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Effects of non-traumatic noise and conductive hearing loss on auditory system function

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Abstract

The effects of traumatic noise-exposure and deafening on auditory system function have received a great deal of attention. However, lower levels of noise as well as temporary conductive hearing loss also have consequences on auditory physiology and hearing. Here we review how abnormal acoustic experience at early ages affects the ascending and descending auditory pathways, as well as hearing behavior.

Hearing disorders of adults experiencing abnormal acoustic experience, such as tinnitus, hyperacusis, and 'hidden hearing loss,' have been the subject of intense investigation, but the origins of these disorders in childhood are poorly understood. Pediatric tinnitus and hyperacusis occur in the presence or absence of early-age hearing loss (Chan et al., 2018), although the prevalence of these hearing disorders is not known. Intriguingly, children are at greater risk for tinnitus if they have a history of noise exposure or conductive hearing loss (CHL) due to otitis media (Mills and Cherry, 1984; Lee and Kim, 2018). Hidden hearing loss, defined as difficulty hearing in noise in the absence of absolute pure tone threshold shifts, is not a commonly reported clinical condition in children per se. However, children presenting with this type of condition may be more generally diagnosed with central auditory processing disorder.

The understanding of how experience and activity influence development and maintenance of sensory systems is heavily influenced by classic studies of the visual system. Those studies revealed an important role of critical periods in formation of ocular dominance columns (Wiesel and Hubel, 1965; Hubel et al., 1977), as well as a number of more complex stimulus characteristics (Daw, 1998). The presence of critical periods makes it important to test for and treat eye problems early in visual development. Similarly, it is important to

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identify which aspects of hearing are subject to acoustic experience, and additionally if they are subject to critical periods, so that appropriate diagnosis and treatment can be developed.

Here we review how abnormal acoustic activity early in life can lead to synaptic and structural changes in the auditory brainstem, which may have behavioral consequences that underlie hearing dysfunctions such as tinnitus, hyperacusis, and hidden hearing loss in children and young adults. Behavioral changes corresponding to similar manipulations of early acoustic experience are also reviewed.

Activity-dependent influences on the afferent pathway during development

Various parts of the auditory pathway are subject to activity-dependent changes in their properties during development. The most dramatic examples come from ablation studies, in which the cochlea is severely damaged or removed prior to hearing onset. Multiple studies in birds and mammals indicate a number of permanent activity-dependent effects on neurons and synapses in the cochlear nucleus, including reduced synapse size, smaller somata, and smaller overall nucleus volume (Rubel et al., 1990; Ryugo, 2015; Tong et al., 2015). Similar effects are seen in models of congenital deafness (Ryugo, 2015) and following knockouts of critical genes expressed in the auditory pathway, including the Shaker-2 potassium channel (Lee et al., 2003), the CaV1.2 calcium channel (Hirtz et al., 2011), and the synaptic proteins bassoon and piccolo (Mendoza Schulz et al., 2014; Butola et al., 2017). In addition, high levels of acoustic stimulation can have severe consequences, including damage to hair cells in the cochlea as well as the more recently recognized phenomenon of synaptopathy (Salvi et al., 2000; Kujawa and Liberman, 2009). However, less is known about the consequences of lower, presumably less-damaging, levels of acoustic exposure. This is important to understand so that clear guidelines can be communicated about what sound levels are genuinely safe for children, having only temporary effects on hearing. On the other end of the spectrum, it is important to understand the consequences of occluded hearing, so that optimal prevention and treatment can be devised for children subject to ear infections (otitis media).

Increased activity

High levels of acoustic stimulation, even non-traumatic, can have a major effect on auditory physiology. In a compelling series of experiments, rats exposed to pure tones at young ages showed increased representation of those frequencies in auditory cortex, and these changes were subject to a critical period (Zhang et al., 2001). Other work suggests that the responses of auditory cortical neurons are highly subject to acoustic experience and training (Dahmen and King, 2007; Pienkowski and Eggermont, 2012). However, it is not clear where specifically in the auditory pathway those changes in response properties first arise.

