Hearing loss and brain plasticity: The hyperexcitability phenomenon

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Abstract

Many aging adults experience some form of hearing problem that may arise from auditory peripheral damage. However, it has been increasingly acknowledged that hearing loss is not only a dysfunction of the auditory periphery but results from changes within the entire auditory system, from periphery to cortex. Damage to the auditory periphery is associated with an increase in excitability of neural populations at various stages throughout the auditory pathway. Here, we review neurophysiological evidence of hyperexcitability, auditory perceptual difficulties that may result from hyperexcitability, and outline open conceptual and methodological questions related to the study of hyperexcitability. We suggest that hyperexcitability alters all aspects of hearing – including spectral, temporal, spatial hearing – and, in turn, impairs speech comprehension when background sound is present. By focusing on the perceptual consequences of hyperexcitability and the potential challenges of investigating hyperexcitability in humans, we hope to bring animal and human electrophysiologists closer together to better understand hearing problems in older adulthood.

Keywords: Hearing loss, aging, hyperexcitability, loss of inhibition, neurophysiology, auditory perception, neural plasticity, speech processing

Introduction

Many aging adults experience some form of hearing problems (Cruickshanks et al., 1998; Feder et al., 2015; Goman and Lin, 2016; Helfer et al., 2017). The loss of sensitivity, particularly at high frequencies, comprises the traditional profile of 'age-related hearing loss' and is commonly associated with impairments of the auditory periphery, including damage of hair cells, spiral ganglion cells, and the stria vascularis (Gratton and Vázquez, 2003; Moore, 2007; Bao and Ohlemiller, 2010; Schmiedt, 2010; Dubno et al., 2013; Plack, 2014; Keithley, 2020). Other impairments include hearing sound in absence of an identifiable source (tinnitus; Anari et al., 1999; Eggermont and Roberts, 2004; McCormack et al., 2016), finding sounds at moderate intensities too loud and distracting (hyperacusis; Anari et al., 1999; Baguley, 2003; Parmentier and Andrés, 2010; Tyler et al., 2014), or experiencing difficulty comprehending speech when background sound is present (Pichora-Fuller, 2003; Pichora-Fuller et al., 2016; Presacco et al., 2019).

Although hearing loss in older adulthood typically arises from dysfunction of the auditory periphery (Gratton and Vázquez, 2003; Moore, 2007; Bao and Ohlemiller, 2010; Schmiedt, 2010; Dubno et al., 2013; Plack, 2014; Moser and Starr, 2016; Keithley, 2020), an increasing amount of evidence suggests that the behavioral consequences of hearing loss may reflect dysfunction of the entire auditory system. Peripheral damage induces neuroplastic changes in downstream brain regions of the auditory pathway, including the cochlear nucleus, superior olivary complex, inferior colliculus, medial geniculate nucleus (thalamus), and auditory cortex (Knipper et al., 2013; Auerbach et al., 2014; Zhao et al., 2016; Salvi et al., 2017). Perhaps the most prominent change is an increase in neuronal excitability (Knipper et al., 2013; Auerbach et al., 2014; Zhao et al., 2016; Salvi et al., 2017). Here, we use the term hyperexcitability to include two related phenomena: 1) an increase in the rate at which neurons in the auditory pathway generate action potentials in the absence of stimulation (i.e., enhanced spontaneous firing rate); and 2) an increase in the number of action potentials generated by these neurons in response to sound (hyperresponsivity; Figure 1).

Previous reviews have detailed the neurophysiological evidence for, and proposed mechanisms underlying hyperexcitability in the auditory systems of animal models of hearing loss (Knipper et al., 2013; Auerbach et al., 2014; Eggermont, 2015; Zhao et al., 2016; Salvi et al., 2017). However, the full extent of the perceptual consequences of hyperexcitability have not been described in as much depth. Moreover, studies conducted in humans – where the study of auditory system hyperexcitability is typically limited to non-invasive measures of hyperresponsivity to sound – have not been commonly integrated within previous reviews. This lack of consolidation across models is a critical oversight that limits our understanding of the causes of hearing impairments in older adults, and slows the development of appropriate treatments.

This review delivers a detailed picture of the potential perceptual consequences of hyperexcitability in the auditory system and provides a foundation from which researchers can

develop targeted approaches for investigating hyperexcitability in humans. The paper is divided into three sections that aim to convey the following messages: firstly, reduced acoustic input leads to hyperexcitability in the central auditory system, regardless of the etiology or nature (conductive/sensorineural) of the hearing loss; secondly, auditory system hyperexcitability likely degrades spectral, temporal, and spatial processing and, in turn, speech comprehension; finally, the non-linear relationship between peripheral damage, hyperexcitability, and hyperresponsivity in the auditory system presents unique challenges that should be considered in the design of human studies.

Hyperexcitability in central auditory regions

In this section, we will review empirical observations of hyperexcitability associated with different experimental manipulations (e.g., sound exposure and drug treatment) and age groups. We will focus on direct measures of hyperexcitability in the central auditory system, such as increased spontaneous firing rates and/or correlated activity among neurons, measured with invasive neurophysiological approaches. We will further focus on indirect measures of hyperexcitability, such as increased neural responses to supra-threshold sounds and enhanced behavioral sensitivity to electrical stimulation, measured using both invasive or non-invasive methods. We will describe animal literature and discuss related work from humans.

Hyperexcitability associated with acoustic injury

Inducing acoustic injury to the auditory system of animals via sound exposure has a long tradition in investigations of hearing function and dysfunction (Saunders et al., 1985; Slepecky, 1986). Sound exposures of varied duration and intensity give rise to varying degrees of auditory peripheral pathology. High-intensity (100 dB SPL or above) exposure to pure tones or noise bursts causes mechanical and metabolic damage of the cochlea, including hair cell loss, damage to the stereocilia, tears in the basilar membrane, rupture of the organ of Corti, metabolic exhaustion, and more (Saunders et al., 1985; Slepecky, 1986). Less intense sound exposure may not cause as much mechanical damage, but may leave scars from degenerating hair cells, alter the morphology of cells, change micromechanical properties of hair cells, and cause metabolic damage (Saunders et al., 1985; Slepecky, 1986). Even sound exposure that does not appear to cause hair cell loss may still degrade the synapses that connect inner hair cells with auditory nerve fibers, potentially impacting the efficiency with which sound waves are translated into electrical signals (Kujawa and Liberman, 2009; Liberman and Kujawa, 2017).

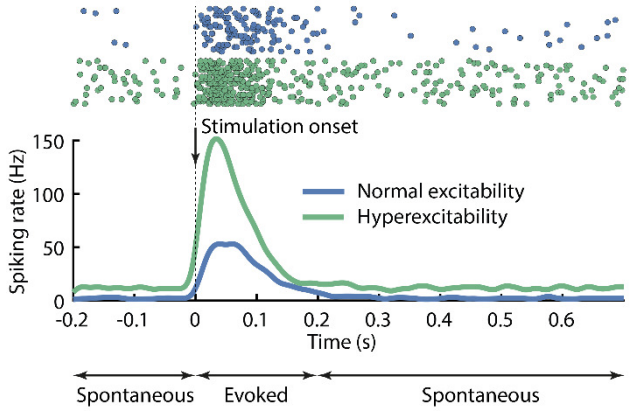

Figure 1: Simulated electrophysiological data of cortical excitability. Data show spontaneous activity (i.e., in absence of experimental acoustic stimulation) and stimulus-evoked activity for simulated neurons under normal and hyperexcitable conditions. Top rows show raster plots, where each dot reflects the occurrence of an action potential (spike). Spike-rate time courses are depicted on the bottom.

