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Article type : Review Article

Title: Axon-glia interactions in the Ascending Auditory System

Short Title: Axon-glia interactions in the Auditory System

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/DNEU.22813

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Abbreviations:

ABR, auditory brainstem response

ALDH1L1, aldehyde dehydrogenase 1 family member L1

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AN, auditory nerve

AP, action potential

APD, auditory processing disorder

ASD, autism spectrum disorder

AVCN, anteroventral cochlear nucleus

BDNF, brain-derived neurotrophic factor

CN, cochlear nucleus

CNS, central nervous system

CMT, Charcot-Marie-Tooth

Cx, connexin

dB SPL, decibels sound pressure level

DTI, diffusor tensor imaging

ErbBR, ErbB receptor

FGF, fibroblast growth factor

GABA, gamma aminobutyric acid

GBC, globular bushy cell

GBS, Guillain-Barre syndrome

GFAP, glial fibrillary acidic protein

GLAST, glutamate/aspartate transporter (also known as EAAT1)

GLT, glutamate transporter

HC, hair cell

HHL, hidden hearing loss

IC, inferior colliculus

IGF1, insulin-like growth factor-1

IHC, inner hair cell

IID, interaural intensity difference

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IP3, inositol trisphosphate

ITD, interaural time difference

KCC4, K/Cl co-transporter 4

KCNQ4, Potassium Voltage-Gated Channel Subfamily Q Member 4

LSO, lateral superior olive

MBP, myelin basic protein

MGN, medial geniculate nucleus

MIF, macrophage migration inhibitory factor

MNTB, medial nucleus of the trapezoid body

MPZ, myelin protein zero

MS, multiple sclerosis

MRI, magnetic resonance imaging

MSO, medial superior olive

NL, nucleus laminaris

NMDA, n-methyl-d-aspartate

NoR, nodes of Ranvier

NRG1, neuregulin 1

NT3, neurotrophin 3

OHC, outer hair cell

OL, oligodendrocyte

OPC, oligodendrocyte precursor cell

PLP1, proteolipid protein 1

PMD, Pelizaeus-Merzbaher disease

PMP22, peripheral myelin protein 22

PNS, peripheral nervous system

SBC, spherical bushy cell

SuppC, supporting cell

SGC, satellite glial cell

SGN, spiral ganglion neuron

SOC, superior olivary complex

Sox10, SRY-Box Transcription Factor 10

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TNF- α, tumour necrosis factor alpha
TRK, tropomyosin receptor kinase
VCN, ventral cochlear nucleus

Acknowledgments: This work was supported in part by NIH/NIDCD R01 DC018500 and R21 DC017916; and the Lynn and Ruth Townsend Professorship of Communication Disorders (G.C.). We thank Gunseli Wallace for critical reading of the manuscript.

Conflict of interest: G.C. is a scientific founder of Decibel Therapeutics, has an equity interest in and has received compensation for consulting. The company was not involved in this study.

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Abstract

The auditory system detects and encodes sound information with high precision to provide a high-fidelity representation of the environment and communication. In mammals, detection occurs in the peripheral sensory organ (the cochlea) containing specialized mechanosensory cells (hair cells) that initiate the conversion of sound-generated vibrations into action potentials in the auditory nerve. Neural activity in the auditory nerve encodes information regarding the intensity and frequency of sound stimuli, which is transmitted to the auditory cortex through the ascending neural pathways. Glial cells are critical for precise control of neural conduction and synaptic transmission throughout the pathway, allowing for the precise detection of the timing, frequency, and intensity of sound signals, including the sub-millisecond temporal fidelity is necessary for tasks such as sound localization, and in humans, for processing complex sounds including speech and music. In this review, we focus on glia and glia-like cells that interact with hair cells and neurons in the ascending auditory pathway and contribute to the development, maintenance, and modulation of neural circuits and transmission in the auditory system. We also discuss the molecular mechanisms of

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these interactions, their impact on hearing and on auditory dysfunction associated with pathologies of each cell type.

Key words:

- Astrocytes
- Auditory system
- Glia
- Hearing loss
- Neuron-glia interactions
- Oligodendrocytes
- Satellite glial cells
- Schwann cells
- Supporting cells

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Introduction

The vertebrate auditory system is the part of the nervous system dedicated to capturing environmental sounds and processing them to extract information about the surroundings and allow for communication between individuals. Using unique mechanosensory cells and specialized synaptic connections, the auditory system is exceptionally proficient at encoding and transmitting a high-fidelity representation of sound frequency and intensity. In mammals, the auditory pathway starts with the organ of Corti located within the cochlea in the inner ear (Fig. 1A). There, inner hair cells (IHCs) transduce sound waves into neural activity through excitatory synapses onto the primary auditory neurons, the type I spiral ganglion neurons (SGNs). These neurons then propagate auditory information to the auditory cortex through an ascending pathway consisting of several nuclei. At every single stage of the pathway, neural cells are in close contact with glia, including the glia-like supporting cells (SuppCs) of the organ of Corti that surround hair cells (HCs) and their synapses with SGNs, Schwann cells that myelinate the peripheral portion of the auditory nerve (AN), satellite glial cells (SGCs) that surround SGN cell bodies, oligodendrocytes (OLs) that myelinate the

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central portion of the AN as well as axons in central auditory pathways, and astrocytes that wrap around synapses in the central portion of the ascending auditory pathway (Fig. 1B). This diverse set of glial cells is critical for precise control of axonal conduction and synaptic transmission at specialized synapses throughout the pathway, facilitating the detection of sub-millisecond changes in the timing of sound signals. This extraordinary temporal fidelity is necessary for tasks such as sound localization, and in humans, for processing complex sounds including speech and music.

This review aims at providing glial biologist information about the auditory system, and auditory scientist information about the roles of glia in the auditory system. We focused on the interactions that glia have with sensory HCs and ascending auditory neurons, as well as their roles in the development, maintenance, and modulation of neural circuits and transmission in the auditory pathway. We also discuss our current understanding of the reciprocal neural-glial interactions that influence development and maintenance of hearing and review the auditory dysfunction associated with pathologies of each cell type.

Supporting cells, the glia of the organ of Corti.

The sensory epithelium of the cochlea, the organ of Corti, contains two types of mechanoreceptive HCs - IHC and outer (OHC) hair cells. IHCs are the principal mechanoreceptor cells for sound detection, whereas OHCs are electromotile cells that amplify the vibrational motion of the organ of Corti and control the gain of auditory responses (Fettiplace 2017). IHCs form ribbon-type glutamatergic synapses with the peripheral axons of type I SGNs, bipolar neurons which give rise to approximately ninety percent of myelinated axons in both the central and peripheral parts of the AN. Specialized exocytosis and endocytosis machinery present at the presynaptic ribbon support sound-evoked synaptic release that is robust and possesses high temporal fidelity (Moser, Grabner et al. 2019). The remaining ten percent of AN myelinated axons belong to brainstem efferent neurons (Ehret 1979, Brown 1987, Campbell and Henson 1988). Each type I SGN innervates a single IHC, while each IHC makes synaptic contact with approximately 10 to 30 type I SGN fibers (Coate, Scott et al. 2019). The AN also contains unmyelinated axons that belong to type II SGNs, smaller caliber afferent

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neurons that innervate OHC. While the roles of type II afferents remain poorly understood, it has been proposed that they signal cochlear damage (Liu, Glowatzki et al. 2015).

Hearing sensitivity is often assessed by measuring auditory brainstem responses (ABRs) to transient sounds. ABRs are auditory evoked far-field responses detected by head-mounted electrodes that represent the synchronous electrical activity of the auditory system at multiple locations along the pathway. A typical ABR waveform from the mouse (Fig. 1C) consists of five major peaks, with peak I corresponding to activity generated by the SGNs within 2 msec following the sound stimulus, and the later peaks II through V corresponding to activity generated by neurons in successive nuclei of the auditory hindbrain. Thresholds are determined by the lowest intensity of sound that produces a recognizable waveform. The peak I amplitude correlates with the number and synchronous firing rate of the type I SGN fibers and can be influenced by changes in IHC-AN synapse numbers and by myelin alterations (see below for details and references). Reductions in ABR peak I amplitudes are considered to reflect a reduction in the efficiency of transmission of information from the cochlea to the CNS.

