Brain Structure and Function (2021) 226:2019–2039
https://doi.org/10.1007/s00429-021-02313-9

REVIEW

Hearing loss and brain plasticity: the hyperactivity phenomenon

Björn Herrmann[1,2] · Blake E. Butler[3,4]

Received: 3 September 2020 / Accepted: 3 June 2021 / Published online: 7 June 2021

Abstract
Many aging adults experience some form of hearing problems 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 also results from changes within the entire auditory system, from periphery to cortex. Damage to the auditory periphery is associated with an increase in neural activity at various stages throughout the auditory pathway. Here, we review neurophysiological evidence of hyperactivity, auditory perceptual difficulties that may result from hyperactivity, and outline open conceptual and methodological questions related to the study of hyperactivity. We suggest that hyperactivity 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 hyperactivity and the potential challenges of investigating hyperactivity in humans, we hope to bring animal and human electrophysiologists closer together to better understand hearing problems in older adulthood.

Keywords Hearing loss · Aging · Hyperactivity · Excitability · 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 that has been extensively studied in animal models (Knipper et al. 2013; Auerbach et al. 2014; Zhao et al. 2016; Salvi et al. 2017) and that is increasingly observed in older human adults with clinical or subclinical hearing loss (Lister et al.

✉ Björn Herrmann
bherrmann@research.baycrest.org

1 Rotman Research Institute, Baycrest, Toronto, ON M6A 2E1, Canada

2 Department of Psychology, University of Toronto, Toronto, ON, Canada

3 Department of Psychology & The Brain and Mind Institute, University of Western Ontario, London, ON, Canada

4 National Centre for Audiology, University of Western Ontario, London, ON, Canada

2011; Alain et al. 2012; Bidelman et al. 2014; Herrmann et al. 2016, 2018; Presacco et al. 2016a, 2019) is neuronal hyperactivity. Here, we use the term hyperactivity to include three 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); (2) an increase in synchronized activity between neurons; and (3) an increase in the number of action potentials and the magnitude of local field potentials generated by neurons in response to sound (hyperresponsivity; Fig. 1).

Previous reviews have detailed the neurophysiological evidence for, and proposed mechanisms underlying hyperactivity 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 hyperactivity has not been described in as much depth. Moreover, studies conducted in humans—where the study of auditory system hyperactivity 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.

The current review delivers a detailed picture of the potential perceptual consequences of hyperactivity in the auditory system and provides a foundation from which researchers can develop targeted approaches for investigating hyperactivity in humans. The paper is divided into three sections that aim to convey the following messages: first, reduced acoustic input leads to hyperactivity in the central auditory system, regardless of the etiology or nature of the hearing loss (conductive/sensorineural); second, auditory system hyperactivity likely degrades spectral, temporal, and spatial processing and, in turn, speech perception; and finally, the non-linear relationship between peripheral

