Ashdin Publishing
Journal of Evolutionary Medicine
Vol. 5 (2017), Article ID 235996, 23 pages
doi:10.4303/jem/235996

Review Article

PERSPECTIVE

The Evolution of Myelin: Theories and Application to Human Disease

Laurence Knowles

Barts and the London School of Medicine and Dentistry, 4 Newark Street, London E1 2AT, UK
Address correspondence to Laurence Knowles, l.j.knowles@smd14.qmul.ac.uk

Received 29 July 2016; Revised 18 December 2016; Accepted 10 January 2017

Abstract Myelin, once thought of as a simple insulating sheath, is now known to be a complex, dynamic structure. It has multiple functions in addition to increasing conduction velocity, including reducing the energetic cost of action potentials, saving space, and metabolic functions. Myelin is also notable for likely having arisen independently at least three times over the course of evolutionary history. This article reviews the available evidence about the evolution of myelin and proposes a hypothesis of how it arose in vertebrates. It then discusses the evolutionary trade-offs associated with myelination and suggests a possible animal model for further study of this phenomenon. Finally, it briefly covers the neural regulation of myelination before discussing possible roles of myelin in human social cognition and evolution, and the relevance of this to human disease.

Keywords evolutionary medicine; myelin; optimization; plasticity; social cognition

1. Introduction

Before Darwin, biology was an exercise in classification. The theory of natural selection, combined with Mendelian genetics to create the "Modern Synthesis", transformed it into a true science with a rigorous theoretical foundation. Clearly, this transformation must affect how we think about medicine as well.

In medicine, the most fundamental part of this transformation is that we can now only understand the design of the human body in the light of evolution. In contrast to engineered systems, evolved organisms have arisen gradually and incrementally in response to a multitude of selective pressures. Thus, components are frequently duplicated or co-opted to perform new functions whilst retaining old ones, and altering any part of the system will have multiple effects. An added layer of complexity arises when we consider that organisms are not assembled, but develop over time; the developmental programme further constrains the options available to natural selection, often resulting in seemingly odd solutions (think of the recurrent laryngeal nerve of the giraffe). Knowledge of evolution helps understand these complexities, from the molecular to population levels. As medicine is built on biology, this is clearly beneficial. There are also more specific applications of evolutionary principles to medicine. One is utilizing these principles to design medical interventions—for example, antibiotic resistance is essentially a phenomena of natural selection and so understanding evolutionary principles can help subvert it [1]; these principles are also being applied to problems like cancer biology [2].

Perhaps surprisingly, one fundamental question where evolutionary principles have not been applied is investigating why humans suffer from diseases [3]. There are likely several reasons for this, not least that evolution is rarely included in medical curricula [4]. When evolutionary explanations are attempted they often fall into several traps, most commonly a "naive adaptationism" whereby any biological feature is explained as a specific adaptation; for example, the argument that vomiting in acute glaucoma is a mechanism to reduce body salt content and hence intraocular pressure [5]. This explanation fails on several levels [6]; the underlying fallacy is to assume that a specific manifestation of a disease is an object of selection. In fact, diseases themselves are rarely shaped by natural selection. What are the biological traits which confer *vulnerability* to disease? [3].

In a famous paper, Tinbergen argued that four types of explanation must be integrated to understand any trait: phylogenic, functional, developmental, and mechanistic [7]. In this article, I will discuss evolutionary medicine using the example of myelin and Tinbergen's criteria as a framework. I will address phylogeny in Section 2, with a review and model of how myelin first evolved. Function will be covered in Section 3, with a discussion of the roles of myelin and how they trade-off against one another. Discussion of mechanism and development will be integrated within these two sections, but specific areas of interest will also be addressed in Sections 4 and 5. Finally, I will discuss the four strands in relation to diseases of myelin and myelination.

2. The evolution of myelin—evidence and models

Once thought of as a simple insulator, we now understand myelin as a dynamic, complex structure serving to speed action potential conduction along axons, conserve space and energy, allow precise temporal coordination of action potentials, and reduce unwanted field potentials. Thus, understanding how it evolved is not simple. First, however, it is worth defining precisely what myelin actually is.

2.1. What is myelin?

Ever since early histologists began investigating nervous systems in the mid 19th century, they noted the presence of lipid-rich axonal sheaths. Over the next hundred years, developments such as osmium staining, birefringence studies, X-ray diffraction, and electron microscopy lead to a detailed understanding of myelin structure and development [8]. Thus, by the 1960s investigators knew that vertebrate myelin consists of lipid-rich segments of glial cell membrane, concentrically wound around the nerve axon with periodic gaps at the "nodes of Ranvier". As more was discovered about the exact morphological parameters of vertebrate myelin, structural knowledge ran far in advance of functional knowledge.

This historical discrepancy is partially at least responsible for the confusion over whether invertebrates have myelin. All phyla except coelenterates have axons ensheathed by glia to some degree [9], but in only some do these sheaths function as vertebrate myelin does. As early as 1879, it was shown that annelid axons had a sheath with equivalent staining properties to vertebrate myelin [10], and several authors showed enhanced conduction speed in such axons. However, it later became apparent that these sheaths vary significantly in morphology from the vertebrate archetype (Section 2.3). These structural differences have lead to the modern misconception that invertebrates do not possess "true" myelin [11,12]. A more useful approach is to define myelin functionally. I will use Hartline's definition ([13], see also [14]), that myelin is

"a multilamellar axonal sheath that increases nerve impulse conduction speed significantly above that of fibers of the same outside diameter that lack the sheath."

This definition has two advantages. It applies across phyla, and it frees us to consider intermediate or ancestral forms of myelin—both clearly useful when discussing evolution. There are, however, disadvantages. It does not consider the other functions of myelin, and if strictly adhered to would exclude the myelin of very small diameter axons in the vertebrate CNS, for example. Practically, measurement of conduction velocity is harder than microscopy and staining, and has been done only in a few species. The latency of stereotyped reflexes is a good proxy for conduction speed, but we must remember that it is a proxy only. However, overall this is the most useful definition for discussion of myelin evolution.

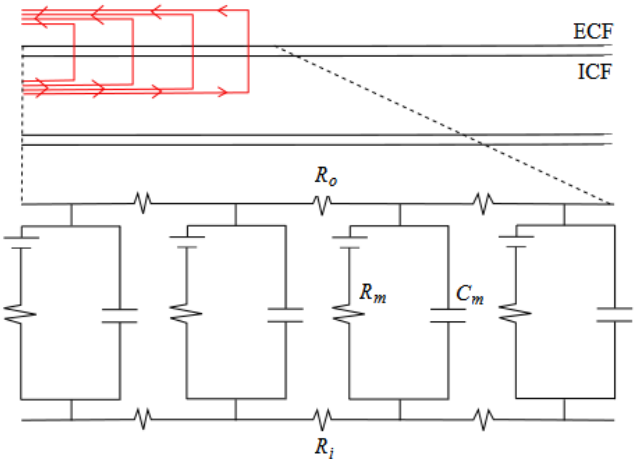

Figure 1: Conduction in unmyelinated nerve. The top schematic shows how action potentials are conducted by passive spread of current (red) to adjacent membrane. The bottom schematic shows the equivalent cable diagram. ECF, extracellular fluid; ICF, intracellular fluid; C_m, transmembrane capacitance; R_m, transmembrane resistance; R_o, external longitudinal resistance; R_i, internal longitudinal resistance. Circuit diagrams redrawn from www.pbrc.hawaii.edu/∼danh/InvertebrateMyelin/.

2.2. Physiology of impulse conduction

The definition above requires us to understand the determinants of conduction velocity in both myelinated and unmyelinated nerve. A useful model is a cable. In unmyelinated axon (Figure 1), current from an action potential spreads passively to the immediately adjacent membrane, where it charges first the transmembrane capacitance and then changes the membrane potential until threshold is reached and the process repeats.

The speed of this process is determined by the membrane length constant and time constant. The length constant, λ, is defined as the distance over which the voltage will decay to $1/e$ of its original value. If a steady current is injected and thus the membrane capacitance is fully charged, then this decay is accounted for by current leakage and so λ is dependent upon R_m and R_i:

$$\lambda \propto \sqrt{\frac{R_m}{R_o + R_i}}.$$

In practice, R_o can be treated as a constant. More important is the fact that, physiologically, current injection is not constant—it occurs fleetingly in the form of action potentials. Thus, current is also needed to charge the membrane capacitance. It turns out that the current needed for this is

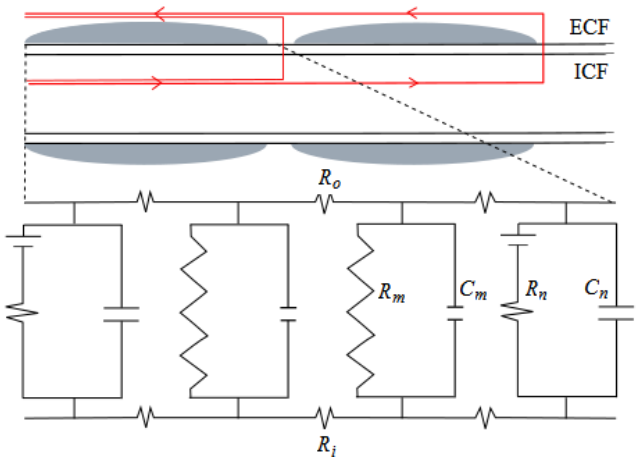

Figure 2: Conduction in myelinated nerve. Schematics, as for Figure 1, demonstrating how internodal myelination leads to saltatory conduction. C_n, transnodal capacitance; R_n, transnodal resistance; all others as for Figure 1.

far greater than the leak current determined by R_m; so under these conditions we can approximate λ as follows:

$$\lambda \propto \sqrt{\frac{2}{C_m R_i}}.$$

The time constant, τ, is defined as the time taken for an increase in membrane potential at any one point spatially to reach $(1-1/e)$ of it's final value, and is proportional to the product of R_m and C_m. Overall, velocity is roughly proportional to the length constant and inversely proportional to the time constant:

$$V \propto \frac{\lambda}{\tau + T},$$

where T represents a constant time delay to account for channel opening.

If we consider how the overall speed of propagation can be increased, it is clear that the length constant should be maximized. The major method of achieving this is by decreasing the internal resistance of the axon (another method to decrease R_i is to have the longitudinal current pass through a nonaxonal substance—see the section on the penaeid shrimp, Section 2.3.3). Hodgkin showed that R_i decreases with the square root of diameter [15]; thus, increasing axon diameter will increase the length constant and thus conduction velocity. Axonal gigantism is the solution adopted by many organisms, most famously the squid. However, it is expensive both in terms of space and energy.

Let us now consider a myelinated axon (Figure 2). At the internodes, myelin greatly reduces the transmembrane capacitance and increases transmembrane resistance. Thus, less current is needed to charge the internodal capacitance, and so current is attenuated less with distance (i.e., λ is increased). Notably the reduced capacitance, rather than the increased transmembrane resistance, is more important functionally; halving capacitance increases conduction speed by 50%, whilst increasing transmembrane resistance by the same amount results in a speed increase of only 2%.

The effect of reduced attenuation with distance is that more current is available for nodal charging. Nodes only have a small surface area to charge, which has the effect of reducing τ. As the nodes are the site of most of the current flow, despite their small area, this also greatly increases conduction velocity.

The overall effect is that current propagates quickly from node to node in a seemingly discrete series of jumps—saltatory conduction [16,17]. Overall, myelinated axons can thus conduct action potentials at roughly 10 times the velocity of an unmyelinated axon of equivalent diameter. The exact determinants of conduction velocity in myelinated axons will be covered in Section 3.

These are the broad functional principles of speed enhancement. Hartline notes that the only two structural features these principles *require* are at least one membrane layer to increase capacitance and a mechanism to regenerate current [13]. As we will see, different organisms have improved upon this basic design in several different ways, but the fundamentals remain similar. The rest of this section will be dedicated to discussing how such minimal speed-enhancing sheaths initially evolved. Myelin does not fossilize, so instead we must use other sources of evidence. I will consider these in turn, before attempting to synthesize a model of initial myelin evolution.

2.3. Phylogeny of myelin

A striking observation about myelin is how widely distributed it is in the animal kingdom (Figure 3). Myelin is present in all vertebrates except the agnathostomes [18], and also in two invertebrate phyla—the annelids and the arthropods—now thought to constitute separate clades [19]; see Table 1.

2.3.1. Vertebrates

Myelin is found almost universally in chordates. The only exceptions are the jawless fish [18], primitive species which lack several features of advanced chordates including a neural crest and advanced features of adaptive immunity. All other chordates have myelin which follows the same basic structural plan (Figure 4).

There are two striking features of vertebrate myelin. Firstly, it is present in all but the smallest axons, unlike in invertebrates where it tends to be associated with specific large axons. Secondly, it differs between the peripheral and central nervous systems (PNS and CNS), produced by Schwann cells and oligodendrocytes, respectively. In the PNS, Schwann cells lie closely apposed to the axon,

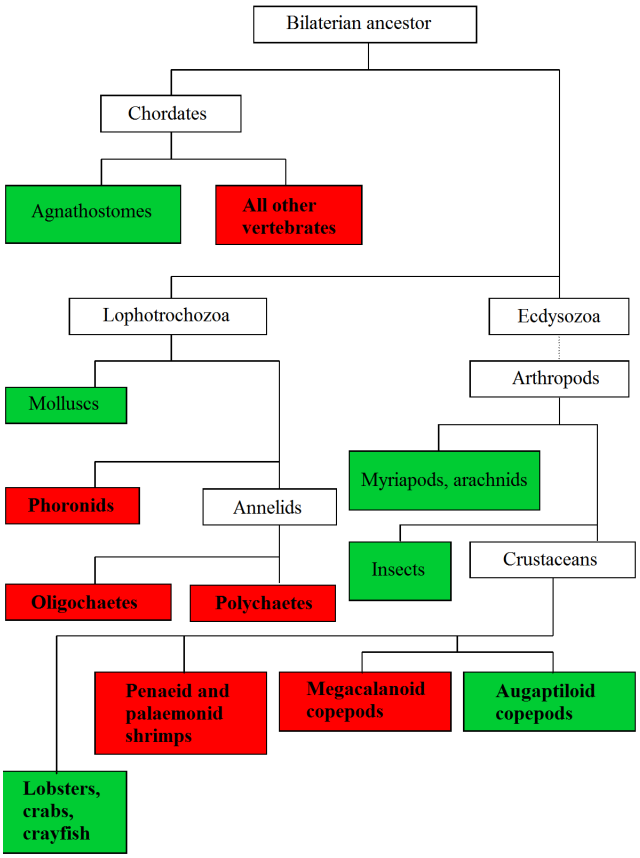

Figure 3: Phylogeny of myelin. An abbreviated phylogenetic tree showing the distribution of myelin in the animal kingdom. Discounting the loss of myelin in an entire phyla, this shows that myelin has likely arisen at least three times independently (possibly four, as it might have arisen twice within crustacea). Red indicates myelin and green indicates no myelin; it should be noted that this diagram simplifies somewhat, and that a red box only indicates that myelin has arisen in some member of that group; not all oligochaetes, for example, are myelinated.

and myelinate one internode each, whilst in the CNS oligodendrocytes send out cytoplasmic processes to up to 50 axons. There are also morphological differences; in the PNS the myelin sheath is thicker relative to axon diameter, with a greater periodicity of spiral wrapping, a layer of Schwann cell cytoplasm external to the node and a basal lamina surrounding the axon [8]. The major difference however is in protein composition (Section 2.5), although there are also differences in lipid profile (see Table 2).

