Oxford Handbooks Online

Glial Cells in the Auditory Brainstem

Giedre Milinkeviciute and Karina S. Cramer

The Oxford Handbook of the Auditory Brainstem
Edited by Karl Kandler

Subject: Neuroscience, Sensory and Motor Systems, Molecular and Cellular Systems
Online Publication Date: Sep 2018 DOI: 10.1093/oxfordhb/9780190849061.013.18

Abstract and Keywords

The auditory brainstem carries out sound localization functions that require an extraordinary degree of precision. While many of the specializations needed for these functions reside in auditory neurons, additional adaptations are made possible by the functions of glial cells. Astrocytes, once thought to have mainly a supporting role in nervous system function, are now known to participate in synaptic function. In the auditory brainstem, they contribute to development of specialized synapses and to mature synaptic function. Oligodendrocytes play critical roles in regulating timing in sound localization circuitry. Microglia enter the central nervous system early in development, and also have important functions in the auditory system's response to injury. This chapter highlights the unique functions of these non-neuronal cells in the auditory system.

Keywords: astrocyte, oligodendrocyte, myelination, conduction velocity, calyx of Held, microglia, nucleus magnocellularis, nucleus laminaris

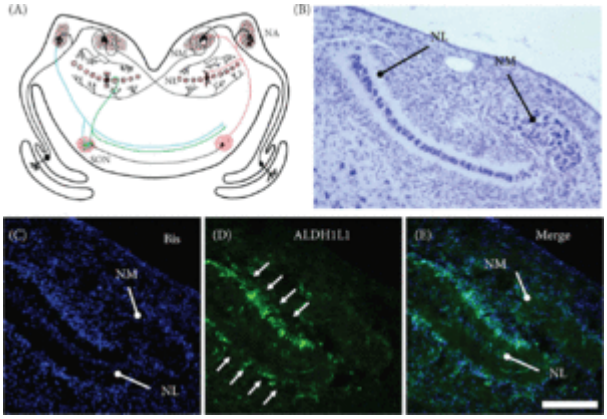
Auditory brainstem function emerges from precise and highly specialized neural circuits. Recent studies have demonstrated the remarkable extent to which the development and function of neuronal circuitry rely on multiple functions of glial cells. Notably, astrocytes (Allen & Eroglu 2017; Chung et al., 2015), oligodendrocytes (Micu et al., 2017), and microglia (Mosser et al., 2017) are known to communicate closely with neurons during development, plasticity, and in response to brain injury. Astrocytes and oligodendrocytes are derived from neural lineages and, like neurons, display diversity appropriate for their specialized functions (Dimou & Simons, 2017; Farmer & Murai, 2017). In addition, they share some unexpected properties with neurons, including the ability to release and respond to neurotransmitters and, in some cases, excitability (Berret et al., 2017; Micu et al., 2017; Perea et al., 2014). Microglia, the immune cells of the brain, are derived from the myeloid lineage and migrate into the central nervous system early in development (Mosser et al., 2017). The highly motile branches of these cells interact dynamically with their environment (Gomez-Nicola & Perry, 2015). However, their gene expression profiles vary with brain region (Grabert et al., 2016), suggesting region-specific functions for subpopulations of microglia.

In this chapter, these aspects of glial cell function are explored in the context of the unique circuits of the auditory brainstem. We consider glial contributions to the formation of auditory brainstem circuits, to the function of synapses and circuits, and to the response of auditory nuclei to injury.

Sound Localization Pathways in Birds and Mammals

Both avian and mammalian animal models have led to insights on auditory brainstem function and on the roles of glial cells. The avian auditory brainstem (Figure 1) displays a well-characterized neuronal pathway from nucleus magnocellularis (NM) to nucleus laminaris (NL). NM, which is homologous to the anteroventral cochlear nucleus, receives input from central projections of cochlear ganglion cells (Rubel & Fritzsch, 2002). NM axons branch and project bilaterally and tonotopically to NL, a laminated nucleus with bitufted dendrites oriented dorsally and ventrally (Figure 1A). The ipsilateral branch makes contacts with dorsal NL dendrites, while the contralateral branch contacts ventral NL dendrites (Hackett et al., 1982; Parks & Rubel, 1975; ; Young & Rubel, 1983). Coincidence detection by NL neurons together with axonal delay lines in the contralateral NM axon are used to reveal interaural time differences (ITDs), which are used to estimate the location of sound sources (Hyson, 2005; Koppl & Carr, 2008; Overholt et al., 1992;. Coincidence detection in NL is improved with inhibitory input, which arises from the superior olivary nucleus (SON) (Burger et al., 2011; Lachica et al., 1994; Ohmori, 2014; Yang et al., 1999). In the developing chick embryo, NL is a single cell thick, and the cell body layer is surrounded by a region of neuropil free of cell bodies (Figure 1B). At the

outer margins of the neuropil, the nucleus is surrounded by a tightly packed layer of glial cells (Figure 1B–E).



Click to view larger

Figure 1. A: Auditory pathways in the chick. Nucleus magnocellularis (NM) receives VIIIth nerve input. NM axons branch and innervate nucleus laminaris (NL) bilaterally, with ipsilateral inputs on dorsal dendrites and contralateral inputs on ventral dendrites. Inhibitory input to NL arises from the superior olivary nucleus (SON). B: Glial cell bodies can be seen in Nissl stained sections in a margin (arrowheads) surrounding the cell-free zone around the NL cell body layer (arrow). C–E: Glial margin around NL is evident at E10 with bisbenzimide staining (bis) and ALDH1L1. Scale bar, 100 µm.

In mammals, ITDs are computed in the medial superior olive (MSO), which is analogous to NL (Grothe, 2003). Lateral MSO dendrites receive ipsilateral input from the ventral cochlear nucleus (VCN) and medial MSO dendrites receive contralateral VCN input. Unlike the chick NL, MSO neurons rely on precisely timed inhibitory input in order to compute ITDs (Brand et al., 2002; Myoga et al., 2014; Pecka et al., 2008). In addition to ITDs, auditory brainstem nuclei are used to compute interaural level differences (ILDs). VCN neurons project contralaterally to the medial nucleus of the trapezoid body (MNTB). The axon terminates in the large calyx of Held, encapsulating the MNTB neuron (Held, 1893; Kuwabara & Zook, 1992; Nakamura & Cramer 2011). MNTB provides inhibitory input to the lateral superior olive (LSO), which receives tonotopically matched excitatory input from VCN. The balance of excitation and inhibition in LSO neurons is used to compute ILDs, which are used to determine the locations of sound sources (Glendenning et al., 1992; Kandler & Gillespie, 2005; Sanes, 1990; Tollin, 2003).

Glial Cells in Auditory Brainstem Development

Astrocytes, microglia, and oligodendrocytes arise in the auditory brainstem with a characteristic time course and morphological features. In some cases, their functions have been critically tested.

Astrocytes and Development of the Chick Auditory Brainstem Pathways

The emergence of glial cells in the developing chick auditory brainstem is evident at the time when NM-NL synapses are forming, at about embryonic day (E)10. Small cells expressing aldehyde dehydrogenase 1, family L1 (ALDH1L1), a marker for astrocytes () are seen in the glial margin around NL (Cahoy et al., 2008; Rotschafer et al., 2016; Figure 1C–E). At this age distinct populations of glial cells are present in the dorsal versus ventral regions of NL during the time of synaptic maturation. Astrocytes expressing glial fibrillary acidic protein (GFAP) emerge after the formation of excitatory connections and just prior to the maturation of inhibitory synapses in NL (Korn & Cramer, 2008) and at the beginning of a period of extensive dendritic remodeling (Smith & Rubel, 1979).

Late appearing GFAP-positive astrocytes may play a role in the maturation of inhibitory inputs. Organotypic slice cultures of the auditory brainstem from an age prior to the maturation of astrocytes were exposed to astrocyte-conditioned medium (ACM) from older brainstems taken at an age when GFAP-positive astrocytes were present. This treatment accelerated the formation of inhibitory inputs, whereas control cultures showed very little change in inhibitory inputs (Korn et al., 2012). These results suggest that astrocytes secrete factors needed for inhibitory synaptogenesis.

A second major role for astrocytes in chick auditory brainstem development appears to be the regulation of dendritic arbor morphology. Dendritic arbor size varies with the tonotopic location of NL neurons, whereby high frequency neurons have numerous short dendrites and low frequency neurons have fewer primary dendrites with longer branches (Smith & Rubel, 1979). This arrangement is thought to optimize the ability of NL neurons to perform computation of ITDs (Agmon-Snir et al., 1998). This gradient of dendritic arbor size emerges from a fairly uniform distribution at a relatively late stage of embryonic development, after the formation of synaptic connections and just after the emergence of GFAP-positive astrocytes. ACM derived from late brainstem astrocytes promoted maturation of these dendritic arbors in organotypic slices (Korn et al., 2011). In this study, the effects varied along the tonotopic axis, suggesting that elements that respond to astrocyte-derived cues reside in the dendrites in tonotopic gradients.

During chick auditory brainstem development, there appears to be significant communication between NM axons, NL dendrites, and the glial cells surrounding NL. We recently showed that cleaved caspase-3 is expressed in axons of the auditory pathway (Rotschafer et al., 2016). When caspase-3 was pharmacologically inhibited in the brainstem in whole embryo cultures, contralateral NM axon branches were mistargeted to dorsal regions of NL. In addition, there was disruption of both the NL cell lamination and the glial cell margin, with numerous ALDH1L1-positive astrocytes found in the normally cell-free NL neuropil region. The mechanism through which axonal caspase-3 non-cell-autonomously influences NL glial cells is not known. Entry of these glial cells into the neuropil region is also seen when the crossed fibers are experimentally severed (Rubel et al., 1981); in this case the disruption is accompanied by rapid atrophy of ventral dendrites. Together, these experiments highlight the importance of signaling between NM

axons and glia surrounding NL. They further suggest that the integrity of both the NL cell lamina and the NL glial margin relies on cues from NM axons.

