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Regulation of Conduction Time along Axons

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Abstract

Timely delivery of information is essential for proper function of the nervous system. Precise regulation of nerve conduction velocity is needed for correct exertion of motor skills, sensory integration and cognitive functions. In vertebrates, the rapid transmission of signals along nerve fibers is made possible by the myelination of axons and the resulting saltatory conduction in between nodes of Ranvier. Myelin is a specialization of glia cells and is provided by oligodendrocytes in the central nervous system. Myelination not only maximizes conduction velocity, but also provides a means to systematically regulate conduction times in the nervous system. Systematic regulation of conduction velocity along axons, and thus systematic regulation of conduction time in between neural areas, is a common occurrence in the nervous system. To date, little is understood about the mechanism that underlies systematic conduction velocity regulation and conduction time synchrony. Node assembly, internode distance (node spacing) and axon diameter - all parameters determining the speed of signal propagation along axons - are controlled by myelinating glia. Therefore, an interaction between glial cells and neurons has been suggested.

This review summarizes examples of neural systems in which conduction velocity is regulated by anatomical variations along axons. While functional implications in these systems are not always clear, recent studies in the auditory system of birds and mammals present examples of conduction velocity regulation in systems with high temporal precision and a defined biological function. Together these findings suggest an active process that shapes the interaction between axons and myelinating glia to control conduction velocity along axons. Future studies involving these systems may provide further insight into how specific conduction times in the brain are established and maintained in development.

Throughout the text, conduction velocity is used for the speed of signal propagation, i.e. the speed at which an action potential travels. Conduction time refers to the time it takes for a specific signal to travel from its origin to its target, i.e. neuronal cell body to axonal terminal.

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Introduction

When signals are conveyed from one neuron to another, temporal accuracy is essential for proper information processing in the nervous system. Exertion of fine motor skills, sensory processing and higher integrative functions require precise regulation of nerve conduction velocity. If the speed of conduction in nerves is altered by illness, impairments of motor, sensory (Compston and Coles, 2002) and possibly cognitive skills follow (Nave, 2010). In the peripheral and central nervous system a specialization of glial cells, the myelin sheath enwrapping of axons, was the last major evolutionary invention for the nervous system of vertebrates (Bullock et al., 1984; Zalc et al., 2008). Myelination of axons, first described in 1854 (Virchow, 1854), increases the speed of conduction significantly by saltatory nerve conduction between nodes of Ranvier (Ranvier, 1871). Qualitative differences of myelination along axons, such as variations in internode distance and myelin sheath thickness, enable systematic regulation of conduction velocity.

Precise temporal signal transmission is of particular importance for the processing of auditory information. One of the important functions of the auditory system is spatial hearing, which enables us to localize sound and to extract acoustic information in a noisy environment (Sound segregation or “cocktail party effect”) (Blauert, 1997), a task that fails with aging. The two main acoustic cues used for these tasks are interaural time differences (ITDs) and interaural intensity differences (IIDs). Processing ITDs and IIDs requires binaural inputs that are temporally correlated. Abnormal timing and synchrony in the auditory brainstem haven been suggested to contribute to auditory neuropathy (Oertel, 2005; Zeng et al., 2005), a form of hearing impairment with normal cochlear conduction but disordered neural conduction (Starr et al., 1996; Starr et al., 2000). Likewise, patients with demyelinating diseases like MS display loss of hearing acuity and impaired temporal processing in the auditory brainstem (Noffsinger et al., 1972; Levine et al., 1993; Rappaport et al., 1994; Jones et al., 2002). At a cellular level, dysmyelination has been shown to cause increase in spike jitter and failures (Kim et al., 2013). Similarly, temporal and speech processing is diminished in elderly listeners who have normal hearing thresholds (Gońdon-Salant and Fitzgibbons, 1993; Anderson et al., 2012).

Systematic timing of signal propagation is a common occurrence in the nervous system and required for proper neural function. A particularly precise timing of neuronal fibers is displayed by the circuits in the auditory brainstem, detecting time disparities in the microsecond range and providing binaural inputs in temporal register. The auditory brainstem of birds and mammals presents a unique opportunity to study the development and mechanisms of CV regulation. The sound localization circuits in the auditory brainstem have temporally precise axonal projections, and a well-defined function. Future experiments may utilize these systems to study the regulation of conduction time in the nervous system,

both during development and at advanced age. The results will contribute to the understanding and treatment of myelin-related diseases – from hereditary leukodystrophies to multiple sclerosis and the degeneration of myelin with age.