2.3.2. Annelids

In the annelids, myelin is found in both polychaete and oligochaete groups, of which the latter is better studied (Figure 5). Nicol described well developed sheaths in three polychaete groups [10], but the latest evidence is that

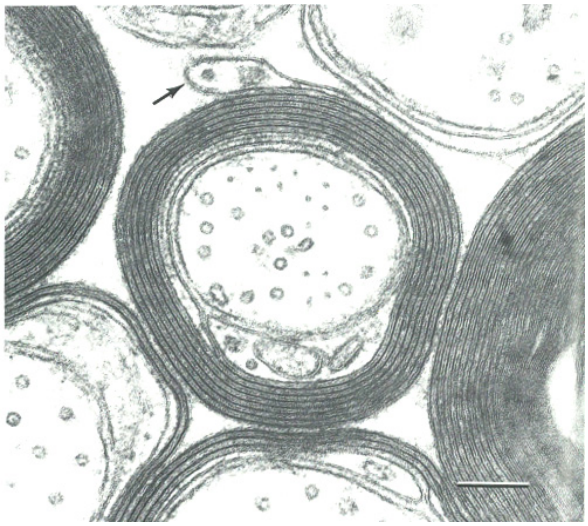

Figure 4: Vertebrate myelin. This figure is an electron micrograph of CNS myelin taken in the spinal cord of an adult dog, illustrating the key features of vertebrate myelin. The myelin sheath is comprised of a spiral wrapping of multiple layers of compacted glial cell membrane. The sheath is periodically interrupted by nodes of Ranvier, which are circumferential areas of exposed membrane at regular intervals. The nodes are sealed with septate junctions. Electron micrograph taken from [8].

these are not true myelin [20]. However, there is electron microscopy evidence in *Vestimentifera* [21]. There is also evidence for primitive myelin sheaths in a related phyla, the phoronids. Intriguingly, phoronid species appear to not have nodes; rather, there is a thin strip of bare axon which presumably allows current regeneration (although not saltatory conduction) [22].

2.3.3. Arthropods

All myelinated arthropods are crustaceans. Within the Crustacea, myelin is arranged concentrically and has been confirmed in several malacostracan and copepod species. Precisely which (if any) other crustacea are myelinated is debated. Roots suggests that crayfish and crabs also have myelin [14], whilst Hartline and Colman include only prawns, shrimps, and copepods [38]. There is evidence that monoclonal antibodies to annelid myelin protein bind to crayfish CNS glia but no direct imaging evidence [39]. Other authors find no evidence for myelination in crayfish, instead arguing that they have *lost* myelin over the course of evolution—an intriguing possibility discussed further below [40]. The sole electron microscopy study suggests that there is myelin in the crab brain [41]. However, it appears very similar to vertebrate myelin, rather than the typical morphology of other crustacea. It is not impossible that crabs evolved radically different myelin morphology,

Table 1: Myelin across species. This table summarizes the evidence for myelination, the specific axons myelinated within an organism and the conduction speeds achieved in the five main groups of myelinated organism; it is informative to compare these conduction velocities with that of the unmyelinated squid giant axon, which with a diameter of 500 μm conducts at around 20 ms^{-1}.

	Vertebrate			Arthropods		
	CNS	**PNS**	**Annelids**	**Penaeid shrimp**	**Megacalanoid copepods**	**Other malacostraca**
Myelination confirmed by:	Electron microscopy [8]	Electron microscopy [8]	Electron microscopy in oligochaetes *E. foetida*, *L. terrestris*, and *B. sowerbyi* and Vestimentifera species; light microscopy suggests myelin sheaths present in other species [14,23]	Electron microscopy [24]	Electron microscopy [25]	Electron microscopy in the palaemonid shrimp; light microscopy for other shrimp species [26,27,28]
Axons myelinated:	The vast majority of CNS axons are myelinated, with the smallest diameter myelinated fibers being 0.2 μm [29]	Most long axons except small "C fibers" of diameter < 1 μm [30]	Three dorsal giant axons, 90 μm diameter	Paired medial giant fibers	Relatively widespread; present in sensorimotor axons of antennae and interneuron circuits	Dosal giant axons and the larger axons of the ventral nerve cord
Conduction speed in myelinated axons:	Up to 50 ms^{-1} in the largest CNS axons [31]	Largest diameter axons (30 μm) conduct at 80–120 ms^{-1}; smallest diameter (1–2 μm) at 10–20 ms^{-1} [32]	30 ms^{-1} [33]	200 ms^{-1} [34]	Not measured	25 ms^{-1} for a 35 μm fiber [35]

Table 2: Composition of isolated human myelin. This table shows the composition of isolated and purified human myelin from both CNS and PNS. CNS figures are based on samples taken from white matter from the centrum semiovale [36], whilst PNS samples are taken from isolated femoral nerve [37].

	CNS		**PNS**	
	(% weight)	(mol/100 mol lipid phosphorus)	(% weight)	(mol/100 mol lipid phosphorus)
Total protein	30.0*	—	28.7*	—
Total lipid	70.0*	—	71.3*	—
Cholesterol	27.7†	129	23.0†	84
Galactolipid	27.5†	59	22.1†	37
– Cerebroside	22.2†	49	—	—
– Sulfatide	3.8†	8	—	—
Phospholipids	43.1†	100	54.9†	100
– Ethanolamine phosphatides	15.6†	38	—	35
– Choline phosphatides	11.2†	25	—	15
– Serine phosphatides	4.8†	11	—	17
– Inositol phosphatides	0.6†	1	—	
– Sphingomyelin	7.9†	18	—	34
Plasmalogens	12.3†	30	—	29

*% weight figures for total protein and total lipid are expressed as a proportion of dry weight.
†% weight figures for all other lipids are expressed as a proportion of total lipid weight.

but it seems unlikely—it is equally possible that these structures are denser versions of the nonmyelinated axon ensheathments found in related species such as lobsters [42]. Ultimately, electrophysiological recordings will be needed to settle the question; a complementary approach would be to use techniques such as microbeam synchrotron X-ray scatter, which have sufficient resolution to examine in detail the morphology and structure of individual myelinated nerve fibers [43].

The first crustacean myelin to be discovered was in palaemonid and other shrimps. Compared to vertebrate and annelid, two features stand out: the concentric organization, and the submyelinic glial cell bodies (Figure 6). This basic plan has been adapted fantastically successfully by

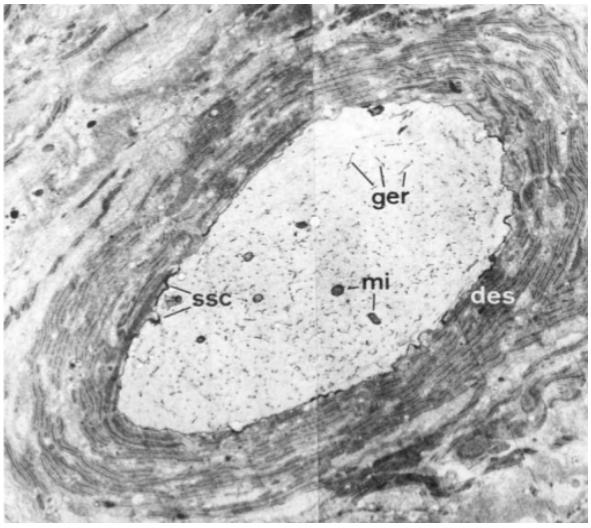

Figure 5: Oligochaete myelin. This figure shows a section through the median giant fiber of the earthworm *Lumbricus terrestris*. Oligochaete myelin is spirally arranged, with varying numbers of lamellae (from 12 to 200 depending on the species) originating from glial cell processes. There are also varying degrees of cytoplasmic extrusion. Rather than circumferential nodes, there are functionally equivalent dorsal "pores", or fenestration nodes, of 10–15 μm in diameter which are sealed by desmosome-like structures, presumably to prevent current shunting. Electron micrograph taken from [33].

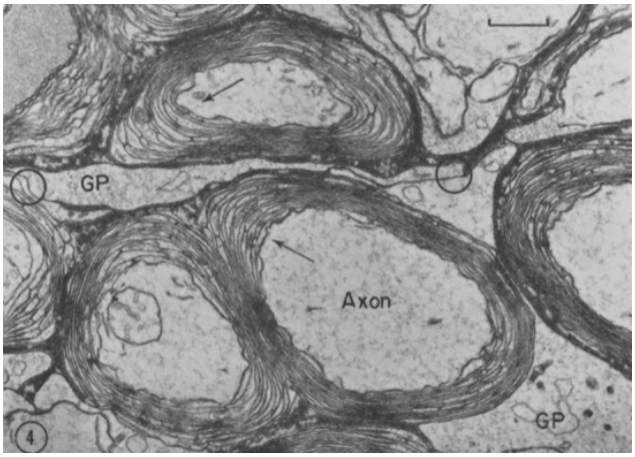

Figure 6: Palaemonid myelin. This figure shows a section through a fiber from the ventral nerve cord of the prawn, *Palaemonetes vulgaris*. Ten to fifty concentric lamellae are arranged to meet in radial "seams", which regularly alternate sides in order to minimize current shunting. Myelinating glia lie closely apposed to the axon submyelinically. Myelin is only compacted in the outer layer. The nodes are similar in structure to vertebrate nodes with similar seals. Electron micrograph taken from [26].

the penaeid shrimp to produce the fastest conduction yet recorded in the animal kingdom [34]. Several structural adaptations to the basic malacostracan model of myelin help achieve this remarkable feat (Figure 7), which is well studied electrophysiologically [24,44,45].

The latest arthropod group with identifiable myelin is the megacalanoid copepods (Figure 8). Copepods are small planktonic organisms with a rapid and sensitive escape response.In a comparative study, it was found that two species, *U. vulgaris* and *N. gracilis*, had response times 2–5 times faster than the other species [46]. Electron microscopy revealed that myelination was present in the three evolutionarily youngest calanoid superfamilies.

Intriguingly copepod myelin seems to be neurally, rather than glially derived, developing by sequential laying down of membrane layers on the inside of the axon membrane [47, 48]. This explains the continuous structure; one possible application of this discovery is discussed in Section 3.

Overall, there is thus good evidence that myelin has arisen independently at least *four* times—in vertebrates, annelids, malacostracan crustaceans, and megacalanoid copepods. The total may well be greater than this—many invertebrate species await both functional (electrophysiological recordings) and structural (electron microscopy and X-ray scattering from single fibers) investigation, both of which are likely to be fruitful areas for future myelin research [49].

2.4. Ecological evidence

One way of understanding the selective pressures driving myelin evolution is to compare the ecology of myelinated and nonmyelinated species. In the case of invertebrates, myelin is almost exclusively found in the context of rapid escape or withdrawal reactions; for example, the rapid anterior withdrawal reflex of earthworms and the escape reflexes of crustacea [50]. However, there are many invertebrates with very fast escape reflexes mediated solely by giant unmyelinated axons. What then drives myelination in some species but not others? One informative example is the copepods, in which myelin has arisen in only the three youngest superfamilies. This allows a relatively direct comparison of two groups of organisms similar in body plan and life history, differing only in myelination status. Older, nonmyelinated superfamilies are restricted in habitat, staying in deeper waters with reduced predation risk during the day and only arising to feed in open water at night [51]. In contrast, myelinated families inhabit open water freely, suggesting that their faster withdrawal reflex makes them less susceptible to predation. Indeed, inhabiting open environments is common amongst myelinated invertebrates—all known myelinated crustacea inhabit pelagic (in marine ecology, "pelagic"

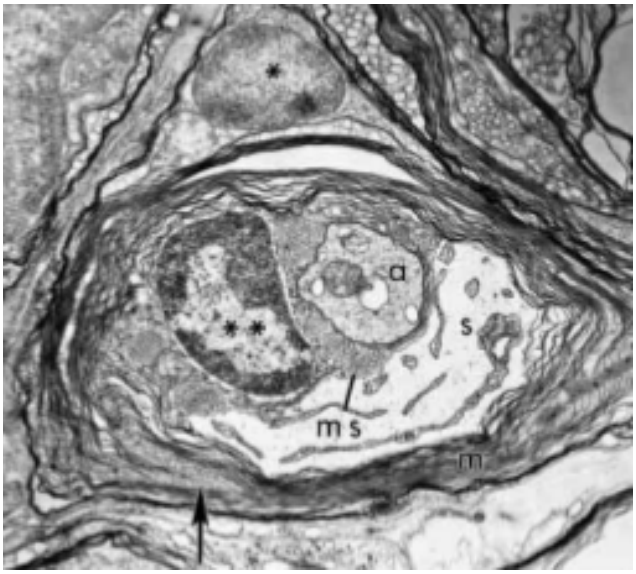

Figure 7: Penaeid myelin. This figure shows a section through a fiber from the ventral nerve cord of the prawn, *Penaeus chinensis*. The broad plan is similar to palaemonids with concentric lamellae and seams (albeit less regularly arranged) but the axon, rather than being tightly enclosed by myelin, is surrounded by a "submyelinic space" with electrolyte composition similar to seawater. This thus provides a very low resistance pathway (the longitudinal resistance is as low as 23 Ω, compared to normal axoplasm resistance of 40 Ω to 60 Ω) for the transmission of current, as well as effectively increasing axon diameter. Penaeids also have two types of specialized node. The first type is fenestrated; they consist of isolated patches of exposed axon, rather than the circumferential nodes of vertebrates and palaemonids. There is also evidence that gaps in the myelin sheath at axon branches and synapses function as nodes. At both these locations, sodium channels are concentrated at very high densities—estimated at between 1,400 to 5,000 channels per μm^2 for synaptic nodes, compared with 100 channels per μm^2 in squid axon [44]—and are highly excitable, providing a substrate for fast saltatory conduction. Electron micrograph taken from [24].