Glial Cells in the Developing Mammalian Auditory Brainstem

ALDH1L1-positive astrocytes are seen in VCN and MNTB at P0 (Dinh et al., 2014) and their populations increase over the next two weeks. Another marker for astrocytes, the calcium binding protein, S100ß, is evident in VCN and MNTB by P6 (Dinh et al., 2014; Saliu et al., 2014), and the expression of GFAP is seen in these nuclei at later postnatal ages. Several studies have demonstrated the presence of astrocytes in the developing calyx of Held. At late ages, when the calyx of Held has formed, ALDH1L1 immunolabeling is associated with the encapsulating calyx around MNTB neurons (Dinh et al., 2014), and ultrastructural studies have demonstrated the interposition of astrocytes between the developing calyx and MNTB neurons (Holcomb et al., 2013). During postnatal development, astrocytic processes invade the calyx, producing numerous fenestrations in a time course that varies with tonotopic position (Ford et al. 2009). Microglia are also evident in the auditory brainstem during early postnatal development. Within MNTB, their branches are seen in close apposition with developing calyces, and their numbers peak at about two postnatal weeks in mice (Dinh et al., 2014). During the first postnatal week in mice, oligodendrocytes are present in both VCN and MNTB (Dinh et al., 2014; Kolson et al., 2016). Myelin basic protein in VCN fibers projecting to MNTB is first expressed at P9 in the rat (Saliu et al., 2014) and P8 in the mouse (Sinclair et al., 2017). Myelin thickness continues to increase until P35, and its maturation is dependent on auditory input (Sinclair et al., 2017). Together these studies highlight the development of glial cells alongside the developing neuronal circuitry in the postnatal auditory brainstem.

Synaptic Functions of Astrocytes in the Auditory Brainstem

Astrocytes have important roles in synaptogenesis and synaptic function. Interestingly, the timing of synaptogenesis has been shown to be related to the arrival of astrocytes in the developing brain (Miller & Gauthier, 2007; Ullian et al., 2001). The involvement of astrocytes in synaptic function is captured in the concept of the “tripartite synapse,” which includes close communication and apposition of the pre- and postsynaptic neurons as well as the astrocyte (Araque et al., 1999; Bosworth & Allen, 2017). Astrocytes respond to neurotransmitter release by elevating the intracellular Ca^{2+} concentration (Cornell-Bell et al., 1990; Cornell-Bell & Finkbeiner, 1991) and releasing their own chemical transmitters (Bezzi et al., 1998; Guthrie et al., 1999). Calcium increase is a necessary step for gliotransmission (Stout & Charles 2003), which results in feedback modulation of neurons and synaptic activity. This tripartite communication system enables astrocytic signals to control the timing, location, and strength of developing synapses (Allen, 2013;

Ullian et al., 2001). Astrocytic molecules including thrombospondins and hevin induce silent synapses (Eroglu et al., 2009; Singh et al., 2016), while glypicans 4 and 6 prompt the formation of active synapses (Allen et al., 2012). In addition to their role in development, astrocytes regulate synaptic maturation through selective strengthening and weakening as well as refinement of neural connections (Risher et al., 2014; van Deijk et al., 2017). Astrocytes can directly phagocytose or remove synapses that have been tagged by microglia, thus contributing to synaptic pruning (Hakim et al., 2014; Tasdemir-Yilmaz & Freeman, 2014).

The involvement of astrocytes in synaptogenesis is facilitated by their location adjacent to synapses in various parts of the brain including the cerebellum, cortex, hippocampus, and brainstem (Satzler et al., 2002; Spacek, 1985; Ventura & Harris, 1999). This strategic positioning allows astrocytes to react rapidly to changes in synaptic activity. Increased synaptic activity leads to expansion of astrocytic volume, growth of astrocytic processes, followed by augmented ensheathment of synapses (Anderson et al., 1994; Genoud et al., 2006; Hawrylak et al., 1993; Jones & Greenough, 1996; Wenzel et al., 1991; Witcher et al., 2007). Astrocytic apposition to pre- and postsynaptic regions facilitates sequestering, releasing, and recycling of neurotransmitters and neuromodulators (Bardoni et al., 2010; Henneberger et al., 2010; Perea & Araque, 2007).

Like principal neurons in the MNTB, glial cells express both ionotropic and metabotropic glutamate receptors (Meguro et al., 1999; Reyes-Haro et al., 2010; Steinhauser & Gallo, 1996). These glial receptors mediate neuron-glia signaling in developing and mature animals (Steinhauser & Gallo, 1996; Vernadakis, 1996), in turn regulating neuronal maturation and synaptic plasticity as well as glial proliferation, differentiation, and gene expression (Condorelli et al., 1993; Gallo et al., 1996). Expression of different types of glutamate receptors can change throughout development and maturation, with occasional overlap. Studies in rats showed that metabotropic glutamate receptor mGluR4a is expressed in calyces of Held prior to hearing onset and expression declines thereafter (Elezgarai et al., 1999; Kandler & Friauf, 1993). The onset of hearing also appears to regulate mGluR3 localization, which shifts from the neuropil toward the cell bodies, in parallel with GFAP immunolabeling (Elezgarai et al., 2001). Taken together, these studies showed that mGluR3 expression in astrocytic processes parallels that of the mGluR4a in calyx of Held synapses and follows the same rise, peak, and decline timeline (Elezgarai et al., 1999). It is possible that astrocytic mGluR3 activates several intracellular mechanisms relevant for the development and maturation of both the neurons and the astrocytes. Additionally, it has been proposed that activation of mGluR3 could function as a way of maintaining glycogen stores for the high-energy levels required for developing and maturing CNS and, in particular, the calyx of Held (Elezgarai et al., 2001; Magistretti et al., 1993; Sorg & Magistretti, 1991).

Some literature suggests that glial transporters are left out of synaptic clefts in the calyx of Held and thus are not necessary for the control of the postsynaptic response (Renden et al., 2005). These data are further supported by the lack of glutamate-mediated uptake currents observed in astrocytes after the stimulation of presynaptic afferents. The slow

inward currents in MNTB astrocytes may be due to increased extracellular potassium levels that follow neuronal activity (Reyes-Haro et al., 2010). Astrocytes in MNTB appear to signal to neurons through D-serine (Panatier et al., 2006), which acts as a co-agonist to evoke NMDA-mediated neuronal slow inward currents (Reyes-Haro et al., 2010). D-serine is only released by astrocytes (Panatier et al., 2006) and its content correlates with the distribution of NMDA receptors (Schell et al., 1995; Schell et al., 1997). These studies highlight the communication between astrocytes and the calyx of Held synapse.

In addition to neuron-glial communication via glutamate receptors, astrocytes are essential for glutamate recycling, which is imperative for the maintenance of neurotransmitter availability (Hertz et al., 1999; Laake et al., 1995; Pow & Robinson, 1994). Glutamate is released in the synaptic cleft and taken up by high-affinity excitatory amino acid transporters (Bak et al., 2006; Danbolt, 2001; Leke & Schousboe, 2016). Glutamate is then converted to glutamine by glutamine synthetase (Norenberg & Martinez-Hernandez, 1979), released from astrocytes and taken up by neurons (Chaudhry et al., 2002) that convert it back to glutamate (Kvamme et al., 2000). This glutamate-glutamine-glutamate cycle ensures a constant supply of glutamate, which is essential for fast and temporally precise high firing frequency (Hermann et al., 2007; Kopp-Scheinpflug et al., 2008) such as that which occurs between the calyx of Held and the MNTB principal neuron (Uwechue et al., 2012). The fenestrated morphology of the calyx of Held allows astroglial processes to closely appose the active sites where glutamate is released and subsequently taken up by astrocytic glutamate transporters terminating the synaptic events (Ford et al., 2009; Gegelashvili & Schousboe, 1997). Inhibition of astrocyte glutamate recycling cycle leads to altered synaptic transmission (Otis et al., 1996; Renden et al., 2005) and disrupts neuronal-glial communication pathway (Uwechue et al., 2012).

Oligodendrocytes and Control of Conduction Time

Auditory brainstem pathways are exquisitely sensitive to the timing of action potentials. In the chick auditory brainstem, coincident input in NL from ipsilateral and contralateral NM occurs for a range of interaural time delays and frequencies. However, NM and NL on each side reside in close proximity, after emerging from a common structure known as the auditory anlage (Book & Morest, 1990; Cramer et al., 2000; Harkmark, 1954). Consequently, the distance from NM to contralateral NL is much greater than the distance to ipsilateral NL. Early studies demonstrated the presence of a looped trajectory in the ipsilateral NM axon branch, and it was postulated that this circuitous pathway brought the conduction times into similar ranges (Young & Rubel, 1983). However, subsequent studies using careful reconstructions demonstrated that in fact, the contralateral axon branch is about twice the length of the ipsilateral axon branch (Seidl et al., 2014). Analysis of the internode distance (between nodes of Ranvier) and axon diameter, both of which are positively correlated with conduction velocity (Brill et al., 1977), revealed differences between the ipsilateral and contralateral NM axon branches that compensate for the disparities in length (Seidl, 2014; Seidl et al., 2014). Long projection segments of axon branches displayed longer internode distances and larger axon diameters than short projection regions. These differences suggest careful regulation of myelination at a subcellular, regional level, and further suggest close communication between axons and myelinating oligodendrocytes.

Adaptations to control conduction time are also evident in the excitatory ITD circuitry in the mammalian auditory brainstem. In gerbils, regulation of internode distance and axon diameter was similarly found to compensate for length disparities in the projection of spherical bushy cells (SBCs) in the VCN to lateral and medial dendrites in ipsilateral and contralateral MSO, respectively (Seidl & Rubel, 2016). While the differences in axon diameter only became evident at about P20, the differences in internodal distance were already established at P10, prior to the time of hearing onset (Woolf & Ryan, 1984). Mechanisms that regulate timing in the inhibitory inputs are not known.

Auditory brainstem circuitry to detect ILDs also relies on precise timing of action potentials. LSO neurons compare excitatory input from the ipsilateral side and inhibitory input from the contralateral side. They receive excitatory input from SBCs in the ipsilateral VCN and tonotopically matched inhibitory input from the ipsilateral MNTB, which is stimulated through the calyx of Held arising in globular bushy cells (GBCs) in contralateral VCN. These inhibitory inputs arise in close temporal proximity, in spite of the longer distance and synaptic delay (Grothe et al., 2010). Morphometric analysis of axons and myelination in SBCs and GBCs in gerbils revealed some new insights into regulation of conduction time (Ford et al., 2015). GBCs showed larger diameter axons and greater internode distance than SBCs. However, GBCs varied according to whether they projected to low frequency, lateral regions of MNTB, or high frequency, medial regions of

MNTB. Lateral GBCs had larger axon diameters and larger node of Ranvier diameters, but shorter internode length. Simulations of conduction time predict that lateral projecting GBCs conduct faster than medial GBCs, consistent with the longer path length of these axons. In addition, spatial aspects of nodes and axon diameter varied with distance from the axon termination; these were found to be optimized for fast, reliable propagation of action potentials to MTNB (Ford et al., 2015).

In the mouse trapezoid body, which includes axons projecting to MNTB, myelination, axon diameter, and conduction velocity mature after hearing onset (Sinclair et al., 2017). While auditory input is needed for normal development of these fibers, reducing input with ear plugs in adult animals resulted in a reduction in large diameter axons and myelin thickness (Sinclair et al., 2017). This study suggests that axon and myelin specializations are regulated in an activity-dependent way throughout the lifespan.

