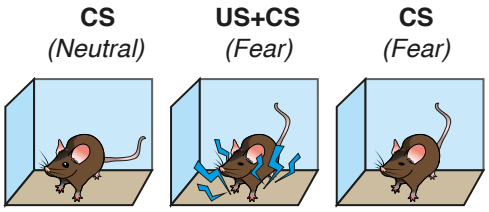


B

	OPC	Newly formed oligodendrocyte	Myelinating oligodendrocyte
Long-term Structural Plasticity	• Direct differentiation to oligodendrocytes (EdU$^-$) • Proliferation then differentiation to oligodendrocytes (EdU+) • Pruning of axon/pre-synapses	• Potentially, secrete factors that induce clustering of nodal proteins on unmyelinated axons	• Modifications of myelin internodal length • Removal/addition of myelin internodes • Secrete factors that induce clustering of nodes
Short-term Functional Plasticity	• Shed NG2 protein (impacts synaptic plasticity)	• Potential role in circuit function (yet to be determined)	• Regulate potassium levels (impacting firing rate) • Metabolic support to maintain fast neuronal firing rate

Figure 2

A

Complex wheel		• Motor skill learning task (motor system) • Walk on a wheel with rungs irregularly spaced • Change locomotor pattern between forelimbs and hindlimbs • Measure running speed
Single-pellet reaching task		• Motor skill learning task (motor system) • Retrieve a difficult to access food pellet using a single forelimb • Refinement of complex motor programmes • Measure number of successful pellet retrievals
Morris water maze		• Spatial memory task (hippocampus) • Reach a platform hidden underneath the water in a large maze • Build a spatial map to “triangulate” and learn the location of the platform using external cues in the environment • Measure time spent in quadrant where the platform was in a probe test
Contextual fear paradigm		• Context-dependent emotional memory (hippocampus) • Predict the occurrence of aversive stimulus • Build a pavlovian association between the aversive stimulus and the context in which it is presented • Measure time expressing the conditioned fear response in the context in the absence of the aversive stimulus

B

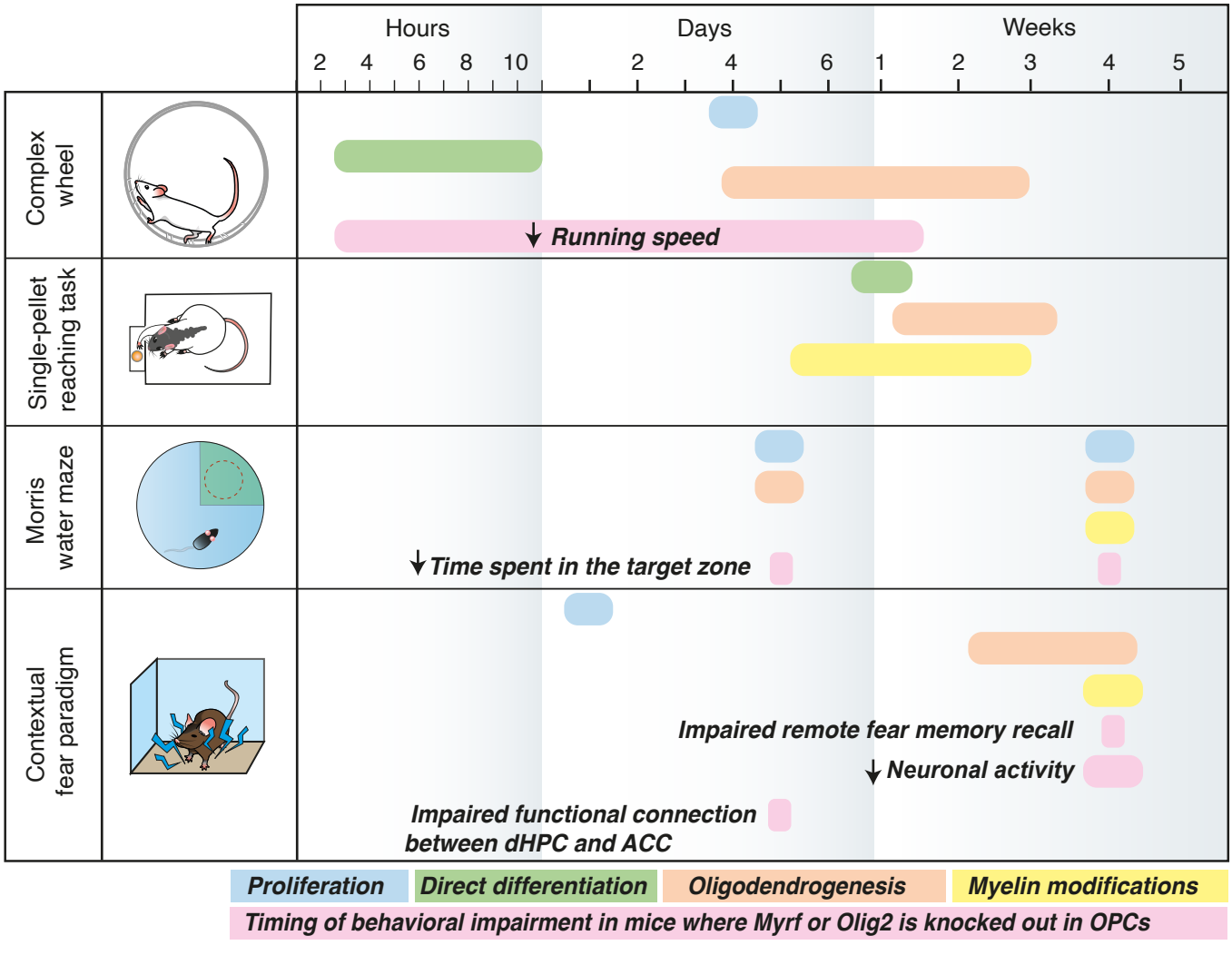


Figure 3