SuppCs in the organ of Corti were traditionally considered to be connective tissue providing structural and homeostatic support. However, recent work has shown that these cells exhibit many characteristics of glia and play glia-like roles (Wan, Corfas et al. 2013). The IHCs and their synapses are surrounded by SuppCs known as inner border and inner phalangeal cells, which express molecules that regulate synaptic development and may function in a manner analogous to that of perisynaptic Schwann cells (Wan, Corfas et al. 2013). Below we discuss the diverse roles that SuppCs play in development and function of the cochlea.

Spontaneous cochlear activity prior to the onset of hearing. While sound evoked responses are not present in early postnatal cochlea of rodents, type I SGNs display spontaneous electrical activity (Walsh and Romand 1992, Jones, Leake et al. 2007). Although IHC intrinsic firing properties likely contribute to early spontaneous activity of SGNs (Johnson, Eckrich et al. 2011, Johnson, Kennedy et al. 2012), several studies indicate a role for SuppCs in modulating this spontaneous activity via ATP-dependent

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signaling. Beginning at birth (P0), ATP released from SuppCs within the developing cochlea activates purinergic receptors on IHCs, leading to IHC depolarization and glutamate release at ribbon synapses, which in turn triggers coordinated bursts of action potentials (APs) in the AN (Tritsch, Yi et al. 2007, Tritsch and Bergles 2010, Tritsch, Zhang et al. 2010). The released ATP also activates purinergic autoreceptors on SuppCs, inducing K+ efflux that potentiates IHC depolarization (Wang, Lin et al. 2015, Babola, Kersbergen et al. 2020). Later in postnatal development, ATP release declines along with spontaneous activity levels in SGNs (Tritsch and Bergles 2010). Spontaneous activity is important for the maturation of auditory neurons (Seal, Akil et al. 2008, Shrestha, Chia et al. 2018, Sun, Babola et al. 2018) as well as refinement of synaptic connections in central auditory pathways (Erazo-Fischer, Striessnig et al. 2007, McKay and Oleskevich 2007, Clause, Kim et al. 2014).

Neuronal survival and outgrowth. HCs have traditionally been considered critical for SGN survival, at least in part due to their expression of neurotrophins such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT3) (Green, Bailey et al. 2012). Indeed, loss of either BDNF or NT3, or their respective cognate receptors trkB and trkC, result in embryonic loss of SGNs, with NT3 KOs exhibiting virtually complete loss of type I SGNs while loss of BDNF results in loss of type II SGNs (Ernfors, Van De Water et al. 1995, Schimmang, Minichiello et al. 1995, Bianchi, Conover et al. 1996, Fariñas, Jones et al. 2001). Nonetheless, a large body of evidence suggests that cochlear SuppCs play an equally important role in SGN biology, including acting as a additional source of BDNF and NT3 in the cochlea (Wiechers, Gestwa et al. 1999, Sugawara, Murtie et al. 2007). Furthermore, data from aged or injured animal indicate a strong correlation between SGN survival and the number of remaining SuppCs, rather than HCs (Leake and Hradek 1988, Xu, Shepherd et al. 1993, McFadden, Ding et al. 2004, Sugawara, Corfas et al. 2005). Notably, experimental ablation of IHCs in two independent mouse model systems, both of which left SuppCs intact, demonstrated survival of SGNs for at least 3 to 4 months post-ablation, suggesting that the intact SuppCs are capable of providing neurotrophic support in the absence of HCs (Zilberstein, Liberman et al. 2012, Tong, Strong et al. 2015). Several studies of human temporal bones have also reported a positive correlation between SuppC and SGN

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survival in the cochlea (Johnsson 1974, Suzuka and Schuknecht 1988). Finally, developmental expression gradients of BDNF and NT3 observed along the length of the cochlea in rodents, including SuppCs, is likely to influence the extension and refinement of fibers toward target HCs (Wiechers, Gestwa et al. 1999, Huang, Thorne et al. 2007, Sugawara, Murtie et al. 2007). These neurotrophin gradients may also modulate synaptic and ion channel protein expression in SGNs and thereby contribute to differences in firing properties in basal versus more apical SGNs (Adamson, Reid et al. 2002, Zhou, Liu et al. 2005, Flores-Otero, Xue et al. 2007).

The ability of SuppCs to impact SGN survival also appears to depend on Neuregulin 1-ErbB receptor (NRG1-ErbBR) signaling, as blockade of SuppC ErbBR signaling results in SGN loss in spite of the presence of intact HCs and SuppCs (Stankovic, Rio et al. 2004). Although SGN loss in this model was originally attributed to an associated decrease in cochlear NT3 expression, more recent work using conditional knockout mice demonstrated normal SGN survival following postnatal loss of NT3 or BDNF in either HCs or SuppCs (Wan, Gómez-Casati et al. 2014). These results suggest that residual neurotrophin expression from either cell type is sufficient for maintenance of SGNs. Other trophic factors that are expressed in postnatal SuppCs, such as insulin-like growth factor-1 (IGF1) or macrophage migration inhibitory factor (MIF), may also contribute to neuronal preservation, as knockout mice for either IGF1 or MIF exhibit SGN loss or altered innervation (Camarero, Avendaño et al. 2001, Okano, Xuan et al. 2011, Bank, Bianchi et al. 2012, Elkon, Milon et al. 2015).

Regulation of synapse formation and regeneration. While postnatal NT3 expression by SuppCs is not required for SGN survival, it is nevertheless critical for normal IHC-AN synaptogenesis. Neonatal knockout of NT3 in cochlear SuppCs results in a significant decrease in the number of IHC ribbon synapses and impaired hearing sensitivity. Conversely, overexpression of NT3 in cochlear SuppCs during the neonatal period results in increases in the number of synapses and better hearing sensitivity (Wan, Gómez-Casati et al. 2014).

Interestingly, studies in numerous animal models have demonstrated that moderate noise exposures can result in the loss of a subset of IHC-AN synapses and an

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associated phenotype known as “hidden hearing loss” (HHL), named for the presence of normal hearing thresholds but decreases in ABR peak I amplitudes at higher stimulus intensities (Liberman and Kujawa 2017, Kohrman, Wan et al. 2019) In adult mice, SuppC overexpression of NT3 promotes regeneration of ribbon synapses and functional recovery after moderate noise overstimulation (Wan, Gómez-Casati et al. 2014). These results have suggested the therapeutic potential of neurotrophins for repair of IHC-AN synapses following noise damage. Indeed, local delivery of NT3 into the cochlea was able to reduce synapse loss following moderate noise exposure (Suzuki, Corfas et al. 2016). The efficacy of NT3 for synapse protection/repair, however, appears to be sensitive to dosage and/or timing of delivery. Although overexpression of NT3 in IHCs via infection with adeno-associated virus prior to noise exposure was able to protect synapses, viral delivery following noise was unable to reproduce the protective effect of direct NT3 injection (Hashimoto, Hickman et al. 2019).

Regulation of neurotransmission. Sound evoked synaptic transmission occurs at IHC–SGN ribbon synapses through release of glutamate and activation of AMPA receptors on the postsynaptic terminal (Fuchs, Glowatzki et al. 2003). Glutamate accumulation and overactivation of glutamate receptors can degrade the fidelity of glutamatergic signaling (Barbour and Häusser 1997) and potentially lead to excitotoxicity-induced withdrawal of the axon terminal and cell death of SGNs (Pujol and Puel 1999, Jäger, Goiny et al. 2000, Oestreicher, Wolfgang et al. 2002, Duan, Chen et al. 2006, Kostandy 2012). Similar to traditional glial cell-neuronal interactions that act to replenish glutamate neurotransmitter levels, the glutamate-glutamine cycle also occurs in the organ of Corti. SuppCs mediate glutamate removal at the IHC afferent synapse through the activity of glutamate/aspartate transporter (GLAST, also known as EAAT1). Glutamate uptake is then followed by conversion of glutamate to glutamine by glutamine synthetase (Usami, Osen et al. 1992). GLAST expression in SuppCs is closely matched to the amount of glutamate released (Furness and Lawton 2003) and the time course of GLAST expression in SuppCs correlates with the electrophysiological onset and maturation of mouse auditory function (Jin, Kikuchi et al. 2003). GLAST-deficient mice experience more pronounced swelling of afferent terminals and exacerbated hearing

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loss after noise exposure than wild types, consistent with enhanced glutamate excitotoxicity (Hakuba, Koga et al. 2000, Glowatzki, Cheng et al. 2006).