There are several molecular pathways through which axons communicate with myelinating oligodendrocytes. They include neurotransmitters, such as glutamate, which is released from axons and taken up by glutamate receptors in oligodendrocytes (Bergles et al., 2000; Kukley et al., 2007). Additionally, the extracellular signal-regulated kinases 1 and 2 (ERK1/2) are crucial parts of the signal transduction pathway that initiates myelination during development, and sustained activation of ERK1/2 can reinstate myelination processes and increase auditory brainstem conduction velocity in adult mice (Jeffries et al., 2016). Oligodendrocyte precursor cells (OPCs) are excitable (De Biase et al., 2010) and later transition to immature pre-myelinating oligodendrocytes (pre-OLs), which attach to axons and retain excitable properties (Bakiri et al., 2011). Recent electrophysiological studies (Berret et al., 2017) demonstrated that pre-OLs in the developing rat MNTB displayed strong sodium currents, expressed $Na_v1.2$, and fired action potentials. This group further showed that a subpopulation of these cells remained through adulthood. Knockdown of $Na_v1.2$ using virally delivered RNA interference led to impaired morphological development of the pre-OLs and a reduction in myelination (Berret et al., 2017). These studies highlight the importance of ongoing neuron-oligodendrocyte communication throughout development.

Glial Cells in Auditory Brainstem Injury

Sensorineural hearing loss can result from a multitude of causes—genetics, exposure to ototoxic drugs, tumors, or other injuries—that compromise the function of hair cells in the cochlea and result in reduced neuronal input to spiral ganglion neurons (SGN). The most commonly used models of sensorineural hearing loss in animals are mechanical cochlear ablation, acoustic trauma or exposure to ototoxic drugs. All of these approaches allow for the study of degenerative and reparative mechanisms in the auditory system.

Loss of Afferent Input

Degeneration of SGNs starts with the loss of acoustic stimulation and initiates a cascade of activity-dependent changes along the auditory ascending pathway (Syka, 2002). Degenerating afferents are seen in the cochlear nucleus (CN) as early as 12–48 hours and disappear between ten days and one month after the lesion (Gentschev & Sotelo, 1973; Morest et al., 1997). As a consequence of reduced or absent stimulation, cell atrophy has been observed in the CN (Moore, 1990; Tierney et al., 1997), as well as alterations to intracellular calcium signaling pathways (Caicedo et al., 1997; Fuentes-Santamaria et al., 2005; Lohmann & Friauf, 1996) and synaptic rearrangements (Du et al., 2012; Muly et al., 2002; Sie & Rubel, 1992). Following injury, synaptogenesis and initiation of axonal sprouting overlaps with degeneration. Recovery of synaptophysin (Benson et al., 1997) and upregulation of growth associated protein 43 (GAP-43), a marker of axonal sprouting, were observed one week after cochlear removal (Fredrich & Illing, 2010). Additionally, deafferentation caused glial proliferation and hypertrophy in the CN of a variety of animal species (Campos Torres et al., 1999; de Waele et al., 1996; Fuentes-Santamaria et al., 2012; Lurie & Durham, 2000; Lurie & Rubel, 1994; Insausti et al., 1999). It is still not entirely clear whether glial cells react to the injury as scavengers, removing the debris from degenerating axons, or whether they act to facilitate reorganization and formation of new synaptic connections and axonal sprouting, or both.

Microglia are activated early in the response to injury (Baizer et al., 2015; Colonna & Butovsky, 2017; Hanisch & Kettenmann, 2007). The microglial response leading to phagocytosis and plasticity has been studied in an experimental model of acoustic trauma. In this study, Baizer et al., (2015) exposed rats to prolonged loud sounds that resulted in the degeneration of the auditory nerve and the subsequent loss of synapses in the CN. The authors used antibodies that selectively identify resting versus activated microglia to characterize microglia in the CN and in the auditory nerve, labeled using silver stain to identify degenerating axons. While there were only minimal numbers of activated microglia in control animals, CN in experimental animals stained strongly for markers of activated microglia, and there was significant overlap between these markers and silver stained degenerating afferents at 30 days after acoustic trauma. This overlap is consistent with a phagocytic scavenging role for microglia, in which microglia act to remove dysfunctional inputs and clear the area for establishment of new synaptic connections (Kettenmann et al., 2013). Degenerating axons and activated microglia remained and showed overlapping regions at 60 days following acoustic trauma. At a six-month time point, evidence for degeneration remained, but the overlap with the activated microglial marker was reduced. At nine months after noise exposure, silver staining was still observed with an overlapping microglial region, but the microglia had shifted their marker profiles. Interestingly, many more activated microglia were observed in the adjacent brainstem (Baizer et al., 2015). These findings support the role of microglia as scavengers in response to injury. However, they do not rule out a role for microglia in plastic changes that occur during and after the time of nerve degeneration. Afferent degeneration and subsequent plasticity occur over a prolonged time course after acoustic

trauma in comparison to the rapid responses after cochlear ablation, suggesting that these injury responses and recovery may be mediated by different mechanisms (Baizer et al., 2015; Morest et al., 1998).

Following bilateral cochlear ablation, a morphological transition in microglia from a quiescent surveying state to an activated amoeboid state was observed as early as 16 hours in the AVCN and PVCN (anterior and posterior VCN) in rats. The activation was characterized by an increase in cross-sectional area of microglial cells and in expression levels of the ionized calcium-binding molecule 1 (Iba-1). The activation peaked at 24 hours post-ablation, gradually declined thereafter, but remained statistically significant until 100 days later (Fuentes-Santamaria et al., 2012). In the unilateral cochlear ablation model, morphological changes in microglia, including compact cell bodies, thickened processes and decreased numbers of distal ramifications, were milder than in bilateral ablation (Janz & Illing, 2014). Microglial cells were observed in close apposition to the CN neurons after unilateral or bilateral cochlear ablations, (Fuentes-Santamaria et al., 2012). This juxtaposition may be related to a role for microglia in synaptic reorganization (Bruce-Keller, 1999; Hildebrandt et al., 2011; Muly et al., 2002) which includes synaptic stripping (Cullheim & Thams, 2007). Activated microglial processes contacted both excitatory and inhibitory synapses in deafferented ipsilateral AVCN and LSO but the cup-like structures partially surrounding the presynaptic endings favored glutamatergic synapses (Janz & Illing, 2014). This proximity is consistent with a role for microglia in a rapid response to neuronal signals following injury and possibly for facilitating axonal sprouting to reinstate synaptic homeostasis (Cullheim & Thams, 2007; Fuentes-Santamaria et al., 2012; Janz & Illing, 2014). It should be noted that microglia dynamically contact synapses in the normal course of surveying their microenvironment, and this contact lasts on the order of minutes (Wake et al., 2009). This contact enables microglia to rapidly detect and respond to any homeostatic deviations in the adult mammalian brain (Janz & Illing, 2014). The frequency and specificity of these ongoing contacts has yet to be compared in control versus experimentally lesioned animals. Such an analysis will be valuable in determining whether microglia-synapse interactions are features of the response to injury.

Microglial activation in response to auditory brainstem denervation is often accompanied by astrocytic activation (Canady & Rubel, 1992; Fuentes-Santamaria et al., 2012; Fuentes-Santamaria et al., 2013) and has been observed in rats (Campos-Torres et al., 2005; Fuentes-Santamaria et al., 2013), chickens (Lurie & Durham, 2000; Lurie & Rubel, 1994) and monkeys (Insausti et al., 1999). GFAP immunostaining peaks one week after bilateral cochlear ablation in rats (Fuentes-Santamaria et al., 2013). It appears that both glial cell types play a part in alteration and repair of auditory brainstem circuitry following cochlear damage, albeit with temporally distinct responses. Microglial transformation usually precedes astroglial changes (Fuentes-Santamaria et al., 2012; Fuentes-Santamaria et al., 2013; ; Fuentes-Santamaria et al., 2017; Janz & Illing, 2014), which may reflect their involvement in different parts of synaptic removal and reorganization. Work in other areas of the nervous system has shown that while microglial cells remove presynaptic boutons, astrocytes may facilitate the formation of

new connections in areas denervated by the lesion (Cullheim & Thams, 2007; Jinno & Yamada, 2011; Reisert et al., 1984; Schiefer et al., 1999). Moreover, in cultured retinal ganglion cells, astrocyte-derived molecular signals were shown to be required for the formation of new functional synapses (Pfrieger & Barres, 1997; Ullian et al., 2001). This view is consistent with the close apposition of microglia and astrocytic processes in deafferented auditory neurons (Fuentes-Santamaria et al., 2012; Fuentes-Santamaria et al., 2013). Taken together, this evidence suggests the critical and coordinated roles of glial cells in synaptic degeneration and repair processes following the loss of afferent input.

Astrocytes have been shown to phagocytose cellular debris in the dentate gyrus and optic nerve as a response to degenerative processes (Bechmann & Nitsch, 1997; Vaughn & Pease, 1970). Numerous proteins become upregulated in response to injury, including some of the matrix metalloproteinases (MMPs). These molecules can cleave the extracellular matrix, altering the environment around neurons and allowing reinnervation to occur (Michaluk & Kaczmarek, 2007; Szklarczyk et al., 2002; Werb, 1997). MMP-9 was found to be upregulated in activated astrocytes following CN deafferentation in rats and occurred early in the degeneration phase (Fredrich et al., 2013). MMP-2 and polysialic acid, which is essential for activity-dependent plasticity (Dityatev et al., 2004; Muller et al., 1996), have been shown to be upregulated during reinnervation. Upregulation was similarly reported for ezrin, a protein that links the cell membrane with the actin cytoskeleton (Fredrich et al. 2013; Tsukita & Yonemura, 1997; Vaheri et al., 1997). Elevated expression of both MMP-9 and ezrin continued independently of the arrival of new GAP-43 positive axons in the denervated areas (Fredrich et al., 2013). GAP-43 has been known to be expressed by newly formed cholinergic collaterals that arrive from the ventral nucleus of the trapezoid body (VNTB) during the regenerative process (Fredrich et al,. 2013; Meidinger et al., 2006) and is thought of as a marker of synaptogenesis (Benowitz & Routtenberg, 1997; Grasselli et al., 2011). When VNTB was lesioned by injections of kainic acid, GAP-43 reactivity in AVCN in response to cochlear ablation was prevented, and reinnervation of the nucleus did not occur. Similarly, MMP-2 did not show its characteristic upregulation. In contrast, VNTB lesion did not affect MMP-9 and ezrin levels. It was thus concluded that these proteins take part in degenerative processes after injury. Astrocytes thus have multiple functions in injury and in regulation of axonal growth and synaptogenesis.