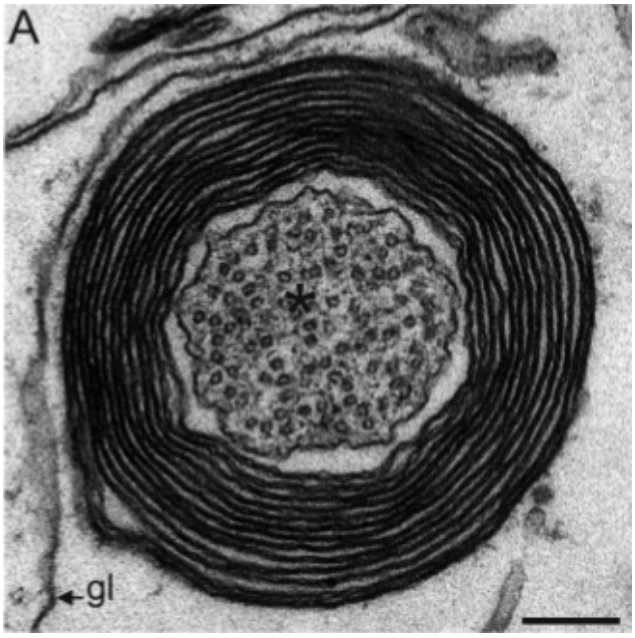

Figure 8: Copepod myelin. This figure shows a section through a nerve fiber of the ventral nerve cord of the copepod *Bestiolina similis*. Myelinated copepods have concentrically arranged myelin consisting of around 60 lamellae, which uniquely are continuous—there are no seams as in other crustacea. Similarly to palaemonids, the myelin is compacted only at the outer layers, with semicompact layers more centrally. Nodes are of the fenestrated type. Electron micrograph taken from [47].

refers to open water zones and "benthic" refers to the seabed) environments, and myelinated annelids generally use withdrawal reflexes to retreat from open ground or seabed. Thus, it is possible that myelination is driven by the additional risk of predation in open environments. This might explain why crayfish, lobsters, and crabs seem to have lost myelin—these organisms have returned to benthic life, where there is a lower predation risk [40, 52]. The sole example of unmyelinated vertebrates—the agnathostomes—also inhabit restricted ecological niches with reduced predation risk. This is just one hypothesis to explain the distribution of myelin in invertebrates—there is a need for further ecological studies in annelids, and it would be particularly interesting to know exactly what pressures lead to such exquisitely fast conduction in the penaeid shrimp. A further question is whether there are any features of the ecology or the life history of insects or molluscs which have lead them to eschew myelination as a strategy.

2.5. Molecular evidence

The molecular structure of vertebrate myelin is well studied, and there is a wealth of information which allows us to make cross-species comparisons of protein composition and structure. The protein composition of invertebrate myelin is obscure. Some components have been identified on electrophoresis which appear to be unrelated to any of the vertebrate proteins [39,54], but almost nothing is known of their function. This is clearly an area where further research would be beneficial; we can speculate that a better understanding of the genetics of invertebrate myelination might shed light on why molluscs and insects have not developed myelin.

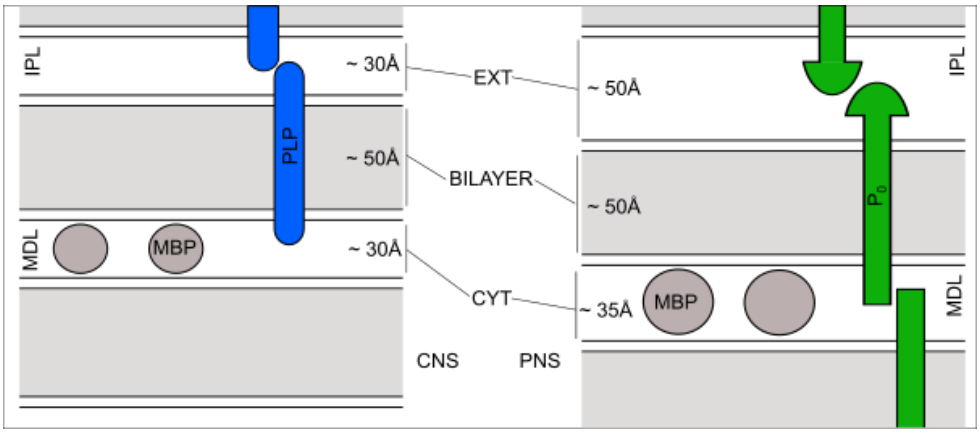

Figure 9: Molecular composition of myelin in the terrestrial vertebrate CNS and PNS. This figure shows a rough schematic of the molecular composition and microstructure of myelin. MBP is responsible for the close apposition of the intracellular membrane surfaces, possibly via interaction with negatively charged lipids localized to the cytoplasmic side of the membrane. This schematic shows an MBP monomer mediating apposition, but there is also plausible evidence that two MBPs may perform this function. Both P_0 and PLP are large ($\sim$ 30 kDa) transmembrane proteins, but they appear unrelated in sequence and structure. P_0 has an immunoglobulin-type extracellular domain which interacts homotypically with the apposing P_0 domain, and the intracellular P_0 domains also probably interact; cells forced to express P_0 thus form a regular myelin-like morphology. Less is known about the functions of the PLPs; there is no crystal structure available, but it is likely that they have an analogous role to P_0. It should also be noted that the bilayer dimensions are the same in PNS and CNS, and that the smaller CNS myelin period is due to cytoplasmic and extracellular changes. See [53] for a detailed discussion; dimensions taken from Figure 6 therein. Note that the two ultrastructural features, the major dense line (MDL) and the intraperiod line (IPL) roughly correlate to the CYT and EXT portions of this schematic. CYT, compacted cytoplasm layer; EXT, apposed extracellular surface.

As mentioned above, vertebrate myelin is formed of layers of compacted (it should be noted that the term "compacted" does not imply the complete absence of cytoplasm, which is an artifact of electron microscopy preparation. X-ray scattering demonstrates that the intermembrane gap is hydrated and accessible to salts and small peptides [55]) glial cell membrane, comprised of specialized lipid and protein components which differ significantly from that of normal cell membranes. In particular, myelin is relatively enriched in lipids (particularly cholesterol and glycosphingolipids) when compared to most membranes. Table 2 (data taken from [36,37,56]) compares the composition of isolated human myelin in both the PNS and CNS based on traditional biochemical analysis; more recently, large scale lipidomic and proteomic analyses have further clarified the nature of myelin components [57].

Whilst the lipid components of myelin differ only slightly (as shown in Table 2, in humans PNS myelin has a relatively greater proportion of phospholipids and a correspondingly lower proportion of cholesterol and galactolipids, with overall a slightly higher ratio of lipid to protein. Across vertebrate species, reported figures also give some differences in lipid composition, but the degree to which this reflects experimental procedures is unclear (see [56]). For a discussion of the functions of various myelin lipids, see [58]), the protein components differ greatly both across species and between the PNS and CNS. Myelin basic protein (MBP) is common to all forms of vertebrate myelin but other major proteins differ significantly. In the CNS of terrestrial vertebrates, the major proteins are the proteolipid proteins (PLPs), whilst in the PNS and CNS of fish P_0 is the main protein; despite their different structures, the two seem to have analogous roles in extracellular apposition (Figure 9) [53,59,60,61,62].

Myelin proteins probably also have nonstructural roles; both P_0 and M6A, a PLP, are hypothesized to have roles in cation homeostasis [63,64], and splice variants of the PLP gene may have roles in oligodendrocyte intracellular trafficking and signaling [65].

This section focuses largely on these three structural proteins, which based on electrophoretic analysis were estimated to comprise around 70% of myelin protein [66]. However, analyses using more modern techniques suggest that this figure might be much lower. Studies utilizing liquid chromatography and mass spectrometry have found that PLP and MBP together comprise only 25% of CNS myelin protein, with 65% comprised of novel myelin associated proteins, and that in the PNS P_0 and MBP together account for only 29% of the total myelin protein, with 50% comprised of novel proteins. Overall, the proteomic

evidence suggests over 1,200 proteins are present in CNS myelin and at least 550 in PNS myelin [67,68,69]. Possible functions of these proteins is an active area of research. However, from an evolutionary and functional perspective we have far more data on the three "canonical" proteins, so I will focus on them.

2.5.1. MBP

The only major myelin protein which arose de novo is MBP, which is not found in agnathans [70]. It seems to be an evolutionary descendant of the *golli* gene, expressed in oligodendrocyte precursors—possible evidence that MBP first arose in cells of the oligodendrocyte lineage. MBP is ubiquitous amongst myelinated vertebrates, with many aspects of structure and expression conserved [71]. Furthermore, the naturally occurring MBP null mutant (the "*shiverer*" phenotype) has severe CNS hypomyelination with absence of the Major Dense Line (MDL) [72] (see Figure 9). However, MBP mutant mice have relatively normal PNS myelination, and there is evidence that this is due to P_0 also contributing to compaction [73]. Another protein which may share this function is peripheral myelin protein 2 (PMP2), a fatty acid binding protein expressed widely (albeit variably) in peripheral myelin and in small amounts centrally. Although structurally unrelated to MBP, they both localize to the (MDL), raising the possibility of shared function; this is supported to a degree by the lipid binding properties of PMP2 [74]. However, knockout experiments have also raised the possibility of a role in lipid homeostasis [75], and the main function of PMP2 remains unclear. From an evolutionary perspective, PMP2 first arose in tetrapods and thus after the origin of vertebrate myelin [76].

2.5.2. P_0

P_0 is the major myelin protein in both the CNS and PNS of aquatic vertebrates. It is a member of the evolutionarily ancient Ig superfamily, and probably arose with the chordates, possibly slightly prior to MBP [76]. P_0 was thus probably the original myelin protein responsible for membrane apposition, a conclusion supported by the fact that experimentally it can (to a degree) replace PLP in the CNS [77]. As mentioned above, P_0 likely also contributes to cytoplasmic compaction and formation of the MDL, further evidence that it could have functioned as one of the earliest myelin proteins. As well as structural functions, P_0 likely regulates the localization and expression of other myelin glycoproteins [78].

2.5.3. PLP

Although P_0 was first used in myelin, PLPs are actually the evolutionarily older proteins, with homologs found across the bilatera; splice variants such as the M6A protein

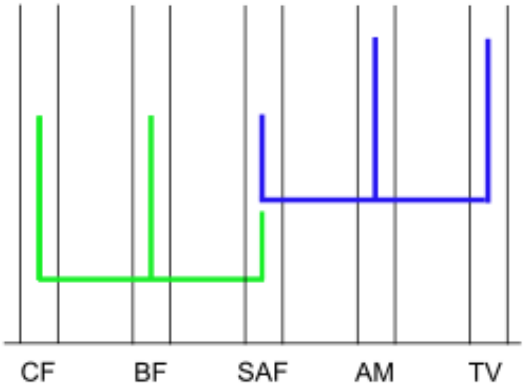

Figure 10: Myelin proteins in vertebrate CNS. This figure summarizes the changes which have occurred in the protein composition of CNS myelin, the major change being the replacement of P_0 with PLP. Key: green, P_0; blue, PLP. CF, cartilaginous fish; BF, bony fish; SAF, semiaquatic fish (e.g., lungfish); AM, amphibia; TV, terrestrial vertebrates.

(related to the DM20 variant) are expressed in fish [79], but not incorporated into myelin [64]. In semiaquatic species both P_0 and proteins closely related to PLP are expressed [80]. In fully terrestrial vertebrates PLP is the major protein in the CNS (Figure 10); it is likely that the event facilitating this switch was the acquisition by the DM20 gene of a novel splice site encoding a second intracellular loop, facilitating localization of PLP to the myelin membrane [64]. Since this switch, PLPs have become more highly conserved [81]. Exactly why this switch was made is debated; one hypothesis is that as PLP myelin is more compact (see Figure 9), P_0 was selected against as it took up more space [68]. However, it has also been hypothesized that as PLP acquired new functions, P_0 was in fact replaced by silent dropout rather than being actively selected against [64]. The possibility of nonstructural functions of PLP is somewhat supported by evidence from genetic knockout models. Naturally occurring PLP mutants (e.g., the "*jimpy*" phenotype) have varying degrees of impairment, with widespread central hypomyelination and oligodendrocyte death [82]. However, structural changes in engineered PLP knockouts are less dramatic than one might expect—in a PLP/DM20 null mouse model, oligodendrocytes were still able to produce large quantities of compact myelin with an IPL, albeit of greatly reduced physical stability [83]. More detailed X-ray diffraction studies of unfixed fibers from PLP null mice reveal swelling of around 40 at the extracellular appositions [84]; when measured, such myelin results in lower conduction velocity and greater action potential thresholds [85]. However, the structural myelin changes in PLP mutants are accompanied by several other changes—defects in axonal transport, a length-dependent axonal

degeneration, and defects of axonal mitochondria have all been observed in PLP mutants [86,87,88]. Ultimately, the question of what drove the P_0 to PLP switch will require greater information on PLP structure and function than we have at present, likely including a crystal structure and greater knowledge of the specific mechanisms of the nonstructural changes mentioned above.

2.6. Developmental evidence

Development and evolution are intricately connected, and so studying the developmental origins of myelinating cells is a key to understanding myelin evolution. Myelination happens in a conserved temporal order reflecting phylogeny—the PNS myelinates before the CNS, and within the CNS older structures such as the spinal cord myelinate before newer ones such as cortex—but differs in rate between species (Section 5). For the whole process to occur, myelinating glia must migrate to the appropriate regions of the nervous system, distinguish between axons which require myelinating and those which do not, and finally construct the myelin sheath itself in the appropriate dimensions and distribution. Furthermore, myelination is a dynamic process occurring throughout life, and dependent upon complex two-way interactions between glia and axons (Section 4). An exhaustive description of these processes is far beyond the scope of this review; there are several comprehensive reviews [12,89,90,91,92]. Here, I will focus on the likely evolutionary origins of myelinating glia.

It is striking that two differently derived cells—oligodendrocytes and Schwann cells—both produce myelin which is overall remarkably similar. Schwann cells are a derivative of the neural crest, a structure of great importance in vertebrate evolution [93]. Schwann cell precursors migrate to and associate with developing peripheral nerves, dependent upon NRG1 signaling. They then develop into immature Schwann cells, which are independent in their survival, and begin selecting axons for myelination, in a process called radial sorting; once a 1:1 axon segment to cell ratio is established, they are referred to as promyelinating Schwann cells. Axonal signaling via the NRG1/ErbB pathway provides the final stimulus for myelination by the Schwann cell [94]. This proceeds via a "spiral wrapping" mechanism, whereby the Schwann cell sends out a process which contacts the axon. Progress of this "inner lip" around the axon creates a loose spiral of extending mesaxon. The extracellular surfaces of this spiral form a regular, closely packed spacing, followed by cytoplasmic narrowing to form compact myelin [95,96]. Schwann cell development is controlled by a genetic network, which although not fully understood has Sox-10, Oct-6, and Krox-20 as key elements [97].

