Grey matter myelination

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Abstract

There is now increasing evidence that myelin is not only generated early in development, but also during adulthood possibly contributing to lifelong plasticity of the brain. In particular, human cortical areas responsible for the highest cognitive functions seem to require decades until they have reached their maximal amount of myelination. Currently, we know very little about the mechanisms and the functions of grey matter myelination. In this emerging field key questions await to be addressed: How long does myelination last in humans? How is grey matter myelination regulated? What is the function of myelin in the grey matter? Does grey matter myelination limit and/or promote neuronal plasticity? Finding answers to these questions will be important for our understanding of normal, but also abnormal cortex function in a number of neurological and psychiatric diseases.

Introduction

Myelin is generated as a lipid-rich, multilayered membrane that wraps around axons to provide electrical insulation and metabolic support (Simons and Nave 2015). Myelin is one of the most abundant membrane structures with a total of around 150 000 km of myelinated fiber length in humans, mostly localized within the white matter (Marner et al. 2003). Whereas the mechanisms and the function of myelin have been intensely studied in the white matter, little is known about grey matter myelination. Grey matter consists predominantly of neuronal cell bodies and dendrites, but is also composed of myelinated axons. Myelination of these axons varies with some axons being incompletely myelinated with myelinated segments interspersed with long, unmyelinated tracts and other axons lacking entirely myelin (Tomassy et al. 2014). In general, cortical areas responsible for the highest cognitive function contain less myelin and require more time to become myelinated (Glasser et al. 2014). Such developmental delay may enhance the impact of postnatal experience on myelination. Indeed, there is no considerable amount of data providing evidence that myelination is not fully determined by intrinsic genetic programs, but also subject to modification by environmental factors (Fields 2008; Forbes and Gallo 2017; Mount and Monje 2017). Here, we will summarize our current understanding of grey matter myelination including its emerging role in shaping neuronal cortical circuits.

How long does myelination last in humans?

The brain develops in a complexly orchestrated sequence of interconnected mechanisms including the maturation and functional specialization of grey matter regions and the establishment of white matter connections. The most rapid changes occur during the last months of gestation and in the first post-natal months (as established by Flechsig and colleagues). However, after this intense phase of non-linear growth, the brain is far from complete. In fact, the brain continues to increase in size until in average ~ 11 years in girls and ~15 years in boys (Giedd and Rapoport 2010). Magnetic resonance imaging (MRI) has been used intensively to follow postnatal brain development during childhood through early adulthood into old age. Such studies have revealed a highly asynchronous pattern of grey and white matter growth and decline.

White matter volume shows a steady increase from birth and even beyond adolescence into middle age peaking at around 40-50 years, after which it continuously declines (Sowell et al. 2003). This increase in volume visualized by MRI is most likely the result of several mechanisms, with myelination representing one of the most striking white matter alterations. Together with post-mortem neuropathological analyses, these studies have described neuroanatomical rules of how myelination progresses (Dubois et al. 2014). In general, the pattern of myelination depends on the hierarchy of connections between the different brain regions (Snaidero and Simons 2014). It starts in areas devoted to the regulation of general brain homeostasis located in the brainstem, from where it proceeds to sensory pathways before moving to motor areas, followed by projection pathway before terminating in association fibers. This sequence results in a wave of myelination proceeding in caudal to rostral direction, and from posterior to anterior and from central to peripheral locations.

When tracked by MRI, grey matter volumes of most cortical areas show inverted U shaped trajectories (Gogtay et al. 2004; Sowell et al. 2003). Grey matter volume increases in the first years after birth, reaching a peak, after which it continuously declines. Depending on the brain region, the rate of grey matter volume loss can be very different. In general, cortical areas associated with basic functions show earlier decline of grey matter density than regions with high level function as language (Sowell et al. 2003). For example, motor and sensory brain regions are the first to loose grey matter density volume, followed by areas involved in spatial orientation and attention, and ending in regions involved in high-order information processing. The exact molecular mechanisms that underlie grey matter density loss are unknown. Synaptic pruning, cell loss and shrinkage are possible mechanisms, but continued

myelination is another likely explanation. As myelination increases white matter volume beyond the time at which the brain increases in size, concomitant loss of grey matter should occur. Indeed, post-mortem studies have provided evidence for protracted myelination within some areas of the human cortex (Benes 1989; Benes et al. 1994). For example, one study quantifying the amount of myelination within different cortical regions in human and chimpanzee post-mortem tissue came to the conclusion that myelination extends beyond late adolescence in humans, but not in chimpanzee (Miller et al. 2012).