Determinants of conduction velocity regulation

Measurements of conduction velocity in axons attracted attention very early in the history of neuroscience. Empirical (Zotterman, 1937; Hursh, 1939; Gasser and Grundfest, 1939; Hutchinson et al., 1970) and theoretical studies (Rushton, 1951) showed a linear relationship between diameter and conduction velocity in myelinated axons. The myelin sheath is provided by specialized glial cells: the oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). The myelin sheath is interrupted in regular intervals by nodes of Ranvier, where sodium channels are present in high density, thereby enabling saltatory conduction (Tasaki, 1939), the basis of fast signal propagation along myelinated axons.

Conduction velocity is influenced by myelin sheath thickness and internode distance (i.e. the distance along the axon between the nodes of Ranvier) (Hursh, 1939), and both parameters are linearly related to axon diameter. Conduction velocity increases with increasing internode distance up to 2000 μm (Brill et al., 1977). Another factor influencing the speed of signal propagation is the composition and density of sodium channels at the nodes of Ranvier (Waxman, 1975) as they influence the onset of the action potential generated at the node. Thus, speed of conduction in myelinated axons is dependent on a number of parameters and variation of any of those parameters can regulate signal propagation speed. These parameters and their influence on conduction velocity have been described in a number of reviews (Waxman, 1975; Waxman and Swadlow, 1977; Waxman, 1980; Waxman, 1997).

Conduction velocity variations in axons

Evolutionary pressures have lead to a maximization of conduction velocity in some axons. However, optimizing nerve fiber function means more than maximizing conduction velocity: Certain neural functions require adjustment of conduction velocity to regulate the relative timing of inputs, which in some cases entails a slowing down or a delay of signal propagation along axons relative to other axonal inputs.

One of the earliest studies on differential conduction velocity described systematic variations in axon diameter of motor axons innervating the mantle of the squid (Pumphrey and Young, 1938). These variations reduced temporal discrepancies as the longer fibers conducted more quickly than the shorter ones. While these differences in diameter do not achieve isochronicity of inputs (the concurrent arrival of inputs at the target), they do ensure nearly simultaneous contraction of the mantle muscles, resulting in a faster reaction time.

Another well-studied example is found in the classical model of the electromotor system in electric fish. In this organ, so-called electrocytes on the body surface provide an electrical discharge used to incapacitate prey. In order to fully deploy its potential, electrocyte discharges need to be synchronized. The electrocytes are connected to a pacemaker nucleus

controlling their deployment and due to their location along the body, the axons providing input from the pacemaker nucleus differ in length. Internode distance along those axons is adjusted so that conduction velocity compensates for different axon lengths and simultaneous firing is achieved (Bennett, 1970; Waxman, 1971; see Figure 1 in Waxman, 1997). In the electric fish Sternarchus, two types of nodes of Ranvier exist: a small, typical type that actively generates spikes, and a larger electrically passive node type that adds capacitance to delay the propagation of action potentials along the axon and modify the waveform of the voltage spike (Waxman et al., 1972). Hence, in addition to the number of nodes of Ranvier along an axon, the structure of nodes can influence conduction velocity.

A particularly elegant example of systematic regulation of conduction velocity in mammals is found in the fibers from the inferior olive (IO) to cerebellar purkinje cells in rats. Purkinje cells in the cerebellar cortex display a high level of spiking synchronicity, supported by electrical coupling of IO cells through gap junctions. In rats, the olivocerebellar path length varies considerably between the different parts of the cerebellar cortex (Sugihara et al., 1993), however their conduction times are fairly equal (Sugihara et al., 1993; Lang and Rosenbluth, 2003). Variations in axon diameter as well as differential myelination contribute to these isochronic inputs (Sugihara et al., 1993; Lang and Rosenbluth, 2003). It should be noted that these findings are not without controversy; these results have not been observed in the cat, suggesting that the isochronicity of the olivocerebellar pathway is due to a restricted brain size in smaller animals (Aggelopoulos et al., 1995; Baker and Edgley, 2006).