In contrast, oligodendrocytes are derived from the neuroepithelium; in the spinal cord, specifically the pMN (progenitor of motor neurons) domain. After motor neuron differentiation, pMN cells undergo a lineage switch to produce oligodendrocyte precursor cells (OPCs), under the control of the Olig-2 gene [98]. Although more difficult to study developmentally, there is evidence for a similar neuron to OPC switch in forebrain tissue, but overall oligodendrocyte development seems to be more heterogenous than Schwann cell development; for example, Olig-1 is required for brain but not spinal cord myelination in mice [99], and there is evidence for three separate "waves" of OPCs. From these diverse origins, OPCs undergo a complex migration route to the appropriate locations of the developing white matter, during which they depend upon various signals including PDGFs, FGFs, and NRG1 and contact-mediated signaling via ECM components [100]. Once in position, terminal differentiation is rapid in mice, but can be delayed for several months in humans [101]. Promoters of terminal differentiation include thyroid hormones and IGF-1, resulting in the expression of Sox-10 under the control of Olig-2. The final stage leading to myelination is myrf (myelin regulating factor) and Olig-1 expression, which leads to expression of myelin proteins. In contrast to peripheral myelination, there are several models of how oligodendrocytes physically wrap axons [89].

Despite their differences both regulatory networks probably evolved through a process of neofunctionalization where ancestral proteins were duplicated, leaving duplicates free to find new roles. Sox-10, Oct-6, Olig-2, and Myrf all have ancestral homologs with developmental functions in *Drosophila* which are conserved in mammals. There is also evidence of whole genome duplication in early vertebrate evolution, which could provide the substrate for such neofunctionalization [81]. This still leaves the question of how two separate cell lineages gained control of the function of myelination. Given the ontogeny, it is unlikely that one gave rise to the other; instead, it seems more plausible that both lineages arose at the same time, and then once the myelination program was developed in one, the other gained control via expression of one of the upstream promoters. As the only common gene Sox-10 would be an obvious candidate, but the exact process remains obscure.

2.7. A hypothesis of myelin evolution

Having covered the different strands of evidence, we are now in a position to construct a hypothesis of how myelin arose in vertebrates. There is not enough evidence to do the same for invertebrates, but what there is will inform our discussion.

I believe that there are two main questions that any such hypothesis must answer. Given the relatively simple functional requirements for a basic speed enhancing sheath, and the small changes which need to be made to loose glial coverings to achieve them, it is easy to see how specific neurons may acquire myelin, evidenced by the

diversity of invertebrate myelin forms. What is less clear is how vertebrates acquired almost universal myelination across afferent sensory, central, and efferent motor axons. This process would need to be almost simultaneous, as if only the PNS were myelinated then an abrupt slowing of transmission would occur at the CNS and vice versa [102]. The second (related) question is how two completely different cell types both acquired the capability to myelinate simultaneously. The hypothesis suggested here aims to answer both these questions.

There is good evidence that the Placoderms—armoured fish, active in the Devonian era—were myelinated, based on inferences from fossilized skulls. The skulls of their immediate ancestors, the Osteostraci, do not show evidence of myelination [102]. Unlike Osteostraci, Placoderms were active predators with hinged jaws. Thus, Zalc has suggested that peripheral myelin arose as an aid to predation as part of the development of neural crest structures (including the jaw), from which Schwann cells are derived [103]. Two points make this unlikely. Firstly, the "slowing down" problem; secondly, it is more likely that myelin arose as an aid to escape predation, rather than facilitate it. That is the situation in modern invertebrates, and conceptually it is easier to see how this could occur. An escape reflex is simple; predation is a more complex task and would require much more widespread and finely calibrated myelination.

The alternate hypothesis is that myelin first arose in "central" neurons, as a means to facilitate escape reflexes. There was probably a high risk to Osteostraci from predatory arthropods [104]. Fish escape using axial muscles, which are innervated by motorneurons which progress only for short distances outside the spinal cord (notably, modern jawless fish without myelin do not exhibit fast escape reflexes). Given the developmental relationship between motorneurons and spinal cord oligodendrocytes, and the restricted spatial areas from which oligodendrocytes arise [105], it is plausible that myelin first evolved in certain restricted central locations to facilitate escape reflexes in fish, and was later adopted peripherally.

My hypothesis is that primitive myelin arose first with some form of wrapping of axial motorneurons by oligodendrocytes (possibly under control of ancestral Olig genes) to facilitate escape responses. There is evidence that mechanisms for sodium channel clustering, required for saltatory conduction, were present before myelin developed [106], so it would only have taken simple modifications to glial sheaths to reduce current loss and increase conduction velocity. Once such primitive myelin had arisen in Osteostraci (notably, this would not leave cranial fossil traces, and so is compatible with the evidence of [102]) the subsequent development of the neural crest and vertebrate predatory behavior would have provided a strong pressure for peripheral myelination to develop, which could have occurred by Schwann cell ancestors gaining control of the myelination program. Once this key event had occurred, myelination would have developed and spread very quickly—both predators and prey would provide reciprocal pressures on one another to increase conduction velocity, a process reminiscent of a "Red Queen" effect (a "Red Queen" effect describes a situation in which increases in evolutionary "equipment" (e.g., myelin increasing conduction velocity) result in no overall improvement in survival—in this case, once prey animals became faster, predators would be under pressure too to develop faster conduction, and so on and so forth; ultimately, as both populations developed rapid conduction in tandem, "success" rates would end up similar [107]). The fact that most of the proteins in myelin—both glial and structural—were co-opted by neofunctionalization rather than arising de novo supports such a hypothesis.

Thus, this hypothesis proposes that early myelinated fish would have both spatially restricted myelin within the CNS, and peripheral myelination. Such a system would allow both predation and rapid escape reflexes. The development of mechanisms to further increase conduction velocity, such as compaction and paranodal sealing (for which there is a convincing computational model [108]) could have either developed simultaneously within the PNS and CNS, or largely in one location before being adopted by the other; in likelihood, the process was a mixture of the two. The final step in this proposed hypothesis was that as the brain and central nervous systems developed, distinct populations of oligodendrocytes gained control of the myelination programme, leading to widespread rather than restricted CNS myelination. The lateness of this expansion in the regions of myelination would explain why, in modern vertebrates, the PNS myelinates before the CNS—the specific regions of the CNS where myelin could have originally arose are an insignificant part of modern ontogeny or have regressed entirely.

There are several parts to this hypothesis which require further detailed evidence to support it. In particular, in the absence of detailed fossil evidence to corroborate or disprove the contention that Osteostraci had myelinated spinal motorneurons as a substrate of escape reflexes, further knowledge of the evolutionary origins of different oligodendrocyte lineages would be invaluable. Discovery of vestigial remnants of such neurons in modern fish species would also be supportive. Further information about Schwann cell origins could also help to substantiate whether they did capture a primitive genetic myelination programme from ancestral oligodendrocytes. In the absence of such evidence, however, I have presented a hypothesis which is consistent with the fossil, ecological, and molecular evidence, and endeavors to provide an explanation of how myelin could arise within both CNS and PNS.

3. Trade-offs and optimization in myelin evolution

In the first section of this essay, I presented a hypothesis of how myelin initially evolved in vertebrates. This focused on speed enhancement, but myelin also has several other functions. In any biological entity with multiple functions there will inevitably be trade-offs between them; not all functions can be performed optimally. In myelin's case, speed enhancement trades off against the need to reduce space and conserve energy. Thus, from the observed parameters of myelin, we can deduce what pressures have been involved in producing it.

This relies on some theoretical assumptions. Firstly, this is an explicitly adaptationist approach. That is, it is assumed that myelination is a trait serving specific functions with parameters shaped by natural selection to maximize these functions—it is adaptive. In an extremely influential paper, Gould and Lewontin strongly criticized adaptationism, noting that there are many constraints on the power of natural selection and many examples of nonadaptive evolution [109]. Genetic drift, allometry, and developmental and environmental constraints are all cited as examples, famously illustrated by the "spandrels of San Marco" (Figure 11).

Gould and Lewontin argued that many features of organisms are analogous to such spandrels, and that it is misleading to try and find adaptive origins for them. This is certainly a danger that we must be aware of, in particular when discussing the evolution of the brain. For example, the tortuous courses of the cranial nerves or the back-to-front arrangement of retinal cell layers are obvious demonstrations of developmental constraints on brain design. Given the vast complexity of brains and the lengthy history of brain evolution, it is likely that there are myriad other such constraints which we are not yet aware of.

However, there are several reasons why it is legitimate to consider myelin an adaptation. Firstly, it has evolved convergently across taxa. Secondly, there is evidence of a steep adaptive gradient and increase in fitness over time—myelinated vertebrates have conclusively out competed the agnathans, for example. Thus, it is legitimate to at least attempt an analysis of myelin in terms of trade-offs. First, however, it is necessary to briefly cover the broad constraints on nervous system design.

3.1. Constraints on nervous system design

The two fundamental currencies of nervous systems are information and energy. At one level this is obvious. Sensory transduction converts energy into information; this information is processed and ultimately converted back to energy as motor output. However, nervous systems also use energy transmitting and processing information, and the faster and more complex computations need to be, the more energy is required. Thus in humans, the brain

Figure 11: The Spandrels of San Marco. Spandrels are the spaces formed by the intersection of two arches upon which a dome is mounted. In San Marco, they are intricately and ingeniously decorated. However, it would be a mistake to argue that the architect designed the spandrels to provide a space for such decoration, despite the fact that that is now one of their functions; they are an inherent byproduct of the construction of the cathedral, and their decorative use is secondary. (It does not detract from Gould's argument that spandrels are in fact two dimensional; the proper term for the San Marco features is pendentives.)

accounts for only 2% of bodyweight but uses 20% of resting metabolism; in mormyrid fish, the figure is 60%. "Bottom up" energy budgets [110,111] have shown that in grey matter the majority of this energy is used in active processes, largely synaptic transmission but also action potential firing. When these budgets are compared with experimentally measured energy use, we see that energy availability severely constrains axonal firing rate [112].

Thus, there is a trade-off between information processing and energy use, both at the level of whole brains and within brains in individual circuits and networks. There are myriad examples of this pressure driving the development of energy efficient adaptations—from energy efficient action potentials and channel parameters to photoreceptors to whole representations in visual cortex [113,114].

A further constraint is space. This is less studied than energy constraints, and it is perhaps less fundamental, but nevertheless important—particularly in nervous systems enclosed within bony cavities. Cajal was the first to note that the forms of neurons seemed to be designed to minimize space, and there has since been interest in spatial efficiency

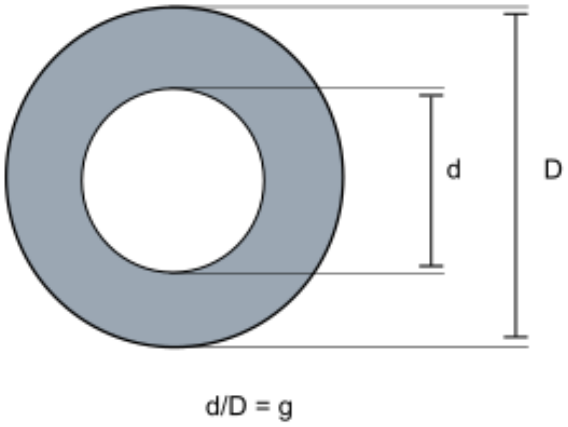

Figure 12: G-ratio. Schematic of a transverse section through a myelinated axon. The g-ratio, defined as the ratio of internal diameter d to external diameter D, should tend towards 0.6 if conduction velocity is to be maximized.

at the whole brain level—the separation into grey and white matter achieves this, as well as the separation of cortex into topographical maps [115, 116].

In the rest of this section, I will discuss how these fundamental constraints apply to myelin.

3.2. Maximizing conduction velocity

Rushton was the first author to address the question of what we would predict the parameters of myelination to be, given an assumed selective pressure—in this case, the need to maximize conduction velocity [117]. Arguing from first principles, he showed that if conduction velocity was to be maximized, the ratio of internal diameter d to external diameter D, the g-ratio, should be 0.6—any lower and the capacitance will not be reduced enough, any higher and the increased internal resistance will outweigh the benefits (Figure 12). This is indeed what is observed in peripheral nerves.

Rushton's paper was seminal in that it was the first to explicitly link a theoretical evolutionary need—to maximize conduction velocity—with the observed structural parameters of myelin. A later generation of biophysically sophisticated models confirmed that for optimum conduction velocity, g should equal 0.6. Furthermore, given this ratio, the main determinant of conduction velocity is axonal diameter, with relative insensitivity to nodal parameters [118]. Thus, to maximize conduction velocity, axons should be of as large a diameter as possible. This is not observed; axons in the CNS vary 100 fold in diameter, and in the CNS the g ratio is not always 0.6. Furthermore, in the CNS very small axons can be myelinated, when by Rushton's calculations conduction would be quicker if they were not. To understand why, we must consider energy use and space constraints.

3.3. Myelin, space, and energy

In myelinated axons, conduction velocity increases proportionally to the total fiber diameter. However, the volume taken up by the axon increases with the square of the diameter, so increasing velocity incurs disproportionate spatial costs. Whilst myelination greatly reduces the space required compared to axonal gigantism, it still represents a nontrivial resource commitment—particularly in the CNS where space is at a premium, and white matter may take up as much as 40% of total brain volume.

Most of the models referred to in Section 3.2 ignored space constraints by holding the external diameter of the axon constant. However, there is ample data to show (particularly in CNS axons) that myelin sheaths can have different parameters to those predicted by "velocity only" models—for example, in guinea pig optic nerve axons, g is often as high as 0.8 [119]. Chomiak and Hu attempted to account for this discrepancy using the idea of "system optimization", defined as "a process through which an optimal solution naturally emerges from a set of alternatives to maximize favorable... outcomes" [120]. They quantified this by modeling the "efficiency index" for various combinations of myelin and axon parameters. Crucially, they varied the relative contribution of wiring volume and conduction velocity to the efficiency index. This process gave g values similar to those observed in central neurons when they set space to be at a premium, and when space constraints were relaxed g values were similar to those in peripheral axons. These results provide quantitative support for the idea that myelination in the CNS may have evolved as much to save space as to maximize conduction velocity. It would be interesting to see whether these results still hold if the volume of the glial architecture necessary for myelination is accounted for.