It is possible that changes at early stages of the auditory pathway could contribute to changes observed in the cortex. A number of studies have examined cellular and synaptic effects of early-age exposure to increased, but non-damaging activity at early stages of the auditory pathway. Auditory nerve synapses onto bushy cells in the cochlear nucleus normally show synaptic depression (Wang and Manis, 2008; Yang and Xu-Friedman, 2008; Cao and Oertel, 2010), most likely as a result of a high probability with which vesicles are

released (Regehr and Stevens, 2001). After a period of constant exposure to loud, non-damaging noise, however, the synapses show less depression, reflecting a decrease in the vesicle release probability (Ngodup et al., 2015). Furthermore, the synapses show an increase in vesicle pool size (assessed physiologically), increased numbers of release sites (assessed anatomically), and lower postsynaptic action potential threshold. These changes appear to enhance the reliability of transmission across the synapse, despite high levels of activity.

The effects observed by Ngodup et al. (2015) may also help explain another emblematic feature of auditory nerve synapses. The levels of depression shown by these synapses normally vary considerably (Yang and Xu-Friedman, 2009), yet synapses that converge onto one bushy cell tend to be rather similar in their levels of depression (Yang and Xu-Friedman, 2012). This similarity suggests release probability is precisely regulated, and acoustically-driven activity is a possible mechanism. An activity-dependent developmental mechanism could account for this, because auditory nerve fibers with similar level sensitivity appear to converge on the same bushy cell (Sento and Ryugo, 1989). Thus, activity-dependent cellular mechanisms may tune synaptic function for normal acoustic conditions.

However, activity-dependent mechanisms that tune synaptic properties could lead to maladaptive changes when the developing auditory system is exposed to abnormal acoustic activity. Synaptic changes early in the auditory pathway could disrupt subsequent processing, and perturb hearing. Therefore, it is important to know what signalling pathways drive synaptic changes, with the ultimate goal of reversing changes that contribute to hearing disorders.

The cellular mechanisms underlying acoustically-driven changes in synaptic function have been studied at synapses in the superior olive. In the medial nucleus of the trapezoid body (MNTB), high levels of acoustic activity lead to de-phosphorylation of a specific class of voltage-gated potassium channels, KV3.1 (Song et al., 2005), which increases their conductance, leading to a faster time constant in MNTB neurons so they can respond more rapidly to high rates of stimulation (Wang et al., 1998). This de-phosphorylation appears to last on the time-scale of minutes, so could be important for rapidly adapting to acoustic conditions. However, it is unlikely to account for the changes in auditory nerve synapses that last for hours to days, suggesting there are multiple mechanisms that modulate synaptic function on different time-scales.

Another question is how acoustic activity induces cellular changes. One factor that might be important is nitric oxide (NO). NO diffuses relatively easily through membranes and intracellular and extracellular space, which makes it a useful long-distance signalling molecule. High rates of stimulation *in vitro* cause release of NO in the MNTB, which causes phosphorylation of KV3 channels, and slowing of spiking in the MNTB neurons (Steinert et al., 2008). Curiously, the effects of activity on KV3 and spiking are opposite to the effects of acoustic activity described by Song et al. (2005) in rats (see previous paragraph). One possible explanation for the different effects of activity on rat and mouse KV3 channels is that mouse KV3.1 lacks the rat phosphorylation site.

NO has additional and complex effects throughout the superior olive through its effects on channels that mediate the hyperpolarization-activated current Ih. NO causes reduced activity of channels containing the HCN1 subunit, but enhanced activity of channels using the HCN2 subunit (Kopp-Scheinpflug et al., 2015). These subunits are differentially distributed throughout the superior olive (Koch et al., 2004), which raises an interesting possibility for how the same induction mechanism (acoustic activity and NO) could yield different expression in different brain areas, depending on their subunit expression. It will be important to explore how these varied areas are actually affected by activity, and which signalling pathways and channels are involved.

Decreased activity

Decreases in activity can also impact auditory function. In children, temporary periods of decreased activity can result from ear infections, formally known as otitis media. Such infections are extremely common, affecting as many as 80% of infants (Whitton and Polley, 2011). Because many brain systems are still developing at such early ages, it raises the possibility of permanent effects on hearing even after the infection clears and cochlear function is (presumably) restored. Clinical tradition often holds that hearing is normal once the infection has cleared up; however, some studies show an association between early hearing deficits and problems with processing speech (Gravel et al., 1996) as well as persistent elevation of thresholds to high frequency sounds (Hunter et al., 1996). Such effects could be a result of long-lasting peripheral or central changes. This has earned the term “amblyaudia” (Whitton and Polley, 2011), by analogy with amblyopia, in which early visual deficits lead to long-term vision problems even after eye problems are corrected. Understanding the long-lasting effects of early childhood conductive hearing loss on stimulus processing in the brain and how complex aspects of hearing are affected could have important implications for how to treat or prevent ear infections.