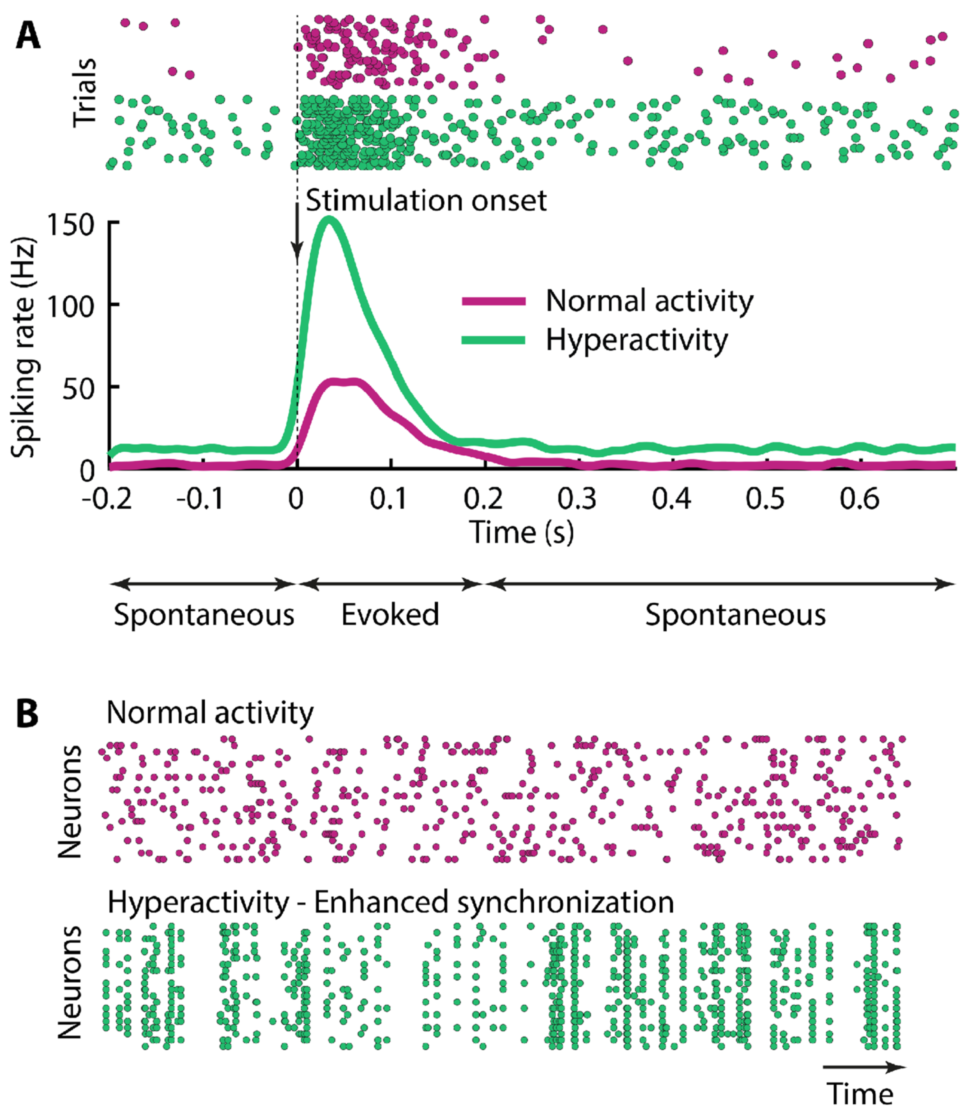

Fig. 1 Simulated electrophysiological data of cortical activity. **A** Simulated data show spontaneous activity (i.e., in the absence of experimental acoustic stimulation) and stimulus-evoked activity for simulated neurons under normal and hyperactive conditions. Top rows show raster plots, where each dot reflects the occurrence of an action potential (spike). Spike-rate time courses are depicted on the bottom. **B** Simulated spike times for several neurons under normal and hyperactive conditions. Synchronization among hyperactive neurons is enhanced (Note that schematic, simulated data are displayed)

damage and hyperresponsivity in the auditory system presents unique challenges that should be considered in the design of human studies that target hyperactivity.

Hyperactivity in central auditory regions

In this section, we will review empirical observations of hyperactivity associated with different experimental manipulations (e.g., sound exposure and drug treatment) and age groups. We will focus on direct measures of hyperactivity 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 hyperactivity, such as increased neural responses to supra-threshold sounds and enhanced behavioral sensitivity to electrical stimulation, measured using invasive or non-invasive methods. We will describe the animal literature and discuss related work from humans.

Hyperactivity 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 exposure (100 dB SPL or above) 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 eliminate 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).

High-intensity sound exposure not only leads to damage of auditory peripheral structures, but also is associated with plastic changes along the auditory neural pathway. 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; Seki and Eggermont 2003; Manzoor et al. 2012; Mulders and Robertson 2013; Wang et al. 2013; Coomber et al. 2014; Kalappa et al. 2014; Eggermont 2015; Fig. 1A). Changes appear to be frequency specific, such that 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 hyperactive. Increased spontaneous activity is often accompanied by enhanced synchronization among neurons (Seki and Eggermont 2003; Norena and Eggermont 2006; Eggermont 2012; Eggermont and Tass 2015; Fig. 1B).