The central auditory systems of animals exposed to high-intensity sounds also undergo drastic changes. Compared to a pre-exposure baseline or to control animals, sound-exposed animals show altered spontaneous firing rates in the cochlear nucleus, inferior colliculus, medial geniculate nucleus (thalamus), and auditory cortex (Zhang and Kaltenbach, 1998; Manzoor et al., 2012; Mulders and Robertson, 2013; Wang et al., 2013; Coomber et al., 2014; Kalappa et al., 2014; Eggermont, 2015; Figure 1). Changes appear to be frequency specific; spontaneous firing rates of neurons that typically respond to the sound frequencies comprising the exposure stimulus are reduced, while neurons whose frequency sensitivities lie outside of those comprising the exposure stimulus become hyperexcitable. High-intensity exposure also results in changes in sound-evoked responses. While acoustic injury leads to smaller responses in neurons of the inferior colliculus of exposed animals compared to non-exposed controls (Popelár et al., 1987; Sun et al., 2012; for a detailed review see Auerbach et al., 2014), hyperresponsivity is observed in neurons of the medial geniculate nucleus (thalamus) and auditory cortex (Popelár et al., 1987; Syka et al., 1994; Sun et al., 2012; Kalappa et al., 2014; Schormans et al., 2019). Hyperexcitability has also been observed following low-intensity sound exposure, where mechanical damage to the cochlea is minimal. Weeks-long continuous sound exposure at intensities that are common in the everyday lives of humans (e.g., ~70 dB SPL) is associated with enhanced spontaneous firing rates in auditory cortex (Munguia et al., 2013) and results in a temporary enhancement of sound-evoked responses in the inferior colliculus (Sheppard et al., 2018).

In sum, a large body of work has demonstrated that damage to the auditory periphery induced by sound exposure is associated with hyperexcitability in the central auditory system and that the degree of damage and subsequent physiological changes depend on the nature of the exposure and the region of the auditory pathway under study.

Hyperexcitability associated with pharmacological treatment

In contrast to the broad pattern of inner ear pathology induced by sound exposure (Saunders et al., 1985; Slepecky, 1986; Liberman and Kujawa, 2017), pharmacological manipulations that induce ototoxicity enable a more fine-grained investigation of the changes in the central auditory system arising from damage to specific peripheral structures, while leaving others intact.

Cisplatin and Carboplatin are chemotherapeutic agents that have been shown to selectively impair outer and inner hair cells in rodent models, respectively (Qiu et al., 2000; Kaltenbach et al., 2002; Zhao et al., 2016). In both cases, ototoxicity is followed by an increase in auditory system hyperexcitability. For example, Cisplatin-induced damage of more than 50% of outer hair cells increases spontaneous firing in the dorsal cochlear nucleus of rodents (Kaltenbach et al., 2002; Rachel et al., 2002). Carboplatin-induced damage to 30-40% of inner hair cells is associated with hyperresponsivity to sound in auditory cortex (Qiu et al., 2000; Salvi et al., 2017). These enhanced responses vanish when 75% of inner hair cells are damaged (Qiu et al., 2000), suggesting that the relationship between the degree of cochlear damage and hyperresponsivity may be non-linear. We will discuss this point in more detail below.

Damage can be specifically restricted to cochlear nerve afferent synapses using Ouabain without damaging hair cells in the cochlea (Schmiedt, 2010; Yuan et al., 2014; Chambers et al., 2016b; Chambers et al., 2016a; Resnik and Polley, 2017; Asokan et al., 2018). Synapse degeneration is associated with a substantial reduction of inputs to central brain regions and results in reduced sound-evoked responses as far along the pathway as the inferior colliculus. However, even with over 90% of synapses degenerated, auditory cortical responses to sound do not differ between Ouabain-treated and control animals (Chambers et al., 2016b; consistent with Carboplatin-induced damage Qiu et al., 2000), indicating that auditory cortex becomes hyperresponsive following afferent synapse loss.

This small sample of studies demonstrates that damage resulting from ototoxic drugs leads to hyperexcitability in the central auditory system. Over 100 drugs have known ototoxic effects that impair hearing in humans, including antibiotics, chemotherapeutics, antimalarials, antiepileptics, anti-inflammatories, and diuretics (Radziwon et al., 2016). However research on ototoxic effects in humans has thus far focused mainly on peripheral and midbrain auditory structures (see review Radziwon et al., 2016).

Hyperexcitability in the aged auditory system

Age-related hearing loss is not a uniquely human phenomenon; animals that grow up in relative quiet and are not exposed to noise nor treated with ototoxic drugs, nevertheless develop inner ear dysfunction as they age. Cochlear dysfunction in aged mammals results from a degeneration of hair cells, spiral ganglion cells, and the stria vascularis (Gratton and Vázquez, 2003; Moore, 2007;

Bao and Ohlemiller, 2010; Schmiedt, 2010; Dubno et al., 2013; Plack, 2014; Keithley, 2020), although it appears that atrophy of the stria is the predominant factor related to aging (Schmiedt, 2010; but see also Wu et al., 2020). As with noise- and drug-induced damage, age-related peripheral impairments are accompanied by hyperexcitability in the central auditory system. A given input to the auditory system activates a larger number of neurons along the auditory pathway (Herrmann et al., 2017; Parthasarathy et al., 2019), and spontaneous activity is increased in the inferior colliculus (Parthasarathy et al., 2019) and auditory cortex of older compared to younger animals (Hughes et al., 2010; Juarez-Salinas et al., 2010; Overton and Recanzone, 2016; Ng and Recanzone, 2018).

In contrast to well-controlled studies in aged animal models, the degree of cochlear damage and subsequent hearing loss observed in older humans reflects the combination of age-related degenerative changes, long-term sound exposure from daily activities (e.g., in train stations, restaurants), occasional episodes of high-intensity sound exposure (e.g., concerts, industrial noise), and side effects from drugs with ototoxic properties (Schmiedt, 2010; Zhao et al., 2016; Ibrahim and Llano, 2019). Hence, humans are exposed to various potential causes of auditory peripheral damage across their lifespans that may give rise to changes in neural excitability. Accordingly, hyperresponsivity to sound has been observed in the auditory cortex of older compared to younger humans (e.g., Anderer et al., 1996; Amenedo and Díaz, 1999; Harkrider et al., 2005; Ross and Tremblay, 2009; Sörös et al., 2009; Lister et al., 2011; Alain et al., 2012; Herrmann et al., 2013b; Bidelman et al., 2014; Herrmann et al., 2018; Herrmann et al., 2019), although most of these studies did not aim to investigate age-related hyperresponsivity specifically. Moreover, older adults with clinical hearing loss (i.e., audiometric pure-tone threshold average of 25 dB HL or greater; Plack, 2014) show even greater increases in cortical excitability than those with normal hearing (Tremblay et al., 2003; Alain et al., 2014; Millman et al., 2017). These observations are consistent with those from noise-exposed, drug-treated, and aged animals, and suggest that auditory cortical hyperexcitability in older humans arises subsequent to peripheral damage.