Another representation of intra-axonal variation of conduction velocity was illustrated in the thalamocortical pathway of mice by Salami and colleagues (Salami et al., 2003). Neurons in the ventrobasal nucleus of the thalamus project to different areas in the cortex and their projections differ widely in length. The axon partitions in the intracortical region, however, cover a similar distance, due to the architecture of the cortical areas. Despite the length difference of the projections, action potentials elicited in the thalamus arrive around the same time at their target. Within cortical areas, conduction velocity slows down about 10-fold in thalamocortical axons, most likely the result of decreased myelination. Thus, the longer, more variable axon segments propagate action potentials quickly, while the shorter, uniform segments contribute most to overall conduction time.

In the retina, variations in conduction velocity minimize conduction time differences among retinal ganglion cell axons (Stanford, 1987). This presumably ensures spatiotemporal representation of the retinal image so that differences between conduction times to the lateral geniculate nucleus are minimized. Another such example is found in the projection from the lateral amygdala to distributed perirhinal sites. Conduction times are similar, despite the fact that the signals must travel different distances (Pelletier and Paré, 2002). The authors hypothesize that these synchronized inputs facilitate Hebbian associations (Hebb, 1949) between coincident, but spatially distributed, activity patterns in the perirhinal cortex.

Cortical areas in both hemispheres of the brain are connected via projections through the corpus callosum. Recent findings show that the axons forming these projections differ in length and possess different fiber caliber (Tomasi et al., 2012). Moreover, axon diameter depends on both the origin and the target of the projection (Innocenti et al., 2013). Although

the exact functional significance is unknown, Innocenti and colleagues speculate that specific conduction times of projections from and within the cerebral cortex contribute to information encoding and processing in the brain through a complex system of lines of communication with specific time computing properties.

Cortical layer V neurons project to a number of different areas, both ipsilaterally and contralaterally, via the corpus callosum. Chomiak et al. showed that conduction velocity in the minor axon branches, connecting the ipsilateral targets, is related to the axonal length from the origin neuron (Chomiak et al., 2008). Conduction velocity is decreased in shorter axons, and vice versa, to allow isochronic spiking at the target nuclei. The much longer, contralateral axon branch is excluded from this strategy: conduction time to the other hemisphere is more than twice as long as the time needed for a signal to reach ipsilateral targets. It thus seems unlikely that this fiber branch undergoes the same temporal adjustment.

Intra-axonal differences, i.e. differences within a single axon, in signal propagation velocity have been suggested in various pathways. In the CNS, direct measurements of response times of antidromically elicited spikes showed that conduction velocity changes between the optic nerve and the optic tract (Baker and Stryker, 1990). This conduction velocity variation takes place presumably takes place in different parts of the same axons, but this was not explicitly determined. In the PNS, differences in internodal length, myelin sheath thickness and axon caliber were found for ventral motor neuron axons (Fraher, 1976; Fraher, 1978a; Fraher, 1978b). Similarly Traub and Mendell (Traub and Mendell, 1988) observed a sequential reduction in conduction velocity for receptor cell axons as they enter the dorsal root and then the spinal cord.

Conduction velocity regulation of axons and thus the specific control of conduction time seem unlikely to be a random occurrence. The exact functional implications of precisely timed inputs in the above-described examples, however, remain undefined.

The auditory system as a model system to study conduction velocity regulation

Auditory brainstem circuitry and function have been especially well described for mammals and birds, and both systems have been used for decades as research models (Friauf and Lohmann, 1999; Rubel and Fritzsch, 2002; Grothe, 2003; Kandler et al., 2009; Grothe et al., 2010; Burger et al., 2011; Ashida and Carr, 2011). Precise temporal signal transmission is of particular importance for the processing of auditory information.

One of the cues used for sound localization and segregation (suppression of unwanted noise, the “cocktail party effect”, which allows us to focus on a single conversation in a noisy room) are interaural time differences (ITD), or the difference in a sound’s arrival time at each ear. ITDs are defined by the speed of sound and the inter ear distance and as a result occur in the microsecond range. The primary circuitry underlying this ability involves ipsilateral and contralateral excitatory collaterals of single axons from monaurally innervated neurons in the cochlear nucleus to binaurally activated ITD-detecting neurons.