Regulation of organ of Corti ionic environment. Ion recycling mechanisms are required in the cochlea to maintain homeostasis, and SuppCs are key players in these pathways. For example, potassium ions (K+) that flow through mechanotransduction channels in HCs during sound stimulation are released through KCNQ4 channels in the HC basolateral membranes and K+ transporter proteins are required for further recycling (Zdebik, Wangemann et al. 2009). Expression of the K-Cl co-transporter protein KCC4 is restricted to SuppCs in the mature cochlea (Boettger, Hübner et al. 2002). Mice with deletion of the *Slc12a7* gene that encodes KCC4 exhibit early progressive degeneration of HCs, SuppCs and SGNs, leading to profound hearing loss, consistent with a critical role for KCC4 in uptake of K+ into SuppCs (Boettger, Hübner et al. 2002).

All cochlear SuppCs are connected by gap junctions that permit small molecule exchange, and this is believed to impact K^+ homeostasis in the inner ear (Zdebik, Wangemann et al. 2009). Gap junctions are formed by connexin (Cx) protein hemichannel complexes on adjacent cells. Cx26 and Cx30 are the major connexin proteins expressed by cochlear SuppCs and mutations in the genes encoding these isoforms have been associated with hearing loss in mice and in humans (Mammano 2018). Most prominently, mutations in the human Cx26 gene (*GJB2*) account for up to 50% of autosomal recessive non-syndromic deafness in many populations (Chan and Chang 2014). Potassium ion homeostasis, however, is unlikely to be the sole critical function for connexins in the cochlea, as several known *GJB2* mutations that are associated with hearing loss appear to form channels capable of small ion passage (Wingard and Zhao 2015). Connexins also mediate passage of larger molecules such as ATP and inositol trisphosphate (IP3), both of which have been linked to intercellular Ca^{2+} signaling in the organ of Corti (Mammano and Bortolozzi 2018). SuppCs release ATP through apical connexin hemichannels, which results in purinergic receptor activation on SuppCs and leads to both the influx of external Ca^{2+} and release of internal Ca^{2+} stores. ATP release from SuppCs has been implicated in the regulation of spontaneous activity in the early postnatal cochlea (see above). Intercellular passage of the second messenger IP3 also occurs through gap junctions, which similarly activates

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Ca^{2+} release from internal stores (Mammano and Bortolozzi 2018). The importance of this pathway is supported by the identification of a human deafness-associated variant in Cx30 that retains permeability to small ions but is deficient in intercellular IP3 transfer and the associated Ca^{2+} response (Schütz, Scimemi et al. 2010). In addition, reduction of connexin-dependent Ca^{2+} signaling has been associated with an immature IHC phenotype, consistent with a role for SuppCs in regulating early sensory cell development (Johnson, Ceriani et al. 2017).

Schwann cells

Schwann cells are derived from precursor cells in the neural crest that migrate to the periphery during embryogenesis, proliferate, associate with axons and adopt myelinating or non-myelinating fates (Salzer 2015). Myelinating Schwann cells elaborate specialized membranes that wrap single axons and form the myelin sheath. Non-myelinating Schwann cells typically bundle multiple smaller caliber unmyelinated axons. A number of extracellular signaling cues and intrinsic transcriptional pathways have been demonstrated to guide these steps from neural crest progenitor to mature Schwann cell in the peripheral nervous system (PNS) (Stolt and Michael 2016). The myelin sheath supports saltatory conduction of neural signals by regulating the assembly and maintenance of neuronal domains that are required for precise localization of voltage gated Na^{+} and K^{+} channels at nodes of Ranvier (NoR) and at terminal heminodes (Rasband 2016).

Schwann cell development in the cochlea. Schwann cell development occurs across an extended time period in the vertebrate cochlea. In humans, immature Schwann cells are associated with AN axons by week 9 of gestation (Locher, Groot et al. 2014). Myelin formation, as evidenced by myelin basic protein (MBP) staining, is present within the cochlear portion of the AN by week 22 (Locher, Groot et al. 2014), consistent with earlier electron microscopy studies that indicate myelin formation is first evident in the peripheral AN segment between weeks 20 and 22 (Lavigne-Rebillard and Pujol 1988, Moore and Linthicum 2001, Ray, Roy et al. 2005). In the mouse, Schwann cell progenitors arrive in the developing inner ear by embryonic day 10.5, when neural progenitor cells begin to differentiate into SGNs (Breuskin, Bodson et al. 2010).

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Myelination by Schwann cells initiates near birth at the cell body of SGNs and progresses centrally toward the PNS-CNS transition zone and peripherally toward the axon terminals between P8 and P10, just days prior to the onset of hearing (Anniko 1983, Wang, Zhang et al. 2013). Immunolocalization studies in rat indicate that, like in other peripheral nerves, maturation of AN myelin continues throughout the first postnatal month, with progressively tighter clustering of Na^+ and K^+ channels, along with associated proteins, at NoRs and terminal heminodes (Kim and Rutherford 2016).

Regulation of SGN migration, maturation, and survival. Several studies suggest that pre-myelinating Schwann cells produce a “stop signal” required for appropriate SGN migration and fiber extension in the cochlea, and that they might contribute to SGN survival during development. Morris and coworkers found that in mice with loss of ErbB2, a receptor tyrosine kinase critical for Schwann cell development, SGN cell bodies migrate to unusual positions in the cochlea and their processes overshoot the sensory epithelia during early development (Morris, Maklad et al. 2006). Similarly, in mice that lack Schwann cells due to Sox10 deletion in neural crest cells, SGN fibers extend peripherally to the lateral part of the cochlea past their normal IHC targets (Mao, Reiprich et al. 2014). Interestingly, ErbB2 KO but not Sox10 KO mice have significant SGN loss, suggesting that Schwann cells are not essential for SGN survival during this developmental stage, and that the neuronal loss in the ErbB2 KO reflects SuppC dysfunction (Stankovic, Rio et al. 2004).

There is also evidence that growth factor pathways mediate critical axon-Schwann cell interactions in the AN, including NRG1-ErbBR signaling, which controls myelin thickness in other peripheral nerves (Garratt, Voiculescu et al. 2000, Michailov, Sereda et al. 2004, Chen, Velardez et al. 2006). All SGNs express NRG1 (Morley 1998, Hansen, Vijapurkar et al. 2001, Stankovic, Rio et al. 2004), and AN Schwann cells express ErbBRs (Hansen, Vijapurkar et al. 2001). We have found that loss of ErbBR signaling in myelinating Schwann cells due to expression of a dominant negative ErbBR results in HHL (Kohrman, Wan et al. 2019, Cassinotti, Kohrman et al. 2020). This dysfunction is associated with deficits in the structure of the terminal heminodes of the AN, consistent with a critical role for the heminodes in ensuring fast, synchronous firing of APs in response to neurotransmitter release from HCs.

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Another example is the fibroblast growth factor (FGF) signaling pathway, which has been shown to regulate multiple functions of Schwann cells, including proliferation, differentiation, regeneration of peripheral nerves following injury, and recovery following demyelination (Davis and Stroobant 1990, Grothe and Nikkhah 2001, Hansen, Vijapurkar et al. 2001). SGNs express FGF-1 and FGF-2 (Lin, Koutnouyan et al. 1993, Pirvola, Cao et al. 1995, Silva, Gomide et al. 2005), while Schwann cells and OLs express a number of FGF receptors, including FGFR1, FGFR2, and FGFR3 (Grothe and Nikkhah 2001, Bansal, Miyake et al. 2002). Wang and co-workers showed that inactivation of FGF signaling in myelinating cells resulted in significant loss of SGNs, accompanied by age-related hearing impairment in adulthood, without apparent loss of glia (Wang, Furusho et al. 2009). Although myelination was not quantitatively assessed in this study, apparent decreases in amplitudes of the sound-evoked responses and increases in their latencies are suggestive of subtle myelination defects. However, since the loss of FGF function occurred in both OLs and Schwann cells, the relative contribution of each myelinating cell type to the observed phenotypes remains to be determined.