It is well established that myelination reduces the energy cost of firing action potentials by reducing membrane capacitance and hence Na^+ flux required. Indeed, central white matter uses roughly 1/3 as much glucose as grey matter [121]. However, it does not necessarily follow that myelination saves energy overall—there are costs associated with the required lipids, proteins, and glial architecture—oligodendrocyte precursor cells, for example, have very high metabolic demands [122]. The major attempt to assess whether the energetic savings of myelination outweigh the costs used a similar "energy budget" calculation to those mentioned above, and concluded that over the lifetime of an organism myelin does not reduce the energy expended by white matter tracts, as the ongoing energy expenditure of maintaining oligodendrocyte resting potentials outweighs the saving on action potential firing for all but the largest axons [123]. This conclusion depends somewhat on the perspective—oligodendrocytes also have other functions, so it is not clear that the resting potential should necessarily be considered a cost of myelination specifically.

Regardless of whether myelination as a whole is energy saving, it is clear that maximizing conduction velocity trades off with energy use in a similar way to the trade-offs with space. Wider axons have a larger membrane area, and so action potentials require more Na^+ flux and hence energy. This trade-off has been demonstrated computationally [124].

3.4. "Optimizing" myelin: theory and experiment

We can thus see that a variety of trade-offs affect the parameters of myelination; increasing conduction velocity has disproportionate costs in terms of energy and space. Such trade-offs pose the question of what "solution", or combination of traits, will maximize adaptive fitness within an organism. We have already seen such an approach with regards to space and g-ratio. However, as we have also seen, a third parameter is the use of energy by myelinated axons. Is it possible to formulate the problem in *three* dimensions—to find out which balance of conduction velocity, space, and energy use would be "optimal" for any given combination of selective pressures?

The concept of an optimum in evolution is difficult. For a feature to be considered a candidate for analysis in these terms, it should show signs of convergent evolution, evidence of steep adaptive gradients, increasing fitness over time and have a relatively simple form-function relationship [125]. Myelin certainly meets the first of these criteria, but the last is more complex. Myelin is the interface between a set of dynamic axon-glia interactions which can complicate the form-function relationships we are interested in. However, copepod myelin is not glially derived, significantly simplifying such relationships. I suggest that it could thus serve as a model to investigate optimal myelination parameters. A full formulation of such a model is beyond the scope of this article, but I will outline here a possible plan for further investigation.

Such investigation would include work to discover the exact determinants of conduction velocity and energy consumption in copepod myelin. This would require multiple strands of evidence including detailed electrophysiological recordings and computer modeling of velocity, and a precise description of the energy costs and savings provided. Further structural evidence would also be vital, particularly as microbeam synchrotron X-ray scatter of unfixed fibers can provide detailed information about the morphology of individual myelinated fibers (as described above). Once this information was gathered, a possible tool to investigate the optimum parameters could be Pareto optimization [126] (Figure 13).

Such an analysis might be particularly productive because of the availability in copepods of well controlled ecological comparisons. This gives us the possibility of cleanly applying an optimal design analysis to a simple physiological function (increasing the velocity of escape reflexes), with a similar ecological control group. Depending upon where copepod myelin was located on the Pareto front, we could infer the pressures that lead to the development of myelin. This could then be related to the differing ecology of myelinated and nonmyelinated copepods.

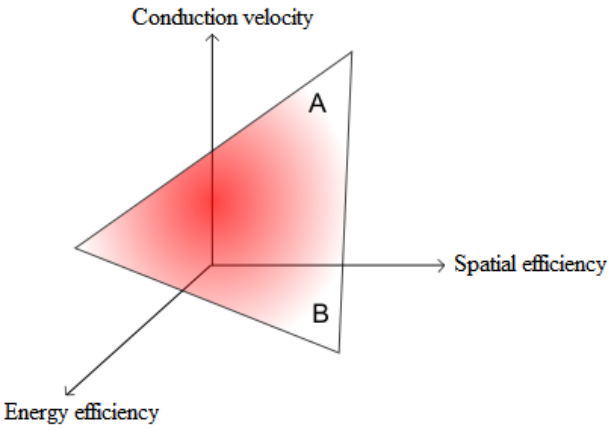

Figure 13: Hypothetical Pareto Front for myelin. Where one phenotype has to perform multiple tasks, there are inevitably trade-offs between them. The "Pareto Front" is the set of all phenotypes in which performance at all tasks cannot be improved. For three parameters (in our case velocity, energy, and space) we can generate a triangular "front" (shaded area) in morphspace across which total performance cannot be improved. (Whether a two-dimensional or three-dimensional space is generated will depend upon the degree to which space use and energy use are correlated). The exact location of the observed phenotype is dependent upon the particular balance of pressures applied to the organism. For example, pressure to increase velocity and conserve space but a relative abundance of energy might lead to a phenotype at position A; strong energy and space constraints but little need for speed to position B.

If this sort of analysis did turn out to be feasible, it would provide a model which links the balance of specific selective pressures to the emergence of myelin in the context of one particular ecological strategy—escape reflexes.

4. Dynamic myelination

In the previous two sections, I have considered myelin rather generally, although differences between central and peripheral myelin have been discussed. This is a simplification, albeit a necessary one to present the arguments of previous sections, but it reflects previous thinking about the *process* of myelination. Although it has long been known that myelin is not a static tissue—for example, structural changes in the myelin membrane were characterized almost 35 years ago [127, 128, 129, 130]—it has generally been assumed that

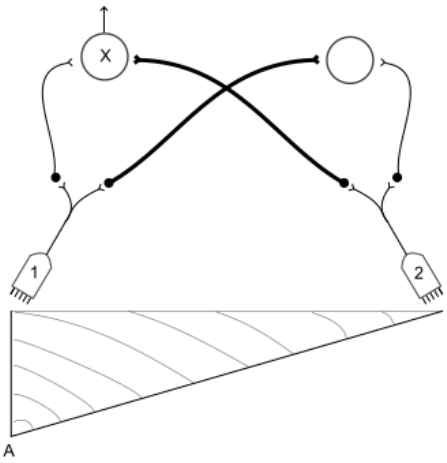

Figure 14: Simplified sound localization circuit. One mechanism of sound localization is the detection of interaural time differences (ITDs). If a sound from source A is off center, it will reach hair cell 1 in the left ear before hair cell 2 in the right ear, leading to an interaural time difference; in this circuit, detected by neuron X. The problem arises when we consider the distances. The ITDs to be detected are typically only a few microseconds. However, the fact that the crossing axon has to travel further (1600 μm further in the chick brainstem, the model system in which this is best studied) should result in a delay of an order of magnitude larger than the ITDs to be detected. However, it has been shown that differential myelination of crossing axons (thicker lines) compensates for this delay and results in isochronic conduction.

once early myelination is complete, the large scale morphology of white matter and the electrophysiological properties of myelinated axons remained relatively constant. However, there is a growing consensus that this is not the case, and that myelin is dynamically regulated by action potential firing throughout life. This is of relevance here for two reasons. Firstly, mechanisms of myelin plasticity may shed light on the evolutionary history of myelin; secondly, the possibility of myelin plasticity is related to questions about learning and cognition, and thus leads on to Section 5.

The benefits of neural regulation of myelin are clear, even reasoning from first principles. As mentioned in Section 3, there is an optimum ratio of myelin to axon. Considering that a single oligodendrocyte may myelinate up to 50 axon segments of widely differing diameters, it is obvious that if this was a preprogrammed process then different signals would have to be sent to each axon—a cumbersome and inflexible process. However, if we postulate a simple local negative feedback system from axon to oligodendrocyte—based for example on conduction velocity—the problem is much simpler, and the solution has the added advantage of flexibility.

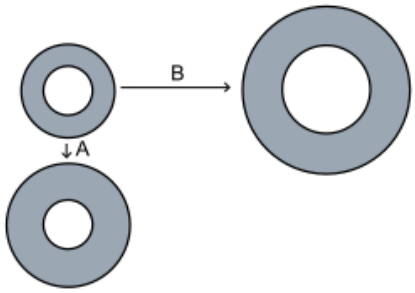

Figure 15: Direct and indirect myelin plasticity. There are two possible forms of myelin plasticity which could account for the diameter changes mentioned above. The first is *direct* plasticity, where diameter changes are due to an increase in myelination alone (A). *Indirect* plasticity is where the underlying change is an increase in axon caliber with myelin simply growing proportionally—that is, g-ratio is maintained (B). These two different phenomena are difficult to distinguish without direct microscopy; similarly, at the level of white matter changes standard MRI will not distinguish either (see Section 4).

Moving from abstract to concrete examples, there is suggestive anatomical and in vitro evidence for such regulation [131, 132]. There are also examples of the parameters of myelination regulating network function. One of the best studied is sound localization in the auditory brainstem, which requires the ability to detect interaural time differences (ITDs) of microsecond durations. Considering the anatomy of the auditory brainstem, these differences should be swamped by the delay due to longer contralateral axons (Figure 14). It has been elegantly shown that systematic decreases in the internodal distance and axon diameter of the shorter ipsilateral axon delay conduction, making detection of coincident binaural inputs possible [133, 134, 135]. Again, a parsimonious hypothesis to explain such a system is neural regulation of myelination. Similar examples are found in the cerebellum and cortex [136, 137].

Importantly, there are two separate phenomena here—changes in internodal distance and fiber diameter. The former is particularly relevant to myelin evolution. There is good evidence that the node of Ranvier is an evolutionary descendant of the axon initial segment (AIS) [106]. Interestingly in the auditory brainstem, the AIS is also plastic, changing length and position in response to sensory input. Could the regulation of internodal distance use the same mechanisms? If so, this would support the notion that myelin evolved by utilization of pre-existing mechanisms, and imply that plasticity may be a more fundamental feature than previously thought. A major question about diameter changes is whether they are due to “direct” or “indirect” myelin plasticity (Figure 15); direct would be a more interesting discovery.

Table 3: Proposed mechanisms of activity-dependent myelination. This table compares multiple proposed mechanisms by which electrical activity in axons might regulate myelination. It should be noted that all are based on in vitro experiments, and generally utilize peripherally derived DRG neurons with central oligodendrocytes.

Proposed mechanism	Tissue used & developmental phase	Experimental evidence	Reference
Reduced neural expression of L1CAM in response to low-frequency stimulation leads to decreased myelination	DRG (PNS); mature Schwann cells	DRG neurons and Schwann cells cultured in vitro; low and high frequency stimulation reduced myelination and L1CAM levels as measured by MBP immunocytochemical staining and mRNA PCR, respectively. Forced upregulation of L1CAM blocked this effect	[138]
Synaptically released adenosine promotes oligodendrocyte differentiation and myelination	DRG neurons; OPCs	Shown via Ca_2^+ imaging that OPCs respond to DRG firing in vitro and express purine receptors. Applied adenosine promotes differentiation and myelination of OPCs.	[139]
Synaptically released ATP cause LIF release by astrocytes promoting oligodendrocyte myelination	DRG neurons (culture contained 13% astrocytes); mature oligodendrocytes	Axons stimulated electrically, releasing ATP and promoting myelination. LIF levels assayed and noted to be increased; anti-LIF antibodies and P_2 receptor block removed the myelin effect. Immunocytochemistry identified astrocytes as the source of LIF	[140]
Synaptically released cAMP promoting oligodendrocyte differentiation	DRG neurons; mature oligodendrocytes	Stimulation of DRG neurons resulted in increased cAMP release and myelination; the effect was blocked by cAMP antagonists and mimicked by cAMP analogues	[141]
Synaptic glutamate release acts on oligodendrocytes to promote myelination.	DRG neurons; OPCs	Stimulation results in synaptic glutamate release; Ca_2^+ imaging shows that glutamate activates OPCs and increased markers of myelination observed. The effect is blocked by treatment with botulinum toxin.	[142]

DRG, dorsal root ganglion; OPCs, oligodendrocyte precursor cells; LIF, leukemia inhibitory factor.

One relevant case is isochronic thalamocortical projections. In mice, isochronicity can be accounted for by *regionally specific* myelination, which is more consistent with direct myelin plasticity [143].

Although undoubtedly interesting, we should not overinterpret the evidence. Direct mechanistic links between neural activity and myelination have not yet been shown, despite a wide range of candidate in vitro mechanisms (Table 3). Furthermore, most work has not distinguished between direct and indirect myelin plasticity. Nevertheless, this is an active area of research showing much promise. The existence of activity-dependent myelin plasticity raises the question of whether such mechanisms might play a role in learning and cognition, and if so, how would this have affected human evolution?

5. Myelin and social cognition

As mentioned above, there is a growing interest in how myelination is related to learning and cognition. For example, following various learning tasks in humans there is increased density of the white matter tracts between the relevant cortical areas [144], correlated with the time spent practicing the task. As already discussed, these sorts of findings could be due to several factors—myelination of unmyelinated axons, concomitant growth of axon and myelin, independent growth of the myelin sheath or a combination of all three [145]. Hopefully, work with more myelin specific measures such as MTR and DTI (Magnetization Transfer Ratio and Diffusion Tensor Imaging, both magnetic resonance metrics which reflect the degree of myelination of white matter and specific microstructural white matter changes, resp.) and histological work will clarify, but meanwhile I will ask the broader question of how learning related changes in myelination might be related to human evolution; particularly the evolution of social cognition.

This is largely a question of ontogeny. Compared to other primates, CNS myelination is delayed in humans [146]. Moreover, this delay seems to be regionally specific; whilst most of the spinal cord and primary sensory cortical areas and tracts are myelinated by age 2 [147], prefrontal and association cortex continue myelination

into early adulthood and even the fourth decade [148, 149]. Such delays in the timing of development are called neoteny, which has been convincingly argued to be a key mechanism of human evolution [150]. In his seminal work on the topic, Gould clearly distinguished between "[the] general, temporal retardation of development [which] has clearly characterized human evolution" and specific adaptations permitted by this retardation. Which is delayed myelination? There is growing evidence suggesting the latter. Firstly, growth in brain mass shows no equivalent delay [151]. More importantly, direct comparison shows that in chimpanzees, postnatal myelination is linear, whilst in humans it is cubic (Figure 16) [152]. This is indication of a specific, evolved delay in myelination in humans. Interestingly, there is also evidence for regionally specific transcriptional neoteny in the human brain [153].

Is the function of this delay related to proposed functions of myelin in learning? Adolescence in humans may be a "critical period" for learning social cognition, analogous to that for the formation of sensory systems in infancy [154]. This was previously thought to be due to grey matter changes and synaptic pruning, but the new understanding of myelin and white matter as a dynamic entity adds a new layer of understanding. The exact way in which myelin contributes is unclear—perhaps dynamic changes in myelin serve to "lock in" grey matter mediated changes, so allowing a greater period in which social learning can occur, or perhaps myelination itself contributes directly to learning.