High-intensity exposure also changes sound-evoked responses. While acoustic injury can lead to smaller sound-evoked responses in neurons of the inferior colliculus of exposed animals compared to non-exposed controls (Popelár et al. 1987; Sun et al. 2012), hyperresponsivity is observed in neurons of the medial geniculate nucleus (thalamus) and auditory cortex (Popelár et al. 1987; Syka et al. 1994; Yang et al. 2011; Sun et al. 2012; Kalappa et al. 2014; Schormans et al. 2019; Wieczerzak et al. 2021; for a detailed review, see Auerbach et al. 2014). Hyperactivity 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 temporary hyperresponsivity to sound 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 hyperactivity 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.

Hyperactivity associated with pharmacological treatment

In contrast to the broad pattern of inner-ear pathology induced by many high-intensity sound-exposure protocols (Saunders et al. 1985; Slepecky 1986), pharmacological manipulations that induce ototoxicity enable a fine-grained investigation of the changes in the central auditory system arising from damage to specific peripheral structures, while leaving others intact (but, see recent examples of sound-exposure protocols that specifically damage nerve synapses; Resnik and Polley 2017; Asokan et al. 2018; Shaheen and Liberman 2018).

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 hyperactivity. 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 nonlinear. 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. 2016a, b; Resnik and Polley 2017, 2021). Synapse degeneration is associated with a 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.

Salicylates are a group of common anti-inflammatory drugs (e.g., aspirin) that, when administered in high doses, are associated with hearing loss and behavioral indices of hyperactivity, most prominently tinnitus and hyperacusis (Day et al. 1989; Yang et al. 2007; Radziwon et al. 2016, 2017; Salvi et al. 2020). A high dose of a salicylate is consistently associated with increased spontaneous firing rates and increased sound-evoked responses in auditory cortex compared to control animals (Yang et al. 2007; Sun et al. 2009; Stolzberg et al. 2012; Salvi et al. 2017). Stronger increases in neural activity are associated with systemic injections of salicylates than with local injections to the cochlea, suggesting that salicylate-induced hyperactivity may not result from changes in cochlear function, but from direct effects on the central auditory structures (Sun et al. 2009).

This small sample of studies demonstrates that damage resulting from ototoxic drugs leads to hyperactivity 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); investigations of auditory cortex—and potential hyperactivity—following ototoxic drugs have not yet been conducted.

Hyperactivity 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 hyperactivity in the central auditory system. A given input to the auditory system activates a larger number of neurons along the auditory pathway (Walton et al. 2002; Herrmann et al. 2017; Parthasarathy et al. 2019), and spontaneous activity is increased in the inferior colliculus (Willott et al. 1988a; 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 aged animal models, the degree of cochlear damage and subsequent hearing loss observed in older human adults reflects a 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), cardiovascular problems (e.g., high blood pressure), and side effects from drugs with ototoxic properties (for reviews see Gates and Mills 2005; 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 activity. 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. 2013a, 2018, 2019; Bidelman et al. 2014), 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 responses to sound 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 hyperactivity in older humans arises subsequent to peripheral damage.

Hyperactivity 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 hyperactivity 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 hyperactivity (Sanes and Kotak 2011; Radziwon et al. 2016; Zhao et al. 2016; Parry et al. 2019). Investigating cortical responses to sound following conductive hearing loss may help disentangle these factors (Teichert et al. 2017; Parry et al. 2019). Conductive hearing loss arises from dysfunction of the middle-ear apparatus that normally transduces airborne sound pressure waves into mechanical vibrations 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.