It remains important to establish how different areas of the central auditory pathway change in response to *transient* decreases in acoustic stimulation. The general principles are still emerging, but it appears that the effects of decreases in acoustic stimulation vary with the specific synaptic connection being studied, and also that the effects differ between binaural and monaural occlusion.

At the start of the auditory pathway, synapses made by auditory nerve fibers in the cochlear nucleus undergo structural changes, and also show changes in the level of synaptic depression following occlusion of the ear. With binaural CHL, auditory nerve synapses onto bushy cells in the cochlear nucleus showed an increase in depression and a smaller vesicle pool, both of which recovered to near normal levels after the occlusion was removed (Zhuang et al., 2017). Furthermore, presynaptic terminals appear to physically shrink during occlusion, similar to changes that are observed following more severe deafness models (Ryugo, 2015). Ultrastructural analyses of auditory nerve synapses from monaurally-occluded rats showed enlarged postsynaptic densities, which grew even larger after the occlusion was removed (Clarkson et al., 2016). Similar hypertrophy has been reported in genetic deafness models (Ryugo et al., 1997; Redd et al., 2002; Ryugo, 2015), indicating that this may be a common consequence of reduced auditory input. In addition to the

hypertrophied postsynaptic densities, there was a corresponding increase in postsynaptic AMPA receptors (Clarkson et al., 2016). Such changes in postsynaptic densities and receptors would most likely yield changes in mEPSC size or kinetics in electrophysiological recordings, but those were not observed by Zhuang et al. (2017). This could be a difference in species (rat *vs.* mouse) or the method of inducing CHL (monaural *vs.* binaural).

There are also important changes downstream of the cochlear nucleus during CHL. The axons formed by bushy cells in the MNTB normally have thick myelin sheaths, but after CHL, myelin is thinner, which may slow axonal conduction velocity and maximum firing rate (Sinclair et al., 2017b). Furthermore, the synapses of globular bushy cells onto inhibitory neurons in the MNTB also change. This synapse, called the calyx of Held, has been widely studied as a model for synaptic function and development (von Gersdorff and Borst, 2002; Schneggenburger and Forsythe, 2006). After monaural CHL, calyces increase the number of terminal swellings (Grande et al., 2014), which most likely correspond to synaptic contacts (Wimmer et al., 2006). However, electrophysiological measurements indicate that the EPSC amplitude and vesicle pool size decrease, even for calyces relaying activity from the ear that is not occluded (Grande et al., 2014). The unoccluded calyx also shows less depression.

There is a parallel between the normal variability in calyces and the changes triggered by CHL. In normal calyces, there is a correlation between morphology and electrophysiological properties such that larger and more complex calyces have smaller EPSCs and less depression (Grande and Wang, 2011). Similarly, a consequence of CHL is larger, complex calyces and reduced depression (Grande et al., 2014), suggesting that the synaptic changes that take place following changes in activity draw on cellular processes that are active in normal synapses. Under normal conditions, bushy cells are expected to show a range of activity levels, depending on their individual intensity sensitivity, so the synaptic terminals they form would vary in activity. If calyces have processes that tune synaptic function to activity level, such processes could be recruited during CHL as well.

Furthermore, these findings underscore that simple synapse morphology does not substitute for direct assessment of electrophysiological properties. Larger calyces that likely have more release sites yet appear to have weaker EPSCs. This is not unexpected, because EPSC amplitude depends on multiple additional factors, including the probability of vesicle release and quantal size, which in this case appear to dominate EPSC amplitude.

It is notable that synapses of auditory nerve fibers and bushy cells show opposite changes following CHL: the endbulb of Held appears to shrink and depression increases, whereas the calyx becomes more elaborate and depression decreases. *In vivo* recordings have not yet confirmed the activity levels in the two cell types, but it seems likely that decreases in acoustic input would reduce activity in both. The opposite changes shown by auditory nerve and bushy cell synapses could reflect their very different roles in the auditory pathway. Endbulbs contact bushy cells, which are excitatory relays, and synaptic changes there appear to reduce excitation (Zhuang et al., 2017). By contrast, calyces contact MNTB neurons, which are inhibitory relays, and synaptic changes there appear to enhance inhibition (Grande et al., 2014), which is effectively the same outcome. Thus, this apparent difference may

reflect a functional similarity. In addition, these contrasting synapses indicate that the effects of reduced activity may need to be specifically assessed at individual synapses, without generalizing findings from a few model synapses.