6. Clinical aspects

In Section 1, I mentioned how misunderstandings can arise when diseases, or even specific features of diseases, are viewed as objects of selection. What *can* be explained in evolutionary terms are traits which predispose to disease. I also mentioned that to fully understand a trait in evolutionary terms, four levels of explanation are required: phylogenetic, functional, developmental, and mechanistic. Having covered these areas in relation to myelin above, we are now in a position to consider to what extent we can use them to understand human vulnerability to neurological and psychiatric disease. Before discussing specifics, it is worth stating that this section is speculative; there is still much we do not know about both the biology of myelin and neurological and psychiatric disease, so the following proposals should be read as hypotheses. These will hopefully serve to illustrate what an evolutionary explanation of disease vulnerability might look like in future. I have selected two areas to discuss, both related to heterochrony in myelination; firstly in relation to certain psychiatric diseases, and secondly in relation to androgens and demyelinating disease.

The phenotype of autism is characterized by an abnormal degree of psychological and cognitive neoteny [159].

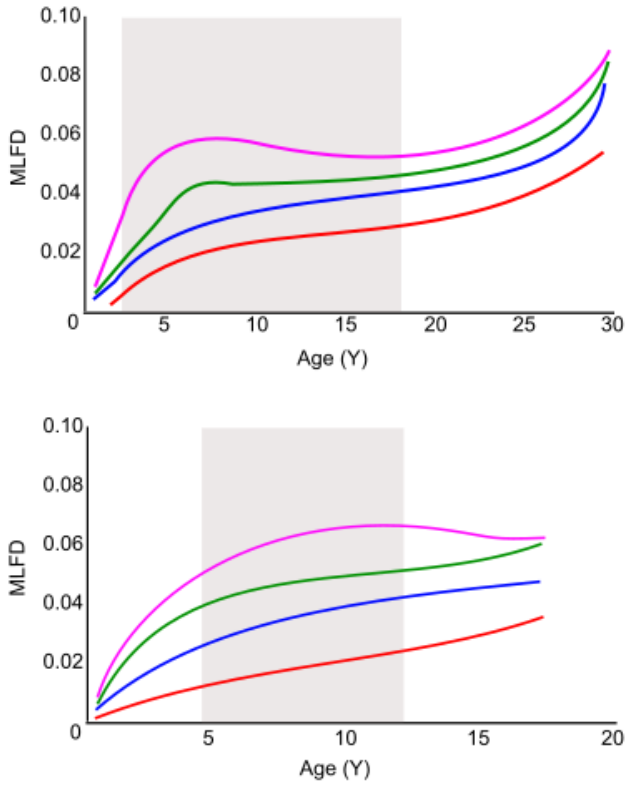

Figure 16: Comparison of myelin growth in human and chimp. This schematic demonstrates the different trajectories of postnatal myelin growth across different cortical areas in humans and chimps, respectively, as measured by MLFD (myelinated fiber length density, units $\mu m/\mu m^3$) calculations. This demonstrates a qualitative difference in myelin trajectory, with a relatively longer delay before full myelination is achieved in humans. The shaded area represents the interval between weaning and maturity. Redrawn from [152]. Key: pink, motor cortex; green, somatosensory cortex; blue, visual cortex; red, frontopolar cortex.

There is also evidence of altered white matter connectivity between limbic, frontal, and temporal structures [160]. A simple "Tinbergian" hypothesis would be that the longer period of myelination in humans, evolved to allow more sophisticated social cognition and learning, allows genes with deleterious effects on myelination more time to act. Hence a general trait—delayed myelination—leads to disease vulnerability in those with genetic risk. This hypothesis links phylogeny, function, and development; we do not yet have an explanation of the mechanism. Similar ideas have been applied to schizophrenia, but in terms of a failure of neoteny, rather than too much [161, 162].

A second area in which we can link disease vulnerability to evolution is the demyelinating diseases (Table 4). Rather than vulnerability due to a species wide trait, as discussed

Table 4: Human diseases of myelin. This table summarizes the broad classes of human myelin disease, based upon pathology. The classification is simplified from [155]; it should be noted that the distinctions are somewhat arbitrary and that in reality these are overlapping categories. For example, progressive multifocal leukoencephalopathy is included amongst the "demyelinating" diseases, despite being essentially noninflammatory; similarly, adrenoleukodystrophy and many of the other leukodystrophies can have inflammatory presentations and components. It should also be noted that this table only includes diseases in which myelin damage is the main or major pathological feature; myelin can be secondarily damaged by almost any disease affecting glia, neurons or vessels, and also in age-related neurodegenerative conditions. This table also excludes psychiatric diseases such as schizophrenia and autism in which neurodevelopmentally-disordered white matter connectivity is increasingly implicated.

Disease class [155]	Disease	Etiology & pathology [156, 157]	Clinical features	Public health burden
Demyelinating diseases—inflammatory and infectious	Multiple sclerosis	Not fully understood; combination of environmental (Vit. D levels, EBV exposure) and genetic (MHC) factors lead to CNS inflammation, demyelination and neurodegeneration	Varied; almost any area of CNS can be affected leading to sensory, motor, cognitive and autonomic symptoms. Most patients initially present with relapsing/remitting disease, which over time becomes progressive; a minority have primary progressive disease	Incidence and prevalence vary geographically; in the UK prevalence is around 165 per 100,000. MS is a chronic and costly disease (estimated $54,244 per patient per year [158]). Most of this cost is due to drug therapy, and a growing problem is lack of available MS drugs in resource-poor settings
	Neuromyelitis Optica	Characterized by confluent demyelination in optic nerve and spinal cord. Possibly due to autoimmune attack of AQP-4 channels	Aggressive demyelinating attacks, which relapse and occur. Primary or secondary progression is rare	Limited knowledge; estimated incidence 0.05 to 0.4 per 100,000, estimated prevalence 0.5 to 0.4 per 100,000
	Acute disseminated encephalomyelitis	Acute, widespread CNS inflammation/demyelination. Postviral etiology	Typically occurs in children/young adults; headache, drowsiness, fits, focal neurological signs	
	Progressive multifocal leukoencephalopathy	Progressive, widespread white matter degeneration secondary to JC virus reactivation following immunosuppression	Progressive global and focal neurological signs, usually on a background of immunosuppression, leading to death by 2–3 years	Rare, although likely to increase in future due to increasing use of immunological therapies in cancer, MS and other autoimmune diseases
	Acute demyelinating polyneuritis (Guillain-Barré syndrome)	Acute PNS polyneuritis associated with primary demyelination. Autoimmune; over half have antecedent infection	Acute onset symmetrical areflexic tetraparesis. Sensory symptoms occur first but are less prominent. Can progress to respiratory involvement	0.6–1.9 per 100,000 incidence annually worldwide. Possibility of a link with Zika virus infection, a major public health crisis in the developing world
	Chronic inflammatory demyelinating polyneuropathy	Chronic inflammatory demyelination of peripheral nerves, autoimmune in origin	Similar to ADP, above; distinguished by slow onset over 2 months or more and relapsing/remitting or chronic course	Estimated prevalence of 2 per 100,000 adults
	Anti-MAG peripheral neuropathy	Distal peripheral demyelination, associated with anti MAG (myelin-associated glycoprotein) IgM	Chronic distal sensory and motor symptoms; the clinical picture is that of a length-dependent process (distinguishing from ADP and CDIP)	Rare
Hereditary and metabolic diseases of myelin (leukodystrophies and hereditary demyelinating peripheral neuropathies)	Metachromatic leukodystrophy	Arylsulphatase A deficiency	All five of these diseases typically present in infancy or early childhood with failure to reach motor milestones, varying progressive focal and global neurological symptoms and often lead to early death. Most also have less severe adolescent/adult variants. They are grouped together as they are all caused by an enzyme deficiency which leads to myelin and white matter degeneration *after* the initial period of in utero myelination is complete	Combined incidence of 1:7,600 live births
	Krabbe disease	α-GCase deficiency		
	Adrenoleukodystrophy	ABCD1 peroxisome transporter mutation; X-linked		
	Canavan disease	Aspartoacylase deficiency		
	Refsum disease	PHYH (peroxisomal enzyme) deficiency		
	Sudanophilic leukodystrophy	PLP mutation; X-linked. Congenital severe hypomelination	Severe global motor and developmental delay; nonprogressive. Lifespan is often roughly 30 years	Rare
	Alexander disease	GFAP (glial fibrillary acidic protein deficiency)	Macrocephaly, spasticity	Rare
	Hereditary motor and sensory neuropathies (demyelinating type); also known as Charcot-Marie-Tooth disease	This is a large group of inherited demyelinating disorders of the PNS. The commonest variants include CMT1A, due to PMP22 duplication on chromosome 17, and CMT1A and Dejerne-Sottas syndrome, both of which can be due to P_0 mutation	Distal weakness, usually presenting in childhood. The severity of the phenotype varies from little to profound disability	Overall prevalence of CMT is around 10 per 100,000; of these, around 2/3 are CMT1, the commonest demyelinating subtype
Acquired toxic and nutritional diseases of myelin	B12 deficiency, anoxia/hypoxia, central pontine myelinolysis			
Traumatic causes of myelin damage	edema, compression, pressure release			

above, this vulnerability is sex-specific. The ratio of females to males who develop MS is 2–5:1, for example. This may well represent an influence of sex steroids; either lower androgens, raised female hormones or both. Interestingly, there are also sex-specific differences in normal white matter development. Post puberty, males have a greater increase in white matter volume, but MTR measurements show that this is due to axon growth and actual myelin volume *decreases*. Within males, this effect is modulated by the androgen receptor (AR), which contains a polyglutamine tract of varying length—males with a "short" AR allele, and thus more efficient transcription of AR genes, show more of an effect (i.e., greater axon growth and less myelination) [163]. Paus interprets this as an effect of testosterone on axonal caliber, citing the example of Kennedy's disease and in vitro research [164]. The proposed mechanism is mediated via AR effects on various axonal transport mechanisms. Interestingly, there is some evidence that myelin proteins are also involved in axonal transport—both natural and experimental PLP mutants result in reduced fast axonal transport and ultimately neuropathy, as does MBP mutation (Section 2.5). If and how these phenomena are related to MS remains to be seen, but the hypothesis can both provide stimuli for further investigation. The AR is well studied in relation to diseases such as prostate cancer, but very little in relation to neurological disease. Triplet repeat expansions are not detected by GWAS studies, and so tend to be neglected when looking for genetic influences on disease; it would be very interesting to see if there is any effect of AR length on MS risk, or in ADL (which in some male paediatric patients has an inflammatory variant very similar to MS).

7. Conclusion

Hopefully, this article has served two purposes. Firstly, to illustrate how an understanding of evolutionary biology can prompt us to think about clinical problems in new ways and from different angles. As I have stated many times already, an evolutionary understanding requires explanations from several different areas of enquiry; such cross fertilization of ideas, methods, and ways of understanding is exactly what often results in progress in areas previously thought intractable. Secondly, I have applied this philosophy to investigate the evolution of myelin. Evidence for the role of myelin and white matter in areas of brain function far beyond simple insulation is accumulating at an astonishing rate; keeping the evolutionary history firmly in mind will be invaluable for making sense of it.

Acknowledgments The author would like to thank Professor Gavin Giovannoni of the Blizard Institute for several illuminating discussions and helpful comments on previous drafts, and would also like to thank the anonymous referees for their insightful comments.

Conflict of interest The author declares that she has no conflict of interest.

References

[1] A. Ross-Gillespie, M. Weigert, S. P. Brown, and R. Kummerli, *Gallium-mediated siderophore quenching as an evolutionarily robust antibacterial treatment*, Evol Med Public Health, 2014 (2014), 18–29.

[2] G. Jansen, R. Gatenby, and C. A. Aktipis, *Opinion: Control vs. eradication: Applying infectious disease treatment strategies to cancer*, Proc Natl Acad Sci U S A, 112 (2015), 937–938.

[3] R. M. Nesse, *Ten questions for evolutionary studies of disease vulnerability*, Evol Appl, 4 (2011), 264–277.

[4] A. Varki, *Nothing in medicine makes sense, except in the light of evolution*, J Mol Med (Berl), 90 (2012), 481–494.

[5] A. Wood, *Darwinian medicine: is vomiting in acute angle closure glaucoma an evolutionary adaptation?*, Med Hypotheses, 71 (2008), 150–151.

[6] S. P. Paşca and R. M. Nesse, *Vomiting is not an adaption for glaucoma (and Darwinian medicine is difficult)*, Med Hypotheses, 71 (2008), 472–473.

[7] N. Tinbergen, *On aims and methods of ethology*, Z Tierpsychol, 20 (1963), 410–433.

[8] C. Raine, *Morphology of myelin and myelination*, in Myelin, P. Morell, ed., Plenum Press, New York, 2nd ed., 1984, 1–50.

[9] B. I. Roots, *A phylogenetic approach to the anatomy of glia*, in Dynamic Properties of Glial Cells, Pergamon Press, New York, 1978, 45–54.

[10] J. A. Nicol, *The giant axons of annelids*, Q Rev Biol, 23 (1948), 291–323.

[11] M. R. Freeman and J. Doherty, *Glial cell biology in Drosophila and vertebrates*, Trends Neurosci, 29 (2006), 82–90.

[12] G. S. Tomassy, L. B. Dershowitz, and P. Arlotta, *Diversity matters: A revised guide to myelination*, Trends Cell Biol, 26 (2016), 135–147.

[13] D. K. Hartline, *What is myelin?*, Neuron Glia Biol, 4 (2008), 153–163.

[14] B. I. Roots, *The phylogeny of invertebrates and the evolution of myelin*, Neuron Glia Biol, 4 (2008), 101–109.

[15] A. L. Hodgkin, *A note on conduction velocity*, J Physiol, 125 (1954), 221–224.

[16] R. S. Lillie, *Factors affecting transmission and recovery in the passive iron nerve model*, J Gen Physiol, 7 (1925), 473–507.

[17] A. F. Huxley and R. Stämpfli, *Evidence for saltatory conduction in peripheral myelinated nerve fibres*, J Physiol, 108 (1949), 315–339.

[18] T. H. Bullock, J. K. Moore, and R. D. Fields, *Evolution of myelin sheaths: Both lamprey and hagfish lack myelin*, Neurosci Lett, 48 (1984), 145–148.

[19] A. Aguinaldo, J. Turbeville, L. Linford, M. Rivera, J. Garey, R. Raff, et al., *Evidence for a clade of nematodes, arthropods and other moulting animals*, Nature, 387 (1997), 489–493.

[20] D. K. Hartline and J. H. Kong, *Axonal sheaths in two reportedly myelinated polychaete nervous systems: Asychis elongata and Capitella sp. I*, Bull Mt Desert Isl Biol Lab Salisb Cove Maine, 48 (2009), 86–87.

[21] M. L. Jones and S. L. Gardiner, *On the early development of the vestimentiferan tube worm Ridgeia sp. and observations on the nervous system and trophosome of Ridgeia sp. and Riftia pachyptila*, Biol Bull, 177 (1989), 254–276.

[22] I. Fernández, F. Pardos, J. Benito, and C. Roldán, *Ultrastructural observations on the phoronid nervous system*, J Morphol, 230 (1996), 265–281.