Myelin-related pathologies in the peripheral auditory system**.** There is increasing evidence that peripheral myelin disorders can lead to auditory neuropathy, a type of hearing loss in which sound detection in the cochlea is normal but transmission of auditory activity to the brain is impaired. This is the case in Guillain-Barre syndrome (GBS), an acute and transient peripheral neuropathy caused by Schwann cell damage due to autoimmune processes (Stathopoulos, Alexopoulos et al. 2015). It has been reported that a portion of GBS patients exhibit abnormal ABRs (Schiff, Cracco et al. 1985, Ropper and Chiappa 1986, Nelson, Gilmore et al. 1988, Ueda and Kuroiwa 2008, Takazawa, Ikeda et al. 2012). Although hearing thresholds gradually recover in some patients, their ABR wave forms show persistent increases in interpeak latencies (Takazawa, Ikeda et al. 2012), consistent with permanent auditory neuropathy. Using a genetic approach to ablate myelinating Schwann cells in mice, we recently demonstrated that transient AN demyelination leads to permanent HHL that is associated with a disruption of the terminal AN heminodes (Wan and Corfas 2017). These defects are consistent with previous modeling and immunostaining studies that

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support the heminodes as the initial spike generators in type I SGNs (Rutherford, Chapochnikov et al. 2012, Kim and Rutherford 2016) and indicate that loss of the normal compacted heminode structure significantly impairs synchronized initiation and conduction of APs (Wan and Corfas 2017, Budak, Zochowski et al. 2019). Thus, heminodal disruption may be the underlying cause of the auditory neuropathy observed in some GBS patients.

Another Schwann cell-related disorder is demyelinating Charcot-Marie-Tooth (CMT), also known as CMT1, in which some patients have been reported to present classic auditory neuropathy characterized by normal OHC function but substantial decreases in hearing sensitivity, often with ABR latency alterations (Rance 2005). CMT is a genetically heterogeneous disorder, and the auditory phenotype in CMT patients is quite variable, likely due to the nature of the affected gene, the mutation type, age, and other genetic modifiers (Morelli, Seburn et al. 2017). For example, evaluation of a cohort of children genetically diagnosed with CMT1, mostly with dominant peripheral myelin protein 22 (PMP22) gene duplication (CMT1A), exhibited relatively normal hearing thresholds but decreased speech understanding in background noise (Rance, Ryan et al. 2012). ABR studies from these patients show altered peak latencies consistent with demyelination and prolonged conduction times in the peripheral AN (Rance, Ryan et al. 2012). Similarly, a large cohort of adult CMT1A patients with normal hearing thresholds was recently found to exhibit HHL, with deficits in speech understanding in background noise that were also associated with other deficits in temporal processing of sound (Choi, Seok et al. 2018). On the other hand, older patients carrying a dominant missense mutation in myelin protein zero (MPZ) gene (CMT1B) were found to exhibit significant threshold increases associated with gross defects in ABR peaks (Starr 2003). Postmortem analysis of the cochlea of one of these patients demonstrated a significant loss of SGNs and demyelination of remaining peripheral fibers, compared with age matched controls (Starr 2003).

Our recent studies on mouse models of CMT1 support the notion that peripheral myelin disorders lead to auditory neuropathy with distinct phenotypes for each mutation (Cassinotti, Ji et al. 2020). CMT1A mice, which carry three copies of the human PMP22 gene (Verhamme, King et al. 2011), exhibit normal hearing thresholds at 4 months of

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age but decreases in ABR peak I amplitudes, indicating an HHL phenotype. This phenotype is associated with defects in the terminal heminode of auditory nerve fibers. In contrast, Trembler-J mice, which carry a dominant missense mutation in PMP22 and serve as a model of CMT1E, exhibit large threshold elevations at 4 months that are associated with hypomyelination and severe loss of peripheral AN fibers and SGN. These features are consistent with the auditory neuropathy previously reported for Trembler-J mice and with the peripheral demyelination caused by direct ablation of Schwann cells with diphtheria toxin at birth (Zhou, Abbas et al. 1995, Zhou, Assouline et al. 1995). Severe to profound threshold elevations are also observed in CMT1E patients (Boerkoel, Takashima et al. 2002, Kovach, Campbell et al. 2002). These CMT phenotypes highlight the critical role of Schwann cell myelination in neurotransmission in the cochlea and in long term AN survival.

Loss of other Schwann cell proteins, including connexins, also result in peripheral neuropathy and auditory dysfunction. Hearing impairment is observed in a subset of individuals with an X-linked form of demyelinating CMT disease (CMT1X), which is caused by any one of a large number of mutations in the gap junction protein Cx32 (*GJB1*) (Kleopa and Scherer 2006). Electrophysiological and pathological studies of peripheral nerves in these patients provide evidence of demyelinating neuropathy with prominent axonal degeneration. Cx32 has been implicated in the gap junction-mediated intracellular transfer of small molecules across myelin layers, as well as in hemichannel passage of ATP from activated neurons, and is expressed in both Schwann cells and OLs (Bortolozzi 2018). Alterations in ABR peak I as well as in central peaks have been observed in different CMT1X patients, consistent with a role for Cx32 in both the peripheral and central auditory systems (Nicholson and Corbett 1996, Bähr, Andres et al. 1999, Giuliani, Holte et al. 2019). Although not associated with general neuropathy, loss of the gap junction protein Cx29 in mice causes AN myelin defects along with a delay in the maturation of auditory thresholds and the prolongation of auditory latencies (Tang, Zhang et al. 2006).

Knowledge of the mechanisms of axon-glial communication provides potential targets for treating neuropathy and myelin disorders. For example, based on the importance of NRG1/ErbBR signaling in modulating myelin development, experimental manipulation of

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this pathway has been tested for efficacy in treating demyelinating neuropathies. Delivery of soluble type I NRG1 via either injected recombinant protein or through expression of a neuronal transgene was found to normalize myelinated axon counts in the sciatic nerve and to improve muscle function in a rat model of CMT1 (Fledrich, Stassart et al. 2014). Similarly, transgenic expression of type III NRG1 in peripheral neurons resulted in partial correction of conduction defects and hypomyelination in the sciatic nerves of two independent mouse models of CMT1 (Belin, Ornaghi et al. 2018, Scapin, Ferri et al. 2018). Manipulation of this pathway must be carefully controlled, however, as overactivation of NRG1/ErbBR signaling can lead to hypermyelination and associated neuropathy (Michailov, Sereda et al. 2004, Belin, Ornaghi et al. 2018).

Acquired and age-related hearing loss. While noise overexposure and some ototoxic drugs have direct damaging effects on HCs, these traumas have also been associated with alterations in Schwann cells and myelin structure. Studies in young rats demonstrated reduced AN myelin thickness and changes in nodal and paranodal dimensions within 4 days of exposure to intense noise sufficient to cause HC damage and permanent threshold shifts (Tagoe, Barker et al. 2014). Similarly, high intensity noise exposure to young adult mice (8 –16 kHz at 106 or 112 dB SPL for 2 h) induced disruption of AN myelin lamellae and heminodal structures within 1 day of exposure, also suggesting direct effects of noise on myelin structure (Panganiban, Barth et al. 2018). Myelin pathologies in AN have been observed in other animal models following either prolonged low level or acute intense sounds, yet in most cases the effects on myelin were evaluated at later time periods following substantial loss of SGN and thus hampering interpretation (Rossi, Robecchi et al. 1976, Coyat, Cazevieille et al. 2019).

Cochlear myelin defects have also been noted in animal models within days following exposure to chemotherapeutic compounds such as cisplatin and carboplatin (Ding, McFadden et al. 2002, van Ruijven, de Groot et al. 2004), consistent with the effects of chemotherapeutic drugs on Schwann cells observed in other peripheral nerves (Carozzi, Canta et al. 2015). Chemotherapeutic compounds also cause CNS damage, including within the central auditory system (Meyers 2008). For example, studies indicate that 5-fluoro-uracil is toxic to OLs *in vitro*, damages central myelin and axons in

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the corpus callosum, and results in increased ABR interpeak latencies, consistent with myelin dysfunction in auditory pathways in mice (Han, Yang et al. 2008).

In addition to HCs, aminoglycoside antibiotic toxicity may directly affect SGNs and peripheral fibers in the cochlea soon after local or systemic delivery, with residual AN fibers often lacking myelin sheaths (Dodson and Mohuiddin 2000, Jiang, Karasawa et al. 2017, Wise, Pujol et al. 2017). Finally, myelin deficits have also been associated with aging in animal models, including thinning and degeneration of myelin on cochlear AN fibers, which correlated with decreases in MBP levels and in ABR peak I amplitudes (Xing, Samuvel et al. 2012). Similar age-associated decreases in MBP levels were also observed in AN from human temporal bone samples (Xing, Samuvel et al. 2012), suggesting that myelin loss could contribute to the temporal processing abnormalities described in aging humans (Plack, Barker et al. 2014, Harris and Dubno 2017).