Hyperexcitability associated with acoustic deprivation

The research reviewed thus far suggests that damage to auditory peripheral structures, whether due to sound exposure, drug treatment, or changes related to aging, is associated with hyperexcitability in downstream brain regions. However, some researchers suggest that it may not be damage per se, but rather the resulting reduction of input to the central auditory system that leads to hyperexcitability (Radziwon et al., 2016; Zhao et al., 2016). While this question has not often been addressed, a recent study in humans attempted to disentangle these factors by comparing cortical responses to sound in people with and without conductive hearing loss (Parry et al., 2019). Conductive hearing loss arises from dysfunction of the middle ear apparatus that normally

amplifies sounds before they reach the cochlea. Conductive hearing loss thus provides a model of reduced input to the auditory system in the absence of cochlear damage. Electroencephalographic recordings from auditory cortex revealed that supra-threshold bone-conducted stimuli – the transmission of which is unaffected by middle ear dysfunction – elicits larger responses in people with conductive hearing loss compared to people without (Parry et al., 2019). This suggests that hyperexcitability in auditory cortex is the result of acoustic deprivation that occurs subsequent to peripheral dysfunction rather than arising from cochlear damage itself.

Mechanisms underlying hyperexcitability

Neurons can be broadly categorized as being either excitatory or inhibitory, and maintaining a balance between excitation and inhibition is crucial for neural function (Wehr and Zador, 2003; Silver, 2010; Froemke and Martins, 2011; Isaacson and Scanziani, 2011; Shew and Plenz, 2013; Whitmire and Stanley, 2016). There are about four times more excitatory neurons than there are inhibitory neurons in auditory cortex (Ouellet and de Villers-Sidani, 2014), but inhibitory neurons are critical for regulating levels of excitation in order to avoid run-away excitation in neural circuits – a pattern of unconstrained excitation that is detrimental to signalling dynamics and which can lead to neuronal death via excitotoxicity (Shew and Plenz, 2013; Moser and Starr, 2016; Hattori et al., 2017; Imam and Hannan, 2017).

Different types of inhibitory neurons can be distinguished in auditory cortex. The most common express either somatostatin (SST), parvalbumin (PV), or vasoactive intestinal polypeptide (VIP). SST-expressing neurons tend to form synapses on dendrites of excitatory neurons, thereby suppressing neuronal inputs. PV-expressing neurons preferentially connect at the cell body of excitatory neurons and inhibit their output (Figure 2A; Ouda et al., 2015; Hattori et al., 2017). VIP-expressing neurons typically synapse with PV and SST neurons and, by inhibiting or disinhibiting them, regulate cortical excitation (Blackwell and Geffen, 2017; Wood et al., 2017). While we will review research on different types of inhibitory neurons (PV and SST specifically, as VIP neurons have been the focus of far less research) and their selective manipulation, we note that interneurons are integrated in complex interactive networks that make inferences about individual cell types difficult (Pfeffer et al., 2013).

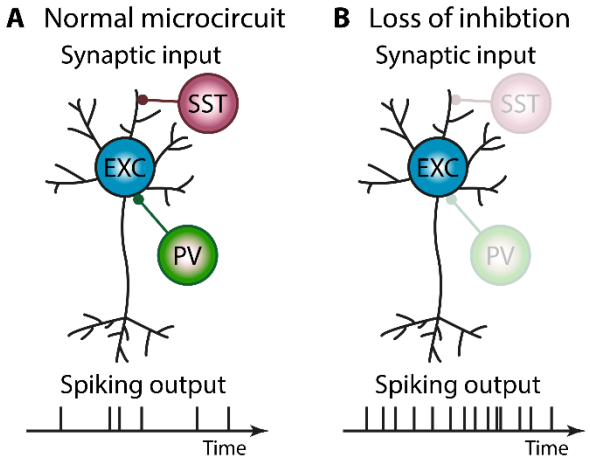

Figure 2: Schematic representation of a loss of inhibition in microcircuits of auditory cortex. A: Normal microcircuit with intact somatostatin (SST) and parvalbumin (PV) inhibitory neurons, regulating the relation between synaptic input and spiking output of an excitatory neuron (EXC). **B:** Microcircuit marked by a loss of SST and PV inhibitory neurons, mirroring observations for the aged auditory cortex (Ouellet and de Villers-Sidani, 2014). A loss of inhibition is associated with increased spiking output.

Hyperexcitability in the central auditory system is predominantly associated with a loss of inhibition (Caspary et al., 2008; Takesian et al., 2009; Auerbach et al., 2014; Ouda et al., 2015; Salvi et al., 2017), although an increase in excitation has also been reported (Kotak et al., 2005; Abolafia et al., 2011; Zhao et al., 2016; Salvi et al., 2017). Sound exposure, ototoxic drug treatment, and aging are all associated with reduced inhibition in the central auditory system compared to young control animals (Rabang et al., 2012; Kamal et al., 2013; Ouellet and de Villers-Sidani, 2014; Resnik and Polley, 2017). For low-intensity sound (Zhou and Merzenich, 2012; Kamal et al., 2013) and ototoxic drug exposure (Resnik and Polley, 2017), this has been attributed to reductions in the number of PV inhibitory neurons. However, in aging animals, the number of both PV and SST interneurons in auditory cortex appears to decrease (Figure 2B; de Villers-Sidani et al., 2010; Martin del Campo et al., 2012; Kamal et al., 2013; Ouellet and de Villers-Sidani, 2014; Cisneros-Franco et al., 2018), whearas other types of inhibitory neurons remain relatively constant in number across the lifespan (Ouellet and de Villers-Sidani, 2014). While inhibitory neuron loss in aging mammals may occur secondary to degradation of the auditory periphery, a loss of inhibition and hyperexcitability could also be the consequence of metabolic vulnerabilities of inhibitory neurons associated with aging processes directly (Ibrahim and Llano, 2019). Inhibitory neurons are metabolically highly demanding, but the cellular energy metabolism supporting inhibitory neurons may decline as we age. This may lead to a selective loss of inhibitory function in central auditory brain regions (Ibrahim and Llano, 2019), and thus presents a mechanism by which auditory hyperexcitability may arise from the aging process in the absence of age-related cochlear degeneration.

That a loss of inhibition – whether through peripheral damage, aging, or a combination thereof – may be a prominent driver of hyperexcitability in auditory circuits is further highlighted by direct manipulations of inhibition. Downregulation of PV- and SST-expressing interneurons function via optogenetic (Aizenberg et al., 2015; Natan et al., 2015; Natan et al., 2017) or

pharmacological approaches (Wang et al., 2002; Llano et al., 2012) increases spontaneous firing rates and sound-evoked responses in auditory cortex. Conversely, drugs that increase inhibition reduce spontaneous activity and supress sound-evoked responses (Manunta and Edeline, 1997; Kaur et al., 2004).