In adult mice, sound-evoked activity in auditory cortex is reduced immediately following the induction of conductive hearing loss through removal of the malleus of the middle ear. However sound-evoked responses appear to recover to normal levels within a few days despite the chronic reduction in peripheral input (Teichert et al. 2017). Conductive hearing loss induced during early development of the auditory system reduces inhibitory activity in auditory cortex, thereby unmasking excitation (Sanes et al. 2010; Sanes and Kotak 2011; Takesian et al. 2012; but see also Rosen et al. 2012). In humans, electroencephalographic recordings from auditory cortex revealed that supra-threshold bone-conducted stimuli—the transmission of which is unaffected by middle-ear dysfunction—elicit larger responses in people with conductive hearing loss compared to people without (Parry et al. 2019). These data suggest that hyperactivity in auditory cortex is the result of acoustic deprivation that occurs subsequent to peripheral dysfunction rather than arising from cochlear damage itself (cf. Bauer et al. 2008).

Mechanisms underlying hyperactivity

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 to avoid run-away excitation in neural circuits—a pattern of unconstrained excitation that is detrimental to signaling dynamics and which can lead to neuronal death via excitotoxicity (Shew and Plenz 2013; 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 (Fig. 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).

Hyperactivity in the central auditory system is commonly associated with a loss of inhibition (Caspary et al. 2005, 2008; Takesian et al. 2009; Sanes et al. 2010; Auerbach et al. 2014; Ouda et al. 2015; Salvi et al. 2017), but increased intrinsic excitation and increased sensitivity to excitatory neurotransmitters also contribute to auditory system hyperactivity (Kotak et al. 2005; Abolafia et al. 2011; Li et al. 2013, 2015; Sturm et al. 2017; Teichert et al. 2017; Balaram

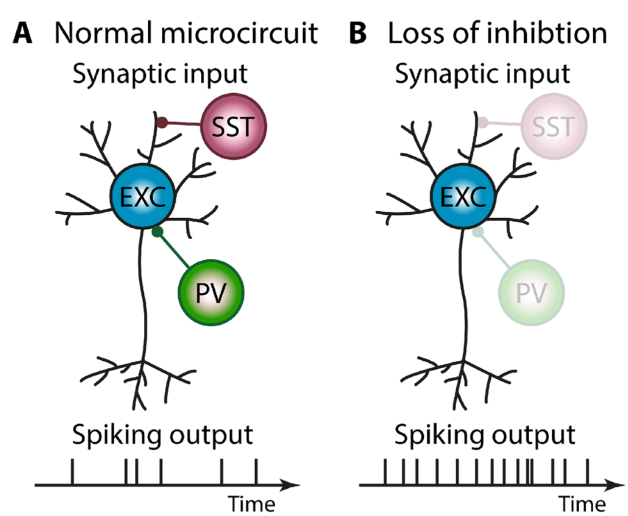

Fig. 2 Schematic representation of a loss of inhibition in microcircuits of auditory cortex. **A** Normal microcircuit with intact somatostatin (SST) and parvalbumin (PV) inhibitory neurons, regulating the relation between synaptic input and spiking output of an excitatory neuron (EXC). **B** Microcircuit 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

et al. 2019). We focus here on the loss of inhibition, as its relationship with cortical hyperactivity has received the most empirical attention, and it has been observed in both animal models and humans (Caspary et al. 2008; Gao et al. 2015; Dobri and Ross 2021).

Sound exposure, ototoxic drug treatment, aging, and acoustic deprivation are all associated with reduced inhibition in the central auditory system compared to control animals (Rabang et al. 2012; Takesian 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 (Fig. 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), whereas other types of inhibitory neurons remain relatively constant in number across the lifespan (Ouellet and de Villers-Sidani 2014). While the loss inhibitory neurons in aging mammals may occur secondary to degradation of the auditory periphery, a loss of inhibition and hyperactivity could also be the consequence of metabolic vulnerabilities of inhibitory neurons associated with aging processes directly (Brown 1984; Ibrahim and Llano 2019; Rogalla and Hildebrandt 2020). Inhibitory neurons are metabolically highly demanding, but the cellular energy metabolism supporting inhibitory neurons may decline with 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 hyperactivity may arise from the aging process in the absence of age-related cochlear degeneration (King et al. 2007; Rogalla and Hildebrandt 2020).