Effects of CHL have also been described in several high-order auditory areas. In the auditory cortex, spontaneous inhibitory currents onto layer 2/3 pyramidal neurons decrease in amplitude following early CHL (Takesian et al., 2012). This effect is subject to a critical period, as CHL on or after postnatal day 19 has little effect (Mowery et al., 2015). Furthermore, the pyramidal neurons themselves undergo changes in intrinsic properties, thereby increasing excitability following CHL, with a critical period that ends by postnatal day 13 (Mowery et al., 2015). These pre- and postsynaptic changes would both increase the efficacy of excitation. It remains to be understood which specific classes of inhibitory interneurons and layer 2/3 pyramidal neurons undergo these changes, and how the spontaneous IPSCs recorded in brain slices relate to activity *in vivo*.

Pyramidal neurons in layer 5 of auditory cortex are also susceptible to CHL. Spontaneous IPSCs increase in amplitude in a critical-period-dependent manner (Mowery et al., 2017), which is opposite to layer 2/3 cortical pyramidal neurons. Layer 5 pyramidal neurons form excitatory synapses onto medium spiny neurons in sensory striatum. These excitatory synapses are enhanced following CHL, while inhibitory inputs onto striatal neurons are reduced, both also subject to a critical period (Mowery et al., 2017). Thus, just as with visual problems, CHL may need to be resolved before auditory critical periods close in children, to avoid disorders in language processing in adults. Identifying synapses that are affected by abnormal acoustic conditions, and determining whether those effects are permanent, may help to account for the childhood hearing disorders described above, and thus provide insights into therapies.

Effects of chronic background noise and conductive hearing loss on olivocochlear efferent feedback pathways

In trying to understand the mechanisms underlying central auditory gain, the effects of brainstem control of cochlear gain must also be considered. Cochlear activity is reduced, and in some circumstances enhanced, by activation of the olivocochlear (OC) neurons projecting from the superior olivary complex to the cochlea and cochlear nucleus. A detailed treatment of the mechanisms underlying OC modulation of cochlear activity can be found in recent reviews and will not be repeated here (Guinan, 2018; Fuchs and Lauer, in press). Briefly, medial OC neurons (MOC) project to outer hair cells from species-specific periolivary regions and reduce outer hair cell-dependent cochlear amplification. Lateral OC neurons (LOC) project to the auditory nerve dendrites contacting inner hair cells and increase or decrease auditory nerve responses. Prior to hearing onset, MOC neurons directly inhibit inner hair cells and later move to form synapses with outer hair cells.

Early studies hypothesized that the OC system affects loudness perception due to the observed gain control effects in the cochlea (Cohen et al., 1988; Collet et al., 1992; Micheyl et al., 1995). However, patients with lesioned olivocochlear bundles in one ear do not typically show abnormal loudness perception (Scharf et al., 1997; Zeng et al., 2000;

Morand-Villeneuve et al., 2002). It is possible that the OC system influences certain aspects of loudness perception, but that central auditory changes underlying abnormal gain obscure the relationship between OC activation strength and psychophysical loudness measurements. It is difficult to parse out the separate contributions of abnormal OC modulation of auditory input to the brain versus compensatory central gain in a behavioral test of loudness perception, particularly since increased central gain could affect the responsiveness of OC neurons.

The OC system has also been hypothesized to play a role in tinnitus and hyperacusis, including hyperacusis experienced by children with autism (Chery-Croze et al., 1993; Geven et al., 2014; Knudson et al., 2014; Riga et al., 2015; Wilson et al., 2017). However, the link between tinnitus and OC function in adults is tenuous at best, and virtually nothing is known about this relationship in children. The nature of the relationship between early age OC system dysfunction and auditory deficits related to abnormal gain remains to be elucidated.