Satellite glial cells. Like most peripheral neurons, SGN cell bodies in the cochlea are enclosed by SGCs. Remarkably, and distinct from all other peripheral ganglia, SGCs create a thin myelin sheath around type I SGN in most vertebrates (Felix 2002). Notably, this is not the case in humans (Tylstedt, Kinnefors et al. 1997, Liu, Edin et al. 2015). The mechanisms that mediate this cell body myelination and its precise physiological impact remain unknown, although biophysical modeling studies have suggested that human type I SGNs have lower spike conduction velocity due to lack of myelin in the soma (Rattay, Lutter et al. 2001, Rattay, Potrusil et al. 2013). Interestingly, high resolution 3D transmission electron microscopy of human cochleae has demonstrated the presence of membrane specializations between groups of SGN soma clustered within common SGCs (Tylstedt and Rask-Andersen 2001). These membrane areas were speculated to contribute to electrotonic cross-transmission that could be related to coding of speech signals.

Several studies have provided evidence that SGCs are important for proper auditory function. SGCs express glutamine synthetase, which is important for metabolizing excess glutamate and preventing excitotoxicity (Eybalin, Norenberg et al. 1996). In addition, deletion of the Saposin B (Sap B) gene, which plays an essential role in the regulation of myelin lipid biosynthesis, results in selective loss of cochlear SGCs in mice

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and is associated with progressive degeneration of SGNs and hearing loss, implicating SGCs in AN maintenance (Akil, Sun et al. 2015). In line with the regenerative ability of SGCs in other sensory ganglia following nerve injury (Elson, Simmons et al. 2004, Donegan, Kernisant et al. 2013, Nascimento, Castro-Lopes et al. 2014), SGCs in the cochlea also regenerate following genetic ablation (Wan and Corfas 2017).

Oligodendrocytes

Oligodendrocytes (OLs) derive from neuroepithelial precursor cells (OPCs) that originate in the ventricular zone of the developing CNS. Intrinsic transcriptional pathways together with extracellular signaling cues guide the migration, proliferation and differentiation of OPCs into mature, myelin-producing OLs (Elbaz and Popko 2019). In contrast to the single nerve fibers wrapped by mature Schwann cells in the periphery, myelinating OLs send out cellular extensions that are capable of wrapping and myelinating multiple CNS axons.

Oligodendrocyte development in the auditory CNS. Myelination of AN central projections and auditory brainstem axons by OLs starts around the time of hearing onset in rodents and humans. In mice, in which hearing onset occurs around P12-P14, OPCs are present in both the AN (Bojrab, Zhang et al. 2017) and the auditory hindbrain (Dinh, Koppel et al. 2014) at birth, while myelination of the central projections of AN are first detectable by P8 near the PNS-CNS transitional zone (Wang, Zhang et al. 2013) (Fig. 1A, B). Myelin formation in the auditory hindbrain and cortex initiates approximately 1 week later (Hackett, Guo et al. 2015, Kolson, Wan et al. 2015). Hearing onset in humans occurs between 24 to 25 weeks of gestation (Birnholz and Benacerraf 1983), with myelination of the central projection of AN as well as the auditory brainstem and midbrain initiating soon after, at 26 to 29 weeks (Moore, Perazzo et al. 1995, Moore and Linthicum 2001). In both humans and mice, myelin maturation in the auditory CNS progresses after hearing onset, coinciding with functional maturation. For example, in the murine auditory brainstem, myelin thickness and axon diameter double in size during the two weeks following hearing onset. Importantly, during this time, conduction velocity in the auditory brainstem also doubles (Sinclair, Fischl et al. 2017). Similarly, in the auditory brainstem and midbrain neurons of humans, increases in myelination are

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observed up to 1 year of age (Moore, Perazzo et al. 1995). In the auditory cortex, myelin signals detected by magnetic resonance imaging (MRI) rapidly increase until 1.5 years of age, then progress at a slower rate until adulthood (Su, Kuan et al. 2008).

Oligodendrocyte function in the auditory CNS. The precise coding and maintenance of timing information of sound stimuli are critical for normal auditory tasks, including spatial hearing and sound localization. Mammals and birds localize sounds in the horizontal plane by comparing the arrival times and intensities through auditory pathways originating at each ear (Grothe and Pecka 2014). Humans are able to discriminate interaural time differences (ITDs) as small as 10 to 20 microseconds (Klumpp and Eady 1956) and interaural intensity differences (IIDs) down to 1 dB SPL (Mills 1960). The circuits in the mammalian central auditory pathway that subserve these sensory processes are depicted in Figure 1B. Neurons in the superior olivary complex (SOC) integrate sound input from each ear. Medial superior olive (MSO) neurons in the SOC play a key role in the ITD detection pathway by comparing the timing of excitatory input from spherical bushy cells (SBCs) in the ipsilateral and contralateral cochlear nuclei (Stotler 1953, Warr 1966, Lindsey 1975, Cant and Casseday 1986) and firing when these binaural inputs arrive within a short time window (Goldberg and Brown 1969, Yin and Chan 1990). In addition to this excitatory input, MSO neurons also receive inhibitory input, most importantly from principal neurons in the medial nucleus of the trapezoid body (MNTB), which fire in response to excitation from single axons of globular bushy cells (GBC) in the contralateral ventral cochlear nucleus (VCN). This contralateral information is transmitted through a large, specialized synapse known as the calyx of Held directly onto the cell bodies of the MNTB principal neurons (Fig. 1D). The fast and precise nature of this synapse is critical for sound processing in the auditory hindbrain (Baydyuk, Xu et al. 2016). Similar integration of excitatory and inhibitory binaural inputs also occurs in lateral superior olive (LSO) neurons in the SOC to detect IIDs (Grothe and Pecka 2014).

Evidence from several model systems suggests that specialized properties of OL-based myelination and their associated axons play a key role in fine tuning the timing of neural transmission in the auditory CNS. Comparisons of ipsilateral and contralateral pathways involved in sound localization suggest that these specializations are likely to influence

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conduction speeds to compensate for inherent differences in fiber projection lengths and synaptic connection numbers between pathways. For instance, in the ITD pathway of gerbils, excitatory projections from SBCs to the contralateral MSO exhibit longer internodes and increased axon diameters relative to those in the shorter ipsilateral projections and are expected to elevate conduction velocity and compensate for the longer contralateral projection distance (Seidl and Rubel 2016). Systematic differences in internode lengths and axon diameters that are associated with conduction velocity variation have also been demonstrated in rodent GBCs, which are part of both the IID and the ITD pathways, and thus seem to compensate for the additional calyx of Held synapse in the contralateral inhibitory circuit in SOC (Ford, Alexandrova et al. 2015). Notably, a recent comparative study between gerbils, which depend upon ITD detection for localization of low frequency sounds, and mice, which rely instead upon IID, demonstrated unique structural specializations of axons and myelin in the localization circuit of each species that correlated with ITD requirements (Stange-Marten, Nabel et al. 2017).

The importance of myelination for temporal processing of sound information in the CNS is highlighted by electrophysiological defects found in Long Evans shaker rats, which carry an insertional mutation of the MBP gene and exhibit little or no condensed myelin in CNS neurons (O'Connor, Goetz et al. 1999). Increased peak I to peak V latencies and decreased peak amplitudes of ABRs to click sound stimuli in the MBP mutants indicated an increased central conduction time and lack of neural synchrony in the auditory hindbrain (Kim, Renden et al. 2013, Kim, Turkington et al. 2013). Additionally, brain slice recordings in the mutants indicated delayed and less reliable AP generation in MNTB principal neurons following high frequency synaptic activation at the calyx of Held. The delays and loss of AP fidelity were associated with altered Na^+ and K^+ channel distribution at NoR and the last heminodes of presynaptic GBC axons (Berret, Kim et al. 2016). These results support previous studies indicating the requirement of normal myelin structure for tight clustering of ion channels at nodes and heminodes in the CNS (Rasband, Peles et al. 1999, Susuki, Chang et al. 2013) and demonstrate its critical role for high fidelity transmission along axons and at nerve terminals in the auditory hindbrain.

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Myelin plasticity in the auditory CNS. A large body of evidence supports a role for neuronal activity and experience in modulating myelin structure in the CNS during development and in the mature organism through multiple mechanisms (Almeida and Lyons 2017, Monje 2018). Many studies have demonstrated that such activity-dependent myelin plasticity impacts behaviors and cognitive function. The coincident timing of myelination and development of auditory processing capabilities, including language acquisition in humans, has suggested that auditory experience impacts myelination to refine sensation during auditory system maturation.