While quantifying inhibitory interneuron function non-invasively in humans is difficult, a loss of inhibition has been documented in older adults with hearing loss compared to those without using magnetic resonance spectroscopy (Gao et al., 2015; but see also discussions in Ouda et al., 2015). The underlying changes in neural subtype distribution are unknown; one study observed no age-related changes in PV inhibitory neurons (Bu et al., 2003), but included only five adults with a median age of 50 and may thus have underestimated the magnitude of PV inhibitory neuron loss associated with aging. Due to inherent technical challenges, further advances in measuring inhibition and quantifying inhibitory neurons in humans will likely rely on indirect inference drawn from measures of hyperresponsivity. Given the large body of work in animals, we suggest that the role of reduced inhibition along the auditory pathway, particularly in auditory cortex, be considered in future human studies.

Summary

In this section, we provided evidence from human and animal studies converging on the idea that damage to the auditory periphery, whether as a result of noise exposure, ototoxicity, the aging process, or some combination thereof, leads to changes throughout the auditory pathway. The most pronounced of these changes is a shift in the balance of excitation and inhibition that results in hyperexcitability of auditory brain structures that can be measured both at rest (as increased spontaneous firing rates) or in the presence of sound (as hyperresponsivity). These functional changes are in accordance with changes that have been observed in the distribution of inhibitory neurons in the auditory system. Moreover, research suggests these structural and functional changes do not arise from cochlear damage per se, but rather, result from decreased input to the system occurring subsequent to that damage.

Hyperexcitability and perception

In this section, we describe the changes in auditory perception that may be associated with a loss of inhibition and subsequent hyperexcitability in the auditory pathway. Empirical research in animals has focused mostly on electrophysiological studies of neuronal function, as described above, with fewer studies designed to assess perception using behavioral approaches. Moreover, very few targeted investigations of hyperexcitability and perception have been undertaken in humans, with the exception of the role of hyperexcitability in tinnitus and hyperacusis. As a

consequence, the associations laid out here between hyperexcitability and auditory perception reflect hypotheses that require additional empirical verification. We begin with a discussion of tinnitus and hyperacusis percepts, and then consider how hyperexcitability might affect complex sound perception by fundamentally altering the encoding of sound features to which auditory pathway neurons are normally highly sensitive.

Tinnitus and hypersensitivity to sound

The perceptual phenomena most closely associated with hyperexcitability are: 1) tinnitus – the perception of sound in absence of an identifiable sound source, which has been attributed to enhanced spontaneous firing rates in the central auditory system of animals following cochlear damage (Kalappa et al., 2014; Eggermont, 2015); and 2) hyperacusis – the sensation that sounds at moderate intensities are too loud (Eggermont and Roberts, 2004; Auerbach et al., 2014), which has been linked to enhanced sound-evoked activity in regions along the auditory pathway, most prominently in auditory cortex (Auerbach et al., 2014). Indeed, tinnitus and hyperacusis comprise the focus of the majority of articles that review, model, or theorize on the perceptual consequences of auditory system hyperexcitability (Eggermont and Roberts, 2004; Knipper et al., 2013; Zeng, 2013; Eggermont, 2015; Zhao et al., 2016; Sheppard et al., 2020).

Behavioral indices of tinnitus have been observed in animals after the type of high-intensity sound exposures known to induce auditory system hyperexcitability (Hayes et al., 2014). For example, exposed animals are poorer at perceiving a gap in noise than animals that were not exposed, where the continuous phantom sound percept of tinnitus is assumed to mask the gap (Turner et al., 2006). Additionally, sound-exposed or ototoxic drug-treated animals categorize periods of silence as containing noise more often than control animals (Stolzberg et al., 2013; Hayes et al., 2014). However, whether the degree of tinnitus correlates with the degree of spontaneous activity in the central auditory system is unknown. Since age-related tinnitus is often accompanied by peripheral hearing loss (Baguley et al., 2013), disentangling the two factors can be challenging.

Behavioral work in animals is also consistent with hypersensitivity to sound following cochlear damage. Cats with cochlear lesions show lower behavioral detection thresholds for electrical stimulation of neurons in the cochlear nucleus, inferior colliculus, and medial geniculate nucleus compared to pre-lesion (Gerken, 1979). Moreover, perceptual thresholds for pure tones are maintained after drug-induced loss of up to 95% of inner hair cells in rodents (Lobarinas et al., 2013; Chambers et al., 2016b), potentially due to enhanced sound-evoked responses in auditory cortex (Qiu et al., 2000). This suggests that hyperresponsivity of auditory neurons may provide the means to maintain sound awareness despite severe cochlear damage (Asokan et al., 2018).

In humans, tinnitus and hyperacusis are often comorbid (Hebert et al., 2013), suggesting a common underlying mechanism. The probability of experiencing both tinnitus (Schaette et al., 2012; Brotherton et al., 2019) and hyperacusis (Fromby et al., 2007; Fournier et al., 2014; Munro et al., 2014; Brotherton et al., 2016, 2017) are increased in adults following temporary sound deprivation via ear plugging. These effects typically vanish a few hours after the ear plug is removed (Schaette et al., 2012; Brotherton et al., 2016) and, while this pattern of results would be predicted by the onset of hyperexcitability, the exact mechanisms underlying the perceptual changes are unknown. There is also evidence of increased sound sensitivity in humans following age-related hearing loss; older adults with clinical hearing loss detect smaller deviations in sound amplitude than older adults without (Füllgrabe et al., 2003; Ernst and Moore, 2012; Sek et al., 2015; Schlittenlacher and Moore, 2016).

Although the perceptual changes described here are consistent with hyperexcitability, investigations directly linking hyperexcitability of the auditory pathway to tinnitus and perceptual hypersensitivity to sound are needed.

Spectral hearing

The ability to accurately perceive sound frequency is critical for the discrimination between two sounds with different spectral profiles, the perception of emotional content of speech, and the segregation of speech from other concurrent sound. Accordingly, neurons along the auditory pathway are frequency-tuned, responding preferentially to some sound frequencies at the expense of others (Moore, 1987; Isaacson and Scanziani, 2011; Noelle O'Connell et al., 2014). Brain regions along the auditory pathway are also organized tonotopically, at least macroscopically (Bandyopadhyay et al., 2010), with neurons tuned to similar sound frequencies being clustered spatially (Kandler et al., 2009; Da Costa et al., 2011; Hackett, 2011; Baumann et al., 2013; Moerel et al., 2014; Saenz and Langers, 2014; Brewer and Barton, 2016).

Accurate perception and discrimination of sound frequency depends critically on narrow frequency tuning – the strong preference of neurons for specific, characteristic frequencies. Neural inhibition shapes this tuning of neurons by modulating the probability of sound frequencies above and below the characteristic frequency eliciting a response (Isaacson and Scanziani, 2011). In auditory cortex, this frequency tuning appears to be mediated largely by PV- and SST- expressing inhibitory interneurons (Aizenberg et al., 2015; Kato et al., 2017). Pharmacological and optogenetic manipulations that specifically modulate the activity of these interneurons have revealed that an increase in inhibition narrows tuning (Kaur et al., 2004; Aizenberg et al., 2015), whereas a decrease in inhibition broadens tuning (Wang et al., 2002; Aizenberg et al., 2015). These changes in tuning have demonstrable perceptual consequences; increasing or decreasing PV

inhibition improves or worsens frequency discrimination, respectively (Aizenberg et al., 2015; SST-expressing interneurons were not tested).