Cochlear ablation leads to effects along the auditory pathway in the CNS. The CN complex is the first auditory structure in the CNS and receives direct input from the auditory nerve. Accordingly, the CN is the first site where the pathological changes in response to the loss of auditory stimulus occur (Fuentes-Santamaria et al. 2012; Fuentes-Santamaria et al. 2013; Janz & Illing 2014). Downstream from the CN, morphological changes of microglia were present in the LSO, with a milder manifestation than that seen in the AVCN at 1 day after the cochlear ablation. By the 7th day, the changes were significant for microglial and astrocytic activation (Janz & Illing, 2014). The ripple of

microglial response along the auditory pathway implies that trans-synaptic effects play a big part in response to the loss of auditory nerve input.

Activation of glial cells after an auditory insult induces the expression of various cellular mediators such as cytokines, consistent with restoration in synaptic homeostasis (Bruce-Keller, 1999; Cullheim & Thams, 2007; Hanisch & Kettenmann, 2007). However, some of these cytokines can have damaging roles and further contribute to inflammatory response (Fujioka et al., 2006; Touzani et al., 2002; Vezzani et al., 2002). It has been shown that blocking certain cytokines synthesized by microglia in the cochlea after noise exposure reduces subsequent hearing impairment in mice (Fujioka et al., 2006; Wakabayashi et al., 2010). Interestingly, not all activity-dependent signaling molecules become upregulated and changes in expression depend on the location of the injury site. Proinflammatory cytokine IL-1β is produced and expressed by activated microglial cells in response to cellular damage (Vezzani et al., 1999; Hanisch, 2002) but does not get upregulated in the VCN after cochlear ablation. Instead, increased expression is observed in deafferented VCN neurons. The same effect is seen with insulin-growth factor 1 (IGF-1) synthesis (Fuentes-Santamaria et al., 2013) in which expression increases after traumatic brain injury or ischemia (Hwang et al., 2004; Madathil et al., 2010; Touzani et al., 1999). Thus, not only glial cells but neurons themselves may augment the production of various activity-dependent signaling molecules in an attempt to re-establish functional connections (Fuentes-Santamaria et al., 2007).

Similar discoveries were made in a rat model of conductive hearing loss in which the tympanic membrane was punctured and the malleus and incus were removed unilaterally. This procedure disrupted the transmission of sound from the middle ear into the cochlea as evidenced by elevated auditory brainstem response (ABR) thresholds and reduction in auditory responses (Fuentes-Santamaria et al., 2014). Activation of microglia was evident one day after surgery, reached its peak by day 4 and microglia resumed their quiescent state by day 15. Surprisingly, activation of astrocytes was not detected. The neurotrophin NT-3, a neurotrophic survival factor expressed in developing and adult auditory system (Hafidi, 1999; Tierney et al., 2001), was found to be upregulated by day 4 in AVCN neurons rather than glial cells. The increased expression of NT-3 coincided with the peak of microglial activation suggesting but only few microglia and astrocytes co-localized NT-3 both in control and experimental groups (Fuentes-Santamaria et al., 2014). Several important conclusions are evident from this study. First, injury to middle ear resulting in reduced auditory input is enough to activate microglia. Second, an astrocytic response may require more severe auditory degeneration (as the one seen in cochlear ablation studies). Third, microglia may be functioning as broad responders, independent of the severity of the injury, e.g., conductive versus sensorineural hearing loss.

Demyelination

The auditory system relies on the precise and rapid neurotransmission that allows the comparison of the arrival of binaural signals on submillisecond scale (Carr et al., 2001). As noted previously, well-timed conduction is normally achieved through regulation of axon diameter and myelination and requires ongoing communication between axons and myelinating oligodendrocytes. However, in a number of neurodegenerative disorders the myelin sheath is disrupted, resulting in impaired nerve conduction and slowed conductance velocity (Kim et al., 2013b; Utzschneider et al., 1994).

Hearing loss is a common comorbid complaint in individuals with multiple sclerosis, which is associated with demyelination (Lewis et al., 2010; Noffsinger et al., 1972; Peyvandi et al., 2010). The Long Evans *shaker* (*LES*) rat is genetically predisposed to loss of myelin basic protein (MBP) and thus serves as an animal model for dysmyelination. In a study to investigate the effect of myelin loss on hearing status, ABRs were recorded in P15-P30 rats and showed increased threshold to high-frequency tone stimulation. These measurements demonstrated the loss of waves II and III in *LES* when compared to control rats and the latencies of waves I and IV were increased (Kim et al., 2013b). Waves I, II, III, and IV represent auditory response in the cochlea/AN, CN, SOC, and lateral lemniscus, respectively (Hall, 2007). Additionally, the action potential (AP) latency, measured as the time between the stimulation of the presynaptic afferent which terminates in the calyx of Held and the peak of postsynaptic AP in the MNTB neuron, was twofold longer and displayed often failures in *LES* rats (Kim et al., 2013b). The rate of failure was severely affected when firing at high frequencies (> 300 Hz) but could follow trains of APs up to 100 Hz without conduction problems (Kim et al. 2013a). The authors did not observe any difference in the pool of available neurotransmitter and no difference in the AP waveform in the stimulated MNTB neuron as well as the structure of the initial segments of MNTB neuron axons in control and *LES* rats. Taken together, these results indicate that the loss of myelin causes a defect in signal transduction in the auditory brainstem by increasing the conduction time and the rate of presynaptic failures (Kim et al., 2013b).

Myelin also contributes to ion channels clustering such as relocation of Na_v at the axon initial segment (AIS). A high density of Na_v channels at the AIS and sustained resurgent Na^+ current at axon heminodes is required for a reliable and precise AP propagation (Berret et al., 2016; Hamada & Kole, 2015). Due to the fact that dysmyelination reduces the reliability and precision of signal transduction (Kim et al., 2013a; Kim et al., 2013b), this group tested the hypothesis that myelin is essential for the final tuning of the AP at the last heminode (Berret et al., 2016). In the calyx of Held, Na_v channels form clusters at the nodes of Ranvier as well as at the last heminode, which separates the myelinated portion of the axon from the non-myelinated calyceal terminal (Leao et al., 2005). In control rats, following the AP Na^+ currents entered at the heminode first and then diffused to the terminal. In contrast, Na^+ currents in *LES* rats entered at the heminode and the terminal at the same time. The general increase of $[Na^+]_i$ was significantly higher at axon heminodes in control than in *LES* rats. However, the decay of Na^+ transient was much slower at heminodes and terminals of *LES* rats. Normally, Na_v channels are clustered in the heminode (10-20 µm away from the terminal) but in *LES* rats this cluster

was much longer and invaded the calyx nerve terminal. The authors showed that it is the loss of $Na_v\beta4$ subunit at the last heminode that actually underlies the disruption of Na_v (Berret et al. 2016). Both $K_v1.2$ and $K_v3.1$ are essential for a consistent AP firing at the calyx of Held (Ishikawa et al., 2003; Johnston et al., 2010) and are located at nodes and perinodes, and at juxtaparanodes, respectively, in wild type rats. $K_v3.1$ expression was increased and dispersed at the heminode and the presynaptic calyceal terminal and $K_{v1}1.2$ expression at juxtaparanodes was completely disrupted in *LES* rats (Berret et al., 2016). The disruption of myelin thus affects not only conduction velocity, but also axonal excitability and reliability, factors that are critical for AP propagation in the auditory system.

Concluding Remarks

The auditory brainstem is a unique and specialized region of the nervous system with exceptionally high demands for synaptic precision and accurate timing. Its development is carefully orchestrated and its circuits are maintained for stable and reliable transmission of nerve impulses. We are now beginning to understand how astrocytes, microglia, and oligodendrocytes contribute to the specificity and specialized features needed for auditory brainstem function. Glial cells have been shown to guide multiple aspects of development. In the auditory brainstem astrocytes assist in the formation of appropriate synapses and in the regulation of dendritic arbors. Both astrocytes and microglia accompany the developing calyx of Held. Astrocytes contribute to auditory synaptic function, and oligodendrocytes communicate with neurons to adjust conduction times to obtain synchrony in sound localization circuits. Glial cells provide support for neural circuits and protect them from injury. In the auditory brainstem, they respond to denervation and acoustic trauma, likely contributing both to elimination of harmful elements and to adaptive generation of novel synapses.

References

Agmon-Snir, H., Carr, C. E., & Rinzel, J. (1998). The role of dendrites in auditory coincidence detection. *Nature*, *393*(6682), 268–272.

Allen, N. J. (2013). Role of glia in developmental synapse formation. *Current Opinion in Neurobiology*, *23*(6), 1027–1033.

Allen, N. J., & Eroglu, C. (2017). Cell biology of astrocyte-synapse interactions. *Neuron*, *96*(3), 697–708.

Allen, N. J., Bennett, M. L., Foo, L. C., Wang, G. X., Chakraborty, C., Smith, S. J., & Barres, B. A. (2012). Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors. *Nature*, *486*(7403), 410–414.

Anderson, B. J., Li, X., Alcantara, A. A., Isaacs, K. R., Black, J. E., & Greenough, W. T. (1994). Glial hypertrophy is associated with synaptogenesis following motor-skill learning, but not with angiogenesis following exercise. *Glia*, *11*(1), 73–80.

Araque, A., Parpura, V., Sanzgiri, R. P., & Haydon, P. G. (1999). Tripartite synapses: Glia, the unacknowledged partner. *Trends in Neuroscience*, *22*(5), 208–215.

Baizer, J. S., Wong, K. M., Manohar, S., Hayes, S. H., Ding, D., Dingman, R., & Salvi, R. J. (2015). Effects of acoustic trauma on the auditory system of the rat: The role of microglia. *Neuroscience*, *303*, 299–311.

Bak, L. K., Schousboe, A., & Waagepetersen, H. S. (2006). The glutamate/GABA-glutamine cycle: Aspects of transport, neurotransmitter homeostasis and ammonia transfer. *Journal of Neurochemistry*, *98*(3), 641–653.

Bakiri, Y., Karadottir, R., Cossell, L., & Attwell, D. (2011). Morphological and electrical properties of oligodendrocytes in the white matter of the corpus callosum and cerebellum. *Journal of Physiology*, *589*(Pt 3), 559–573.

Bardoni, R., Ghirri, A., Zonta, M., Betelli, C., Vitale, G., Ruggieri, V., Sandrini, M., & Carmignoto, G. (2010). Glutamate-mediated astrocyte-to-neuron signalling in the rat dorsal horn. *Journal of Physiology*, *588*(Pt 5), 831–846.

Bechmann, I., & Nitsch, R. (1997). Astrocytes and microglial cells incorporate degenerating fibers following entorhinal lesion: A light, confocal, and electron microscopical study using a phagocytosis-dependent labeling technique. *Glia*, *20*(2), 145–154.

Benowitz, L. I., & Routtenberg, A. (1997). GAP-43: An intrinsic determinant of neuronal development and plasticity. *Trends in Neuroscience*, *20*(2), 84–91.