Imaging studies in humans support a relationship between sensory-evoked activity and myelin levels in the auditory CNS. MRI studies showed that white matter to gray matter ratios are lower in the Heshl's gyrus and superior temporal gyrus of congenitally deaf individuals relative to normal hearing controls (Emmorey, Allen et al. 2003, Hribar, Suput et al. 2014). Changes in white matter microstructure in the temporal lobes of deaf subjects relative to hearing controls have also been detected by diffusor tensor imaging (DTI), which measures water diffusion properties to estimate brain structural features (Kim, Park et al. 2009, Hribar, Suput et al. 2014). Increasing sensory input, (auditory enrichment), has been associated with enhanced levels of CNS myelination. In rats, age-related decreases in myelin gene expression in the auditory cortex were partially reversed by auditory enrichment in an operant conditioning paradigm (Villers-Sidani, Alzghoul et al. 2010). Similarly, DTI evaluations in humans have demonstrated a positive correlation between more extensive white matter connections in the corpus callosum and both the extent of musical training and the age of training initiation (Bengtsson, Nagy et al. 2005, Steele, Bailey et al. 2013). Using mice, Sinclair and colleagues found that eliciting a hearing loss (50 dB SPL threshold elevation) with ear plugs at the time of normal hearing onset results in thinner myelin wrapping axons projecting to the MNTB of the auditory brainstem (Sinclair, Fischl et al. 2017). Similar deficits were observed following ear plugging of mature mice, suggesting that activity is also important in the maintenance of myelin.

Several mechanisms have been proposed to underlie the impact of neuronal activity and experience on CNS myelination, including impacts on OPC proliferation and differentiation (Foster, Bujalka et al. 2019). Trophic factors expressed by active neurons

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such as BDNF and NRG1 have been shown to stimulate myelination by OLs (Roy, Murtie et al. 2007, Taveggia, Thaker et al. 2007, Xiao, Wong et al. 2010, Wong, Xiao et al. 2013, Venkatesh, Johung et al. 2015) and experience-dependent changes in the levels of NRG1 expression have been shown to underlie the impact of social isolation on prefrontal cortex myelin maturation (Makinodan, Rosen et al. 2012). Likewise, sustained genetic activation in OLs of ERK1/2 kinases, which are part of the intracellular signaling pathway initiated by NRG1-ErbBR engagement (Mei and Nave 2014), results in increased myelin thickness in the CNS and decreased latencies in ABR brainstem peaks (Jeffries, Urbanek et al. 2016).

Neurotransmitters such as ATP and glutamate released by active neurons may also impact myelination. *In vitro* studies indicated an indirect effect of neuronal ATP release, which induces the release of leukemia inhibitory factor (a cytokine with pro-myelinating activity), from astrocytes, which in turn stimulates myelin formation by OLs (Ishibashi, Dakin et al. 2006). OPCs express a variety of voltage-gated ion channels and neurotransmitter receptors, including AMPA, NMDA, and GABA receptors (de Biase, Nishiyama et al. 2010). In multiple regions of the CNS, subsets of these progenitors also receive synapse-like input from either glutamatergic excitatory and GABAergic inhibitory neurons (Bergles, Roberts et al. 2000, Lin and Bergles 2003, Ziskin, Nishiyama et al. 2007). A recent study provided evidence that OPC excitability contributes to their own maturation and myelination (Berret, Barron et al. 2017). This paper showed that a subset of pre-OLs in the MNTB of P7-P14 rats fire APs in response to glutamatergic transmission from nearby neurons, and these APs depend upon the voltage-gated Na^+ channel Nav1.2. Moreover, shRNA-mediated knockdown of Nav1.2 blocks this Na^+ current and results in altered OL cellular extensions and a decrease in MBP levels, consistent with an impact of activity on pre-OL development and myelination.

In addition to modulating neural transmission through effects on myelination, OL-nerve interactions also appear to impact synaptic plasticity at the calyx of Held synapse via BDNF-trkB signaling (Jang, Gould et al. 2019). Building on prior studies that demonstrated release of BDNF from OLs in response to glutamate in the cortical CNS (Bagayogo and Dreyfus 2009), Jang and co-workers verified BDNF expression by OLs

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in the MNTB and demonstrated decreased glutamate release from presynaptic neurons in slice preparations from mice that lack BDNF expression in pre-myelinating OLs (Jang, Gould et al. 2019). These conditional *Bdnf* knockouts also exhibited defects in neural synchrony in the auditory brainstem. The rescue of glutamatergic transmission in the knockouts by local delivery of either BDNF or trkB agonists suggests a mechanism by which BDNF secretion from OLs near the calyx of Held modulates neurotransmitter release from the GBC terminal and supports a modulating role for activity-dependent regulation of presynaptic properties by OLs in the central auditory system.

Oligodendrocyte pathology and hearing impairments. CNS myelin disorders can affect auditory function, as might be expected given the impact of myelin on conduction velocity and timing in neuronal circuits. Studies of these disorders have provided insights into how myelin impacts processing of auditory signals and the nature of hearing defects that arise due to abnormal CNS myelination. While a number of case reports indicate increases in hearing thresholds in multiple sclerosis (MS) patients that present with lesions in CNS auditory regions (Drulovic, Ribaric-Jankes et al. 1993, Bergamaschi, Romani et al. 1997), larger controlled studies failed to validate those observations (Doty, Tourbier et al. 2012). Sudden sensorineural hearing loss has also been described in MS patients, but typically resolves over time (Hellmann, Steiner et al. 2011). Although MS does not appear to result in consistent decreases in auditory sensitivity, subtler defects in hearing that involve losses in temporal auditory processing have been associated with the disorder. Common abnormalities in MS patients include increases in ABR I to V peak latencies that are consistent with myelin deficits in the auditory brainstem. MS patients often exhibit decreased abilities in binaural hearing tasks such as detection of ITDs and IIDs, suggesting impairment of sound localization pathways (Furst and Levine 2015).

Defects in CNS myelin development may also underlie auditory dysfunction. Auditory processing disorder (APD) is a heterogeneous developmental disorder characterized by perceptual problems including deficits in speech comprehension, spatial hearing, and attention. The normal cochlear thresholds often present in individuals diagnosed with APD has suggested that the source of the disorder lies within defects in the central auditory system. Associations between APD and abnormalities in the temporal

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characteristics of speech-evoked ABRs (Rocha-Muniz, Befi-Lopes et al. 2012, Rocha-Muniz, Befi-Lopes et al. 2014) have led to the hypothesis that decreases in the precision of AP firing and conduction in auditory pathways contribute to perceptual dysfunction (Kopp-Scheinpflug and Tempel 2015). Consistent with this notion, myelin abnormalities have been observed in APD patients in brain regions involved in auditory processing. For example, an increased mean diffusion in auditory cortex was observed by DTI in children diagnosed with APD, consistent with a potential disruption of thalamo-cortical communication (Farah, Schmithorst et al. 2014). The same DTI study also found white matter structural abnormalities in the prefrontal cortex and anterior cingulate, which are areas of the brain closely tied to attention and top–down information processing. This suggests that altered myelination in these structures may underlie difficulties in attending to auditory stimuli in APD.

The transmembrane proteolipid protein 1 (PLP1) is a major constituent of myelin in OL. Loss of function mutations in the human X-linked *PLP1* gene generally result in spastic paraplegia, a progressive neuronal degenerative disorder affecting mainly spinocerebellar and lateral corticospinal tracts, while missense mutations with apparent toxic gain of function effects underlie Pelizaeus-Merzbacher Disease (PMD), a more severe leukodystrophy disorder characterized by hypomyelination (Garbern 2007). PMD patients typically have speech difficulties that are associated with normal cochlear function (ABR thresholds and peak I amplitudes) but dyssynchrony of later ABR peaks and delayed and/or reduced myelin levels in the auditory brainstem and higher auditory pathways (Kuan, Sano et al. 2009, Coticchia, Roeder et al. 2011, Morlet, Nagao et al. 2018). Defects in CNS myelination may also influence the auditory dysfunction observed in other neurological disorders. For example, many individuals diagnosed with autism spectrum disorder (ASD) exhibit alterations in several aspects of auditory perception including loudness detection and complex speech comprehension (O'Connor 2012). ASD patients also often exhibit reduced detection of temporal features of auditory stimuli such as gaps in sounds (Foss-Feig, Schauder et al. 2017) as well as decreased white matter properties in several brain regions, including the corpus callosum and temporal lobes (Travers, Adluru et al. 2012). Defects in CNS myelin and auditory processing have also been associated with psychiatric disorders such as

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schizophrenia, bipolar disorder, and chronic depression (Kahkonen, Yamashita et al. 2007, Fields 2008, McLachlan, Phillips et al. 2013, Zenisek, Thaler et al. 2015).