The protective effects of OC activation against acute, damaging sound exposure in adulthood have been well documented (Fuente, 2015), but less is known about these effects in juveniles. Accelerated age-related hearing loss has also been associated with abnormal OC neuron excitability and abnormal synaptic morphology in the cochlea (Fu et al., 2010; Lauer et al., 2012; Zachary and Fuchs, 2015; Sinclair et al., 2017a). Remarkably, OC neurons appear to leave the outer hair cells and recapitulate an early developmental state in which they form inhibitory synapses directly with the inner hair cells (Fu et al., 2010; Lauer et al., 2012; Zachary and Fuchs, 2015). This reinnervation of inner hair cells may both exacerbate the hearing loss by inhibiting hair cell activity (Zachary and Fuchs, 2015) and protect the remaining auditory nerve synapses from accruing further excitotoxic damage (Nouvian et al., 2015). Conductive hearing loss also yields age-related changes in OC innervation, with reduced LOC and auditory nerve innervation in ears with conductive hearing loss compared to intact ears observed approximately 1 year after tympanic membrane removal (Liberman et al., 2015). It is unknown if impaired acoustic experience at early ages produces similar forms of plasticity in the OC system.

Studies of the effects of early-age acoustic experience on OC neuron form and function are scant but emerging. Central auditory inputs from the IC to OC neurons show a loss of precision in models of hereditary early-onset progressive deafness and congenital deafness (Suthakar and Ryugo, 2017). At present, nothing else is known about the effects of abnormal acoustic experience on the synaptic inputs to OC neurons.

Several studies have investigated the interaction between ‘non-damaging’ environmental noise exposure and the OC system in juvenile and young adult mice. Preliminary studies indicate that MOC synapse morphology remains normal after early-age noise exposure identical to that used by Ngodup et al. (2015), in that there is no difference in the number or area of presynaptic MOC terminals in noise-housed versus control cochleas (Villavisanis et al., 2018). In contrast, LOC terminals appear to be upregulated in some frequency regions (Villavisanis et al., 2018). Experiments using more intense repeated daily noise exposures also indicate an upregulation of LOC activity, specifically dopaminergic, in exposed cochleas (Wu et al., 2018). Relatedly, lesions of the OC fiber bundle increase susceptibility

to damage from chronic background noise in young adult mice (Maison et al., 2013). These experiments demonstrate both the potential for early-age activity-dependent plasticity in OC neurons and its importance in protecting the auditory system against the effects of chronic noise. Ongoing studies will elucidate the impact of these effects on auditory nerve and central auditory function and behavior.

Mutant mouse strains with abnormal OC activity represent an additional means of introducing increased or decreased auditory activity during development and throughout the lifespan. Mice missing the α9 subunit of the nicotinic acetylcholine receptor subunit (α9nAChR$^{-/-}$) lack classic MOC cochlear suppression effects (Vetter et al., 1999). α9nAChR$^{-/-}$ mice show hyperactive acoustic startle responses when brief silent periods precede a startle-eliciting stimulus and auditory brainstem timing abnormalities in response to rapidly presented stimuli, despite normal hearing thresholds (May et al., 2002; Lauer and May, 2011). These effects are exacerbated in animals raised in a noisy vivarium (Lauer and May, 2011). Abnormal modification of the acoustic startle response by short noisebursts has also been observed in α9nAChR$^{-/-}$ mice and in mice with a gain of function mutation in the α9nAchR that increases MOC activity (Allen and Luebke, 2017). Mice missing the α-calcitonin gene-related protein, which have reduced cochlear activity related to abnormal LOC function, also show abnormal inhibition of the acoustic startle response. In aggregate, these studies indicate that the OC system is involved in modulating acoustic startle activity and, potentially, hyperacusis-like conditions.

The effects of moderate levels of noise and temporary earplugging on hearing by animals

A key question is how the activity-dependent changes observed in the afferent and efferent pathways influence functional hearing. Many studies using different types of moderate acoustic exposures have shown that animals can have normal auditory brainstem response (ABR) thresholds but differences in physiological response properties at various locations in the auditory system (e.g. Stanton and Harrison, 1996; Noreña et al., 2006; Pienkowski and Eggermont, 2010). A few studies have demonstrated the functional changes in other measures of auditory acuity following either these moderate noise exposures or temporary earplugs. It is clear from these studies that normal ABR thresholds do not mean the animals are unaffected by moderate disruptions to their auditory systems, as both temporary and permanent deficits in auditory acuity are widely reported. Specifically, normal tone detection thresholds do not mean that auditory acuity is normal.

