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REVIEW ARTICLE

Evolution of glial wrapping: A new hypothesis

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Abstract

Animals are able to move and react in numerous ways to external stimuli. Thus, environmental stimuli need to be detected, information must be processed and finally an output decision must be transmitted to the musculature to get the animal moving. All these processes depend on the nervous system which comprises an intricate neuronal network and many glial cells. In the last decades, a neurono-centric view on nervous system function channeled most of the scientific interest toward the analysis of neurons and neuronal functions. Neurons appeared early in animal evolution and the main principles of neuronal function from synaptic transmission to propagation of action potentials are conserved during evolution. In contrast, not much is known on the evolution of glial cells that were initially considered merely as static support cells. Although it is now accepted that glial cells have an equally important contribution as their neuronal counterpart to nervous system function, their evolutionary origin is unknown. Did glial cells appear several times during evolution? What were the first roles glial cells had to fulfil in the nervous system? What triggered the formation of the amazing diversity of glial morphologies and functions? Is there a possible mechanism that might explain the appearance of complex structures such as myelin in vertebrates? Here, we postulate a common evolutionary origin of glia and depict a number of selective forces that might have paved the way from a simple supporting cell to a wrapping and myelin forming glial cell.

KEYWORDS

evolution, glia, myelin

1 | ANIMAL BRAINS HARBOR TWO MAJOR CELL TYPES

Fossil records demonstrate that evolution of metazoan animals started more than 650 million years ago with the appearance of Demospongiae, primitive Porifera (sponges) lacking true tissues, and organs (Leys & Hill, 2012; Love et al., 2009). Shortly thereafter, the first nervous systems and muscles evolved to sense external and internal stimuli and subsequently adjust the behavior of the animal. Although it is still under debate whether nervous systems evolved once or twice (Jékely, Paps, & Nielsen, 2015; Marlow & Arendt, 2014; Moroz et al., 2014; Ryan et al., 2013), in all nervous systems neurons collect information and connect themselves in amazingly complex circuits. All neurons use similar voltage gated sodium and potassium channels to generate action potentials, release neurotransmitters to finally control movements. Thus, neurons residing in the nervous system, or the brain, use evolutionary conserved mechanisms to direct behavior, thoughts and emotions of the animal, which over the last century resulted in a neurono-centric view of brain function.

However, it is long known, since Virchow's first descriptions of glial cells in 1846 and 1858 and Deiter's first drawing

of an astrocyte (1865) that the nervous system harbors two closely interacting cell types: neurons and glial cells (Deiters, 1865; Virchow, 1846, 1858). Moreover, in some mammalian nervous systems, glial cells can even outnumber neurons (Herculano-Houzel, 2014). The importance of glia may be reflected by the increase in their relative number during evolution. In Drosophila, glial cells and neurons can be counted easily and are found in a ratio of 1:10 (Beckervordersandforth, Rickert, Altenhein, & Technau, 2008; Kremer, Jung, Batelli, Rubin, & Gaul, 2017). Counting of neural cells in much larger brains of rodents or humans is more challenging and for the human brain ratios from 1:1 to 10:1 have been reported (von Bartheld, Bahney, & Herculano-Houzel, 2016).

Although there is no doubt that a nervous system generally harbors two major cell types, glia is often overlooked when it comes to the question of how often and when the nervous system evolved (Arendt, Tosches, & Marlow, 2016; Miller, 2009; Varoqueaux & Fasshauer, 2017). On the one hand, Virchow placed these cells on the scientific agenda (Virchow, 1858). On the other hand, he down played their significance by introducing the name Glia, which means cement or glue and suggests a minor role in the functionality of the nervous system. Today, we realize that glial cells are indeed an important and decisive constituent of the nervous system. In the following, we will consider the interplay of glia and neurons as driving force of the evolution of elaborated computing devices as we find them in our own brain, focusing on the origin of wrapping glial cells and myelin.