In the avian brainstem, the circuit responsible for encoding sub-millisecond ITDs consists of axonal delay lines innervating an array of coincidence detector neurons. Information from the ears is transferred to neurons in nucleus magnocellularis (NM), a part of the avian cochlear nucleus, on each side of the brainstem. Individual NM axons bifurcate and project to both the ipsilateral nucleus laminaris (NL) and the contralateral NL. Thus, NL coincidence detector neurons receive inputs from both ears. The circuit comprised by NM and NL embodies a modified Jeffress model (Jeffress, 1948; Overholt et al., 1992; Köppl and Carr, 2008; Seidl et al., 2010), in which external arrival time differences are matched by an internal delay line. NL neurons form a bilateral map of sound source locations (Figure; Carr and Konishi, 1990; Overholt et al., 1992; Köppl and Carr, 2008; for review see Palmer, 2004; Burger et al., 2011). Equivalent interaural delays occur when a sound stimulus originates from straight ahead, arriving at both ears simultaneously and leading to an ITD of 0 μs. Action potential (AP) travel times have to be regulated precisely to ensure coincident arrival of information within several microseconds at individual detector neurons in NL. NM neurons send out a circuitous, but short axon branch to the ipsilateral NL and a much longer axon branch to the contralateral NL (Figure; Seidl et al., 2010). The length difference between these axon branches exceeds 1600 μm, making coincident arrival of inputs at 0 ITD a challenge. In fact, coincident binaural inputs would be impossible at any naturally occurring ITD. Anatomical data describes variations in axon diameter and distance between nodes of Ranvier between ipsilateral and contralateral inputs to NL, suggesting that axon length differences are counterbalanced by differences in conduction velocity (Seidl et al., 2010). Direct measurements of conduction velocity confirm this hypothesis and show that signal propagation is twice as fast in the longer, contralateral axon (Seidl et al., 2013). Thus, within one axon, conduction velocities differ systematically between two branches enabling coincidence detection in the microsecond range.

These findings in the chicken auditory brainstem were foreshadowed by a study in the barn owl (Carr and Konishi, 1990). Here, differences between the ipsilateral and contralateral NM axon branches were found but were not as dramatic as in the chicken. Carr and Konishi also reported variations in axon diameter and internode distances and speculated that these anatomical variations might provide a means to regulate conduction times (Carr and Konishi, 1990).

In the mammalian auditory brainstem variations in axon diameter and internode distance have been found as well. While the exact mechanism of ITD processing in mammals is still being resolved (for review see Joris and Yin, 2007; Grothe et al., 2010; Portfors and von Gersdorff, 2013), it appears to involve a strong, temporally precise inhibitory input in addition to binaural excitatory coincidence detection onto neurons in the medial superior olive (MSO) (Brand et al., 2002; Pecka et al., 2008). This inhibitory projection from the ipsilateral medial nucleus of the trapezoid body (MNTB) is driven by an excitatory input from the contralateral cochlear nucleus. Recent findings have revealed caliber and internode variations that would selectively speed up the excitatory inputs to MNTB compared to those to MSO (Ford et al., 2012). These findings support the hypothesis that inhibitory inputs to MSO are precisely timed in relation to the contralateral excitatory inputs targeting the same nucleus, suggesting a role for inhibition in shaping ITD tuning of MSO neurons. These findings are not without precedence in the mammalian auditory brainstem: in the cat,

binaural axonal inputs to the lateral superior olive, (LSO), involved in the processing of interaural level differences (ILD, occurring when sound is louder at one ear over the other) have been shown to differ in diameter as well (Warr, 1966; Brownell, 1975; Spangler et al., 1985; Spirou et al., 1990; Smith et al., 1991; Smith et al., 1993; reviewed in Joris and Yin, 1998).