That a loss of inhibition—whether through peripheral damage, aging, or a combination thereof—may be an important driver of hyperactivity 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, 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; Dobri and Ross 2021; 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 reviewed evidence from animal and human 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 hyperactivity of auditory brain structures that can be measured both at rest (as increased spontaneous firing rates and increased synchronization among neurons) 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.

Hyperactivity and perception

In this section, we describe the changes in auditory perception that may be associated with a loss of inhibition and subsequent hyperactivity 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 the relationship between hyperactivity and auditory perception using behavioral approaches. Moreover, very few targeted investigations of hyperactivity and perception have been undertaken in humans, with the exception of the role of hyperactivity in tinnitus and hyperacusis. As a consequence, the associations laid out here between hyperactivity and auditory perception reflect hypotheses that require additional empirical verification. We begin with a discussion of tinnitus and hyperacusis percepts, and then consider how hyperactivity 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 hyperactivity are: (1) tinnitus—the perception of sound in the absence of an identifiable sound source, which has been attributed to enhanced spontaneous firing rates and increased synchrony among neurons in the central auditory system of animals following cochlear damage (Bauer et al. 2008; Eggermont 2012, 2015; Kalappa et al. 2014); and (2) hyperacusis—the sensation that sounds at moderate intensities are too loud (Eggermont and Roberts 2004; Auerbach et al. 2014; Thomas et al. 2019a), 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 hyperactivity and related phenomena (Eggermont and Roberts 2004; Eggermont 2012, 2015; Knipper et al. 2013, 2020; Zeng 2013; Zhao et al. 2016; Sedley 2019; 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 hyperactivity (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; but see Radziwon et al. 2015 for counter evidence). 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). 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 (Sedley 2019), and some evidence suggests that increased spontaneous activity may be insufficient to explain tinnitus (Hayes et al. 2021). Indeed, a recent human neuroimaging study suggests that cortical hyperactivity is less prevalent in individuals with hearing loss *and* tinnitus than in those with hearing loss alone (Koops et al. 2020). Other mechanisms underlying tinnitus have also been proposed, but are beyond the scope of the current review (see Weisz et al. 2005; Sedley et al. 2016; Sedley 2019; Knipper et al. 2020; Hayes et al. 2021).

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 awareness of sound in quiet despite severe cochlear damage (Asokan et al. 2018; Resnik and Polley 2021). In contrast, hyperactivity—specifically, increased synchronized activity—appears to impair sensitivity to sound in background noise by increasing neural noise in auditory cortex (Resnik and Polley 2021).

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 hyperactivity, the exact mechanisms underlying the perceptual changes are unknown. Functional imaging in humans further indicates hyperactivity in auditory cortex in people with tinnitus (Koops et al. 2020). Tinnitus, however, does not appear to affect perception of speech in noise, frequency discrimination, or temporal-modulation detection (Zeng et al. 2020, but see also Ivansic et al. 2017). 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 (Bacon and Gleitman 1992; Füllgrabe et al. 2003; Ernst and Moore 2012; Sek et al. 2015; Schlittenlacher and Moore 2016; but see Rosen et al. 2012 for results in early developmental hearing loss).

Although the perceptual changes described here are consistent with hyperactivity, investigations directly linking hyperactivity 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; Ramachandran et al. 1999; Miller et al. 2002; Bartlett et al. 2011; Schreiner et al. 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, 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).

While less is known about the perceptual consequences of a loss of inhibition and hyperactivity, aged animals and animals with peripheral injury due to sound exposure or drug treatment also exhibit broadened tuning or tuning with reduced specificity (Turner et al. 2005; Barsz et al. 2007; Izquierdo et al. 2008; Leong et al. 2011). Reorganization of tonotopic maps, where neurons shift their frequency preference to lower frequencies, has been observed as well (Fig. 3; Willott 1986; Willott et al. 1988b; 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 is 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. 2019b).