[23] C. D. Drewes and R. O. Brinkhurst, *Giant nerve fibers and rapid escape reflexes in newly hatched aquatic oligochaetes, Lumbriculus variegatus (Family Lumbriculidae)*, Invertebr Reprod Dev, 17 (1990), 91–95.

[24] K. Xu and S. Terakawa, *Fenestration nodes and the wide submyelinic space form the basis for the unusually fast impulse*

conduction of shrimp myelinated axons, J Exp Biol, 202 (1999), 1979–1989.

[25] T. M. Weatherby, A. D. Davis, D. K. Hartline, and P. H. Lenz, *The need for speed. II. Myelin in calanoid copepods*, J Comp Physiol A, 186 (2000), 347–357.

[26] J. E. Heuser and C. F. Doggenweiler, *The fine structural organization of nerve fibers, sheaths, and glial cells in the prawn, Palaemonetes vulgaris*, J Cell Biol, 30 (1966), 381–403.

[27] W. Holmes, *The giant myelinated nerve fibres of the prawn*, Philos Trans R Soc Lond B Biol Sci, 231 (1942), 293–311.

[28] K. Hama, *Some observations on the fine structure of the giant nerve fibers of the earthworm, Eisenia foetida*, J Biophys Biochem Cytol, 6 (1959), 61–66.

[29] C. Hildebrand, S. Remahl, H. Persson, and C. Bjartmar, *Myelinated nerve fibres in the CNS*, Prog Neurobiol, 40 (1993), 319–384.

[30] M. A. Matthews, *An electron microscopic study of the relationship between axon diameter and the initiation of myelin production in the peripheral nervous system*, Anat Rec, 161 (1968), 337–351.

[31] B. Freeman, *Myelin sheath thickness and conduction latency groups in the cat optic nerve*, J Comp Neurol, 181 (1978), 183–196.

[32] S. G. Waxman and M. V. Bennett, *Relative conduction velocities of small myelinated and non-myelinated fibres in the central nervous system*, Nat New Biol, 238 (1972), 217–219.

[33] J. Günther, *Impulse conduction in the myelinated giant fibers of the earthworm. Structure and function of the dorsal nodes in the median giant fiber*, J Comp Neurol, 168 (1976), 505–531.

[34] K. Kusano, *Electrical activity and structural correlates of giant nerve fibers in Kuruma shrimp (Penaeus japonicus)*, J Cell Physiol, 68 (1966), 361–383.

[35] W. Holmes, R. J. Pumphrey, and J. Z. Young, *The structure and conduction velocity of the medullated nerve fibres of prawns*, J Exp Biol, 18 (1941), 50–54.

[36] W. T. Norton, S. E. Poduslo, and K. Suzuki, *Subacute sclerosing leukoencephalitis. II. Chemical studies including abnormal myelin and an abnormal ganglioside pattern*, J Neuropathol Exp Neurol, 25 (1966), 582–597.

[37] N. Spritz, H. Singh, and B. Geyer, *Myelin from human peripheral nerves. Quantitative and qualitative studies in two age groups*, J Clin Invest, 52 (1973), 520–523.

[38] D. K. Hartline and D. R. Colman, *Rapid conduction and the evolution of giant axons and myelinated fibers*, Curr Biol, 17 (2007), R29–R35.

[39] B. Cardone and B. I. Roots, *Monoclonal antibodies to proteins of the myelin-like sheath of earthworm giant axons show cross-reactivity to crayfish CNS glia: An immunogold electron microscopy study*, Neurochem Res, 21 (1996), 505–510.

[40] Z. Faulkes, *Turning loss into opportunity: the key deletion of an escape circuit in decapod crustaceans*, Brain Behav Evol, 72 (2008), 251–261.

[41] J. H. Mcalear, N. S. Milburn, and G. B. Chapman, *The fine structure of Schwann cells, nodes of Ranvier and Schmidt-Lanterman incisures in the central nervous system of the crab, Cancer irroratus*, J Ultrastruct Res, 2 (1958), 171–176.

[42] B. B. Geren and F. O. Schmitt, *The structure of the Schwann cell and its relation to the axon in certain invertebrate nerve fibers*, Proc Natl Acad Sci U S A, 40 (1954), 863–870.

[43] H. Inouye, J. Liu, L. Makowski, M. Palmisano, M. Burghammer, C. Riekel, et al., *Myelin organization in the nodal, paranodal, and juxtaparanodal regions revealed by scanning x-ray microdiffraction*, PLoS One, 9 (2014), e100592.

[44] K. Hsu and S. Terakawa, *Fenestration in the myelin sheath of nerve fibers of the shrimp: A novel node of excitation for saltatory conduction*, J Neurobiol, 30 (1996), 397–409.

[45] S. Terakawa and K. Hsu, *Ionic currents of the nodal membrane underlying the fastest saltatory conduction in myelinated giant nerve fibers of the shrimp Penaeus japonicus*, J Neurobiol, 22 (1991), 342–352.

[46] P. H. Lenz, D. K. Hartline, and A. D. Davis, *The need for speed. I. Fast reactions and myelinated axons in copepods*, J Comp Physiol A, 186 (2000), 337–345.

[47] C. H. Wilson and D. K. Hartline, *Novel organization and development of copepod myelin. ii. nonglial origin*, J Comp Neurol, 519 (2011), 3281–3305.

[48] C. H. Wilson and D. K. Hartline, *Novel organization and development of copepod myelin. i. ontogeny*, J Comp Neurol, 519 (2011), 3259–3280.

[49] T. H. Bullock, *The natural history of neuroglia: an agenda for comparative studies*, Neuron Glia Biol, 1 (2004), 97–100.

[50] M. J. Zoran and C. D. Drewes, *Rapid escape reflexes in aquatic oligochaetes: variations in design and function of evolutionarily conserved giant fiber systems*, J Comp Physiol A Neuroethol Sens Neural Behav Physiol., 161 (1987), 729–738.

[51] T. L. Hayward and J. A. Mcgowan, *Pattern and structure in an oceanic zooplankton community*, Am Zool, 19 (1979), 1045–1055.

[52] S. Y. Espinoza, L. Breen, N. Varghese, and Z. Faulkes, *Loss of escape-related giant neurons in a spiny lobster, Panulirus argus*, Biol Bull, 211 (2006), 223–231.

[53] H. Inouye and D. A. Kirschner, *Evolution of myelin ultrastructure and the major structural myelin proteins*, Brain Res, 1641 (2016), 43–63.

[54] B. I. Roots, B. Cardone, and P. Pereyra, *Isolation and characterization of the myelin-like membranes ensheathing giant axons in the earthworm nerve cord*, Ann N Y Acad Sci, 633 (1991), 559–561.

[55] D. A. Kirschner and C. J. Hollingshead, *Processing for electron microscopy alters membrane structure and packing in myelin*, J Ultrastruct Res, 73 (1980), 211–232.

[56] W. T. Norton and W. Cammer, *Isolation and characterization of myelin*, in Myelin, P. Morell, ed., Plenum Press, New York, 2nd ed., 1984, 147–195.

[57] G. Gopalakrishnan, A. Awasthi, W. Belkaid, O. De Faria Jr., D. Liazoghli, D. R. Colman, et al., *Lipidome and proteome map of myelin membranes*, J Neurosci Res, 91 (2013), 321–334.

[58] S. Schmitt, L. C. Castelvetri, and M. Simons, *Metabolism and functions of lipids in myelin*, Biochim Biophys Acta, 1851 (2015), 999–1005.

[59] M. Simons, E. M. Krämer, C. Thiele, W. Stoffel, and J. Trotter, *Assembly of myelin by association of proteolipid protein with cholesterol- and galactosylceramide-rich membrane domains*, J Cell Biol, 151 (2000), 143–154.

[60] L. Shapiro, J. P. Doyle, P. Hensley, D. R. Colman, and W. A. Hendrickson, *Crystal structure of the extracellular domain from P_0, the major structural protein of peripheral nerve myelin*, Neuron, 17 (1996), 435–449.

[61] D. D'Urso, P. J. Brophy, S. M. Staugaitis, C. S. Gillespie, A. B. Frey, J. G. Stempak, et al., *Protein zero of peripheral nerve myelin: Biosynthesis, membrane insertion, and evidence for homotypic interaction*, Neuron, 4 (1990), 449–460.

[62] R. L. Avila, M. D'Antonio, A. Bachi, H. Inouye, M. L. Feltri, L. Wrabetz, et al., *P0 (protein zero) mutation S34C underlies instability of internodal myelin in S63C mice*, J Biol Chem, 285 (2010), 42001–42012.

[63] K. Kitagawa, M. Sinoway, C. Yang, R. Gould, and D. Colman, *A proteolipid protein gene family: Expression in sharks and rays and possible evolution from an ancestral gene encoding a pore-forming polypeptide*, Neuron, 11 (1993), 433–448.

[64] W. Möbius, J. Patzig, K. A. Nave, and H. B. Werner, *Phylogeny of proteolipid proteins: divergence, constraints, and the*

evolution of novel functions in myelination and neuroprotection, Neuron Glia Biol, 4 (2008), 111–127.

[65] A. T. Campagnoni and R. P. Skoff, *The pathobiology of myelin mutants reveal novel biological functions of the MBP and PLP genes*, Brain Pathol, 11 (2001), 74–91.

[66] M. B. Lees and S. W. Brostoff, *Proteins of myelin*, in Myelin, P. Morell, ed., Plenum Press, New York, 2nd ed., 1984, 197–224.

[67] O. Jahn, S. Tenzer, and H. B. Werner, *Myelin proteomics: molecular anatomy of an insulating sheath*, Mol Neurobiol, 40 (2009), 55–72.

[68] P. de Monasterio-Schrader, O. Jahn, S. Tenzer, S. Wichert, J. Patzig, and H. Werner, *Systematic approaches to central nervous system myelin*, Cell Mol Life Sci, 69 (2012), 2879–2894.

[69] J. Patzig, O. Jahn, S. Tenzer, S. P. Wichert, P. de Monasterio-Schrader, S. Rosfa, et al., *Quantitative and integrative proteome analysis of peripheral nerve myelin identifies novel myelin proteins and candidate neuropathy loci*, J Neurosci, 31 (2011), 16369–16386.

[70] H. B. Werner, *Do we have to reconsider the evolutionary emergence of myelin?*, Front Cell Neurosci, 7 (2013), 217.

[71] S. Nawaz, J. Schweitzer, O. Jahn, and H. B. Werner, *Molecular evolution of myelin basic protein, an abundant structural myelin component*, Glia, 61 (2013), 1364–1377.

[72] A. Roach, N. Takahashi, D. Pravtcheva, F. Ruddle, and L. Hood, *Chromosomal mapping of mouse myelin basic protein gene and structure and transcription of the partially deleted gene in shiverer mutant mice*, Cell, 42 (1985), 149–155.

[73] R. Martini, M. H. Mohajeri, S. Kasper, K. P. Giese, and M. Schachner, *Mice doubly deficient in the genes for P0 and myelin basic protein show that both proteins contribute to the formation of the major dense line in peripheral nerve myelin*, J Neurosci, 15 (1995), 4488–4495.

[74] V. Majava, E. Polverini, A. Mazzini, R. Nanekar, W. Knoll, J. Peters, et al., *Structural and functional characterization of human peripheral nervous system myelin protein P2*, PLoS One, 5 (2010), e10300.

[75] J. Zenker, M. Stettner, S. Ruskamo, E. Domènech-Estévez, H. Baloui, J. J. Médard, et al., *A role of peripheral myelin protein 2 in lipid homeostasis of myelinating Schwann cells*, Glia, 62 (2014), 1502–1512.

[76] R. M. Gould, T. Oakley, J. V. Goldstone, J. C. Dugas, S. T. Brady, and A. Gow, *Myelin sheaths are formed with proteins that originated in vertebrate lineages*, Neuron Glia Biol, 4 (2008), 137–152.

[77] X. Yin, R. C. Baek, D. A. Kirschner, A. Peterson, Y. Fujii, K. A. Nave, et al., *Evolution of a neuroprotective function of central nervous system myelin*, J Cell Biol, 172 (2006), 469–478.

[78] W. Xu, D. Manichella, H. Jiang, J. M. Vallat, J. Lilien, P. Baron, et al., *Absence of P0 leads to the dysregulation of myelin gene expression and myelin morphogenesis*, J Neurosci Res, 60 (2000), 714–724.

[79] M. Yoshida and D. R. Colman, *Parallel evolution and coexpression of the proteolipid proteins and protein zero in vertebrate myelin*, Neuron, 16 (1996), 1115–1126.

[80] T. V. Waehneldt, J. Malotka, N. J. Karin, and J.-M. Matthieu, *Phylogenetic examination of vertebrate central nervous system myelin proteins by electro-immunoblotting*, Neurosci Lett, 57 (1985), 97–102.

[81] J. Schweitzer, T. Becker, M. Schachner, K. A. Nave, and H. Werner, *Evolution of myelin proteolipid proteins: Gene duplication in teleosts and expression pattern divergence*, Mol Cell Neurosci, 31 (2006), 161–177.

[82] I. D. Duncan, J. P. Hammang, S. Goda, and R. H. Quarles, *Myelination in the jimpy mouse in the absence of proteolipid protein*, Glia, 2 (1989), 148–154.

[83] M. Klugmann, M. H. Schwab, A. Pühlhofer, A. Schneider, F. Zimmermann, I. R. Griffiths, et al., *Assembly of CNS myelin in the absence of proteolipid protein*, Neuron, 18 (1997), 59–70.

[84] R. L. Avila, H. Inouye, R. C. Baek, X. Yin, B. D. Trapp, M. L. Feltri, et al., *Structure and stability of internodal myelin in mouse models of hereditary neuropathy*, J Neuropathol Exp Neurol, 64 (2005), 976–990.

[85] R. Gutiérrez, D. Boison, U. Heinemann, and W. Stoffel, *Decompaction of CNS myelin leads to a reduction of the conduction velocity of action potentials in optic nerve*, Neurosci Lett, 195 (1995), 93–96.

[86] I. Griffiths, M. Klugmann, T. Anderson, D. Yool, C. Thomson, M. H. Schwab, et al., *Axonal swellings and degeneration in mice lacking the major proteolipid of myelin*, Science, 280 (1998), 1610–1613.

[87] J. M. Edgar, M. McLaughlin, D. Yool, S. C. Zhang, J. H. Fowler, P. Montague, et al., *Oligodendroglial modulation of fast axonal transport in a mouse model of hereditary spastic paraplegia*, J Cell Biol, 166 (2004), 121–131.

[88] X. Yin, G. J. Kidd, N. Ohno, G. A. Perkins, M. H. Ellisman, C. Bastian, et al., *Proteolipid protein-deficient myelin promotes axonal mitochondrial dysfunction via altered metabolic coupling*, J Cell Biol, 215 (2016), 531–542.