Conduction velocity properties of axons providing inputs to primary binaural centers are regulated systematically. Plasticity in ITD and ILD processing can be induced during development and in adulthood by deprivation of meaningful acoustic cues (Seidl and Grothe, 2005; Siveke et al., 2012). This plasticity in response patterns correlates with qualitative changes of inhibitory axonal inputs that depend on normal auditory experience during development (Kapfer et al., 2002; Werthat et al., 2008). Precise timing of excitatory axonal inputs is important for both ITD and ILD coding (ITD: Rose et al., 1966; Goldberg and Brown, 1969; ILD: Joris and Yin, 1995; Park et al., 1996; Park et al., 1997; Tollin, 2003). Deprivation of acoustic cues may also cause a change in the development of myelination and contribute to alteration of timing properties of afferent inputs to MSO and LSO. Therefore, myelin plasticity may play a role in shaping ITD and ILD processing as well. Recent data suggest that myelination can be a substrate for adult plasticity (Liu et al., 2012). It is, thus, possible that changes in myelination can be induced by unnatural acoustic environments during adulthood and result in altered responses of the auditory system (Siveke et al., 2012).

Regulation of conduction time in the auditory system is different from other systems for two reasons. First, adjustment of conduction time serves a known biological function, the encoding of ITDs. The circuitry comprised by NM and NL embodies a Jeffress model of sound localization for which the timing of inputs is crucial (Jeffress, 1948). Second, conduction time regulation needs to be more precise, as ITDs occur in the sub-millisecond range. For the chicken (Calford and Piddington, 1988), and likewise for small mammals like the gerbil (Maki and Furukawa, 2005), the maximum ITD occurring between the two ears is less than 200 μs. If the timing of inputs were off by more than that, no binaural coincidence detection would occur at NL. Hence, precise adjustment of conduction times is a prerequisite. The differential regulation of conduction time in the avian auditory brainstem is remarkable because it takes place in two major branches of a single axon. This sets it apart from differential regulation in the mammalian auditory brainstem (projections with different origin and target) and other systems, where differential regulation occurs along the same axon or in terminal axon branches that make out only a small part of total axon length.

Because of the aforementioned characteristics, the auditory system in birds and mammals presents an interesting model system to study mechanisms and development of internode distance regulation.

Mechanisms of internode distance regulation

Axon diameter, internode distance, and myelin sheath thickness all influence the speed of action potential propagation. Moreover, these factors are to a certain degree correlated with each other. As node assembly, node spacing, and axon diameter are controlled by

myelinating glia (de Waegh et al., 1992; Garcia et al., 2003; Court et al., 2004; Susuki and Rasband, 2008), the key to understanding conduction velocity regulation lies most likely with glial cells and their interaction with axons.

Traditionally, growth during development and the ensuing stretching of axons is thought to be responsible for determining the distance between nodes of Ranvier (Hiscoe, 1947; Schlaepfer and Myers, 1973; Friede et al., 1981; Friede et al., 1985; Hildebrand et al., 1989; Hildebrand et al., 1996). Consequently, the determining factor in internode elongation should be the developmental time period, during which myelination occurs coincident with axonal growth. Such a passive mechanism has major implications on the ability to repair damage after demyelination caused by neurological disease and trauma. Remyelination would not have access to the same processes to control internode distance in adult organisms after growth, and thus the elongation of axons, has stopped. A recent study by Horner and colleagues, however, provides evidence for a dynamic remyelination that is independent of axonal growth (Powers et al., 2013). Here, myelin that is restored by oligodendrocytes after spinal cord injury in mice does not differ from myelin in control animals with respect to internode distance and myelin sheath thickness. Myelin sheath length increased over the course of 6 months to achieve control values. This suggests that establishing internode length may involve a process that does not require lengthening of axons.

Much knowledge about internode distance and its relation to axon diameter has been gained from studies in the PNS, where Schwann cells provide myelination. Myelin formed by Schwann cells is similar to myelin formed by oligodendrocytes in certain aspects, such as composition of Na^+ channels at the node, anchoring proteins at the node and paranode, as well as K^+ channels at the juxtaparanode (Peles and Salzer, 2000). There are, however, fundamental characteristics that separate oligodendrocyte-mediated myelin from that formed by Schwann cells: Schwann cells can only provide one internode per axon, whereas oligodendrocytes extend several processes, each of which myelinates distinct internodes, often on different axons (Baumann and Pham-Dinh, 2001). A local regulation between axon segments and oligodendrocyte processes has been suggested to affect myelin sheath thickness: In rats, myelin sheaths of different thickness are provided by the same oligodendrocyte. The existence of polyribosomes and/or rough endoplasmic reticulum in oligodendrocyte processes near the myelinated axons suggests a local mechanism in myelin formation (Waxman and Sims, 1984). Nerve growth factor (NGF) stimulates myelination by Schwann cells but inhibits oligodendrocyte-mediated myelination (Chan et al., 2004). After birth, the brain is less susceptible to growth than the rest of the body (Thompson, 1917; Moore, 1983). Hence the degree of change needed for internodes may differ between the PNS and the CNS.