2 | NEURONS AND GLIAL CELLS EVOLVED AT THE SAME TIME

At the onset of animal evolution, epithelial structures were developed as found today in Porifera, which lack discernible neuronal cell types (Bullock & Horridge, 1965). However, Porifera harbor up to 16 distinct cell types including those that form sensory cilia (Leys, 2015; Mah & Leys, 2017). Even in such primitive multicellular organisms, coordinated and coherent responses to external cues are possible, which require some form of communication among the different cells (Elliott & Leys, 2007; Lavrov & Kosevich, 2018; Nakayama et al., 2015; Nickel, Scheer, Hammel, Herzen, & Beckmann, 2011). Indeed, classic neurotransmitters such as glutamate or GABA exist and glutamate-induced contractions were shown (Elliott & Leys, 2010). Moreover, the major protein components required for secretion and signaling receptors have already appeared in this early stage of evolution and metabotropic glutamate, dopamine, and serotonin receptors are all encoded in the Porifera genome—although these animals lack clear neurons (Riesgo, Farrar, Windsor, Giribet, & Leys, 2014; Srivastava et al., 2010).

In Porifera, epithelial cells are able to feed from the environment through endocytosis at the apical cell domain (Figure 1a). The formation of sensory cilia, which are present in Porifera, caused morphological specializations of the apical cell domain (Mah & Leys, 2017). This quite likely caused restrictions in feeding from the external world by endocytosis compared to normal neighboring epithelial cells. Such ur-sensory cells[1] had therefore to be metabolically supported by neighboring epithelial cells (Figure 1b).

Considering that the first neurons may have been sensory cells and that such cells require special metabolic care by their neighbors, we speculate that an epithelial "neural stem cell" underwent asymmetric cell division to generate an ur-neuron and an ur-glial cell. As a general theme in evolution, such progenitor cells require the activity of proneural and neurogenic genes (Baker & Brown, 2018). Indeed, these two gene families are already present in Cnidaria (jellyfish, sea anemone, and hydra) (Busengdal & Rentzsch, 2017; Galliot et al., 2009; Marlow, Roettinger, Boekhout, & Martindale, 2012). Moreover, in the sea anemone *Nematostella vectensis*, special neural progenitor cells have been identified that respond to the same molecules as neural progenitor cells in flies or man. In an apparently asymmetric cell division, these progenitor cells generate neurons and a still uncharacterized second cell type (Busengdal & Rentzsch, 2017). These cells might correspond to the most primitive nonneuronal support cells, which eventually developed into the first glial cells.

Thus, we postulate that neurons and glial cells evolved at the same time to meet one of the biggest challenges neuronal cells are facing: nutrient supply.

3 | GLIAL CELLS PROVIDE METABOLIC SUPPORT

Due to their morphological specializations, neurons had to meet the big challenges of organizing metabolic supply and became more and more dependent on the metabolic support by accompanying cells (Magistretti & Allaman, 2015, 2018; Nave, 2010b; Pellerin & Magistretti, 1994; Tsacopoulos & Magistretti, 1996; Volkenhoff et al., 2015). The first glial function to evolve, according to our model, was the ability to provide metabolic support to neurons (Figure 1b). This may also be the reason why primitive glial cells are not so easy to recognize. For example, recent single-cell RNA-seq experiments in *Nematostella vectensis* revealed an astonishing diversity of neuronal cell types, but glial transcriptome signatures as found in vertebrates were not reported for this sea anemone (Sebé-Pedrós et al., 2018). But how should a glial transcriptome signature be recognized? Mammalian CNS glial cells, astrocytes and oligodendrocytes, are transcriptionally diverse and no clear universal glial marker has been identified yet (Cahoy et al., 2008; Zhang et al., 2014). Although some glial differentiation markers such as glutamine synthetase are expressed in Nematostella (Roots, 1981; Sebé-Pedrós et al.,