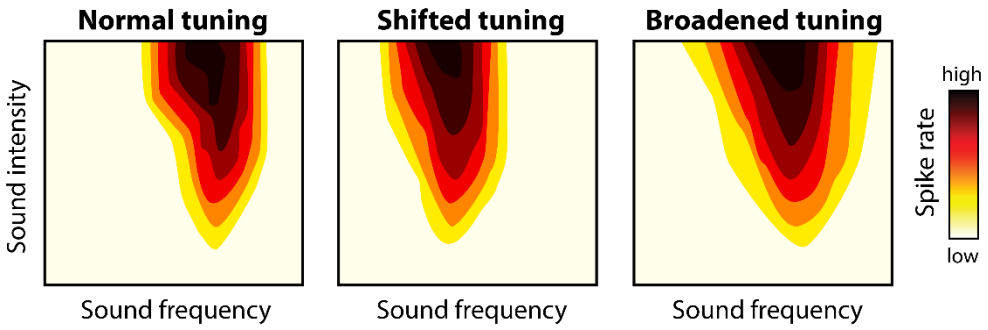

Figure 3: Schematic frequency-response areas. Normal, shifted, and broadened frequency tuning.

While less is known about the perceptual consequences, aged animals and animals with peripheral injury due to sound exposure or drug treatment also exhibit broadened tuning or tuning with reduced specificity. Reorganization of tonotopic maps, where neurons shift their frequency preference to lower frequencies, has been observed as well (Figure 3; Norena et al., 2003; Turner et al., 2005; de Villers-Sidani et al., 2010; Zhou and Merzenich, 2012; Chambers et al., 2016a; Resnik and Polley, 2017). Thus, cochlear pathology associated with aging and sound exposure gives rise to changes in neural tuning that are comparable to those occurring when inhibition is specifically suppressed (Wang et al., 2002; Aizenberg et al., 2015); this consistent with the loss of PV and SST interneurons described above (Martin del Campo et al., 2012; Kamal et al., 2013; Ouellet and de Villers-Sidani, 2014; Resnik and Polley, 2017). These changes are not limited to severe peripheral damage; frequency tuning of neurons in auditory cortex broadens even after a few weeks of sound exposure at levels that humans typically encounter (65-70 dB SPL; Zhou and Merzenich, 2012; Thomas et al., 2019).

As described above, direct evidence of changes in inhibitory interneuron distribution and function is limited in aging and hearing-impaired humans. Accordingly, few studies have provided demonstrable links between hyperexcitability and frequency perception. However, broadening of neural tuning is consistent with decreased frequency discrimination acuity observed in older adults with and without hearing loss (Turner and Nelson, 1982; Nelson and Freyman, 1986; Clinard et al., 2010). Moreover, it has been reported that severe hearing loss leads to tonotopic map reorganization in human auditory cortex (Wolak et al., 2017), however, this finding is not consistent across studies (see Saenz and Langers, 2014; Ouda et al., 2015). Tonotopic map reorganization (Mühlnickel et al., 1998) and broadened frequency tuning (Sekiya et al., 2017) have also been observed (albeit inconsistently) in individuals with tinnitus. In contrast, frequency-

specific adaptation in auditory cortex – a unique form of frequency tuning – appears to be unaltered in older compared to younger adults, despite concurrent hyperresponsivity that suggests a loss of inhibition (Herrmann et al., 2013b). Together, these studies suggest that, at least in some individuals, frequency tuning in auditory brain regions and the neuronal inhibition governing it are altered by peripheral damage in a way that would be expected to affect perception.

In sum, frequency discrimination behavior in aging animals and animals with hearing loss is affected in a manner consistent with changes in the frequency-tuning of neurons in auditory cortex – changes that are likely the result of reduced inhibition and hyperexcitability. Deficits in frequency discrimination behavior are well established in older humans, but the currently available data are insufficient to directly link these perceptual deficits to neural hyperexcitability and altered frequency tuning.

Spatial hearing

Most auditory signals that reach a listener's ears consist of a mixture of sounds from spatially distinct sources. A listener must isolate a sound source of interest (e.g., speech) from the mixture and segregate it from sounds originating from other locations in order to track and attend it over time. Hearing loss and processes related to aging impair spatial hearing abilities (Brown, 1984; Abel et al., 2000; Koehnke and Besing, 2001), leading to a significant behavioral detriment that may be tied to auditory system hyperexcitability.

The accurate perception of sound source location is thought to depend on narrow spatial tuning that relies on primary (King et al., 2007) and posterior-dorsal regions of auditory cortex (Rauschecker and Tian, 2000; Arnott et al., 2004; Rauschecker and Scott, 2009; Woods and Alain, 2009; Herrmann et al., 2011; Rauschecker, 2011). Neurons in posterior auditory cortex are spatially tuned such that they respond preferentially to sounds originating from one location at the expense of other locations (Figure 4; Woods et al., 2006; Juarez-Salinas et al., 2010).

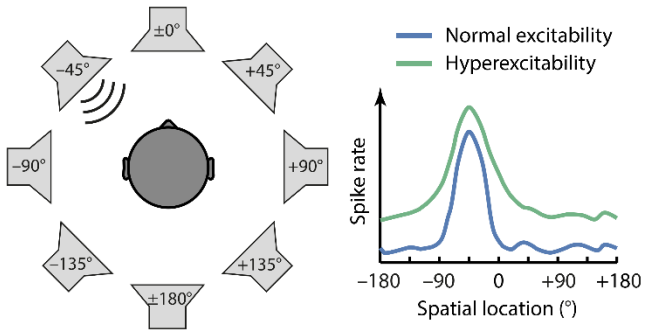

Figure 4: Simulated sound-evoked activity depicting spatial tuning for normal cortical excitability and hyperexcitability. Left: Schematic of a person positioned at the center of surrounding speakers. **Right:** Spatial tuning centered at –45 degrees.

Electrophysiological recordings from monkeys demonstrate that age-related hyperexcitability extends from primary auditory cortex into spatially-tuned posterior auditory cortex (Juarez-Salinas et al., 2010), suggesting a loss of inhibition in these regions as individuals age. Increased hyperexcitability in posterior auditory cortex also coincides with broadened spatial tuning (Juarez-Salinas et al., 2010) that would be expected to decrement spatial acuity. Accordingly, reduced behavioral performance in spatial hearing task have been reported in aged rats (Brown, 1984) and humans (Abel et al., 2000; Koehnke and Besing, 2001) compared to younger listeners.

Thus, hyperexcitability following peripheral damage appears throughout auditory cortex, including dorsal-stream regions that are crucial to spatial hearing. The loss of inhibition that underlies these changes also results in broadened spatial tuning of neurons in these dorsal areas, which may underlie behavioral decrements observed in aged humans. However, a direct link between hyperexcitability and the perception of sound location is currently missing.