How is the position of nodes of Ranvier along axons determined? An early event in the establishment of nodes of Ranvier is the formation of a junction at the paranode between the axon and the glial sheet and sodium channel clustering at the node (Poliak and Peles, 2003; Sherman and Brophy, 2005; Salzer et al., 2008; Susuki and Rasband, 2008). The formation of a paranodal junction and sodium channel clustering at the node appear linked, however the exact mechanism is unclear. At least for the CNS, myelination does not seem to be a prerequisite for node formation, as contact between oligodendrocytes and the neurites of

retinal ganglion cells is not necessary for the induction of sodium channel clustering (Kaplan et al., 1997). Similarly, axon diameter can be controlled by oligodendrocytes in the absence of myelination (Sánchez et al., 1996). Conversely, individual axons have been shown to profoundly regulate the myelinating potential of single oligodendrocytes (Almeida et al., 2011).

Some insight about node formation might come from an axonal neighbor, the axon initial segment (AIS). The AIS and the nodes of Ranvier share the molecular composition of ion channels, anchoring proteins and other classes of proteins (Ogawa and Rasband, 2008; Rasband, 2010). Na^+ and K^+ channel clustering at the AIS further suggests that nodes of Ranvier are evolutionary derivatives of the AIS (Hill et al., 2008). A series of excellent studies recently demonstrated plasticity at the AIS: in the avian auditory brainstem, the position of the AIS is tuned for optimal function in a sound localization circuit (Kuba et al., 2006). The same neurons respond with change in AIS length and position after sensory deprivation (Kuba et al., 2010). Similar results have been reported in dissociated neurons of mammals, suggesting that plasticity at the AIS may be a universal mechanism to regulate neuronal excitability (Grubb and Burrone, 2010; Evans et al., 2013).

Information processing in the auditory brainstem of mammals and birds, together with the synchronized current discharge in electrical fish, present the highest level of temporal precision in any neural system. Considering the temporal resolution needed to differentiate and encode ITDs that differ by only a few microseconds, it is intriguing to speculate about an active process that adjusts conduction time along axons conveying information from the ears. In the avian auditory brainstem, conduction velocity is regulated differentially within two branches of the same axon to overcome a dramatic fiber length difference and achieve isochronic inputs (Seidl et al., 2010; Seidl et al., 2013). Myelination of the delay line circuit of the barn owl occurs at a time in development when auditory responses are present (Kubke and Carr, 2000) and coincides with the period of head growth and attainment of stable ITD cues (Cheng and Carr, 2007). Therefore, myelination in this circuit may be affected by the electrical activity of NL neurons and/or signals of axons from NM.

We can only speculate how a systematic arrangement of conduction velocities is achieved during development. Sensory inputs appear to play a role in myelination. In the visual system, deprivation or enhancement of sensory inputs cause a change in myelination (Gyllensten and Malmfors, 1963; Tauber et al., 1980). Similar to barn owls, acoustically evoked activity is present in chickens (Jackson and Rubel, 1978) when myelination occurs (Hartman et al., 1979; Macklin and Weill, 1985; Korn and Cramer, 2008). Therefore the contribution of sensory activity to systematic regulation of internode distance seems possible.

If sensory activity influences myelination, how is oligodendrocyte myelination around axons controlled? Electrical activity of CNS axons has been shown to affect proliferation and differentiation of myelinating glia (Demerens et al., 1996; Stevens et al., 2002; Ishibashi et al., 2006); likely by the release of glutamate from synaptic vesicles along axons that promotes myelin induction (Wake et al., 2011). Moreover, oligodendrocytes are electrically active as well (Káradóttir et al., 2008) and their membrane potential can influence

conduction velocity (Yamazaki et al., 2007). Recently, Teneurin-4 has been identified as a regulator of oligodendrocyte differentiation and myelination (Suzuki et al., 2012) and, as it is expressed in the auditory brainstem, it might play a role in functional myelination (Kenzelmann-Broz et al., 2010).