[89] N. Snaidero and M. Simons, *Myelination at a glance*, J Cell Sci, 127 (2014), 2999–3004.

[90] K. A. Nave and H. B. Werner, *Myelination of the nervous system: mechanisms and functions*, Annu Rev Cell Dev Biol, 30 (2014), 503–533.

[91] K. R. Monk, M. L. Feltri, and C. Taveggia, *New insights on Schwann cell development*, Glia, 63 (2015), 1376–1393.

[92] K. K. Bercury and W. B. Macklin, *Dynamics and mechanisms of CNS myelination*, Dev Cell, 32 (2015), 447–458.

[93] C. Gans and R. G. Northcutt, *Neural crest and the origin of vertebrates: a new head*, Science, 220 (1983), 268–273.

[94] J. D. Robertson, *The ultrastructure of adult vertebrate peripheral myelinated nerve fibers in relation to myelinogenesis*, J Biophys Biochem Cytol, 1 (1955), 271–278.

[95] R. P. Bunge, M. B. Bunge, and M. Bates, *Movements of the Schwann cell nucleus implicate progression of the inner (axon-related) Schwann cell process during myelination*, J Cell Biol, 109 (1989), 273–284.

[96] A. Peters, S. L. Palay, and H. D. Webster, *The cellular sheaths of neurons*, in Fine Structure of the Nervous System: Neurons and Their Supporting Cells, Oxford University Press, New York, 3rd ed., 1991, 212–272.

[97] C. C. Stolt and M. Wegner, *Schwann cells and their transcriptional network: Evolution of key regulators of peripheral myelination*, Brain Res, 1641 (2016), 101–110.

[98] H. Li and W. D. Richardson, *Evolution of the CNS myelin gene regulatory program*, Brain Res, 1641 (2016), 111–121.

[99] J. Dai, K. K. Bercury, J. T. Ahrendsen, and W. B. Macklin, *Olig1 function is required for oligodendrocyte differentiation in the mouse brain*, J Neurosci, 35 (2015), 4386–4402.

[100] S. Mitew, C. M. Hay, H. Peckham, J. Xiao, M. Koenning, and B. Emery, *Mechanisms regulating the development of oligodendrocytes and central nervous system myelin*, Neuroscience, 276 (2014), 29–47.

[101] S. A. Back, N. L. Luo, N. S. Borenstein, J. J. Volpe, and H. C. Kinney, *Arrested oligodendrocyte lineage progression during human cerebral white matter development: dissociation between the timing of progenitor differentiation and myelinogenesis*, J Neuropathol Exp Neurol, 61 (2002), 197–211.

[102] B. Zalc, D. Goujet, and D. Colman, *The origin of the myelination program in vertebrates*, Curr Biol, 18 (2008), R511–R512.

[103] B. Zalc, *The acquisition of myelin: An evolutionary perspective*, Brain Res, 1641 (2016), 4–10.

[104] H. Li and W. D. Richardson, *The evolution of Olig genes and their roles in myelination*, Neuron Glia Biol, 4 (2008), 129–135.

[105] W. D. Richardson, H. K. Smith, T. Sun, N. P. Pringle, A. Hall, and R. Woodruff, *Oligodendrocyte lineage and the motor neuron connection*, Glia, 29 (2000), 136–142.

[106] A. S. Hill, A. Nishino, K. Nakajo, G. Zhang, J. R. Fineman, M. E. Selzer, et al., *Ion channel clustering at the axon initial segment and node of Ranvier evolved sequentially in early chordates*, PLoS Genet, 4 (2008), e1000317.

[107] L. Van Valen, *A new evolutionary law*, Evol. Theory, 1 (1973), 1–30.

[108] A. M. Castelfranco and D. K. Hartline, *The evolution of vertebrate and invertebrate myelin: a theoretical computational study*, J Comput Neurosci, 38 (2015), 521–538.

[109] S. J. Gould and R. C. Lewontin, *The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme*, Proc R Soc Lond B Biol Sci, 205 (1979), 581–598.

[110] D. Attwell and S. B. Laughlin, *An energy budget for signaling in the grey matter of the brain*, J Cereb Blood Flow Metab, 21 (2001), 1133–1145.

[111] C. Howarth, P. Gleeson, and D. Attwell, *Updated energy budgets for neural computation in the neocortex and cerebellum*, J Cereb Blood Flow Metab, 32 (2012), 1222–1132.

[112] S. B. Laughlin and T. J. Sejnowski, *Communication in neuronal networks*, Science, 301 (2003), 1870–1874.

[113] H. Alle, A. Roth, and J. R. Geiger, *Energy-efficient action potentials in hippocampal mossy fibers*, Science, 325 (2009), 1405–1408.

[114] J. E. Niven, J. C. Anderson, and S. B. Laughlin, *Fly photoreceptors demonstrate energy-information trade-offs in neural coding*, PLoS Biol, 5 (2007), e116.

[115] G. Mitchison, *Axonal trees and cortical architecture*, Trends Neurosci, 15 (1992), 122–126.

[116] D. B. Chklovskii, T. Schikorski, and C. F. Stevens, *Wiring optimization in cortical circuits*, Neuron, 34 (2002), 341–347.

[117] W. A. Rushton, *A theory of the effects of fibre size in medullated nerve*, J Physiol, 115 (1951), 101–122.

[118] J. W. Moore, R. W. Joyner, M. H. Brill, S. D. Waxman, and M. Najar-Joa, *Simulations of conduction in uniform myelinated fibers. Relative sensitivity to changes in nodal and internodal parameters*, Biophys J, 21 (1978), 147–160.

[119] J. Guy, E. Ellis, K. Kelley, and G. Hope, *Spectra of G ratio, myelin sheath thickness, and axon and fiber diameter in the guinea pig optic nerve*, J Comp Neurol, 287 (1989), 446–454.

[120] T. Chomiak and B. Hu, *What is the optimal value of the g-ratio for myelinated fibers in the rat CNS? A theoretical approach*, PLoS One, 4 (2009), e7754.

[121] L. Sokoloff, M. Reivich, C. Kennedy, M. H. Des Rosiers, C. S. Patlak, K. D. Pettigrew, et al., *The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat*, J Neurochem, 28 (1977), 897–916.

[122] T. J. Yuen, J. C. Silbereis, A. Griveau, S. M. Chang, R. Daneman, S. P. Fancy, et al., *Oligodendrocyte-encoded HIF function couples postnatal myelination and white matter angiogenesis*, Cell, 158 (2014), 383–396.

[123] J. J. Harris and D. Attwell, *The energetics of CNS white matter*, J Neurosci, 32 (2012), 356–371.

[124] K. M. Stiefel, B. Torben-Nielsen, and J. S. Coggan, *Proposed evolutionary changes in the role of myelin*, Front Neurosci, 7 (2013), 202.

[125] K. D. Farnsworth and K. J. Niklas, *Theories of optimization, form and function in branching architecture in plants*, Funct Ecol, 9 (1995), 355–363.

[126] O. Shoval, H. Sheftel, G. Shinar, Y. Hart, O. Ramote, A. Mayo, et al., *Evolutionary trade-offs, Pareto optimality, and the geometry of phenotype space*, Science, 336 (2012), 1157–1160.

[127] P. P. da Silva and R. G. Miller, *Membrane particles on fracture faces of frozen myelin*, Proc Natl Acad Sci U S A, 72 (1975), 4046–4050.

[128] C. J. Hollingshead, D. L. Caspar, V. Melchior, and D. A. Kirschner, *Compaction and particle segregation in myelin membrane arrays*, J Cell Biol, 89 (1981), 631–644.

[129] D. A. Kirschner, C. J. Hollingshead, C. Thaxton, D. L. Caspar, and D. A. Goodenough, *Structural states of myelin observed by x-ray diffraction and freeze-fracture electron microscopy*, J Cell Biol, 82 (1979), 140–149.

[130] D. L. Caspar, V. Melchior, C. J. Hollingshead, and D. A. Kirschner, *Dynamics of myelin membrane contacts*, Soc Gen Physiol Ser, 34 (1980), 195–211.

[131] B. Zalc and R. D. Fields, *Do action potentials regulate myelination?*, Neuroscientist, 6 (2000), 5–13.

[132] C. Demerens, B. Stankoff, M. Logak, P. Anglade, B. Allinquant, F. Couraud, et al., *Induction of myelination in the central nervous system by electrical activity*, Proc Natl Acad Sci U S A, 93 (1996), 9887–9892.

[133] A. H. Seidl, E. W. Rubel, and D. M. Harris, *Mechanisms for adjusting interaural time differences to achieve binaural coincidence detection*, J Neurosci, 30 (2010), 70–80.

[134] A. H. Seidl, E. W. Rubel, and A. Barría, *Differential conduction velocity regulation in ipsilateral and contralateral collaterals innervating brainstem coincidence detector neurons*, J Neurosci, 34 (2014), 4914–4919.

[135] A. H. Seidl and E. W. Rubel, *Systematic and differential myelination of axon collaterals in the mammalian auditory brainstem*, Glia, 64 (2016), 487–494.

[136] E. J. Lang and J. Rosenbluth, *Role of myelination in the development of a uniform olivocerebellar conduction time*, J Neurophysiol, 89 (2003), 2259–2270.

[137] G. S. Tomassy, D. R. Berger, H. H. Chen, N. Kasthuri, K. J. Hayworth, A. Vercelli, et al., *Distinct profiles of myelin distribution along single axons of pyramidal neurons in the neocortex*, Science, 344 (2014), 319–324.

[138] B. Stevens, S. Tanner, and R. D. Fields, *Control of myelination by specific patterns of neural impulses*, J Neurosci, 18 (1998), 9303–9311.

[139] B. Stevens, S. Porta, L. L. Haak, V. Gallo, and R. D. Fields, *Adenosine: A neuron-glial transmitter promoting myelination in the CNS in response to action potentials*, Neuron, 36 (2002), 855–868.

[140] T. Ishibashi, K. A. Dakin, B. Stevens, P. R. Lee, S. V. Kozlov, C. L. Stewart, et al., *Astrocytes promote myelination in response to electrical impulses*, Neuron, 49 (2006), 823–832.

[141] M. Malone, D. Gary, I. H. Yang, A. Miglioretti, T. Houdayer, N. Thakor, et al., *Neuronal activity promotes myelination via a cAMP pathway*, Glia, 61 (2013), 843–854.

[142] H. Wake, P. R. Lee, and R. D. Fields, *Control of local protein synthesis and initial events in myelination by action potentials*, Science, 333 (2011), 1647–1651.

[143] M. Salami, C. Itami, T. Tsumoto, and F. Kimura, *Change of conduction velocity by regional myelination yields constant latency irrespective of distance between thalamus and cortex*, Proc Natl Acad Sci U S A, 100 (2003), 6174–6179.

[144] R. D. Fields, *Change in the brain's white matter*, Science, 330 (2010), 768–769.

[145] F. Ullén, *Is activity regulation of late myelination a plastic mechanism in the human nervous system?*, Neuron Glia Biol, 5 (2009), 29–34.

[146] T. Sakai, A. Mikami, M. Tomonaga, M. Matsui, J. Suzuki, Y. Hamada, et al., *Differential prefrontal white matter*

development in chimpanzees and humans, Curr Biol, 21 (2011), 1397–1402.

[147] B. A. Brody, H. C. Kinney, A. S. Kloman, and F. H. Gilles, *Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination*, J Neuropathol Exp Neurol, 46 (1987), 283–301.

[148] P. I. Yakovlev and A. R. Lecours, *The myelogenetic cycles of regional maturation of the brain*, in Regional Development of the Brain in Early Life, A. Minkowski, ed., Blackwell Scientific Publications, Oxford, 1967, 3–70.

[149] G. Bartzokis, P. H. Lu, K. Tingus, M. F. Mendez, A. Richard, D. G. Peters, et al., *Lifespan trajectory of myelin integrity and maximum motor speed*, Neurobiol Aging, 31 (2010), 1554–1562.

[150] S. J. Gould, *Ontogeny and Phylogeny*, Harvard University Press, Cambridge, MA, 1977.

[151] B. Bogin, *Evolutionary perspective on human growth*, Annu Rev Anthropol, 28 (1999), 109–153.

[152] D. J. Miller, T. Duka, C. D. Stimpson, S. J. Schapiro, W. B. Baze, M. J. McArthur, et al., *Prolonged myelination in human neocortical evolution*, Proc Natl Acad Sci U S A, 109 (2012), 16480–16485.

[153] M. Somel, H. Franz, Z. Yan, A. Lorenc, S. Guo, T. Giger, et al., *Transcriptional neoteny in the human brain*, Proc Natl Acad Sci U S A, 106 (2009), 5743–5748.

[154] S. J. Blakemore and S. Choudhury, *Development of the adolescent brain: implications for executive function and social cognition*, J Child Psychol Psychiatry, 47 (2006), 296–312.

[155] C. Raine, *The neuropathology of myelin diseases*, in Myelin, P. Morell, ed., Plenum Press, New York, 2nd ed., 1984, 259–310.

[156] A. Compston, *Multiple sclerosis and other demyelinating diseases*, in Brain's Diseases of the Nervous System, M. Donaghy, ed., Oxford University Press, New York, 11th ed., 2001, 909–957.

[157] U. Traugott and C. Raine, *The neurology of myelin diseases*, in Myelin, P. Morell, ed., Plenum Press, New York, 2nd ed., 1984, 311–335.

[158] G. Adelman, S. G. Rane, and K. F. Villa, *The cost burden of multiple sclerosis in the United States: a systematic review of the literature*, J Med Econ, 16 (2013), 639–647.

[159] B. Crespi, *Developmental heterochrony and the evolution of autistic perception, cognition and behavior*, BMC Med, 11 (2013), 119.

[160] S. H. Ameis and M. Catani, *Altered white matter connectivity as a neural substrate for social impairment in Autism Spectrum Disorder*, Cortex, 62 (2015), 158–181.

[161] M. Brüne, *Neoteny, psychiatric disorders and the social brain: Hypotheses on heterochrony and the modularity of the mind*, Anthropol Med, 7 (2000), 301–318.

[162] J. K. Burns, *An evolutionary theory of schizophrenia: cortical connectivity, metarepresentation, and the social brain*, Behav Brain Sci, 27 (2004), 831–855.

[163] J. S. Perrin, P. Y. Hervé, G. Leonard, M. Perron, G. B. Pike, A. Pitiot, et al., *Growth of white matter in the adolescent brain: role of testosterone and androgen receptor*, J Neurosci, 28 (2008), 9519–9524.

[164] T. Paus, *Growth of white matter in the adolescent brain: Myelin or axon?*, Brain Cogn, 72 (2010), 26–35.