Maps of cortical myelin content have been generated using ratios of T1-weighted (T1w) and T2-weighted (T2w) imaging intensities (Glasser and Van Essen 2011). Such studies concur with previous histological neuropathological studies in humans and show that primary cortical areas such as motor, somatosensory, visual, and auditory cortices are more heavily myelinated than association areas. The cortex of the most heavily myelinated areas tends to be thinner, with higher densities of neurons, but with less complex dendritic arbors. Lightly myelinated areas are in general associated with higher brain functions using neurons with large dendritic arbors and more synapses (Collins et al. 2010; Glasser and Van Essen 2011). There are also striking metabolic differences between those areas. Even if lightly myelinated areas contain fewer neurons, these regions appear to be metabolic more active with higher rates of aerobic glycolysis (Vaishnavi et al. 2010). When such myelin maps are generated and compared across humans, chimpanzee and macaques, interesting differences are observed. Whereas the macaques cortex is relatively enriched in highly myelinated areas, human brains have in particular expanded the regions containing little myelin such as the prefrontal, inferior parietal and lateral temporal cortex (Donahue et al. 2018).

In particular these lightly myelinated areas are those, in which myelin is formed late and slowly. Following grey matter density in such areas across the entire human life span using MRI, reveals striking patterns. For example, the superior frontal cortex shows a steady decline until the age of ~ 60 years, after which the cortical thinning reaches a plateau (Sowell et al. 2003). The maturation of these lightly myelinated cortical areas in the human cortex raises some important questions: Does myelination contribute to the thinning of the cortex? When does myelination terminate in the human cortex? Is there evidence for very late myelination continuing even until the age of ~60?

While developmental processes such as synaptic pruning or loss of dendritic arbors are likely to contribute to grey matter maturation proceeding myelination, the effect of related changes occurring during aging is unclear. Do degenerative processes such as loss of synapses and

dendrites release inhibitory signals for myelination? Do maturation and aging processes intermingle in the brain? Even if there is no answer to these questions yet, and we still do not know how long myelination continues in the human grey matter and how this affects brain function and aging, it is clear that white and grey matter remodeling is a lifelong process.

It is interesting to note that the pattern of neurofibrillary changes which gradually develops in the course of Alzheimer's disease, bears a striking resemblance to the inverse sequence of cortical myelination with the lightly myelinated areas, in which myelin is formed late and slowly, being affected first (Braak and Braak 1996). The significance of this finding is unknown. Some authors have suggested that the breakdown of this late-stage myelin promotes the buildup of toxic fibrils (Bartzokis 2004).

How are different layers of the grey matter myelinated?

The human cerebral cortex is only 2-3 millimeter thick, but folded in such a way that it forms a large sheet with a surface area of 0.12 m^2 accounting for 40 per cent of the brain mass (Toro et al. 2008). One distinctive feature of the cortex is its organization into six layers, which can be divided into three functional parts consisting of the supragranular layer (layer I/II-III), the granular layer (layer IV) and the infragranular layer (layer VI) (Lodato and Arlotta 2015). The supragranular layer contains predominantly neurons that project their axons to other cortical areas of the same hemisphere (associative) or to the opposite hemisphere (commissural). The granular layer receives thalamocortical connections from the specific thalamic nuclei, whereas the infragranular layers connect the cerebral cortex with subcortical regions. The pyramidal cells are the main cell type within layers III and V. The cortex displays unique cytoarchitectural characteristics across its surface, such as distinct regional differences in the type, size, shape and density of neurons (Amunts and Zilles 2015). These features allowed Brodmann to distinguish 52 different areas within the cortex. These pioneering cytoarchitectural maps created by Brodmann are well known to neuroscientist and still widely used to define anatomical structures within the brain.