As described above, direct evidence of changes in inhibitory interneuron distribution and function is limited in aged humans and humans with hearing impairment. Accordingly, few studies have provided demonstrable links between hyperactivity and frequency perception. However, broadening of neural tuning is consistent with decreased frequency discrimination acuity and frequency-modulation detection observed in older adults with and without hearing loss (Turner and Nelson 1982; Nelson and Freyman 1986; Moore and Skrodzka 2002; Clinard et al. 2010; Moore 2014; Moore et al. 2019). Decreased frequency-modulation detection, in turn, is associated with reduced speech-in-noise perception (Holmes and Griffiths 2019; Parthasarathy et al. 2020). Moreover, it has been reported that severe hearing loss leads to tonotopic map reorganization in human auditory cortex (Wolak et al. 2017; Koops et al. 2020); however, this finding is not consistent across studies (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 in individuals with tinnitus (albeit inconsistently; e.g., Koops et al. 2020). 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. 2013a). 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 aged 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 hyperactivity. Deficits in frequency

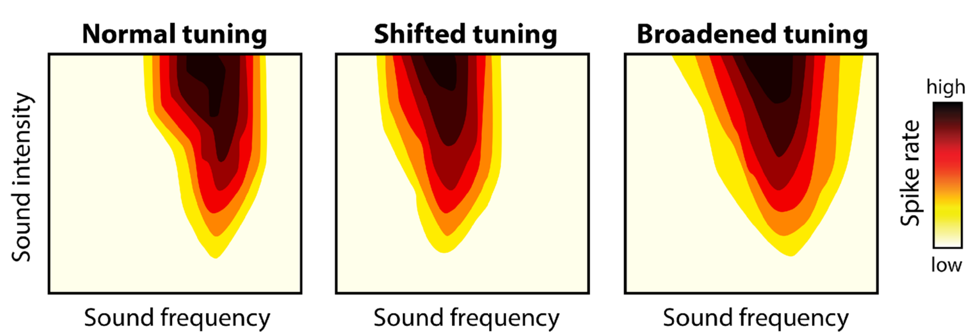

Fig. 3 Schematic frequency–response areas. Normal, shifted, and broadened frequency-tuning. (Note that schematic data are displayed)

discrimination behavior are well established in older humans, but the currently available data are insufficient to directly link these perceptual deficits to neural hyperactivity 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 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 hyperactivity.

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 (Fig. 4; Woods et al. 2006; Juarez-Salinas et al. 2010).

Electrophysiological recordings from monkeys demonstrate that age-related hyperactivity 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. Hyperactivity 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.

In sum, hyperactivity 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 hyperactivity and the perception of sound location is currently missing.

Temporal sensitivity

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 remain the topic of much research, and are 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. 2013b; 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

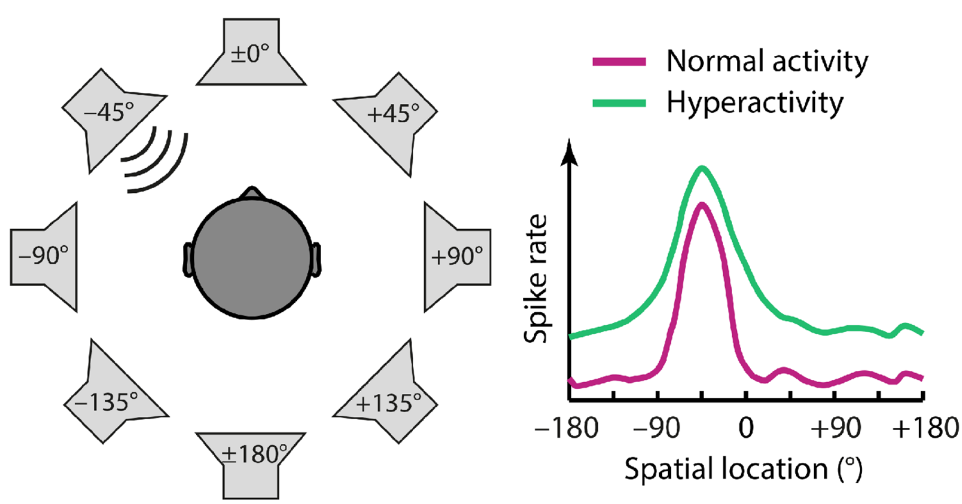

Fig. 4 Schematic of sound-evoked activity depicting spatial tuning for normal cortical activity and hyperactivity. Left: Schematic of a person positioned at the center of surrounding speakers. Right: Spatial tuning centered at − 45°. (Note that schematic data are displayed)