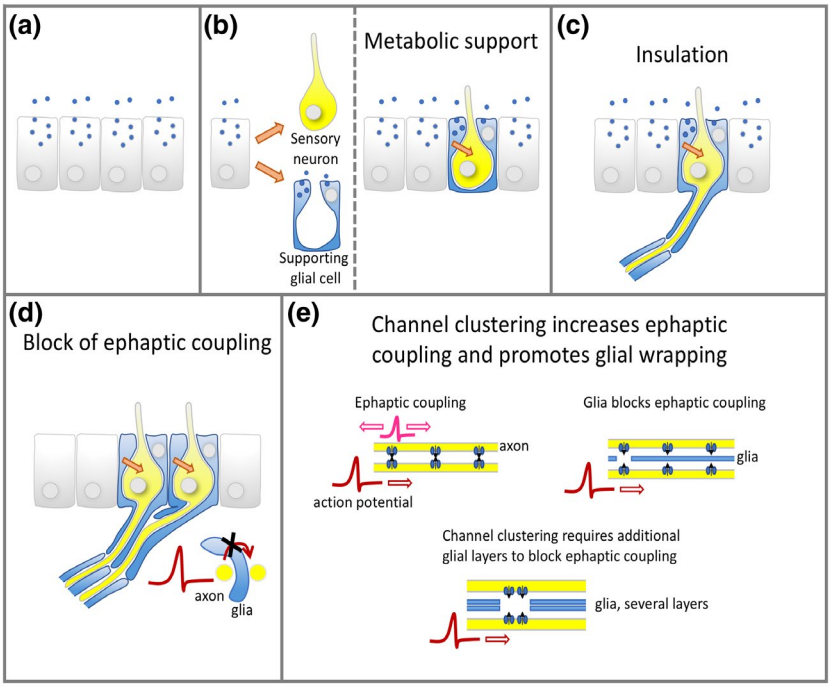

FIGURE 1 Evolution of glial wrapping. Model explaining the early evolution of wrapping glial cells. (a) Primitive organisms lacking nervous systems comprised of epithelia. All cells were able to feed from their environment by endocytosis. Blue dots indicate nutrients taken up by the cell at the apical cell membrane. (b) One epithelial cell gained the ability to divide asymmetrically to generate a sensory neuron (yellow) and a supporting glial cell (blue). The reorganization of the apical cell domain of the sensory neuron prevented feeding from the environment. Nutrients had to be delivered by the neighboring glial cell (orange arrow). (c) As the neuron started to develop an axon, it was accompanied by glial processes which allowed the growth of axonal diameter. (d) In axon bundles, glial processes efficiently blocked ephaptic coupling between neighboring axon. (e) Clustering of voltage gated ion channels resulted in an increase of conductance speed and an increased likelihood of ephaptic coupling by increasing the electric fields. Additional glial wraps separated the axons further to again block ephaptic coupling

2018), we will have to wait for further molecular and morphological analyses to determine whether the cells expressing these genes are directly neighboring neurons.

A clear and unique glial sequence signature might also be difficult to extract for early glial cells since the relevant metabolic enzymes and transporters required to exert the glial support functions are expressed by all other cells of the organism, too. Thus, the only criterion to define early glia may be its close association with neurons and its lineage. We would therefore postulate that in Cnidaria, cells neighboring neuronal cell types act as primitive glial cells by providing metabolic support and possibly spatial isolation from the remaining cells. Examples may be seen in the lens eyes of Cubozoa (box jellyfish), where photoreceptors are accompanied by pigment cells that may be considered as glial support cells (Gehring, 2005; O'Connor et al., 2010), or in the special ectodermal cells that compartmentalize axons in the jellyfish nervous system (Garm, Poussart, Parkefelt, Ekström, & Nilsson, 2007; Mackie & Meech, 1995) (see below). Definite proof would require ablation of these ur-glial cells, which should cause some form of neurodegeneration.

4 | THE EVOLUTION OF MORE PRECISE AND FASTER NERVOUS SYSTEMS

In a next evolutionary step, neurons started to more precisely deliver their signaling cargo. For this, long processes developed from the primitive sensory cells to, for example, reach muscle cells. Here, local communication between the two cell types was organized in special zones that evolved into synapses (Varoqueaux & Fasshauer, 2017). The exocytosis machinery required to release signaling molecules (neurotransmitters) depends on voltage controlled Ca^{2+} entry (Senatore, Raiss, & Le, 2016). Next voltage-gated sodium and potassium channels evolved to convey information from the soma to the synapse, which act as universal information transmission tools in all neurons known to date. As the ancestors of neurons acquired the ability to generate fast changes in their membrane potential they could easily transmit information to distant target cells. To further improve the functionality of the nervous system, only a few set screws are required. Among these is that information had to be transmitted as fast and as precise as possible to react better than competitors. As

we will discuss below, such an advance in nervous system function requires a close interplay of neurons and glial cells.