Temporal sensitivity – periodicity processing

A sound originating from a given source is not only spectrally and spatially unique but also has a unique profile with which its amplitude and frequency fluctuate over time. In speech, for example, low- and high-frequency amplitude and frequency modulations reflect the envelope and fine-structure of a sound, respectively (Rosen, 1992). The relative contributions of envelope and fine structure to the perception of complex sounds like speech remains the topic of much research, and is beyond the scope of this review (but see Drullman, 1995; Lorenzi et al., 2006; Shamma and Lorenzi, 2013). Nevertheless, successful tracking of amplitude and frequency modulations across frequencies is considered crucial for the segregation of sounds from different sources and ultimately for speech comprehension in the presence of other sounds (Kerlin et al., 2010; Giraud and Poeppel, 2012; Edwards and Chang, 2013; Peelle and Davis, 2013).

Neurons along the auditory pathway are sensitive to acoustic periodicity, in that their activity synchronizes with a sound's amplitude and frequency fluctuations (Picton et al., 2003; Anderson et al., 2012; Herrmann et al., 2013a; Henry et al., 2014; Goossens et al., 2016; Parthasarathy et al., 2019). Electrophysiological work in animals and humans increasingly points to frequency-dependent changes in neural synchronization associated with aging and hearing loss. Auditory neurons synchronize more strongly with lower-frequency periodicities and less strongly with higher-frequency periodicities in aged compared to young rodents (Figure 5; Palombi et al., 2001; Schatteman et al., 2008; Overton and Recanzone, 2016; Herrmann et al., 2017; Parthasarathy et al., 2019). Similar changes have been observed following continuous exposure to sound at low-to-moderate intensities (~65 dB SPL; Zhou and Merzenich, 2012). Both enhanced low-frequency (Purcell et al., 2004; Goossens et al., 2016; Presacco et al., 2016a; Herrmann et al., 2019) and

decreased high-frequency synchronization (Purcell et al., 2004; Anderson et al., 2012; Clinard and Tremblay, 2013) have also been reported for older compared to younger humans, although low-frequency enhancements may not necessarily scale with the degree of peripheral hearing loss (Goossens et al., 2019; Herrmann et al., 2019; Presacco et al., 2019; but see Millman et al., 2017). Modeling and empirical measurements of neural activity suggests that a loss of inhibition could underlie this bidirectional change, although the effects of inhibition on synchronization appear complex and non-linear (Yang and Pollak, 1997; Backoff et al., 1999; Rabang et al., 2012).

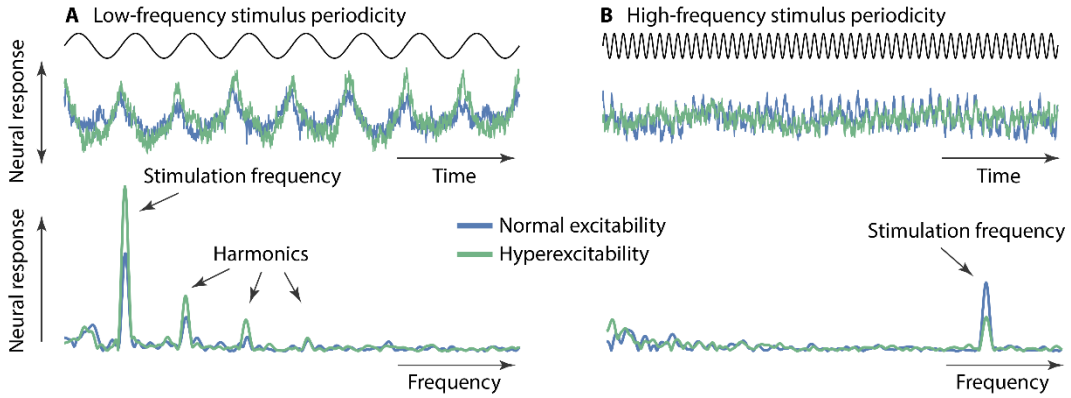

Figure 5: Simulated neural activity depicting neural synchronization to periodicity in sound for normal excitability and hyperexcitability. Panel A and B show simulated activity for low- and high-frequency stimulus periodicities, respectively. **Top:** Stimulus periodicity and simulated activity time courses. **Bottom:** Frequency spectra (from a fast Fourier transform) of the simulated response time courses. Peaks in the spectra indicate that neural activity synchronized with the periodicity in the acoustic signal. Peaks at harmonic frequencies emerge when time courses of synchronized neural activity are not fully sinusoidal.

In line with these changes in neural synchronization, individuals with unilateral hearing impairment perceive low-frequency amplitude modulations (4–32 Hz) as fluctuating more strongly in their hearing-impaired compared to their non-impaired ear (Moore et al., 1996), while discrimination of higher-frequency pure tones (500-1000 Hz) declines with age and hearing loss (Turner and Nelson, 1982; Nelson and Freyman, 1986; Clinard et al., 2010). However, because the relationship between low-frequency and high-frequency periodicity cues is not fully understood, the behavioral consequences of a bidirectional shift in neural synchronization on real-world listening are hard to predict. Reduced higher-frequency synchronization has been associated with poorer speech-in-noise perception (Anderson and Kraus, 2010; but see Presacco et al., 2016a), but the mechanism underlying this behavioral deficit is unknown. Additionally, enhanced low-frequency synchronization has been linked to poor speech intelligibility, specifically when a modulated masker sound is present (Millman et al., 2017; Goossens et al., 2018), suggesting that hyperexcitability makes ignoring irrelevant, fluctuating sounds more difficult.

Summary

The work reviewed in this section suggests that hyperexcitability (or the loss of inhibition underlying it) may contribute to a variety of perceptual phenomena that are common among normally aging adults and individuals with hearing loss. Hyperexcitability has long been hypothesized to underlie tinnitus and hyperacusis (Eggermont and Roberts, 2004; Knipper et al., 2013). But there is growing evidence that a loss of inhibition and hyperexcitability also affect spectral, spatial, and periodicity processing, altering responses to complex auditory signals like speech, and increasing interference from background sounds (Millman et al., 2017; Goossens et al., 2018). Since listening in acoustically challenging environments relies heavily on these processes, it is not be surprising that speech perception in noise declines with age and hearing loss (Pichora-Fuller, 2003; Presacco et al., 2016a, 2019). Hence, it is becoming increasingly clear that peripheral damage and associated plasticity along the auditory pathway fundamentally alter how sounds are represented neurally and how they are perceived. Yet, research linking hyperexcitability to perception remains underdeveloped.

Open questions and ongoing challenges in the study of hyperexcitability

Despite the increasing evidence of hyperexcitability following auditory peripheral damage, and the clear hypotheses regarding how perceptual impairments could arise secondary to hyperexcitability, open questions remain. In many cases, the types of investigations necessary to fill the knowledge gaps outlined in the previous two sections face considerable conceptual, experimental, and methodological challenges that we will attempt to highlight in the following sections. Indeed, a fulsome understanding of the role of inhibition and hyperexcitability in reshaping neural representations of sound and subsequent behaviors following peripheral degeneration will require additional study in both animal models of hearing loss and in human listeners. Critically, the ability to integrate findings across models, and the development of innovative approaches to the measurement of hyperexcitability are necessary to move this field forward.

Open question 1: What is the functional role of auditory system hyperexcitability?