Roughly at the same time, Oskar and Cecile Vogt pioneered another method of architectonic cortex mapping. This discipline is called myeloarchitectonics and is based on description of myelinated fibers distribution in the cortex (Braitenberg 1962; Hopf 1968; Nieuwenhuys et al. 2015). While cytoarchitectonics has and is still receiving much attention, myeloarchitectonics has been neglected and forgotten for over 100 years. Vogt (1910) realized that myelinated fibers show distinct patterns of radially and tangentially orientated bundles. The radial fibers

represent efferent projections mainly originating in layer III and V, and afferents projections terminating in layer III and IV. The tangential fibers are heavily myelinated transverse layers, the so-called band of Baillinger, that are found in layer IV and V. These layers represent mainly efferent axon collaterals running 200-300 μm below the cell bodies of the pyramidal cells from which they originate. Based on these patterns, the Vogts were able to distinguish four principal myeloarchitectonic categories: a bistriate type, characterized by the presence of two clearly separated horizontal myelin-rich bands; an unistriate and an unitostriate type, both characterized by one band, but of different size; and an astriate type, which is so heavily myelinated that no bands are seen (Figure 1). Based on visual inspection of stained myelinate fibers, the Vogts were able to identify 185 different areas. In some cortical areas the boundaries are sharp and clearly distinguishable, whereas in other only subtle differences are seen (Nieuwenhuys 2013). The transitions in myeloarchitecture are often accompanied differences in cytoarchitecture. For example, large pyramidal neurons with extensive collateral contribute more to the intracortical myelin content than small ones. More lightly myelinated areas tend to have lower neuronal cell density and more complex intracortical circuitry with large dendritic trees. Thus, cytoarchitecture and myeloarchitecture are closely linked and are just a description of different aspects of cortex structure. If so, why do we need to advance our understanding of myeloarchitecture in brain? One reason is that myeloarchitecture will give us information on the function of the cortex beyond the cellular composition. It can teach us how myelination is affected by environmental influences, age and disease. In addition, changes in myeloarchitecture can possibly be imaged non-invasively using MRI in humans.

It is now becoming increasingly clear, that with the advent of new high-resolution MRI methods, it will become feasible to resolve myelin density in the cortex, and with these advances the neglected science of myeloarchitectonics needs to be revitalized (Amunts and Zilles 2015; Dinse et al. 2015). For example, comparisons of high-resolution *in vivo* T1 and postmortem T2 MRI, one cell body stain, and two myelin stains showed that the MRI signal mainly reflects the variation of myelin density throughout the different cortical layers (Eickhoff et al. 2005). Furthermore, using high angular resolution diffusion imaging, specific myeloarchitectonic features, such as the transverse myelinated stripes, were visualized (Aggarwal et al. 2015). Moreover, using T1w/T2w ratio imaging at high resolution, detailed cortical myelin density maps have been generated that show ~180 different areas, matching exactly with the number of myeloarchitectonic areas defined by the Vogts (Van Essen et al. 2012). These studies are encouraging as they indicate that a window to cortical myelin may

open up in the near future that may allow us to image non-invasively and longitudinally grey matter myelination in humans in health and disease. However, at the same time it is clear that MRI lacks the resolution to visualize layers and boundaries between and within different cortical areas.

How are the different neurons within the grey matter myelinated?

The most ambitious goal in myeloarchitectonics is to obtain comprehensive maps of myelin distribution resolving the distribution of individual sheaths within neuronal circuits. Such studies require high-resolution three dimensional images of large volumes - data that can only be provided by electron microscopy analyses. Using high-throughput electron microscopy serial reconstruction data sets of the somatosensory cortex of adult mice, the myelination was traced along axons located in layers II/III to VI (Tomassy et al. 2014). As already apparent from histochemical staining of myelin, the coverage of myelin is higher on axons in the deeper as compared to superficial cortical layers with a total coverage of myelin of ~60% in layer V-VI as compared to ~35% on layer II/III. The most striking observation, however, is the pattern of how myelin is arranged on axons arising from layer II/III neurons. Myelin sheath length is highly variable with sheaths ranging from ~20 to 60 µm that are separated by large gaps up to ~60 µm in length. In addition, the distance between the axon hillock and the beginning of the first internode is unusually long covering a distance of ~100 µm. This pattern of intermittent myelination observed in the grey matter is very different from how myelin is arranged within most white matter fiber tracts. A possible explanation for this heterogeneity of myelination profiles is that different neuronal subtypes regulate their own myelination profile. Indeed, mouse models, in which the cortical migration of neurons is impaired, give raise to aberrant positioning of deep-layer neurons into the upper layer with increased myelination of these superficial layers (Tomassy et al. 2014). These experiments provide evidence that pyramidal layers of the upper and deep layers carry intrinsic information on how myelination is regulated along their axonal surfaces.