Oliver et al. (2011) found differences in the ABR waveforms of rat pups exposed to 70 dB, 250 ms sinusoidally amplitude modulated (SAM) tones for 16 hours per day between days P9 and P17, and control rats. When ABRs were measured at days P32 and P112, waveforms of exposed rats had decreased latencies and increased amplitudes at and above the frequencies of the stimuli used in the exposures relative to the controls. Although the differences in ABR waveforms between control and exposed rats were significant, ABR thresholds did not differ for either clicks or pure tones, similar to the findings of the studies mentioned and those from Furman et al. (2013). Furman et al. (2013) exposed guinea pigs

(*Cavia porcellus*) for 2 hours to 4–8 kHz noise at 106 dB SPL. The resulting ABR audiograms were normal 10 days after exposure. The suprathreshold auditory nerve responses were reduced in amplitude, a reduction attributed to the loss of low spontaneous activity fibers. In sum, noise exposures lead to several types of changes in auditory processing that do not result in differences in basic auditory acuity, as demonstrated by the ABR audiogram.

The perception of timing information seems to be the most affected auditory process following moderate temporary or permanent modified acoustic input. Tees (1967b) found that rats raised with bilateral earplugs from days P0-P60 had difficulty discriminating between patterns containing temporal differences, but not frequency differences. A similar earplug paradigm revealed difficulty by the rats in learning a duration discrimination task but not an intensity discrimination task (Tees, 1967a). More recently, Zhou and Merzenich (2012) exposed adult rats to 65 dB pulsed noise bursts for 2 months. The rats later had a diminished ability to discriminate between different rates of sound stimulus presentation, a deficit that persisted for at least six weeks following the cessation of the noise. Responses of cortical neurons were significantly altered, but the changes were independent of the rate of the noise bursts. Thus, it appears that several different types of altered auditory input can disrupt temporal processing, though the central mechanisms could be quite different.

Several studies have found that animals with early-age bilateral conductive hearing loss (CHL) also show difficulties in auditory temporal processing. Rosen et al. (2012) compared behavioral detection thresholds for SAM stimuli in Mongolian gerbils (*Meriones unguiculatus*) with CHL and controls. When sensation level was controlled (to account for the moderate levels of hearing loss), the CHL gerbils had trouble detecting slow SAM relative to the controls, while detection of fast SAM did not differ. The differences in SAM detection across modulation rate correlated with responses by auditory cortex neurons: there were fewer neurons with low SAM detection thresholds than high SAM thresholds in the CHL group relative to the control group. von Trapp et al. (2017) found a similar difference in the discrimination of modulation rate in Mongolian gerbils with CHL. Their CHL gerbils took longer to train on the discrimination task than controls and they were less sensitive than the controls at the 4 Hz modulation rate but not the 32 Hz modulation rate. The CHL gerbils improved significantly as testing progressed, however. As described above, Lauer and May (2011) found that temporal processing in mice lacking a functional MOC system was affected by prolonged moderate noise exposure throughout development, independent of hearing loss and acoustic trauma.

Binaural auditory acuity can also be affected by modifications to auditory input. Monaurally earplugging young guinea pigs for 11 days and then removing the earplugs resulted in chance performance levels in a directional response task, even three weeks later (Clements and Kelly, 1978). Moore et al. (1999) found a decrement in free-field binaural unmasking levels in ferrets (*Mustela putorius*) that were monaurally earplugged for 7–15 months. Performance for both adult- and infant-plugged ferrets recovered, but recovery took almost two years. Thus, temporal processing of auditory stimuli in the binaural domain can also be affected.

One study has found that not all complex stimuli are equally effective in demonstrating temporal resolution deficits following moderate noise exposure. Ranasinghe et al. (2012) found that the behavioral discrimination of speech did not change in rats that were speech reared or pulsed-noise reared. Rats were exposed to 65 dB stimuli from day P9 through day P38, then trained beginning on day P50. Exposed and control groups did not differ in any behavioral measure of spectral or temporal properties of speech sounds, despite a myriad of neural changes in the auditory system. This lone study on speech perception highlights the need for more work in this field. Most studies of altered auditory feedback in animals highlight problems that humans have in understanding speech in noisy environments after hearing loss, but this study indicates that drawing parallels between some animal models and humans may not be straightforward.

There are stark differences in how effective altered acoustic environments are on auditory acuity later in life, depending on when the alterations occur and how long they last. Patchett (1977) found that differences in pattern discrimination performance in rats raised in 75–78 dB white noise depended on when and for how long the noise was present. Rats who experienced the noise from age P0-P60 took twice as long to reach criterion than those who were raised in the noise from days P60-P120, from P30-P60, and from P0-P30. Thus, “normal” (at least non-white-noise) auditory exposure is necessary between days P0 and P60 for normal pattern perception in rats. In chicks (*Gallus domesticus*), “normal” auditory experience is required between days 1 and 3–4 (Kerr et al., 1979). Chicks exposed to repeated 800 Hz tones starting on day 1 had significant deficits in discrimination of frequency relative to chicks who started exposure at 3–4 days. Earplugged chicks from embryonic day 18 to post-hatch days 3–4 had deficits that were similar to the chicks exposed to tones.