Astrocytes

Astrocytes account for approximately 20-40% of the glial population across different regions in the CNS and play a range of supportive and regulatory roles that contribute to neuronal development, synaptic plasticity and responses to neuronal damage (Bartheld, Bahney et al. 2016). These cells elaborate highly branched processes that interact with neural structures, including synapses, and express ion channels, extracellular matrix proteins, growth factors and cytokines that appear to mediate their influence on neurons (Schiweck, Eickholt et al. 2018). Of note, astrocytes are chemically excitable via expression of a variety of neurotransmitter receptors (Nimmerjahn and Bergles 2015).

Astrocytes and development in the central auditory pathway. Astrocytes have been linked to the postnatal development of the central auditory system (Cramer and Rubel 2016). Immunostaining of astrocyte-associated marker proteins including the intermediate filament glial fibrillary acidic protein (GFAP), the calcium binding protein S100β, and aldehyde dehydrogenase 1 family member L1 (ALDH1L1), revealed the emergence of a diverse pattern of astrocyte cell types in VCN and MNTB of rodents across the three week postnatal developmental period (Dinh, Koppel et al. 2014, Saliu, Adise et al. 2014). At P14, just after the time of hearing onset and when auditory brainstem pathways are approaching maturity, all astrocyte markers were expressed in the VCN and MNTB, with GFAP-positive processes found in both locations while GFAP-positive cell bodies remained outside of these nuclei (Dinh, Koppel et al. 2014). In the MNTB, cell bodies of ALDH1L1-positive and S100β-positive astrocytes were present near principal neurons and calyces of Held, the excitatory terminal of GBC axons on principal neurons, while GFAP-positive processes were often present near the calyces (Dinh, Koppel et al. 2014) (Fig. 1D). This heterogeneous population of astrocytes present during auditory hindbrain maturation has suggested that distinct classes of astrocytes carry out different developmental functions, with early emerging astrocytes participating in neuronal refinement and synaptogenesis and later emerging astrocytes influencing neurotransmission (Dinh, Koppel et al. 2014, Cramer and Rubel 2016).

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It has been suggested that interactions between astrocytic processes and the pre- and post-synaptic membranes of the calyx of Held influence the development and function of this critical auditory synapse. Spontaneous Ca^{2+} transient currents in astrocytes appear to elicit slow inward currents in post-synaptic principal neurons in early postnatal brain slice recordings in MNTB (Reyes-Haro, Muller et al. 2010). These astrocyte-mediated currents, known as gliotransmission, correlate with astrocytic Ca^{2+} activity and seem to be NMDA receptor-mediated. Glutamate release from the presynaptic GBCs mediates fast excitatory synaptic transmission at the calyces of Held. Group II metabotropic glutamate receptors (mGluRs) are expressed in astrocytic processes at the maturing calyces of Held, suggesting that synaptic transmission may also influence astrocyte function during this time (Elezgarai, Bilbao et al. 2001).

Astrocytes play key homeostatic roles in the CNS, including biosynthetic recycling of the neurotransmitter glutamate at synapses (Verkhratsky, Nedergaard et al. 2015). Studies in the developing postnatal MNTB of rats and gerbils demonstrated that the glutamate transporters GLAST and GLT are selectively localized in astrocyte processes ensheathing the calyx of Held (Renden, Taschenberger et al. 2005, Ford, Grothe et al. 2009). This is likely to aid in limiting glutamate diffusion between adjacent terminals during this period of structural and functional remodeling of the calyx. Similar to SuppCs in the cochlea and other glia, glutamate taken up by astrocytes in the MNTB is converted to glutamine; release of glutamine by astrocytes provides a precursor for biosynthetic replenishment of glutamate in adjacent neurons (Uwechue, Marx et al. 2012).

Astrocytes appear to influence neuronal development in the avian auditory hindbrain through release of modulatory factors (Cramer and Rubel 2016). Neurons in nucleus laminaris (NL), which are involved in ITD pathways of sound localization in chicks, display a gradient of dendritic arborization that systematically changes during development of the auditory circuits (Parks and Rubel 1975). Morphological alterations in dendrites coincide with the appearance of GFAP-positive astrocytes, which led researchers to assess the contribution of glial cells to branch order and dendritic morphometric features in NL neurons (Korn, Koppel et al. 2011). Studies in embryonic brainstem slices indicated that conditioned media from cultured embryonic astrocytes

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promoted the formation of a normal gradient of dendritic morphology in NL neurons, suggesting that astrocytes are an important source of molecules capable of modulating dendritic branching and reorganization during development (Korn, Koppel et al. 2011). Similar brainstem slice experiments also support a role for astrocyte-derived factors in regulating the final numbers of inhibitory synapses on NL neurons, which in turn facilitate more precise binaural coincidence detection (Korn, Koppel et al. 2012).

Astrocyte involvement in auditory system damage. Glial cells, including astrocytes and microglia, participate in complex adaptive responses to neurological injury and disease, including local inflammation as well as degenerative and neural protective activities (Schiweck, Eickholt et al. 2018). CNS injuries often lead to an increase in reactive astrocytes, which serve to dampen inflammatory responses and increase neuronal viability (Faulkner, Herrmann et al. 2004). Glial responses to injury often produce a "scar" composed of astrocytes, microglia and associated extracellular matrix material. Such glial scars, while containing the extent of injury, also appear to limit the ability of neural regeneration (Bradbury and Burnside 2019). A number of studies support the involvement of astrocytes and other glia following damage or peripheral sensory loss in the auditory system.

In a model of acute injury by compression of the central portion of the AN in rats, Sekiya and colleagues observed GFAP-positive reactive astrocytes along with markers of glial scar formation in the vicinity of the injured site, which also extended beyond the PNS-CNS transitional zone boundary into the cochlea (Sekiya, Holley et al. 2015). The injury resulted in partial degeneration of SGNs that was associated with ABR threshold elevations. Interestingly, the authors reported that transplantation of auditory neuroblast cells onto the surface of the injured nerves resulted in neurons capable of forming glutamatergic synapses with HCs in the organ of Corti and extending processes into the auditory hindbrain. Rats receiving the neuroblasts exhibited modest recovery of central ABR peak thresholds relative to sham-treated controls. The transplanted cells were closely associated with GFAP-positive processes, suggesting that the reactive astrocytes may have provided neural guidance cues, similar to the glia-guided migration of neurons in the developing cortex (Marín and Rubenstein 2003).

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Disruption of cochlear function decreases afferent AN signaling in the cochlear nucleus (CN) and leads to activity-dependent alterations in central auditory pathways, including neural degeneration and rewiring of circuits (Gold and Bajo 2014). Activated glial responses involving astrocytes and microglia have often been observed following loss of AN nerve input in mammals and birds during development and in the adult, consistent with a damage response (Lurie and Rubel 1994, de Waele, Torres et al. 1996, Janz and Illing 2014). For example, the neural degeneration in ipsilateral CN that follows unilateral cochlear ablation leads to loss of normal VCN connections to the contralateral MNTB (Trune 1982, Hashisaki and Rubel 1989, Mostafapour, Cochran et al. 2000). Interestingly, following cochlear ablation during early postnatal development, neurons of the intact VCN have been shown to send branches that form new calyceal contacts with the denervated MNTB (Moore and Kowalchuk 1988, Kitzes, Kageyama et al. 1995, Hsieh, Hong et al. 2007). Dinh and co-workers observed that these new synapses exhibited closely apposed astrocytes, suggesting that glial cells are involved in reorganizing the new calyces (Dinh, Koppel et al. 2014). In contrast to manipulations during development, loss of afferent synapses in VCN following cochlear ablation in the mature animal leads to re-innervation of VCN cells by axon collateral sprouting from SOC-derived neurons (Kraus and Illing 2004). Molecular studies of astrocyte markers during this reorganization suggested two phases of glial cell responses, one associated with AN and synaptic degeneration and the second associated with reinnervation and new synapse formation (Fredrich, Zeber et al. 2013).