The loss of inhibition giving rise to hyperexcitability along the auditory pathway is commonly referred to as a process that *compensates* for reduced inputs from damaged peripheral structures to central brain regions to maintain sensation (Caspary et al., 2008; Schaette and McAlpine, 2011; Knipper et al., 2013; Auerbach et al., 2014; Chambers et al., 2016a; Möhrle et al., 2016; Salvi et al., 2017). Homeostatic mechanisms are thought to underlie this compensatory adjustment in excitability (Caspary et al., 2008; Auerbach et al., 2014), by stabilizing and maintaining optimal

levels of excitability in neural circuits such that both low levels of excitability and run-away excitability are avoided. These homeostatic mechanisms operate across many levels, from synaptic changes to changes at the whole-brain network level (Turrigiano, 1999; Turrigiano and Nelson, 2000; Turrigiano, 2012; Keck et al., 2017). Accordingly, the term 'compensation' has recently been adopted by human cognitive neuroscientists to describe, for example, enhanced sound-evoked activity observed in older people and people with hearing loss (Bidelman et al., 2014; Herrmann et al., 2016; Presacco et al., 2016b, a; Goossens et al., 2018, 2019).

The use of the term 'compensation' to describe homeostatic mechanisms can give rise to considerable confusion. The fields of psychology and cognitive neuroscience commonly use 'compensation' to refer to behavioral or neurological adaptations that arise to offset a perceptual deficit (Bäckman and Dixon, 1992; Salthouse, 1995). In the case of hearing loss, 'compensation' is thus commonly used to refer to a breadth of adaptative strategies that help maintain or restore the perception of sound. Homeostatic compensation, however, seeks to maintain optimal levels of excitability in neural circuits without consideration of perceptual consequences (Turrigiano, 1999; Turrigiano and Nelson, 2000; Turrigiano, 2012; Nahmani and Turrigiano, 2014); indeed, homeostatic compensation may actually impair auditory perception (as described above). Thus, the term 'compensation' must be clearly defined when studying hyperexcitability in sensory circuits.

Many observations of hyperexcitability following peripheral damage could be considered to reflect homeostatic compensation, however, this idea is increasingly debated (Herrmann et al., 2016; Asokan et al., 2018; Cisneros-Franco et al., 2018; Ibrahim and Llano, 2019; Rogalla and Hildebrandt, 2020). While enhanced spontaneous activity has been observed at essentially all levels of the auditory pathway following peripheral damage (Kaltenbach et al., 2002; Rachel et al., 2002; Eggermont, 2015; Parthasarathy et al., 2019), the effects on sound-evoked activity are not as straightforward. For example, sound-evoked neural activity can be suppressed in the inferior colliculus, and enhanced in auditory cortex following peripheral damage (Hughes et al., 2010; Auerbach et al., 2014; Chambers et al., 2016b; Herrmann et al., 2016; Zhao et al., 2016). If homeostatic mechanisms underlie these changes, this would suggest they are not equally successful across brain regions.

An alternative view arises from observed similarities between damage-induced hyperexcitability in auditory brain regions and the excitability levels in the developing auditory system (Cisneros-Franco et al., 2018). Reduced inhibition may return auditory brain regions to a state of increased neural plasticity (Herrmann et al., 2016; Hattori et al., 2017; Cisneros-Franco et al., 2018; Thomas et al., 2019) that resembles early developmental periods during which inhibitory circuits have not yet matured and new connections between neurons can be formed efficiently (Cisneros-Franco et al., 2018). Indeed, a reduction of inhibition is thought to foster Hebbian

learning (Hattori et al., 2017) and new neural connections are formed in auditory cortex following peripheral hearing loss that give rise to visual and somatosensory functions (Allman et al., 2009; Ptito et al., 2012). However, homeostatic and Hebbian mechanisms may be intertwined at the molecular level (Turrigiano and Nelson, 2000) and disentangling them will present a significant future challenge.

Open question 2: How does lifelong hearing experience influence damage & hyperexcitability?
Accumulated sound exposure over the lifespan is thought to significantly contribute to hearing loss in older people (Schmiedt, 2010; Wu et al., 2020). The exact nature of this relationship has been the focus of substantial interest recently based on the observations that even low-intensity sound exposure can damage inner hair cell synapses (Kujawa and Liberman, 2009; Liberman and Kujawa, 2017), and that this type of cochlear degeneration is poorly captured by clinical hearing assessment tools in humans (Schaette and McAlpine, 2011; Plack et al., 2014). As described above, peripheral damage – including that which arises from sound exposure – may lead to a loss of inhibition and hyperexcitability in the auditory pathway (Auerbach et al., 2014; Zhao et al., 2016; Salvi et al., 2017). Concerts, urban streets, bars, restaurants, schools, train stations, hospitals, and industrial workplaces are only a few examples of acoustic environments that humans encounter regularly in which sound levels are comparable to those that induce hyperexcitability in noise-exposed animals (Hopkins, 1994; Olsen, 1998; Tsai et al., 2009). We may thus expect many humans to exhibit hyperexcitability along their auditory pathway reflecting frequent exposures.

However, it has also been demonstrated that, under certain circumstances, sound exposure may have a protective function. For example, routine exposure to sounds at low (~46 dB; Fukushima et al., 1990) or moderate-to-high intensities (e.g., 80 dB SPL; Canlon et al., 1988; Yoshida and Liberman, 2000; Niu et al., 2004, 2007) – often referred to as enriched acoustic environments – can reduce the damage induced by subsequent traumatic, high-intensity sounds. In fact, the protective effects of auditory enrichment can even mitigate sound-induced peripheral damage when presented *after* high-intensity exposure (Niu et al., 2004; Norena and Eggermont, 2006; Noreña et al., 2006; Niu et al., 2007). In humans, enriched acoustic environments have also been shown to reduce perceptual hypersensitivity to sound (Norena and Chery-Croze, 2007) and have been used to treat tinnitus (Henry et al., 2006; Jastreboff, 2007).

This presents a paradox: how can enriched environmental exposure exert a protective function while noise exposure at the same amplitude and duration results in considerable peripheral damage? The answer may lie in the sound structure; exposure to unmodulated, continuous noise leads to hyperexcitability and increased plasticity in auditory cortex, whereas exposure to sound with more naturalistic, structured properties, such as amplitude modulation, does not (Zhou and Merzenich, 2012; Thomas et al., 2019). As such, it is possible that humans' everyday environments

may protect them (to some extent) from occasional high-intensity sound exposure, and that this could explain why investigations of the impact of recreational sound exposure on hearing function have revealed mixed results (Prendergast et al., 2017a; Prendergast et al., 2017b; but see Liberman et al., 2016; Imam and Hannan, 2017). It may ultimately be critical to distinguish between sounds that may be more harmful for the auditory system, such as occupational or industrial sounds with broad-band, unmodulated, continuous properties, and sounds like music and speech, which elicit structured, correlated neural activity which may be less harmful (Thomas et al., 2019).

Open question 3: How does hyperexcitability change as function of hearing loss severity?