Benson, C. G., Gross, J. S., Suneja, S. K., & Potashner, S. J. (1997). Synaptophysin immunoreactivity in the cochlear nucleus after unilateral cochlear or ossicular removal. *Synapse*, *25*(3), 243–257.

Bergles, D. E., Roberts, J. D., Somogyi, P., & Jahr, C. E. (2000). Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. *Nature*, *405*(6783), 187–191.

Berret, E., Kim, S. E., Lee, S. Y., Kushmerick, C., & Kim, J. H. (2016). Functional and structural properties of ion channels at the nerve terminal depends on compact myelin. *Journal of Physiology*, *594*(19), 5593–5609.

Berret, E., Barron, T., Xu, J., Debner, E., Kim, E. J., & Kim, J. H. (2017). Oligodendroglial excitability mediated by glutamatergic inputs and Nav1.2 activation. *Nature Communications*, *8*(1), 557.

Bezzi, P., Carmignoto, G., Pasti, L., Vesce, S., Rossi, D., Rizzini, B. L., Pozzan, T., & Volterra, A. (1998). Prostaglandins stimulate calcium-dependent glutamate release in astrocytes. *Nature*, *391*(6664), 281–285.

Book, K. J., & Morest, D. K. (1990). Migration of neuroblasts by perikaryal translocation: Role of cellular elongation and axonal outgrowth in the acoustic nuclei of the chick embryo medulla. *Journal of Comparative Neurology*, *297*(1), 55–76.

Bosworth, A. P., & Allen, N. J. (2017). The diverse actions of astrocytes during synaptic development. *Current Opinion in Neurobiology*, *47*, 38–43.

Brand, A., Behrend, O., Marquardt, T., McAlpine, D., & Grothe, B. (2002). Precise inhibition is essential for microsecond interaural time difference coding. *Nature*, *417*(6888), 543–547.

Brill, M. H., Waxman, S. G., Moore, J. W., & Joyner, R. W. (1977). Conduction velocity and spike configuration in myelinated fibres: Computed dependence on internode distance. *Journal of Neurology, Neurosurgery, and Psychiatry*, *40*(8), 769–774.

Bruce-Keller, A. J. (1999). Microglial-neuronal interactions in synaptic damage and recovery. *Journal of Neuroscience Research*, *58*(1), 191–201.

Burger, R. M., Fukui, I., Ohmori, H., & Rubel, E. W. (2011). Inhibition in the balance: Binaurally coupled inhibitory feedback in sound localization circuitry. *Journal of Neurophysiology*, *106*(1), 4–14.

Cahoy, J. D., Emery, B., Kaushal, A., Foo, L. C., Zamanian, J. L., Christopherson, K. S., … Barres, B. A. (2008). A transcriptome database for astrocytes, neurons, and oligodendrocytes: A new resource for understanding brain development and function. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(1), 264–278.

Caicedo, A., d'Aldin, C., Eybalin, M., & Puel, J. L. (1997). Temporary sensory deprivation changes calcium-binding proteins levels in the auditory brainstem. *Journal of Comparative Neurology*, *378*(1), 1–15.

Campos Torres, A., Vidal, P. P., & de Waele, C. (1999). Evidence for a microglial reaction within the vestibular and cochlear nuclei following inner ear lesion in the rat. *Neuroscience*, *92*(4), 1475–1490.

Campos-Torres, A., Touret, M., Vidal, P. P., Barnum, S., & de Waele, C. (2005). The differential response of astrocytes within the vestibular and cochlear nuclei following unilateral labyrinthectomy or vestibular afferent activity blockade by transtympanic tetrodotoxin injection in the rat. *Neuroscience*, *130*(4), 853–865.

Canady, K. S., & Rubel, E. W. (1992). Rapid and reversible astrocytic reaction to afferent activity blockade in chick cochlear nucleus. *Journal of Neuroscience*, *12*(3), 1001–1009.

Carr, C. E., Soares, D., Parameshwaran, S., & Perney, T. (2001). Evolution and development of time coding systems. *Current Opinion in Neurobiology*, *11*(6), 727–733.

Chaudhry, F. A., Reimer, R. J., & Edwards, R. H. (2002). The glutamine commute: Take the N line and transfer to the A. *Journal of Cell Biology*, *157*(3), 349–355.

Chung, W. S., Allen, N. J., & Eroglu, C. (2015). Astrocytes control synapse formation, function, and elimination. *Cold Spring Harbor Perspectives in Biology*, *7*(9), a020370.

Colonna, M., & Butovsky, O. (2017). Microglia function in the central nervous system during health and neurodegeneration. *Annual Review of Immunology*,35, 441–468.

Condorelli, D. F., Dell'Albani, P., Amico, C., Kaczmarek, L., Nicoletti, F., Lukasiuk, K., & Stella, A. M. (1993). Induction of primary response genes by excitatory amino acid receptor agonists in primary astroglial cultures. *Journal of Neurochemistry*, *60*(3), 877–885.

Cornell-Bell, A. H., & Finkbeiner, S. M. (1991). Ca^{2+} waves in astrocytes. *Cell Calcium*, *12*(2–3), 185–204.

Cornell-Bell, A. H., Finkbeiner, S. M., Cooper, M. S., & Smith, S. J. (1990). Glutamate induces calcium waves in cultured astrocytes: Long-range glial signaling. *Science*, *247*(4941), 470–473.

Cramer, K. S., Fraser, S. E., & Rubel, E. W. (2000). Embryonic origins of auditory brain-stem nuclei in the chick hindbrain. *Developmental Biology*, *224*(2), 138–151.

Cullheim, S., & Thams, S. (2007). The microglial networks of the brain and their role in neuronal network plasticity after lesion. *Brain Research Review*, *55*(1), 89–96.

Danbolt, N. C. (2001). Glutamate uptake. *Progress in Neurobiology*, *65*(1), 1–105.

De Biase, L. M., Nishiyama, A., & Bergles, D. E. (2010). Excitability and synaptic communication within the oligodendrocyte lineage. *Journal of Neuroscience*, *30*(10), 3600–3611.

de Waele, C., Campos Torres, A., Josset, P., & Vidal, P. P. (1996). Evidence for reactive astrocytes in rat vestibular and cochlear nuclei following unilateral inner ear lesion. *European Journal of Neuroscience*, *8*(9), 2006–2018.

Dimou, L., & Simons, M. (2017). Diversity of oligodendrocytes and their progenitors. *Current Opinion in Neurobiology*, *47*, 73–79.

Dinh, M. L., Koppel, S. J., Korn, M. J., & Cramer, K. S. (2014). Distribution of glial cells in the auditory brainstem: Normal development and effects of unilateral lesion. [Research Support, N.I.H., Extramural]. *Neuroscience*, *278*, 237–252.

Dityatev, A., Dityateva, G., Sytnyk, V., Delling, M., Toni, N., Nikonenko, I., Muller, D., & Schachner, M. (2004). Polysialylated neural cell adhesion molecule promotes remodeling and formation of hippocampal synapses. *Journal of Neuroscience*, *24*(42), 9372–9382.

Du, X., Chen, K., Choi, C. H., Li, W., Cheng, W., Stewart, C., … Kopke, R. D. (2012). Selective degeneration of synapses in the dorsal cochlear nucleus of chinchilla following acoustic trauma and effects of antioxidant treatment. *Hearing Research*, *283*(1–2), 1–13.

Elezgarai, I., Bilbao, A., Mateos, J. M., Azkue, J. J., Benitez, R., Osorio, A., … Grandes, P. (2001). Group II metabotropic glutamate receptors are differentially expressed in the medial nucleus of the trapezoid body in the developing and adult rat. *Neuroscience*, *104*(2), 487–498.

Elezgarai, I., Benitez, R., Mateos, J. M., Lazaro, E., Osorio, A., Azkue, J. J., … Grandes, P. (1999). Developmental expression of the group III metabotropic glutamate receptor mGluR4a in the medial nucleus of the trapezoid body of the rat. *Journal of Comparative Neurology*, *411*(3), 431–440.

Eroglu, C., Allen, N. J., Susman, M. W., O'Rourke, N. A., Park, C. Y., Ozkan, E., … Barres, B. A. (2009). Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. *Cell*, *139*(2), 380–392.

Farmer, W. T., & Murai, K. (2017). Resolving astrocyte heterogeneity in the CNS. *Frontiers in Cellular Neuroscience*, *11*, 300.

Ford, M. C., Grothe, B., & Klug, A. (2009). Fenestration of the calyx of Held occurs sequentially along the tonotopic axis, is influenced by afferent activity, and facilitates glutamate clearance. *Journal of Comparative Neurology*, *514*(1), 92–106.

Ford, M. C., Alexandrova, O., Cossell, L., Stange-Marten, A., Sinclair, J., Kopp-Scheinpflug, C., … Grothe, B. (2015). Tuning of Ranvier node and internode properties in myelinated axons to adjust action potential timing. *Nature Communications*, *6*, 8073.

Fredrich, M., & Illing, R. B. (2010). MMP-2 is involved in synaptic remodeling after cochlear lesion. *Neuroreport*, *21*(5), 324–327.

Fredrich, M., Zeber, A. C., Hildebrandt, H., & Illing, R. B. (2013). Differential molecular profiles of astrocytes in degeneration and re-innervation after sensory deafferentation of the adult rat cochlear nucleus. *European Journal of Neuroscience*, *38*(1), 2041–2056.

Fuentes-Santamaria, V., Alvarado, J. C., & Juiz, J. M. (2012). Long-term interaction between microglial cells and cochlear nucleus neurons after bilateral cochlear ablation. *Journal of Comparative Neurology*, *520*(13), 2974–2990.

Fuentes-Santamaria, V., Alvarado, J. C., Henkel, C. K., & Brunso-Bechtold, J. K. (2007). Cochlear ablation in adult ferrets results in changes in insulin-like growth factor-1 and

synaptophysin immunostaining in the cochlear nucleus. *Neuroscience*, *148*(4), 1033–1047.

Fuentes-Santamaria, V., Alvarado, J. C., Gabaldon-Ull, M. C., & Manuel Juiz, J. (2013). Upregulation of insulin-like growth factor and interleukin 1beta occurs in neurons but not in glial cells in the cochlear nucleus following cochlear ablation. *Journal of Comparative Neurology*, *521*(15), 3478–3499.

Fuentes-Santamaria, V., Alvarado, J. C., Taylor, A. R., Brunso-Bechtold, J. K., & Henkel, C. K. (2005). Quantitative changes in calretinin immunostaining in the cochlear nuclei after unilateral cochlear removal in young ferrets. *Journal of Comparative Neurology*, *483*(4), 458–475.