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 (Fig. 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). Overall firing rate may also be increased in older compared to younger animals for sounds with periodic amplitude modulations, especially for slower modulation rates (Palombi et al. 2001; Walton et al. 2002). However, neural synchronization in inferior colliculus and thalamus appears to be reduced for all stimulation frequencies when over 95% of afferent fibers are eliminated through drug manipulations in animals (Chambers et al. 2016a, b).

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 suggest 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).

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 hyperactivity makes ignoring irrelevant, fluctuating sounds more difficult.

Finally, neural and perceptual sensitivity to short gaps—that is, periods of silence—in a sound have long been considered a measure of temporal resolution of the auditory system (Frisina et al. 2001; Fitzgibbons and Gordon-Salant 2010; Walton 2010), and the ability to detect gaps appears to be a good predictor of speech comprehension abilities (Gordon-Salant and Fitzgibbons 1993). Work in rodents shows reduced neural responses to gaps in the inferior colliculus of older compared to younger animals and in animals exposed to sound (Walton et al. 1998; Allen et al. 2003;

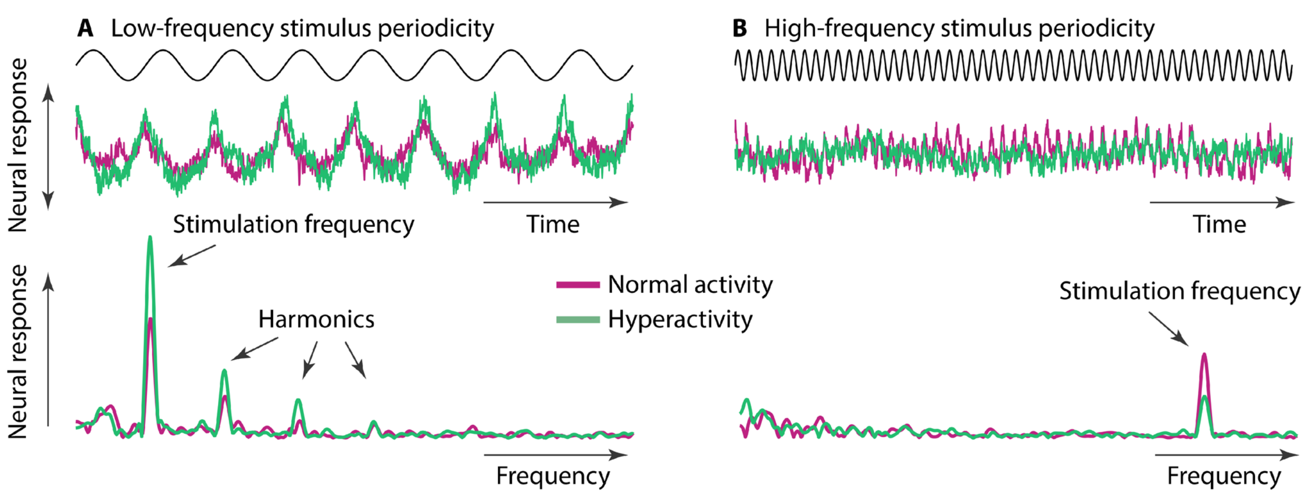

Fig. 5 Simulated neural activity depicting neural synchronization to periodicity in sound for normal activity and hyperactivity. Panel **A** and **B** show simulated activity for low- and high-frequency stimulus periodicities, respectively. Top: Stimulus periodicity and simulated activity time courses. 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. (Note that schematic, simulated data are displayed)