In cnidarian species, we find simple nervous systems that might resemble the evolutionary intermediate described above where all of the major components defining a neuron are in place. Indeed, the complex gene repertoire of the sea anemone *Nematostella vectensis*, a cnidarian representative, is even more related to the human genome than to the fly genome (Putnam et al., 2007). Ctenophores (comb jellyfish) are a sister group of the cnidarian jellyfish and share a gelatinous body. However, they may be more closely related to the bilaterians, as they have mesoderm and true muscle cells. The genome sequence of Ctenophores sparked speculation as to whether neurons have evolved twice, since it placed Ctenophores at the base of metazoan evolution (Moroz et al., 2014; Ryan et al., 2013). Thus, Poriferea (and Placozoa) must have either lost neurons or Cnidaria and Bilateria must have evolved neurons independently (Marlow & Arendt, 2014). However, the current sequence analysis is not yet conclusive and thus, the question whether neurons evolved more than once remains unsettled.

5 | GLIAL CELLS INCREASE INFORMATION TRANSFER SPEED

Possibly, early sensory neurons detected prey and communicated this to their neighboring cells by paracrine signaling. The precision of information transfer increased when neurons started to generate processes to reach and directly contact distant target cells such as muscle cells. In Cnidaria, axons leave the epithelium and travel through the mesoglea separating the ectodermal cell layer from the endodermal cell layer to meet contractile cells (Figure 1c) (Buzgariu, Haddad, Tomczyk, Wenger, & Galliot, 2015; Kerfoot, Mackie, Meech, Roberts, & Singla, 1985; Norekian & Moroz, 2019). In this scenario, the need of metabolic supply for the neuron and its process continued, which presumably sparked the formation of supporting glial cell sheets, which additionally provide insulation to the axon and later in evolution turn into myelin.

We postulate that the intimate interaction of an insulating glial cell with its target axon also provides the means to generate larger caliber axons. However, not all axons that contact glial processes grow equally in diameter (Hess, 1958; Matzat et al., 2015; Peters, Palay, & Webster, 1991; Stork et al., 2008). In addition, target size and thus, possibly, neuronal activity influence axonal caliber (Voyvodic, 1989). Thus, the axon itself is able to instruct the glial cell to provide more or less metabolic support, which concomitantly would result in a selective growth of active axons.

Axonal growth also has some direct consequences on neuronal physiology since it feeds back on axonal conduction velocity, which increases in dependence of the axonal diameter (Castelfranco & Hartline, 2016; Hartline & Colman, 2007; Hodgkin & Huxley, 1952). In other words, the close interaction of glial cells and neurons not only fostered the survival of the neuron, but in addition, provided the means to react faster to external stimuli, which appears as a powerful selection criterion.

6 | GLIAL CELLS REGULATE PRECISION OF INFORMATION TRANSFER

A broad spectrum of sensory neurons devoted to detect changes in light, temperature, olfactory, or mechanical stimuli, allowed to extract a wealth of information from the external as well as internal environment. At the same time an increase in the number of sensory neurons of a given modality allowed the animal to detect stimuli with a higher spatial resolution. The increased number of sensory neurons resulted in the formation of several axons that most likely projected together in fascicles toward their target (Figure 1d). Naked, neighboring axons are able to excite each other via local field effects and it has been speculated already a long time ago that primitive ur-glial cells were first needed to suppress electric interactions between closely apposed axons (Horridge, Chapman, & MacKay, 1962) (Figure 1d). Glial wrapping therefore entails neurons with an increase in precision of neuronal information transmission, which likely has been a second driving force in glial evolution (Figure 1e).