Fuentes-Santamaria, V., Alvarado, J. C., Lopez-Munoz, D. F., Melgar-Rojas, P., Gabaldon-Ull, M. C., & Juiz, J. M. (2014). Glia-related mechanisms in the anteroventral cochlear nucleus of the adult rat in response to unilateral conductive hearing loss. *Frontiers in Neuroscience*, *8*, 319.

Fuentes-Santamaria, V., Alvarado, J. C., Melgar-Rojas, P., Gabaldon-Ull, M. C., Miller, J. M., & Juiz, J. M. (2017). The role of glia in the peripheral and central auditory system following noise overexposure: Contribution of TNF-alpha and IL-1beta to the pathogenesis of hearing loss. *Frontiers in Neuroanatomy*, *11*, 9.

Fujioka, M., Kanzaki, S., Okano, H. J., Masuda, M., Ogawa, K., & Okano, H. (2006). Proinflammatory cytokines expression in noise-induced damaged cochlea. *Journal of Neuroscience Research*, *83*(4), 575–583.

Gallo, V., Zhou, J. M., McBain, C. J., Wright, P., Knutson, P. L., & Armstrong, R. C. (1996). Oligodendrocyte progenitor cell proliferation and lineage progression are regulated by glutamate receptor-mediated K+ channel block. *Journal of Neuroscience*, *16*(8), 2659–2670.

Gegelashvili, G., & Schousboe, A. (1997). High affinity glutamate transporters: Regulation of expression and activity. *Molecular Pharmacology*, *52*(1), 6–15.

Genoud, C., Quairiaux, C., Steiner, P., Hirling, H., Welker, E., & Knott, G. W. (2006). Plasticity of astrocytic coverage and glutamate transporter expression in adult mouse cortex. *PLoS Biology*, *4*(11), e343.

Gentschev, T., & Sotelo, C. (1973). Degenerative patterns in the ventral cochlear nucleus of the rat after primary deafferentation. An ultra-structural study. *Brain Research*, *62*(1), 37–60.

Glendenning, K. K., Baker, B. N., Hutson, K. A., & Masterton, R. B. (1992). Acoustic chiasm V: inhibition and excitation in the ipsilateral and contralateral projections of LSO. *Journal of Comparative Neurology*, *319*(1), 100–122.

Gomez-Nicola, D., & Perry, V. H. (2015). Microglial dynamics and role in the healthy and diseased brain: A paradigm of functional plasticity. *Neuroscientist*, *21*(2), 169–184.

Grabert, K., Michoel, T., Karavolos, M. H., Clohisey, S., Baillie, J. K., Stevens, … McColl, B. W. (2016). Microglial brain region-dependent diversity and selective regional sensitivities to aging. *Nature Neuroscience*, *19*(3), 504–516.

Grasselli, G., Mandolesi, G., Strata, P., & Cesare, P. (2011). Impaired sprouting and axonal atrophy in cerebellar climbing fibres following in vivo silencing of the growth-associated protein GAP-43. *PLoS ONE*, *6*(6), e20791.

Grothe, B. (2003). New roles for synaptic inhibition in sound localization. *Nature Review Neuroscience*, *4*(7), 540–550.

Grothe, B., Pecka, M., & McAlpine, D. (2010). Mechanisms of sound localization in mammals. *Physiology Reviews*, *90*(3), 983–1012.

Guthrie, P. B., Knappenberger, J., Segal, M., Bennett, M. V., Charles, A. C., & Kater, S. B. (1999). ATP released from astrocytes mediates glial calcium waves. *Journal of Neuroscience*, *19*(2), 520–528.

Hackett, J. T., Jackson, H., & Rubel, E. W. (1982). Synaptic excitation of the second and third order auditory neurons in the avian brain stem. *Neuroscience*, *7*(6), 1455–1469.

Hafidi, A. (1999). Distribution of BDNF, NT-3 and NT-4 in the developing auditory brainstem. *International Journal of Developmental Neuroscience*, *17*(4), 285–294.

Hakim, Y., Yaniv, S. P., & Schuldiner, O. (2014). Astrocytes play a key role in Drosophila mushroom body axon pruning. *PLoS ONE*, *9*(1), e86178.

Hall, J. W. (2007). *New Handbook of Auditory Evoked Responses*. Boston, MA: Pearson.

Hamada, M. S., & Kole, M. H. (2015). Myelin loss and axonal ion channel adaptations associated with gray matter neuronal hyperexcitability. *Journal of Neuroscience*, *35*(18), 7272–7286.

Hanisch, U. K. (2002). Microglia as a source and target of cytokines. *Glia*, *40*(2), 140–155.

Hanisch, U. K., & Kettenmann, H. (2007). Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience*, *10*(11), 1387–1394.

Harkmark, W. (1954). Cell migrations from the rhombic lip to the inferior olive, the nucleus raphe and the pons; a morphological and experimental investigation on chick embryos. *Journal of Comparative Neurology*, *100*(1), 115–209.

Hawrylak, N., Chang, F. L., & Greenough, W. T. (1993). Astrocytic and synaptic response to kindling in hippocampal subfield CA1. II. Synaptogenesis and astrocytic process increases to in vivo kindling. *Brain Research*, *603*(2), 309–316.

Held, H. (1893). Die zentrale Gehörleitung. *Archiv für Anatomie, Physiologie und Anatomie*, *17*, 201–248.

Henneberger, C., Papouin, T., Oliet, S. H., & Rusakov, D. A. (2010). Long-term potentiation depends on release of D-serine from astrocytes. *Nature*, *463*(7278), 232–236.

Hermann, J., Pecka, M., von Gersdorff, H., Grothe, B., & Klug, A. (2007). Synaptic transmission at the calyx of Held under in vivo like activity levels. *J Neurophysiology*, *98*(2), 807–820.

Hertz, L., Dringen, R., Schousboe, A., & Robinson, S. R. (1999). Astrocytes: Glutamate producers for neurons. *Journal of Neuroscience Research*, *57*(4), 417–428.

Hildebrandt, H., Hoffmann, N. A., & Illing, R. B. (2011). Synaptic reorganization in the adult rat's ventral cochlear nucleus following its total sensory deafferentation. *PLoS ONE*, *6*(8), e23686.

Holcomb, P. S., Hoffpauir, B. K., Hoyson, M. C., Jackson, D. R., Deerinck, T. J., Marrs, G. S., … Spirou, G. A. (2013). Synaptic inputs compete during rapid formation of the calyx of Held: A new model system for neural development. [In Vitro Research Support, N.I.H., Extramural]. *Journal of Neuroscience*, *33*(32), 12954–12969.

Hwang, I. K., Yoo, K. Y., Park, S. K., An, S. J., Lee, J. Y., Choi, S. Y., … Won, M. H. (2004). Expression and changes of endogenous insulin-like growth factor-1 in neurons and glia in the gerbil hippocampus and dentate gyrus after ischemic insult. *Neurochemistry International*, *45*(1), 149–156.

Hyson, R. L. (2005). The analysis of interaural time differences in the chick brain stem. *Physiology Behavior*, *86*(3), 297–305.

Insausti, A. M., Cruz-Orive, L. M., Jauregui, I., Manrique, M., & Insausti, R. (1999). Stereological assessment of the glial reaction to chronic deafferentation of the cochlear nuclei in the macaque monkey (Macaca fascicularis). *Journal of Comparative Neurology*, *414*(4), 485–494.

Ishikawa, T., Nakamura, Y., Saitoh, N., Li, W. B., Iwasaki, S., & Takahashi, T. (2003). Distinct roles of Kv1 and Kv3 potassium channels at the calyx of Held presynaptic terminal. *Journal of Neuroscience*, *23*(32), 10445–10453.

Janz, P., & Illing, R. B. (2014). A role for microglial cells in reshaping neuronal circuitry of the adult rat auditory brainstem after its sensory deafferentation. *Journal of Neuroscience Research*, *92*(4), 432–445.

Jeffries, M. A., Urbanek, K., Torres, L., Wendell, S. G., Rubio, M. E., & Fyffe-Maricich, S. L. (2016). ERK1/2 Activation in preexisting oligodendrocytes of adult mice drives new

myelin synthesis and enhanced CNS function. *Journal of Neuroscience*, *36*(35), 9186–9200.

Jinno, S., & Yamada, J. (2011). Using comparative anatomy in the axotomy model to identify distinct roles for microglia and astrocytes in synaptic stripping. *Neuron Glia Biology*, *7*(1), 55–66.

Johnston, J., Forsythe, I. D., & Kopp-Scheinpflug, C. (2010). Going native: Voltage-gated potassium channels controlling neuronal excitability. *Journal of Physiology*, *588*(Pt 17), 3187–3200.

Jones, T. A., & Greenough, W. T. (1996). Ultrastructural evidence for increased contact between astrocytes and synapses in rats reared in a complex environment. *Neurobiology of Learning and Memory*, *65*(1), 48–56.

Kandler, K., & Friauf, E. (1993). Pre- and postnatal development of efferent connections of the cochlear nucleus in the rat. *Journal of Comparative Neurology*, *328*(2), 161–184.

Kandler, K., & Gillespie, D. C. (2005). Developmental refinement of inhibitory sound-localization circuits. *Trends in Neuroscience*, *28*(6), 290–296.

Kettenmann, H., Kirchhoff, F., & Verkhratsky, A. (2013). Microglia: New roles for the synaptic stripper. *Neuron*, *77*(1), 10–18.

Kim, J. H., Renden, R., & von Gersdorff, H. (2013a). Dysmyelination of auditory afferent axons increases the jitter of action potential timing during high-frequency firing. *Journal of Neuroscience*, *33*(22), 9402–9407.

Kim, S. E., Turkington, K., Kushmerick, C., & Kim, J. H. (2013b). Central dysmyelination reduces the temporal fidelity of synaptic transmission and the reliability of postsynaptic firing during high-frequency stimulation. *Journal of Neurophysiology*, *110*(7), 1621–1630.

Kolson, D. R., Wan, J., Wu, J., Dehoff, M., Brandebura, A. N., Qian, J., … Spirou, G. A. (2016). Temporal patterns of gene expression during calyx of Held development. *Developmental Neurobiology*, 76, 166–189.

Kopp-Scheinpflug, C., Tolnai, S., Malmierca, M. S., & Rubsamen, R. (2008). The medial nucleus of the trapezoid body: comparative physiology. *Neuroscience*, *154*(1), 160–170.

Koppl, C., & Carr, C. E. (2008). Maps of interaural time difference in the chicken's brainstem nucleus laminaris. *Biological Cybernetics*, *98*(6), 541–559.

Korn, M. J., & Cramer, K. S. (2008). Distribution of glial-associated proteins in the developing chick auditory brainstem. *Developmental Neurobiology*, *68*(8), 1093–1106.