The mostly inhibitory interneurons comprise approximately 20% of the cortical neuronal population and, in contrast to their excitatory glutamatergic principal cells, they form mostly short range projections within local circuits and have therefore been thought to be less dependent on myelin for its function. However, by combining light microscopy-based array tomography and large volume electron microscopy data sets, extensive myelination of interneurons was revealed in mice (Micheva et al. 2016). These are predominantly parvalbumin-positive basket cells that are especially prominent in the middle cortical layers

and constitute around half of the myelinated axons in layer II/III. Interestingly, some migrating interneurons secrete fractalkine to directly promote oligodendrogensis and myelination during development (Voronova et al. 2017). Reconstructions showed that the distribution of myelin on these basket cells is intermittent with large parts being unmyelinated. These intermittent myelin profiles have also been detected on parvalbumin-positive basket in the human cortex, which also show myelinated segments preferentially localizing to the axon arbor near the cell body and with relatively short internodes (~25 μm) interspersed at axonal branch points followed by unmyelinated segments (Stedehouder et al. 2017). Furthermore, myelinating satellite oligodendrocytes around layer V neurons have been identified forming few wraps of myelin around their proximal axon (Battefeld et al. 2016). What are the electrophysiological or circuit-level consequences of having discontinuous myelination? One possibility is that these isolated sheaths have no circuit-level function and are only present to provide metabolic support to axon. Another explanation is that isolated sheaths induce subtle differences in action potential conduction, thereby, shaping neuronal cortical circuit function.

How is grey matter myelination regulated?

The different pattern, extent and timing of myelination in the grey as compared to the white matter, raises the question whether distinct mechanisms of myelin biogenesis exist in different regions of the CNS. Myelination of white matter tracts has been extensively studied in mice in regions such as the spinal cord and the optic nerve. It occurs in several steps including OPC generation, proliferation, cell migration, differentiation, axonal ensheathment and myelination (Bercury and Macklin 2015; Chang et al. 2016; Snaidero and Simons 2017). Myelination in the optic nerve is rapid and is largely completed within ~2-3 weeks in mice (Snaidero et al. 2014). Within a very short time window OPCs proliferate and differentiate into premyelinating oligodendrocytes, which form large number of processes that do not yet wrap nearby axons. These premyelinating oligodendrocytes are generated in such a large number that only around half of the cells manage to myelinate axons while the remaining are eliminated by apoptosis (Barres et al. 1992). Premyelinating oligodendrocytes are distinguished by their high expression of the breast carcinoma amplified sequence 1 (BCAS1) and ectonucleotide pyrophosphatase/phosphodiesterase 6 (ENPP6) protein, which serve as markers for oligodendrocytes in an intermediate stage of differentiation, between early progenitors and mature cells (Fard et al. 2017; Xiao et al. 2016). Most likely these premyelinating oligodendrocytes have a narrow time window, in which they compete for

survival factors possibly secreted by or expressed on unmyelinated axons (Czopka et al. 2013). Such a mechanism ascertains that the number of surviving premyelinating oligodendrocytes is matched to the axonal surface requiring myelination. Even if wasteful in nature, it is a powerful mechanism to generate fully myelinated axonal tracts in areas of the brain that depend on saltatory nerve conduction. In the optic nerve, all axons will eventually become myelinated and there is therefore very little room for regulatory axonal cues determining its extent of myelination, except of a supra-threshold axon caliber (Mayoral et al. 2018). Once myelination is terminated, OPC proliferation and differentiation is reduced, but not completely eliminated. The low rate of continuous OPC proliferation and differentiation is most likely necessary for myelin maintenance (Hughes et al. 2013). As the survival rate of myelin-forming oligodendrocytes in the optic nerve is around 50-60% over 20 months, new oligodendrocytes have to be generated in adult mice to ensure that axons remain fully myelinated (Tripathi et al. 2017).