Conclusion

In the past few decades, enormous progress has been made in the myelin field. It will be exciting to find out more about interactions between axon and glial cells and how these interactions shape myelin plasticity. Recent studies suggest that an activity-dependent process may shape the organization of myelin along an axon, but it is currently unknown how internode distances are regulated. Future experiments are needed to establish how specific internode distances are arranged during development, what is needed for the maintenance of specific conduction times. Another interesting question will be if conduction times of networks change with age. Understanding these mechanisms has implications for the formation and regulation of myelinated axons throughout life and for mechanisms that may need to be considered for their repair. Demyelinating diseases like multiple sclerosis lead to are responsible for the breakdown of precise conduction velocity regulation, thereby compromising motor skills and sensory processing (Compston and Coles, 2002). Cognitive functions may be susceptible to oligodendrocyte defects also (Nave, 2010), as myelination shows plasticity in adulthood triggered by social interactions (Liu et al., 2012) and transmission along transcallosal projections seems to be timed precisely (Tomasi et al., 2012; Innocenti et al., 2013). Knowledge about the development and mechanisms of conduction regulation in axons may lead to new therapies for neurological and neuropsychiatric diseases.

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Highlights

- This review presents neural systems where axon conduction times are systematically regulated.
- Recent studies in the auditory system are highlighted where high temporal precision is achieved.
- Mechanisms of neuron-glia interaction may achieve activity-dependent plasticity of myelin.

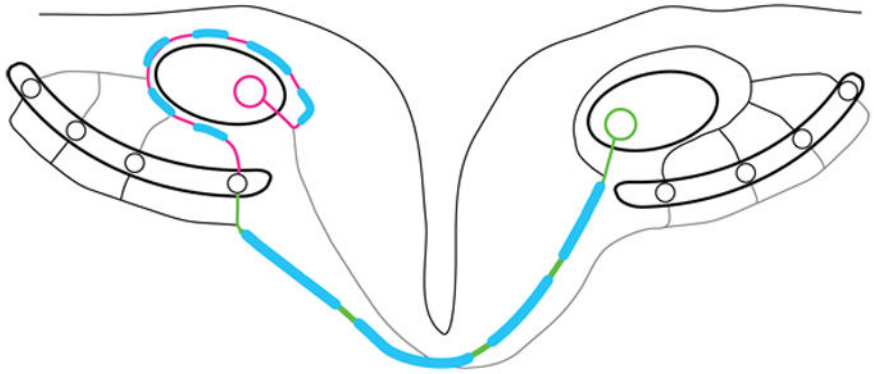

Figure 1.

Figure Differential regulation of conduction velocity in two major branches of single axon Nucleus magnocellularis (NM) and nucleus laminaris (NL) embody a modified Jeffress model (Jeffress, 1948) where contralateral NM axons form a delay line on the ventral side of a NL cell line. This delay line sequentially slows down the contralaterally evoked sound signal and enables coincidence with the ipsilateral inputs that creates no delay between terminals. Depending on the ITD presented, coincident inputs occur at a different location in NL, rendering the NL cell line a map or sound source location along the azimuth (Carr and Konishi, 1990; Köppl and Carr, 2008). The ipsilateral and contralateral axon branches of the NM axon display a length difference of more than 1600 μm. Conduction velocities in the ipsilateral and contralateral branches are adjusted utilizing variations in internode distance and axon diameter so that conduction times achieve isochronicity in the microsecond range. In the shorter axon branch, internode distance and axon diameter are shorter and thinner, respectively, than in the longer axon branch. The differential regulation of conduction time in the sub-millisecond range between two major collaterals of a single axon to fulfill a well-described biological function is unprecedented (Seidl et al., 2010). Note that both axon segments are part of a single NM axon. Magenta, ipsilateral axon branch; green, contralateral axon branch; blue, myelin sheath.