Korn, M. J., Koppel, S. J., & Cramer, K. S. (2011). Astrocyte-secreted factors modulate a gradient of primary dendritic arbors in nucleus laminaris of the avian auditory brainstem.

[Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *PLoS ONE*, *6*(11), e27383.

Korn, M. J., Koppel, S. J., Li, L. H., Mehta, D., Mehta, S. B., Seidl, A. H., & Cramer, K. S. (2012). Astrocyte-secreted factors modulate the developmental distribution of inhibitory synapses in nucleus laminaris of the avian auditory brainstem. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *Journal of Comparative Neurology*, *520*(6), 1262–1277.

Kukley, M., Capetillo-Zarate, E., & Dietrich, D. (2007). Vesicular glutamate release from axons in white matter. *Nature Neuroscience*, *10*(3), 311–320.

Kuwabara, N., & Zook, J. M. (1992). Projections to the medial superior olive from the medial and lateral nuclei of the trapezoid body in rodents and bats. *Journal of Comparative Neurology*, *324*(4), 522–538.

Kvamme, E., Roberg, B., & Torgner, I. A. (2000). Phosphate-activated glutaminase and mitochondrial glutamine transport in the brain. *Neurochemistry Research*, *25*(9–10), 1407–1419.

Laake, J. H., Slyngstad, T. A., Haug, F. M., & Ottersen, O. P. (1995). Glutamine from glial cells is essential for the maintenance of the nerve terminal pool of glutamate: Immunogold evidence from hippocampal slice cultures. *Journal of Neurochemistry*, *65*(2), 871–881.

Lachica, E. A., Rubsamen, R., & Rubel, E. W. (1994). GABAergic terminals in nucleus magnocellularis and laminaris originate from the superior olivary nucleus. *Journal of Comparative Neurology*, *348*(3), 403–418.

Leao, R. M., Kushmerick, C., Pinaud, R., Renden, R., Li, G. L., Taschenberger, H., … von Gersdorff, H. (2005). Presynaptic Na^+ channels: locus, development, and recovery from inactivation at a high-fidelity synapse. *Journal of Neuroscience*, *25*(14), 3724–3738.

Leke, R., & Schousboe, A. (2016). The glutamine transporters and their role in the glutamate/GABA-glutamine cycle. *Advances in Neurobiology*, *13*, 223–257.

Lewis, M. S., Lilly, D. J., Hutter, M. M., Bourdette, D. N., McMillan, G. P., Fitzpatrick, M. A., & Fausti, S. A. (2010). Audiometric hearing status of individuals with and without multiple sclerosis. *Journal of Rehabilitation Research and Development*, *47*(7), 669–678.

Lohmann, C., & Friauf, E. (1996). Distribution of the calcium-binding proteins parvalbumin and calretinin in the auditory brainstem of adult and developing rats. *Journal of Comparative Neurology*, *367*(1), 90–109.

Lurie, D. I., & Rubel, E. W. (1994). Astrocyte proliferation in the chick auditory brainstem following cochlea removal. *Journal of Comparative Neurology*, *346*(2), 276–288.

Lurie, D. I., & Durham, D. (2000). Neuronal death, not axonal degeneration, results in significant gliosis within the cochlear nucleus of adult chickens. *Hearing Research*, *149*(1–2), 178–188.

Madathil, S. K., Evans, H. N., & Saatman, K. E. (2010). Temporal and regional changes in IGF-1/IGF-1R signaling in the mouse brain after traumatic brain injury. *Journal of Neurotrauma*, *27*(1), 95–107.

Magistretti, P. J., Sorg, O., Yu, N., Martin, J. L., & Pellerin, L. (1993). Neurotransmitters regulate energy metabolism in astrocytes: implications for the metabolic trafficking between neural cells. *Developmental Neuroscience*, *15*(3–5), 306–312.

Meguro, R., Ohishi, H., Hoshino, K., Hicks, T. P., & Norita, M. (1999). Metabotropic glutamate receptor 2/3 immunoreactivity in the developing rat cerebellar cortex. *Journal of Comparative Neurology*, *410*(2), 243–255.

Meidinger, M. A., Hildebrandt-Schoenfeld, H., & Illing, R. B. (2006). Cochlear damage induces GAP-43 expression in cholinergic synapses of the cochlear nucleus in the adult rat: a light and electron microscopic study. *European Journal of Neuroscience*, *23*(12), 3187–3199.

Michaluk, P., & Kaczmarek, L. (2007). Matrix metalloproteinase-9 in glutamate-dependent adult brain function and dysfunction. *Cell Death and Differentiation*, *14*(7), 1255–1258.

Micu, I., Plemel, J. R., Caprariello, A. V., Nave, K. A., & Stys, P. K. (2017). Axo-myelinic neurotransmission: A novel mode of cell signalling in the central nervous system. *Nature Review Neuroscience*.

Miller, F. D., & Gauthier, A. S. (2007). Timing is everything: Making neurons versus glia in the developing cortex. *Neuron*, *54*(3), 357–369.

Moore, D. R. (1990). Auditory brainstem of the ferret: Early cessation of developmental sensitivity of neurons in the cochlear nucleus to removal of the cochlea. *Journal of Comparative Neurology*, *302*(4), 810–823.

Morest, D. K., Kim, J., & Bohne, B. A. (1997). Neuronal and transneuronal degeneration of auditory axons in the brainstem after cochlear lesions in the chinchilla: Cochleotopic and non-cochleotopic patterns. *Hearing Research*, *103*(1–2), 151–168.

Morest, D. K., Kim, J., Potashner, S. J., & Bohne, B. A. (1998). Long-term degeneration in the cochlear nerve and cochlear nucleus of the adult chinchilla following acoustic overstimulation. *Microscopy Research and Technique*, *41*(3), 205–216.

Mosser, C. A., Baptista, S., Arnoux, I., & Audinat, E. (2017). Microglia in CNS development: Shaping the brain for the future. *Progress in Neurobiology*, *149–150*, 1–20.

Muller, D., Wang, C., Skibo, G., Toni, N., Cremer, H., Calaora, V., … Kiss, J. Z. (1996). PSA-NCAM is required for activity-induced synaptic plasticity. *Neuron*, *17*(3), 413–422.

Muly, S. M., Gross, J. S., Morest, D. K., & Potashner, S. J. (2002). Synaptophysin in the cochlear nucleus following acoustic trauma. *Experimental Neurology*, *177*(1), 202–221.

Myoga, M. H., Lehnert, S., Leibold, C., Felmy, F., & Grothe, B. (2014). Glycinergic inhibition tunes coincidence detection in the auditory brainstem. *Nature Communications*, *5*, 3790.

Nakamura, P. A., & Cramer, K. S. (2011). Formation and maturation of the calyx of Held. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S. Review]. *Hearing Research*, *276*(1–2), 70–78.

Noffsinger, D., Olsen, W. O., Carhart, R., Hart, C. W., & Sahgal, V. (1972). Auditory and vestibular aberrations in multiple sclerosis. *Acta Otolaryngologica Supplement*, *303*, 1–63.

Norenberg, M. D., & Martinez-Hernandez, A. (1979). Fine structural localization of glutamine synthetase in astrocytes of rat brain. *Brain Research*, *161*(2), 303–310.

Ohmori, H. (2014). Neuronal specializations for the processing of interaural difference cues in the chick. *Frontiers in Neural Circuits*, *8*, 47.

Otis, T. S., Wu, Y. C., & Trussell, L. O. (1996). Delayed clearance of transmitter and the role of glutamate transporters at synapses with multiple release sites. *Journal of Neuroscience*, *16*(5), 1634–1644.

Overholt, E. M., Rubel, E. W., & Hyson, R. L. (1992). A circuit for coding interaural time differences in the chick brainstem. *Journal Neuroscience*, *12*(5), 1698–1708.

Panatier, A., Theodosis, D. T., Mothet, J. P., Touquet, B., Pollegioni, L., Poulain, D. A., & Oliet, S. H. (2006). Glia-derived D-serine controls NMDA receptor activity and synaptic memory. *Cell*, *125*(4), 775–784.

Parks, T. N., & Rubel, E. W. (1975). Organization and development of brain stem auditory nuclei of the chicken: Organization of projections from n. magnocellularis to n. laminaris. *Journal of Comparative Neurology*, *164*(4), 435–448.

Pecka, M., Brand, A., Behrend, O., & Grothe, B. (2008). Interaural time difference processing in the mammalian medial superior olive: The role of glycinergic inhibition. *Journal Neuroscience*, *28*(27), 6914–6925.

Perea, G., & Araque, A. (2007). Astrocytes potentiate transmitter release at single hippocampal synapses. *Science*, *317*(5841), 1083–1086.

Perea, G., Sur, M., & Araque, A. (2014). Neuron-glia networks: Integral gear of brain function. *Frontiers in Cellular Neuroscience*, *8*, 378.

Peyvandi, A., Naghibzadeh, B., & Ahmady Roozbahany, N. (2010). Neuro-otologic manifestations of multiple sclerosis. *Archives of Iranian Medicine*, *13*(3), 188–192.

Pfrieger, F. W., & Barres, B. A. (1997). Synaptic efficacy enhanced by glial cells in vitro. *Science*, *277*(5332), 1684–1687.

Pow, D. V., & Robinson, S. R. (1994). Glutamate in some retinal neurons is derived solely from glia. *Neuroscience*, *60*(2), 355–366.

Reisert, I., Wildemann, G., Grab, D., & Pilgrim, C. (1984). The glial reaction in the course of axon regeneration: A stereological study of the rat hypoglossal nucleus. *Journal of Comparative Neurology*, *229*(1), 121–128.

Renden, R., Taschenberger, H., Puente, N., Rusakov, D. A., Duvoisin, R., Wang, L. Y., … von Gersdorff, H. (2005). Glutamate transporter studies reveal the pruning of metabotropic glutamate receptors and absence of AMPA receptor desensitization at mature calyx of Held synapses. *Journal of Neuroscience*, *25*(37), 8482–8497.

Reyes-Haro, D., Muller, J., Boresch, M., Pivneva, T., Benedetti, B., Scheller, A., … Kettenmann, H. (2010). Neuron-astrocyte interactions in the medial nucleus of the trapezoid body. *Journal of General Physiology*, *135*(6), 583–594.

Risher, W. C., Patel, S., Kim, I. H., Uezu, A., Bhagat, S., Wilton, D. K., … Eroglu, C. (2014). Astrocytes refine cortical connectivity at dendritic spines. *eLife*, *17*, 3.

Rotschafer, S. E., Allen-Sharpley, M. R., & Cramer, K. S. (2016). Axonal cleaved Caspase-3 regulates axon targeting and morphogenesis in the developing auditory brainstem. *Frontiers in Neural Circuits*, *10*, 84.

Rubel, E. W., & Fritzsch, B. (2002). Auditory system development: primary auditory neurons and their targets. *Annual Review of Neuroscience*, *25*, 51–101.