Much less is known about myelination in the cortex, but the available data indicate that many mechanisms are shared. Overproduction of premyelinating oligodendrocytes and competition for survival factors is also seen in the cortex. For example, in the rat cortex, 20-30% of the premyelinating oligodendrocytes die by postnatal day 21 (Trapp et al. 1997). In addition, intravital imaging of oligodendrocyte differentiation in the adult mouse cortex shows that only 22% of the premyelinating oligodendrocytes are successfully integrated in circuits by forming new myelin sheaths, while most are eliminated by cell death (Hughes et al. 2018). Extrinsic factors may play more dominant role in the regulation of myelination in the grey as compared to the white matter. Axonal diameter could be one factor that determines whether an axon will be myelinated or not (Bechler et al. 2015) (Lee et al. 2012a). As many myelinated and unmyelinated axons are found in the range between 0.2µm and 0.8µm in the cortex other factors must exist. Axonally-expressed neuregulin regulated by experience could be such a cue (Lundgaard et al. 2013) (Makinodan et al. 2012).

In addition, oligodendrocyte-intrinsic mechanisms controlling oligodendrocyte survival have recently been discovered (Sun et al. 2018) (Meireles et al. 2018). The transcription factor EB (TFEB), previously identified as a master regulator of lysosomal biogenesis, is crucially involved in this process by controlling the activation of pro-apoptotic genes. TFEB expression in oligodendrocytes induces PUMA induction and Bax-Bak activation to promote programmed cell death. In the absence of TFEB the ‘brake’ is removed and as a consequence oligodendrogenesis and myelination is enhanced. This does not only result in precocious, but

also in ectopic myelination, which is particular obvious in upper cerebral cortical and in the cerebellar molecular layers. Ectopic myelination has also been observed in mouse spinal cord grey matter (dorsal horn), when myelin production is increased by oligodendrocyte-specific *Pten* deletion (Almeida et al. 2018). Notably, by targeting *Pten* in cerebellar granular neurons axon caliber is increased and naturally unmyelinated axons become myelinated (Goebbels et al. 2016). In addition, to axonal caliber size regulation, it is possible that the grey matter is enriched in inhibitory factors that prevent myelination of most of its axons. For example, surface molecules such as the junction adhesion molecule 2 (JAM2) are expressed on the soma and dendrites acting as inhibitory myelin-guidance molecules (Redmond et al. 2016).

A striking feature of myelin biogenesis in the cortex is the time it takes. Longitudinal two-photon imaging of oligodendrocytes showes that myelination occurs for at least 12 months with only half of the final myelin generated until 4 months of age (Hill et al. 2018; Hughes et al. 2018). These data concur with the observation that $BCAS1^+$ premyelinating cells are generated until at least 1 year of age in mice (Fard et al. 2017). In humans $BCAS1^+$ cells were mainly found in the first year of postnatal white matter development, but were also present, at low levels, in the frontal human cortex into adulthood. Whereas adult myelination in the optic nerve or in the spinal cord occurs at low rate to maintain fully myelinated fibers, adult myelination appears to be of different purpose in the cortex. Cortical myelin is remarkably stable, but some remodeling occurs, characterized by retraction or extension of internodes (Dutta et al. 2018; Hill et al. 2018; Hughes et al. 2018; Young et al. 2013). Nevertheless, most of the myelin that is generated during adulthood supplements existing myelin resulting in a continuous expansion of the amount of myelin. Even if this process continuous for a long period it is not sufficient to eliminate the intermittent pattern of sparsely myelinated axons in the cortex completely (Hughes et al. 2018). Lifelong cortical myelination raises the question of the underlying role for brain function. It is possible that cortical myelin contributes to the adaption or maturation of neuronal circuits (de Hoz and Simons 2015; Fields 2014). Myelin placed on axons with a discontinuous pattern of segments may generate subtle differences in action potential conduction sufficient to change timing differences in cortical circuits. If myelin contributes to the maturation and the plasticity of neuronal networks, it must be regulated by neuronal signals. Indeed, optogenetic or pharmacogenetic stimulation of neuronal activity increases myelination (Gibson et al. 2014; Mitew et al. 2018). In addition, skilled motor training or sensory stimulation in adult mice or rats promotes oligodendrocyte generation and myelination (McKenzie et al. 2014; Sampaio-Baptista et al. 2013). Conversely, sensory deprivation leads to hypomyelination (Hill et al. 2014; Liu et al. 2012;