Sun et al. (2011b) measured gap-induced pre-pulse inhibition of the acoustic startle reflex in rats raised in continuous 70 dB SPL white noise from P7 for 2–3 months. They were housed in quiet for a few weeks and thresholds were measured again. There were initial significant gap detection deficits in the noise-reared rats relative to controls. Two weeks after noise cessation, the rats that had been in the noise for only 2 months improved significantly, while the rats that had been in the noise for 3 months did not. Adult rats that underwent the same noise exposure showed normal gap detection thresholds later, suggesting that the rat’s age at noise onset was also important for causing the temporal acuity deficits. Buran et al. (2014) similarly found that bilateral CHL induced in young or old Mongolian gerbils led to differences in frequency modulation detection thresholds. Thresholds were elevated in both groups relative to controls, but the deficits were greater in the adult-onset hearing loss gerbils than the juvenile onset hearing loss gerbils, even though there were no differences in the overall audibility of the stimuli by the two groups. Buran et al. (2014) suggested a parallel of their results to those from human listeners who sometimes show better auditory acuity with longer durations of auditory deprivation, and highlighted possible differences in the stimulus cues that the different age groups were using to improve behavioral performance.

Mowery et al. (2015) induced mild hearing loss in Mongolian gerbils by inserting earplugs between days P11 and P23. The gerbils were then trained on an operant conditioning task to

detect a 4 kHz pure tone. The earplugs increased thresholds by 28 dB. Within six days of earplug removal, all subjects had recovered to control threshold levels. Caras and Sanes (2015) similarly earplugged Mongolian gerbils for 12 days, this time spanning either days P11 to P23 or days P23 to P35. Mongolian gerbils earplugged later showed normal amplitude modulation (AM) detection thresholds within 15 days of plug removal, while gerbils reared with the early earplugging showed no such improvements in thresholds 15 days later. Taken together, the two studies demonstrate that different types of auditory acuity have different sensitive periods, and that the severity and duration of acuity deficits caused by early auditory deprivation also differs across auditory tasks.

Knudsen et al. (1984) mapped the sensitive period for the development of accurate sound localization in barn owls (*Tyto alba*). Barn owls raised with an earplug that was later removed showed sound localization errors after removal. As accurate interaural time difference and interaural level difference cues had time to recover, sound localization accuracy recovered. Moreover, the later the plugs were removed, the slower the recovery time. If plugs were removed after 38–42 weeks, sound localization never recovered. Adult barn owls given earplugs also showed deficits in sound localization accuracy, but they recovered quickly when the plugs were removed.

In contrast to barn owls, ferrets reared with an earplug show no deficits in sound localization accuracy, even immediately after earplug removal (King et al., 2000). Discriminating between two broadband sounds from different locations was also difficult for ferrets monaurally earplugged as adults but not those occluded as infants. Another difference from barn owls is that adult ferrets given earplugs show deficits in sound localization accuracy that remained even after the earplugs were removed. Whether the differences between ferrets and barn owls are due to differences in methods, species, or both, remains to be seen.

An important series of studies has attempted to determine if the deficits caused by early auditory deprivation can be reversed. Pan et al. (2011) reared rats under pulsed noise conditions from P7 to P35, then tested them on their ability to discriminate sound azimuth. Discrimination performance was poor relative to normally reared rats. Some of the rats were then moved to a normal acoustic environment, some were placed in a passive noise environment, and some were trained to discriminate sounds from a specific location for water reinforcement, from days P41 to P75. The third group of rats was able to improve azimuth discrimination performance relative to the other two groups, suggesting the importance of attention for inducing functional changes to the auditory system after acoustic trauma. Attention was a likely factor for adult barn owls allowed to hunt for their food, which in turn increased plasticity in the optic tectum (Bergan et al., 2005). Zhu et al. (2014) and Green et al. (2017) similarly showed that acoustically enriched post-trauma environments can help to recover frequency discrimination and gap detection deficits, respectively, caused by damaging noise rearing.