Passive influences of one axon on the activity of a neighboring axon are known as ephaptic coupling effects, which clearly affect the precision of neuronal transmission (Arvanitaki, 1942; Krnjevic, 1986; Rasminsky, 1980). On the one hand, ephaptic coupling allows to synchronize firing axons within one unit (Anastassiou & Koch, 2015; Anastassiou, Perin, Markram, & Koch, 2011; Han et al., 2018). On the other hand, ephaptic coupling will impair precision across different axon fibers and might be the cause of paroxysmal dystonia (episodic movement disorders) observed in patients suffering from demyelinating diseases such as multiple sclerosis (Bokil, Laaris, Blinder, Ennis, & Keller, 2001; Mehanna & Jankovic, 2013; Ostermann & Westerberg, 1975). It has also been proposed that Lhermitte's sign, an electric shock running through the back and the four limbs upon bending the head forward, a characteristic sign of multiple sclerosis, may be the consequence of ephaptic coupling of demyelinated axons touching each other (Lhermitte & Bollak, 1924; Smith & McDonald, 1999).

Do we find evidence for glial cells blocking ephaptic coupling in primitive organisms? Although Cnidaria are considered to have no glial cells, some species with a ring shaped, symmetric central nervous system have special ectodermal cells, which could well be glial-like cells, that send out specialized processes to compartmentalize groups of axons (Garm et al.,

2007; Mackie & Meech, 1995). Such compartment formation may be a consequence of the need to block ephaptic coupling among different axons, and it will be interesting to see a direct test of this hypothesis using electrophysiology.

In conclusion, we postulate that neuron–glia interaction promoted an increase in axonal growth which according to the physical laws underlying electric conduction, results in an increased signaling speed (Cohen et al., 2019; Hodgkin & Huxley, 1952). Concomitantly, neuron-glia interaction provided the means for a more precise information transmission by blocking ephaptic coupling of neighboring axons. These processes provided selective advantages from beginning of nervous system evolution and thus should be present in modern species.

7 | EVOLUTION OF MYELIN

During evolution of animals the blocking of ephaptic coupling by glia contributes to both speed and precision of neuronal signaling and thus constitutes a significant selection criteri. How to further increase conductance speed? The option to develop giant axons is constrained by space limitations (Hartline & Colman, 2007; Zalc & Colman, 2000; Zalc, Goujet, & Colman, 2008). Alternatively, ion channels can be clustered along the axonal membrane to achieve faster conductance speed. Such clustering has been beautifully documented for voltage-gated ion channels but also thermosensitive and mechanosensitive two-pore domain potassium (K2P) channels at the nodes of Ranvier found in myelinated nerves (Amor et al., 2014; Brohawn et al., 2019; Hill et al., 2008; Kanda et al., 2019). Interestingly, clustering of voltage-gated ion channels is also found in unmyelinated C-fibers in the mammalian nervous system where it allows micro-saltatory conductance (Neishabouri & Faisal, 2014) and has been reported to occur along axons of the invertebrate Aplysia (Johnston, Dyer, Castellucci, & Dunn, 1996). In rodents, it has been reported that clustering of Nav ion channel prior to myelin deposition is sufficient to increase velocity of propagation of action potential (Freeman et al., 2015).

Importantly, the local concentration of channels causes stronger electric fields (Hichri, Abriel, & Kucera, 2018). This in turn requires increased glial wrapping to spatially separate an axon from its neighbors to prevent ephaptic coupling (Figure 1e). Thus, ephaptic coupling provides the evolutionary trigger for an increased wrapping efficiency, which eventually resulted in the formation of compact myelin as we know it from vertebrates.

Based on the above-mentioned considerations, glial cells are posed to develop a supporting sheath around axons, to make them bigger in diameter and to block electrical cross-talk between axons. Indeed, in most invertebrates we find glial cells that form only simple glial wraps around axons or axon bundles (Bullock & Horridge, 1965), which is in line with these functions. However, higher vertebrates evolved complex multiple glial wrapping in the form of myelin and concomitantly evolved saltatory conduction (Castelfranco & Hartline, 2016). This speeded up information transmission even further to promote the development of very large animals such as giraffes or even dinosaurs (Weil et al., 2018; Zalc, 2016). Myelin is defined as a compacted, glial derived, lipid-rich multilamellar sheath wrapped around a stretch of axon. How and when could myelin appear in the vertebrate lineage?