Makinodan et al. 2012). Data obtained from zebrafish demonstrated, that ablated myelin sheaths grow back at the same position and length as before, suggesting that axons directly control myelin remodelling (Auer et al. 2018). These mechanisms are compelling, but whether they occur in the adult human cortex is unknown.

The dynamics of oligodendrocyte formation and myelination are difficult to study in humans. However, a study using nuclear bomb test-derived ^{14}C for oligodendrocyte birth dating has provided some valuable insights (Yeung et al. 2014). These experiments revealed that stable numbers of oligodendrocytes are reached within the white matter at the age of 5. These cells generated until the age of 5 are long-lived with an annual exchange rate of only 0.32% (~1 out of 300 being replaced per year). Mathematical modelling of the ^{14}C data in the grey matter shows a much prolonged expansion phase as compared to the white matter. Stable numbers are not reached until the fourth decade, followed by an annual turnover of 2.5%. The small number of new oligodendrocytes generated in adult humans, is consistent with the low levels of proliferating OPCs as assessed by expression analysis of Ki67 to mark cell divisions (Yeung et al. 2014). Furthermore, when brain autopsies of patients were analysed that had received the thymidine analog IdU in adult age as a radiosensitizer, mature oligodendrocytes were only very rarely found, providing further evidence that generation of new oligodendrocytes is a rare event in adulthood. Nevertheless, there is extensive data suggesting that myelination during adulthood is as an adaptive process and in response to learning. For example, practicing piano, playing baduk or juggling, acquiring specific visuomotor skills or learning a new language have been associated with new myelin formation (Zatorre et al. 2012). One drawback, however, is that these experiments are based on MRI, which so far lacks sequences specific for myelin. Even if adaptive myelination is now an established concept in mice, we do not know whether it exists in humans. In mice, oligodendrogenesis is profoundly increased when animals are, for example, exposed to enhanced sensory experience, resulting in the formation new myelin sheaths within the somatosensory cortex (Hughes et al. 2018). Two photon imaging shows that not only the generation of new but also the rate of oligodendrocytes successfully integrated into circuits is enhanced. Thus, in the adult brain it seems that even without stimulation OPCs continue to divide and differentiate, but the barrier to full integration in mature circuits is high. As a consequence, most cells are eliminated by programmed cell death. Upon stimulation, however, the barrier is lowered and a larger fraction of the cells survive and form new myelin sheaths. Whether a similar mechanism operates in humans is difficult to find out, but the low number of proliferating cells within the human brain indicates that this may not be the case (Yeung et al. 2019) (Jakel

et al. 2019). Instead, a relatively large number of $BCAS1^+$ premyelinating cells have been detected within the human cortex that persists until old age (Fard et al. 2017). Thus, it is possible that adaptive myelination is carried out by resident premyelinating oligodendrocytes in adult humans. Such a cell proliferation independent scenario implies that there is a limited reservoir of cells available for adult myelination as the capacity for replenishment is low.

What is the function of grey matter myelination?