Hyperexcitability in human auditory cortex is most commonly measured indirectly as hyperresponsivity to sound (e.g., Alain et al., 2014; Bidelman et al., 2014; Herrmann et al., 2016). However, hyperresponsivity changes as a function of the degree of auditory deprivation (Figure 6). It may be tempting to interpret decreased responsivity to sound following severe cochlear damage as evidence against hyperexcitability in auditory brain regions. However, one must be mindful that peripheral damage also affects signal generation at the cochlea. Animals with a mild to moderate noise-induced or age-related hearing loss show hyperresponsivity in auditory cortex (Hughes et al., 2010; Auerbach et al., 2014). However, as the degree of peripheral damage increases – for example, when 80-90% of hair cells are lost – hyperresponsivity is offset by a dramatic reduction in signal transduction, and cortical responses are no larger than those observed in unexposed animals (Qiu et al., 2000; Chambers et al., 2016b; Salvi et al., 2017). In the extreme case of complete peripheral damage, signal transduction is lost and auditory cortex becomes non-responsive to sound (Figure 6).

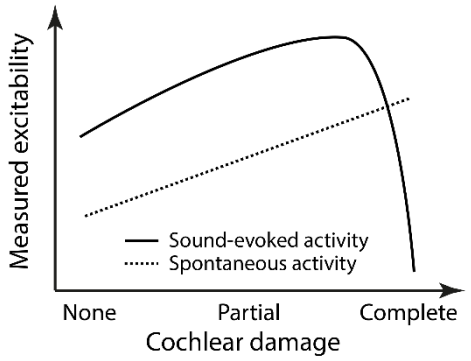

Figure 6: Hypothetical depiction of auditory cortical excitability as a function cochlear damage. The solid line reflects cortical excitability measured indirectly using sound stimulation. The dashed line reflects cortical excitability measured directly via spontaneous neuronal activity or indirectly via electric stimulation of auditory cortex.

Thus, hyperresponsivity to sound may only be a useful proxy for hyperexcitability when sufficient peripheral integrity exists to facilitate sound transduction. Indeed, behavioral thresholds for electrical stimulation of auditory thalamic neurons (bypassing peripheral damage) are improved after complete, or almost complete peripheral damage compared to a pre-damage control (Gerken, 1979), suggesting hyperresponsivity in auditory circuits that would not be evident using

acoustic stimulation. Unfortunately, techniques that measure spontaneous neural activity or behavioral responses to electrical stimulation are not typically applicable in humans.

How long hyperexcitability in auditory cortex persists following complete auditory deprivation is also unclear. Based on research on other biological tissue (Cannon and Rosenblueth, 1949), hyperexcitability of neurons in auditory cortex is expected to persist for at least several weeks after complete denervation. However, this is likely an underestimate, as neurons in auditory cortex are integrated into larger networks, including non-auditory brain regions, that continue to deliver synaptic inputs to auditory cortex following hearing loss. Indeed, the persistence of non-auditory inputs to auditory brain regions is hypothesized to underlie the preservation of normal patterns of connectivity in auditory cortex, even following profound early-onset hearing loss (Chabot et al., 2015; Butler et al., 2016; Butler et al., 2018). Moreover, the way in which excitability changes over time is also likely dependent on the degree of peripheral damage and subsequent hearing loss.

In sum, current measures of hyperresponsivity to sound are likely non-linear, such that the absence of *measurable* hyperresponsivity associated with aging or hearing loss may not imply the absence of hyperexcitability. This is particularly relevant for studies of older human adults and people with hearing loss that often rely on non-invasive recordings of event-related potentials like the P1 and N1 (e.g., Laffont et al., 1989; Anderer et al., 1996; Sörös et al., 2009; Bidelman et al., 2014; Stothart and Kazanina, 2016; Henry et al., 2017) that originate from auditory cortex (Näätänen and Picton, 1987; Huotilainen et al., 1998; Maess et al., 2007; Herrmann et al., 2018). The development of measures designed to capture hyperexcitability more directly from human listeners is an important first step toward understanding how hyperexcitability is shaped by the degree of hearing loss.

Open question 4: How do experimental design choices impact measures of hyperexcitability?

In addition to its dependence on the degree of peripheral damage, hyperresponsivity to sound also varies as a function of stimulus characteristics. For example, as described above, hyperexcitable auditory neurons in aged and noise-exposed animals show reduced neural synchronization specifically for higher-frequency periodicities (Zhou and Merzenich, 2012; Herrmann et al., 2017). Studies using high-frequency periodic stimuli may thus underestimate hyperexcitability, and observe different effects compared to studies that present stimuli with low-frequency periodicities.

Another example involves the relationship between neural responsivity and the temporal presentation dynamics of auditory stimuli. Neurons in the auditory pathway undergo adaptation – a reduction in neural response to sound due to sustained stimulation (Whitmire and Stanley, 2016) – and require time to recover full responsivity after responding to sound. This recovery time appears to be shortened in older compared to younger adults (de Villers-Sidani et al., 2010; Mishra

et al., 2014; Herrmann et al., 2016; Herrmann et al., 2019). Thus, sounds presented in short succession may lead to inputs to a larger proportion of adapted neurons in individuals with normal hearing compared to aged individuals or individuals with hearing loss. As a result, studies with different stimulation rates may confound hyperexcitability and neural recovery times, and may come to different conclusions.

This short list of examples is not exhaustive – they simply serve as a reminder that a loss of inhibition in the central auditory system may not always manifest as response enhancements to sound and that careful consideration of experimental design is required for the meaningful study of neural inhibition, hyperexcitability, and perception.

Summary

In this section, we reviewed open questions in the study of hyperexcitability, and outlined some of the challenges inherent to their study. First, we highlighted the ongoing debate surrounding the relative contributions of homeostatic mechanisms that stabilize the level of excitation within neuronal circuits and Hebbian mechanisms that support the formation of new connections between neurons efficiently to hyperexcitability in the auditory system. Second, we discussed the paradox that sound exposure can have damaging *and* protective effects on peripheral auditory function, suggesting that spectral and temporal properties of exposure sounds may play an underappreciated role in whether and how sound exposure impairs hearing. Finally, we highlighted the non-linear relationship between peripheral damage, hyperexcitability, and hyperresponsivity to sound and between experimental factors and hyperresponsivity to sound. These non-linearities pose a challenge for investigations of how hyperexcitability interacts with the degree of hearing loss in humans, where hyperexcitability is measured non-invasively as hyperresponsivity to sound.

Conclusions

Hearing loss in older adulthood is associated with a broad range of perceptual impairments that include a loss of sensitivity, tinnitus, hyperacusis, problems locating sounds, difficulties with speech comprehension in noise, and more. Traditionally, many of these perceptual deficits have been associated with damage to the cochlea in the auditory periphery. However, an increasing amount of evidence, mostly from studies in animals, suggests that hearing dysfunction results from changes in the entire auditory system, from the periphery to cortex. The most prominent change following peripheral degeneration is an increase in excitability of downstream brain regions in the auditory pathway. In this paper, we have a) reviewed the causes and neurophysiological mechanisms underlying hyperexcitability, showing that hyperexcitability does not arise from cochlear damage per se, but rather, result from decreased input to the system occurring subsequent

to that damage; b) suggested that hyperexcitability alters all aspects of auditory perception – including spectral, spatial, and temporal hearing – and, in turn, speech comprehension abilities when background sound is present; and c) discussed the need for further understanding of the functional role of hyperexcitability, and outlined some of the most important open questions in the study of hyperexcitability in humans. Our hope is that this review provides a foundation from which researchers can develop targeted approaches for investigating hyperexcitability in humans.

Acknowledgements

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