In the last century, before the success of Drosophila genetics enticed many scientists from other models, a great diversity of invertebrate species were analyzed for the presence of myelin-like structures, but findings appeared largely forgotten (Figure 2). Hess described myelin in the cockroach, *Periplaneta americana*, a blattodean species (Hess, 1958), and McAlear in the crab, *Cancer irroratus* a crustacean species, (McAlear, Milburn, & Chapman, 1958). In 1959, Wigglesworth analyzed *Rhodnius prolixus*, a hemipteran species, and concluded that peripheral Schwann cell-like glial cells generated myelin sheath around lateral motor axons (Wigglesworth, 1959). At the same time, Hama studied the nervous system of the earthworm *Eisenia foetida*, an Annelid, and reported multilayered, spiral wraps around some giant axons resembling myelin-like multilamellar sheaths (Hama, 1959), a finding which was confirmed later (Roots & Lane, 1983). Some years later leeches (*Hirudo medicinalis*, annelida) were analyzed and again myelin-like glial cells were observed (Coggeshall & Fawcett, 1964; Kuffler & Potter, 1964; Van Harreveld, Khattab, & Steiner, 1969). Myelin was also found in the ventral nerve cord of prawns (*Palaemonetes vulgaris*) (Heuser & Doggenweiler, 1966), lobster (Govind & Lang, 1976), and shrimp (*Penaeus japonicus*) (Hama, 1966) as well as in squids where Geren and Schmitt reported 3–6 Schwann cell layers around a giant fiber (Geren & Schmitt, 1954). In summary, these reports demonstrate a rather broad distribution of myelin or related myelin-like structures in many invertebrate animal species. However, it is of note that not all annelids or crustaceans have wraps of membrane around their axons (Figure 3; also see Figure 3 in Hartline & Colman, 2007).

Myelin as we know it from mammalian species is associated with very fast propagation of action potentials by providing the means for saltatory conduction. Is there a similar increase in conductance speed determined for myelinate invertebrate axons? Myelinated fibers of the shrimp *(Penaeus setiferus, Penaeus japonicus)* show no morphologically discernible nodes of Ranvier, yet, exhibit a conduction velocity greater than 90 m/s, which is comparable to conduction speed in myelinated mammalian axons (Hama, 1966; Kusano, 1966). In contrast, node-like structures were detected in small sea prawns (*Palaemonetes vulgaris*) (Heuser & Doggenweiler, 1966; see Roots, 1984, for