A long-lasting activated glial response (increased number of astrocytes and microglia processes) has been observed in the CN of mature rats following deafening by loud noise exposure, prior to any evidence of overt AN degeneration (Fuentes-Santamaria, Alvarado et al. 2017). Glial processes were found in close apposition to VCN neurons and synapses, along with increased expression of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α). This glial response may be related to the increased spontaneous firing rate in CN neurons that is frequently observed following noise trauma (Kaltenbach and Afman 2000, Vogler, Robertson et al. 2011). Following deafening of neonatal rats, glial activation has also been correlated with increased neuronal activity in the inferior colliculus (IC), a central auditory nucleus that receives

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input from both the periphery and higher level pathways (Rosskothen-Kuhl, Hildebrandt et al. 2018). These findings suggest that glial remodeling contributes to auditory system plasticity following sensory loss.

Deafness-associated plasticity, including increased spontaneous activity and synchrony in central auditory system nuclei, has also been implicated in tinnitus, an often-debilitating condition characterized by the sensation of phantom sounds (Shore, Roberts et al. 2016). A recent study has suggested an association of microglial activation and increased TNF-α expression with excitatory-inhibitory synaptic imbalance in the auditory cortex following noise-induced deafness in mice (Wang, Zhang et al. 2019). Pharmacological and genetic inhibition of TNF-α resulted in a decrease in microglial activation and normalized synaptic firing in the cortex, together with reduced behavioral evidence of tinnitus in deafened animals. Although the use of behavioral studies to evaluate tinnitus in animal models remains controversial (Jones and May 2017), this study suggests that neuroinflammatory responses to noise could influence auditory system plasticity and thus may also impact development of tinnitus.

Conclusions. The auditory system provides a tractable experimental model to investigate the roles of glia and neuron-glia interactions in health and disease. The accessibility of the auditory system for in vivo recordings at the physiological and behavioral levels, in conjunction with the growing toolbox for genetic manipulation of sensory HCs, neurons and glia, provide opportunities to interrogate the molecular and cellular mechanisms of neuron-glia interactions. As a note of caution, however, a number of studies have underscored the importance of careful consideration of genetic regulatory elements in these approaches, as promoters typically considered specific for particular glial subtypes can be expressed more broadly in both neurons and glia (Wan and Corfas 2017, Brandebura, Morehead et al. 2018). Similarly, a more detailed understanding of the role of glia on hearing should provide insight into deafness and other disorders that affect the auditory system, including peripheral neuropathies and tinnitus, and is also likely to suggest novel approaches for treatment.

Further comparative investigations of glial interactions within the auditory system through use of high resolution imaging of animal model and human specimens will also

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be useful to identify any subtle species-specific differences that may underlie functional divergence (Liu, Edin et al. 2015, Liu, Glueckert et al. 2020). Similarly, proteomic and single cell transcriptional studies of auditory tissue from humans and animals will provide a sharper picture of molecular mechanisms involved in glial function (Schmitt, Pich et al. 2017, Petitpré, Wu et al. 2018, Shrestha, Chia et al. 2018, Sun, Babola et al. 2018, Lin, Ren et al. 2019). In addition to providing insight into basic processes such as sensory information processing, a more precise understanding of axon-glia interactions in the auditory system is likely to impact development of future regeneration and neural implant treatment strategies for hearing loss.

Figure 1. The auditory pathway.

(A) Schematic representation of the auditory periphery, including glial cells associated with SGNs (supporting cells, Schwann cells, satellite glial cells, oligodendrocytes). Oligodendrocyte myelination of SGN axons begins at the CNS–PNS transition zone (arrows).

(B) Schematic representation of the central auditory pathway highlighting ITD and IID circuitry at the level of the pons. VCN SBCs (blue) extend excitatory projections to the LSO and MSO in the SOC. VCN GBCs (green) extend excitatory projections to the MNTB, which then send inhibitory projections (red) to the LSO and MSO. Auditory information then passes through several subsequent nuclei including the IC before reaching the MGN and projecting to the auditory cortex.

(C) Auditory system function can be measured using auditory brainstem responses (ABR). This method uses electrodes to detect evoked electrical potentials along the early auditory pathway, from the cochlea through the midbrain. The summating potential (SP) reflects activation of IHCs, peak I corresponds to evoked potentials in SGNs while later peaks generally correspond to evoked potentials in CN (peak II), SOC (peak III), and IC (peaks IV and V) in the mouse (Henry 1979, Land, Burghard et al. 2016). The magnitude of peak I amplitudes correlates with the number and synchronous firing rate of the SGN fibers.

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(D) Calyx of held synapse in MNTB is formed by a highly fenestrated calyx ending of the presynaptic GBC axon and the postsynaptic soma of the MNTB principal cell (principal cell projections not shown). Astrocytes are in close proximity to the principal cell soma and extend processes into the spaces between calyceal elements (Ford, Grothe et al. 2009, Reyes-Haro, Muller et al. 2010). Figure 1B is adapted from (Cope, Baguley et al. 2015). Figure 1C is adapted from (Kohrman, Wan et al. 2019). AVCN: anteroventral cochlear nucleus; LSO: lateral superior olive; MSO: medial superior olive; GBC: globular bushy cell; SBC: spherical bushy cell; SOC: superior olivary complex; MNTB: medial nucleus of the trapezoid body; MGN: medial geniculate nucleus; IHC: inner hair cell; SGN: spiral ganglion neuron.

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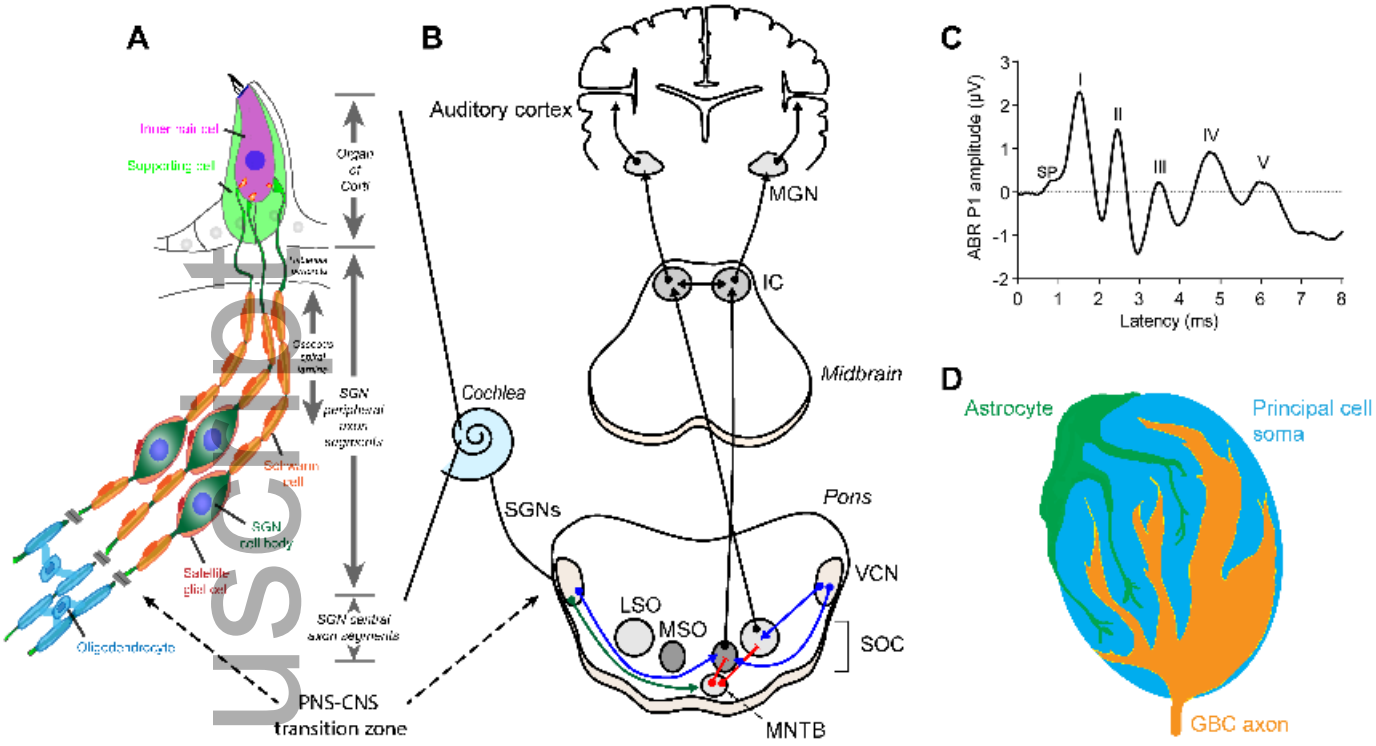

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