While it is well established that the major function of myelin is to increase the propagation of action potentials along axons by allowing saltatory nerve conduction, this function of myelin may not apply to all axons. The intermittent myelin pattern along inhibitory basket cell axons in the cortex and along descending axons of excitatory pyramidal cells indicates that rapid saltatory nerve conduction velocity cannot be the function of myelin on these axons. Instead and because of the high tonic activity and the high energy demands, the fast-spiking basket cells may require myelin for metabolic reasons (Micheva et al. 2016). It is possible that basket cells have a need for metabolic oligodendroglial assistance, for example to obtain lactate as an energy source and to siphon excess amounts of extracellular potassium (Battefeld et al. 2016; Funfschilling et al. 2012; Lee et al. 2012b).

In contrast to axons that transmit information along 'one-way' tracts, as for example in the spinal cord or in the optic nerve, the function of myelin in more complex circuits may differ. The main task of myelin in these circuits is not to speed up nerve conduction to maximal values, but to synchronize conduction velocity to the need of the entire network. Precision of spike timing is a critical parameter in neuronal network function. Changes in conduction velocity - as they may occur by the addition of intermittent myelin segments - will affect the absolute time it takes for a spike to arrive (Pajevic et al. 2014). Myelination could for example be generated in such a way that oscillating neuronal networks are generated. In addition to spike arrival, myelin also influences relative measures that are considered to be important for temporal coding, such as first spike latency and interspike interval. Adjustment of relative spike timing can be used to code information in certain neuronal networks. For example, it can serve as a mechanism for adjusting interaural time differences to achieve binaural coincidence detection (Ford et al. 2015; Seidl et al. 2010).

Long unmyelinated axonal segments may not only be used to fine-tune conduction speed, but also to allow coordinated transmission between their unmyelinated segments (de Hoz and

Simons 2015). Such parallel fiber interactions are termed ephaptic from a Greek word meaning to touch.

Another way to explain the differences in myelin content between different brain regions is to consider the function of myelin as growth inhibitor (Filbin 2003; McGee et al. 2005; Schnell and Schwab 1990). It is well known, that myelin provides a non-permissive environment for axonal and synaptic growth. This concept is well established in the field of CNS regeneration, where a number of different myelin-associated inhibitors imped axonal regeneration. One function of myelin could be to prevent aberrant axonal sprouting and synapse formation. Cortical areas that are more plastic and require more synapse remodeling are in general less myelinated and require much more time until myelination is completed. The developmental delay of myelination may enhance the impact of postnatal experience on neuronal remodeling. Only when the most complex tasks have been acquired and neuronal remodeling is terminated, myelination may put a seal on neuronal plasticity to consolidate the acquired skills.

Conclusion

In the emerging field of grey matter myelination several key questions await to be addressed. New patterns of intermittent myelin have been described, but its function remains elusive. It is conceivable that continuous and lifelong addition of new myelin sheaths regulate oscillations and synchrony of neuronal activity into adulthood. These ideas raise the question of how neurons and oligodendrocytes communicate to regulate such functions. Do OPCs sense the demand of axons for myelin or is myelination regulated by survival factors at the level of pre-myelinating oligodendrocytes? Currently, we lack specific axonal cues that determine how and which axons will be myelinated. As a consequence, models have been proposed suggesting that myelination occurs by default. One possibility is, indeed, that myelin is placed randomly into neuronal circuits continuing until the network has achieved its desired function. Alternatively, specific axonal signals coordinate myelination to generate precise patterns. It is very likely, that the regulation of grey matter myelination is more complex and requires more specific cues. In this review, we have also discussed the possible function of myelin as an inhibitor of neuronal circuit plasticity. This idea arises from the inverse correlation of the amount of myelin and the plasticity of the cortical region. It is clear that testing these different hypotheses require new tools that allow us to disrupt myelination selectively. Such methods will also be important to understand the possible contribution of myelin pathology for psychiatric diseases such as schizophrenia and autism.

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Figure Legend

Representation of cytoarchitectonic and myeloarchitectonic layers in cortex, according to Vogt 1903. (b) Schematics of the four types of myeloarchitectonic layer structures, according to Vogt 1910. These are the bistriate type, characterized by the presence of two clearly separated horizontal myelin-rich bands; an unistriate and an unitostriate type, both characterized by one band, but of different size; and an astriate type, which is so heavily myelinated that no bands are seen. Images are modified from Nieuwenhuys et al. 2013 and reproduced with permission from the publisher.

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