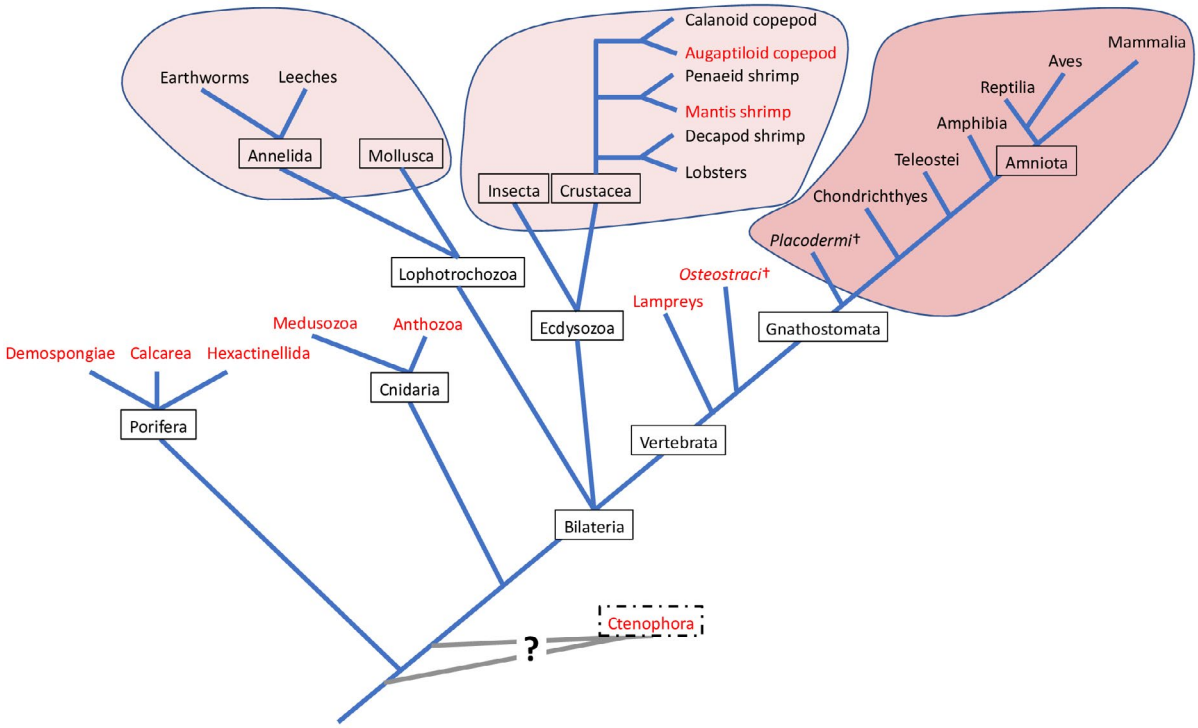

FIGURE 2 Simplified phylogenic tree showing species with myelin or myelin-like structures. All gnatostomata are myelinated (dark purple shading). Among craniate, agnatan are not myelinated and appear in red. Names in italic indicate fossils for which we assume they were myelinated (e.g., Placodermi) or not (e.g., Osteostraci). Cnidarians, Ctenophores, and Porifera are nonmyelinated species. Question marks indicate the uncertain evolutionary position of the Ctenophores. Among Lophotrochozoan (leeches and earthworm) myelin-like structures have been described (light pink shading). Similarly, for several insect and crustacean species, myelin-like structures were described (light pink shading) and species in which myelin-like structures have not been described appear in red. This schematic representation is inspired and modified from Figure 3 in Salzer & Zalc, 2016 and Figure 3 in Hartline & Colman, 2007

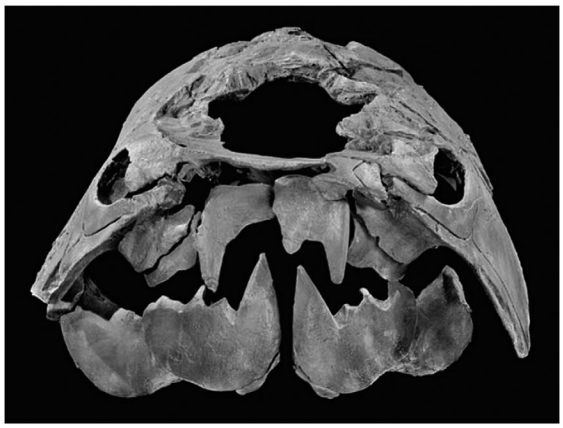

FIGURE 3 Frontal view of a fossil specimen of placoderm from Morocco illustrating the presence of the neural crest derivative the hinged jaw, which acquisition is concomitant with that of a compact myelin sheath in vertebrates. (Photograph by D. Goujet) [Correction added on April 30, 2020, after first online publication: "Spitzberg" was changed to "Morocco" in the legend]

discussion). Moreover, in the earthworm and in shrimps (*Penaeus chinensis* and *Penaeus japonicus*) circular or fenestrated nodes that regularly disrupt the continuity of the glial sheath around the axon were observed that might provide the basis for the extremely fast conductance rates (Castelfranco & Hartline, 2016; Günther, 1973, 1976; Hsu & Terakawa, 1996; Xu & Terakawa, 1999). However, it is not known whether voltage-gated ion channels concentrate below these windows. Using myelin-like sheath around axons the penaeid shrimp achieved speed of conduction of nerve impulse of 200 m/s, the highest speed of conduction reported among living species, twice more rapid than in the fastest reported myelinated axons in vertebrates (Hartline & Colman, 2007). Therefore, not only structural aspects of myelin itself, but also its physiological consequences in accelerating conductance speed by saltatory conduction are found in invertebrates, indicating that possibly vertebrate myelin has much older evolutionary roots than previously thought. However, based on the diversity of different myelin structures ranging from compacted glial sheaths to purely axonal differentiations myelin possibly appeared several times independently during evolution (Castelfranco & Hartline, 2016; Wilson & Hartline, 2011a).