Finally, Zheng (2012) found that adult rats exposed to white noise for 30 days showed impaired abilities to discriminate between small pitch changes but not large pitch changes relative to control rats. Surprisingly, when tested in a white noise background, the noise exposed rats showed no decrements in performance compared to the control rats. It appears

that the noisy rearing environment actually *aided* the animals during the noisy testing condition. This study has interesting implications for our understanding of what a 'normal' acoustic environment might really be for animals living in increasingly noisy worlds.

In summary, while altered auditory exposures often reveal no differences in simple measures of auditory acuity, many other deficits can be seen after some (but not all) experimental manipulations. The key factors involved in determining the deficits include the auditory task, the animal's age, and the nature of the altered auditory input. The deficits may result in poor abilities for animals to communicate complex situations with one another, severely hindering their survival rates in the wild. Unfortunately, these studies are scarce, especially within a single animal model, limiting our understanding about the effects of altering auditory input on auditory function.

Early-Age Conductive Hearing Loss and Audiogenic Seizures

A distinctive behavioral consequence of sound deprivation at early ages in rodents is increased susceptibility to audiogenic seizure (AGS). Chen et al. (1973) reported that AGS can be induced in mice by destruction of tympanic membranes (TM) at postnatal days 14 to 21 (P14–21). When these animals were exposed to loud sound (~120 dB SPL), they exhibited seizure-like activity, i.e. running at full speed ("wild running"), followed by rhythmic muscle spasms ("clonicity") or rigid muscles ("tonicity") (Ross and Coleman, 2000; Faingold, 2002). The incidence and severity of seizures was greater in 14-day-old mice compared to 21-day-old mice (Chen and Gates, 1973; Chen et al., 1973), indicating the maturational stage of the mouse influenced AGS.

The age-dependence of AGS was studied in rats. Sun et al. (2011a) found that after bilateral rupture of the TM at P16, over 80% of the rats developed AGS when exposed to loud sounds two weeks later. Similar results were found after monaural TM rupture. TM-damaged rats also showed significant increases in sensitivity to sound loudness (Sun et al., 2014). However, damaging the TM after P45 did not cause AGS in any rats. These results suggest that hearing loss during a critical period can increase the susceptibility of rodents to AGS.

Multiple auditory areas have been investigated to understand how TM damage leads to AGS (Faingold, 2002). Coleman et al. (1999) found that ABRs were elicited with shorter latencies, suggesting faster processing time in the auditory brainstem. In addition, c-Fos staining revealed that activity in the inferior colliculus was enhanced in rats after TM damage (Friauf, 1992; Sun et al., 2011a). Furthermore, TM-damaged rats showed lower expression of δ and α6 GABA receptor subunits in the inferior colliculus compared to controls (Sun et al., 2014). Interestingly, AGS could be blocked by treatment with vigabatrin, an inhibitor of GABA-transaminase that increases the ambient GABA concentration in the brain (Willmore et al., 2009). Taken together, these results suggest hearing loss caused by TM damage or other insults leads to reduced central inhibition, and thereby increased activity in the inferior colliculus during loud noise exposure.

While rodents demonstrate AGS following TM damage, such an extreme effect is not observed in children following otitis media and its associated CHL. Even so, a decrease in

central inhibition has been implicated in the development of tinnitus and hyperacusis (Richardson et al., 2012; Sedley et al., 2015; Caspary and Llano, 2017). It remains a strong possibility that early CHL in children leads to similar long-lasting changes in central auditory pathways, which could contribute to tinnitus or hyperacusis later in life.

Summary and Conclusions

In sum, moderate changes in acoustically-driven activity have measurable effects in auditory afferent and efferent pathways, and some of these changes contribute to changes in hearing behavior. It will be important to understand the signalling mechanisms underlying cellular changes, so that therapies may be found to reverse detrimental changes that otherwise would have permanent effects on hearing. It will also be important to establish additional animal models in which the contributions of early age manipulations to acoustic experience can be directly linked with behavioral deficits. This will be important for understanding childhood hearing dysfunction and improving treatments for children that undergo abnormal acoustic experience.

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- Hearing can be adversely affected by increases or decreases in acoustic activity.
- Behavioral studies in animals reveal diverse effects on multiple aspects of hearing.
- Physiological study of the auditory pathway has found several areas affected by abnormal activity.
- Some of these areas may underlie the behavioral changes, and thus may be useful therapeutic targets.