Rubel, E. W., Smith, Z. D., & Steward, O. (1981). Sprouting in the avian brainstem auditory pathway: Dependence on dendritic integrity. *Journal of Comparative Neurology*, *202*(3), 397–414.

Saliu, A., Adise, S., Xian, S., Kudelska, K., & Rodriguez-Contreras, A. (2014). Natural and lesion-induced decrease in cell proliferation in the medial nucleus of the trapezoid body during hearing development. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Journal of Comparative Neurology*, *522*(5), 971–985.

Sanes, D. H. (1990). An in vitro analysis of sound localization mechanisms in the gerbil lateral superior olive. *Journal of Neuroscience*, *10*(11), 3494–3506.

Satzler, K., Sohl, L. F., Bollmann, J. H., Borst, J. G., Frotscher, M., Sakmann, B., & Lubke, J. H. (2002). Three-dimensional reconstruction of a calyx of Held and its postsynaptic

principal neuron in the medial nucleus of the trapezoid body. *Journal of Neuroscience*, *22*(24), 10567–10579.

Schell, M. J., Molliver, M. E., & Snyder, S. H. (1995). D-serine, an endogenous synaptic modulator: Localization to astrocytes and glutamate-stimulated release. *Proceedings of the National Academy of Sciences USA*, *92*(9), 3948–3952.

Schell, M. J., Brady, R. O., Jr., Molliver, M. E., & Snyder, S. H. (1997). D-serine as a neuromodulator: Regional and developmental localizations in rat brain glia resemble NMDA receptors. *Journal of Neurosciences*, *17*(5), 1604–1615.

Schiefer, J., Kampe, K., Dodt, H. U., Zieglgansberger, W., & Kreutzberg, G. W. (1999). Microglial motility in the rat facial nucleus following peripheral axotomy. *Journal of Neurocytology*, *28*(6), 439–453.

Seidl, A. H. (2014). Regulation of conduction time along axons. *Neuroscience*, *276*, 126–134.

Seidl, A. H., & Rubel, E. W. (2016). Systematic and differential myelination of axon collaterals in the mammalian auditory brainstem. *Glia*, *64*(4), 487–494.

Seidl, A. H., Rubel, E. W., & Barria, A. (2014). Differential conduction velocity regulation in ipsilateral and contralateral collaterals innervating brainstem coincidence detector neurons. *Journal of Neuroscience*, *34*(14), 4914–4919.

Sie, K. C., & Rubel, E. W. (1992). Rapid changes in protein synthesis and cell size in the cochlear nucleus following eighth nerve activity blockade or cochlea ablation. *Journal of Comparative Neurology*, *320*(4), 501–508.

Sinclair, J. L., Fischl, M. J., Alexandrova, O., Hebeta, M., Grothe, B., Leibold, C., & Kopp-Scheinpflug, C. (2017). Sound-evoked activity influences myelination of brainstem axons in the trapezoid body. *Journal of Neuroscience*, *37*(34), 8239–8255.

Singh, S. K., Stogsdill, J. A., Pulimood, N. S., Dingsdale, H., Kim, Y. H., Pilaz, L. J., … Eroglu, C. (2016). Astrocytes assemble thalamocortical synapses by bridging NRX1alpha and NL1 via Hevin. *Cell*, *164*(1–2), 183–196.

Smith, D. J., & Rubel, E. W. (1979). Organization and development of brain stem auditory nuclei of the chicken: Dendritic gradients in nucleus laminaris. *Journal of Comparative Neurology*, *186*(2), 213–239.

Sorg, O., & Magistretti, P. J. (1991). Characterization of the glycogenolysis elicited by vasoactive intestinal peptide, noradrenaline and adenosine in primary cultures of mouse cerebral cortical astrocytes. *Brain Res*, *563*(1–2), 227–233.

Spacek, J. (1985). Three-dimensional analysis of dendritic spines. III. Glial sheath. *Anatomy and Embryology*, *171*(2), 245–252.

Steinhauser, C., & Gallo, V. (1996). News on glutamate receptors in glial cells. *Trends Neuroscience*, *19*(8), 339–345.

Stout, C., & Charles, A. (2003). Modulation of intercellular calcium signaling in astrocytes by extracellular calcium and magnesium. *Glia*, *43*(3), 265–273.

Syka, J. (2002). Plastic changes in the central auditory system after hearing loss, restoration of function, and during learning. *Physiology Review*, *82*(3), 601–636.

Szklarczyk, A., Lapinska, J., Rylski, M., McKay, R. D., & Kaczmarek, L. (2002). Matrix metalloproteinase-9 undergoes expression and activation during dendritic remodeling in adult hippocampus. *Journal of Neuroscience*, *22*(3), 920–930.

Tasdemir-Yilmaz, O. E., & Freeman, M. R. (2014). Astrocytes engage unique molecular programs to engulf pruned neuronal debris from distinct subsets of neurons. *Genes & Development*, *28*(1), 20–33.

Tierney, T. S., Russell, F. A., & Moore, D. R. (1997). Susceptibility of developing cochlear nucleus neurons to deafferentation-induced death abruptly ends just before the onset of hearing. *Journal of Comparative Neurology*, *378*(2), 295–306.

Tierney, T. S., Doubel, T. P., Xia, G., & Moore, D. R. (2001). Development of brain-derived neurotrophic factor and neurotrophin-3 immunoreactivity in the lower auditory brainstem of the postnatal gerbil. *European Journal of Neuroscience*, *14*(5), 785–793.

Tollin, D. J. (2003). The lateral superior olive: a functional role in sound source localization. *Neuroscientist*, *9*(2), 127–143.

Touzani, O., Boutin, H., Chuquet, J., & Rothwell, N. (1999). Potential mechanisms of interleukin-1 involvement in cerebral ischaemia. *Journal of Neuroimmunology*, *100*(1–2), 203–215.

Touzani, O., Boutin, H., LeFeuvre, R., Parker, L., Miller, A., Luheshi, G., & Rothwell, N. (2002). Interleukin-1 influences ischemic brain damage in the mouse independently of the interleukin-1 type I receptor. *Journal of Neuroscience*, *22*(1), 38–43.

Tsukita, S., & Yonemura, S. (1997). ERM (ezrin/radixin/moesin) family: From cytoskeleton to signal transduction. *Current Opinion in Cell Biology*, *9*(1), 70–75.

Ullian, E. M., Sapperstein, S. K., Christopherson, K. S., & Barres, B. A. (2001). Control of synapse number by glia. *Science*, *291*(5504), 657–661.

Utzschneider, D. A., Archer, D. R., Kocsis, J. D., Waxman, S. G., & Duncan, I. D. (1994). Transplantation of glial cells enhances action potential conduction of amyelinated spinal cord axons in the myelin-deficient rat. *Proceedings of the National Academy of Sciences USA*, *91*(1), 53–57.

Uwechue, N. M., Marx, M. C., Chevy, Q., & Billups, B. (2012). Activation of glutamate transport evokes rapid glutamine release from perisynaptic astrocytes. *Journal of Physiology*, *590*(10), 2317–2331.

Vaheri, A., Carpen, O., Heiska, L., Helander, T. S., Jaaskelainen, J., Majander-Nordenswan, P., … Turunen, O. (1997). The ezrin protein family: Membrane-cytoskeleton interactions and disease associations. *Current Opinion in Cell Biology*, *9*(5), 659–666.

van Deijk, A. F., Camargo, N., Timmerman, J., Heistek, T., Brouwers, J. F., Mogavero, F., … Verheijen, M. H. (2017). Astrocyte lipid metabolism is critical for synapse development and function in vivo. *Glia*, *65*(4), 670–682.

Vaughn, J. E., & Pease, D. C. (1970). Electron microscopic studies of wallerian degeneration in rat optic nerves. II. Astrocytes, oligodendrocytes and adventitial cells. *Journal of Comparative Neurology*, *140*(2), 207–226.

Ventura, R., & Harris, K. M. (1999). Three-dimensional relationships between hippocampal synapses and astrocytes. *Journal of Neuroscience*, *19*(16), 6897–6906.

Vernadakis, A. (1996). Glia-neuron intercommunications and synaptic plasticity. *Progress in Neurobiology*, *49*(3), 185–214.

Vezzani, A., Conti, M., De Luigi, A., Ravizza, T., Moneta, D., Marchesi, F., & De Simoni, M. G. (1999). Interleukin-1beta immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainate application: Functional evidence for enhancement of electrographic seizures. *Journal of Neuroscience*, *19*(12), 5054–5065.

Vezzani, A., Moneta, D., Richichi, C., Aliprandi, M., Burrows, S. J., Ravizza, T., … De Simoni, M. G. (2002). Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. *Epilepsia*, *43 Suppl*, *5*, 30–35.

Wakabayashi, K., Fujioka, M., Kanzaki, S., Okano, H. J., Shibata, S., Yamashita, D., … Okano, H. (2010). Blockade of interleukin-6 signaling suppressed cochlear inflammatory response and improved hearing impairment in noise-damaged mice cochlea. *Neuroscience Research*, *66*(4), 345–352.

Wake, H., Moorhouse, A. J., Jinno, S., Kohsaka, S., & Nabekura, J. (2009). Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. *Journal of Neuroscience*, *29*(13), 3974–3980.

Wenzel, J., Lammert, G., Meyer, U., & Krug, M. (1991). The influence of long-term potentiation on the spatial relationship between astrocyte processes and potentiated synapses in the dentate gyrus neuropil of rat brain. *Brain Research*, *560*(1–2), 122–131.

Werb, Z. (1997). ECM and cell surface proteolysis: regulating cellular ecology. *Cell*, *91*(4), 439–442.

Witcher, M. R., Kirov, S. A., & Harris, K. M. (2007). Plasticity of perisynaptic astroglia during synaptogenesis in the mature rat hippocampus. *Glia*, *55*(1), 13–23.

Woolf, N. K., & Ryan, A. F. (1984). The development of auditory function in the cochlea of the mongolian gerbil. *Hearing Research*, *13*(3), 277–283.

Yang, L., Monsivais, P., & Rubel, E. W. (1999). The superior olivary nucleus and its influence on nucleus laminaris: A source of inhibitory feedback for coincidence detection in the avian auditory brainstem. *Journal of Neuroscience*, *19*(6), 2313–2325.

Young, S. R., & Rubel, E. W. (1983). Frequency-specific projections of individual neurons in chick brainstem auditory nuclei. *Journal of Neuroscience*, *3*(7), 1373–1378.

Giedre Milinkeviciute

Giedre Milinkeviciute, Department of Neurobiology and Behavior, University of California, Irvine

Karina S. Cramer

Karina S. Cramer, Department of Neurobiology and Behavior, University of California, Irvine