There are some differences between invertebrate and vertebrate myelin. While the latter is highly organized and compacted, the invertebrate sheath appears irregular. Likewise, no molecular similarity has been identified so far comparing vertebrate and invertebrate myelin (Pereyra & Roots, 1988; Waehneldt, 1990). However, the different forms of invertebrate

myelin may share some molecular properties as monoclonal antibodies generated against earthworm myelin-like sheaths, cross-reacted with crayfish glia forming myelin-like structures (Cardone & Roots, 1996). Myelin, however, may also have different evolutionary origins. Copepods are very small marine organisms that show a rather unusual form of myelination. Here, the axon itself forms lamellar sheaths that eventually engulf the entire axon (Davis, Weatherby, Hartline, & Lenz, 1999; Wilson & Hartline, 2011a, 2011b). The mode of axon insulation highlights that the need of blocking ephaptic coupling between axons might be higher than the need of metabolic coupling of the neuron with its neighbors.

In the beginning, we have emphasized that a prime evolutionary task of glial cells is to provide neurons with metabolites via metabolite transporters. Such metabolic coupling is also observed between axons and myelin forming glial cells (Fünfschilling et al., 2012; Lee et al., 2012; Saab et al., 2016). In vertebrate myelin, transport of metabolites from the cell soma to the axon can be accomplished by gap junctional coupling or cytoplasmic bridges as seen in the Schmidt–Lanterman incisures (Nave, 2010a; Nave & Trapp, 2008; Nave & Werner, 2014). In invertebrate myelin, similar structures may be present; however, in case of a pure neuronal myelin formation mode as observed in some copepods (Wilson & Hartline, 2011a), we assume that glial support is efficiently blocked. Thus, the gain in fitness obtained by such structures must be very high and must exceed the needs for metabolic supply. Indeed, comparing escape responses in myelinate and amyelinate copepod species demonstrated that the escape speed is identical in the two classes, but the navigation precision during the escape response is dramatically lower in the amyelinate species (Buskey, Strickler, Bradley, Hartline, & Lenz, 2017). The evolutionary advantage of myelination may therefore not only be an increase in conduction speed but also in precision of neuronal signaling.

8 | DATING THE ORIGIN OF COMPACT MYELIN IN VERTEBRATE

Although it is generally accepted that vertebrates are myelinated, it has to be stressed that in fact, not all vertebrates are myelinated. Based on the presence or absence of a hinged jaw, craniates are divided in two groups: Agnatha (jawless fish) and Gnathostomata, those organisms whose neural crest first produced a hinged jaw. Among living species, hagfishes and lampreys (Agnathans), are not myelinated, while all members of the Gnathostomes infraphylum are myelinated (Figure 2). This observation leads to hypothesize that the dual, apparently unrelated acquisitions of compact myelin and a hinged jaw occurred at the same time in evolution (Zalc & Colman, 2000). This raised the question of what was the first myelinated vertebrate? A logical answer to this question, has been proposed using the most sophisticated experimental animals (Devonian fossil fishes) and tools (21st century millimeter rulers and a magnifying lens) available (Zalc et al., 2008). Placoderms, particularly wicked-looking fish (Figure 3), and jawless ostracoderms reigned the Devonian oceans 443–359 million years ago (Gai, Donoghue, Zhu, Janvier, & Stampanoni, 2011). Measurements of fossilized oculomotor nerve foramina in both organisms reveal that the nerves in both fish were of equal diameter; however, and remarkably, the imprints of oculomotor nerve on the inner face of the skull of placoderms was 10 times longer than its ostracoderm counterpart. This implies that placoderms were able to sustain impressively longer nerve lengths possibly because they were myelinated, and therefore able to conduct the nerve impulse by rapid saltatory conduction. Acquisition of compact myelin by vertebrates can therefore be dated back to the late Devonian period, some 425 million years ago.

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END NOTE

[1] Ur-cells refer to ancestors of a given cell type by analogy to the Bible's Ur of the Chaldees, birth place of Abraham.

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