Sturm et al. 2017). In humans, older adults exhibit enhanced responses to gaps in auditory cortex compared to younger listeners, indicating that the auditory system is hyperresponsive (Ross et al. 2010; Lister et al. 2011; but see Harris et al. 2012). Accordingly, behavioral gap-detection thresholds are typically larger for older compared to younger human adults (Glasberg et al. 1987; Schneider et al. 1994, 1998; Snell 1997; Snell and Frisina 2000; Humes et al. 2009; Harris et al. 2012). However, sensorineural hearing loss may not additionally contribute to changes in gap-detection thresholds beyond effects of aging (Moore and Glasberg 1988; Fitzgibbons and Gordon-Salant 1996; Gordon-Salant and Fitzgibbons 1999, but see Moore et al. 1992), suggesting that peripheral damage and associated hyperactivity may not contribute substantially to gap-detection performance. This is further corroborated by the observation that salicylate, a drug known to induce auditory system hyperactivity (see above), does not seems to affect behavioral gap-detection performance in animals (Radziwon et al. 2015).

Summary

The work reviewed in this section suggests that hyperactivity (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. Hyperactivity 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 hyperactivity also affects 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). Whereas hyperactivity may benefit sound awareness in quiet situations, it appears to impair sound sensitivity when background noise is present (Resnik and Polley 2021). Since listening in acoustically challenging environments relies heavily on spectral, spatial, and periodicity processing, it is not 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 hyperactivity to perception remains underdeveloped.

Open questions and ongoing challenges in the study of hyperactivity

Despite the increasing evidence of hyperactivity following auditory peripheral damage, and the clear hypotheses regarding how perceptual impairments could arise secondary to hyperactivity, 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 hyperactivity 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 hyperactivity are necessary to move this field forward.

Open question 1: what is the functional role of auditory system hyperactivity?

The loss of inhibition giving rise to hyperactivity 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 neuronal activity (Caspary et al. 2008; Sanes et al. 2010; Auerbach et al. 2014; Teichert et al. 2017), by stabilizing and maintaining excitability 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, 2012; Turrigiano and Nelson 2000; 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. 2016a, b; 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 adaptive strategies that help maintain or restore the perception of sound. Homeostatic compensation, however, stabilizes and maintains neuronal excitability without consideration of perceptual consequences (Turrigiano 1999, 2012; Turrigiano and Nelson 2000; 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 hyperactivity in sensory circuits.

Many observations of hyperactivity 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). Whereas 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 hyperactivity in auditory brain regions and the activity 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; Cisneros-Franco and de Villers-Sidani 2019; Thomas et al. 2019b) 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 and hyperactivity?

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 not fully captured by standard hearing assessment tools in humans, such as pure-tone audiometry (Schaette and McAlpine 2011; Plack et al. 2014; but see recent approaches Liberman et al. 2016; Mepani et al. 2020; Parthasarathy et al. 2020). As described above, peripheral damage—including that which arises from sound exposure—may lead to a loss of inhibition and hyperactivity 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 hyperactivity in noise-exposed animals (Hopkins 1994; Olsen 1998; Tsai et al. 2009). We may, thus, expect many humans to exhibit hyperactivity 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; Oliver et al. 2011)—often referred to as enriched acoustic environments—can reduce the damage induced by subsequent traumatic, high-intensity sounds and improve auditory processing. 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, 2007; Norena and Eggermont 2006; Noreña et al. 2006). 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 hyperactivity 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. 2019b). Enriched environmental exposure to a temporally complex sound, compared to a less complex sound, has also been shown to improve temporal processing acuity in the auditory midbrain (Dziorny et al. 2020). 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. 2019b; Dziorny et al. 2020).

Open question 3: how does hyperactivity change as function of hearing loss severity?

Hyperactivity 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, a decrease in inhibition and hyperresponsivity changes as a function of the degree of auditory deprivation (Qiu et al. 2000; Resnik and Polley 2017; Fig. 6). It may be tempting to interpret decreased responsivity to sound following severe cochlear damage as evidence against hyperactivity 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 the 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). However, in the extreme case of complete peripheral damage, signal transduction is lost and auditory cortex becomes non-responsive to sound (Fig. 6).

Thus, hyperresponsivity to sound may only be a useful proxy for hyperactivity when sufficient peripheral integrity

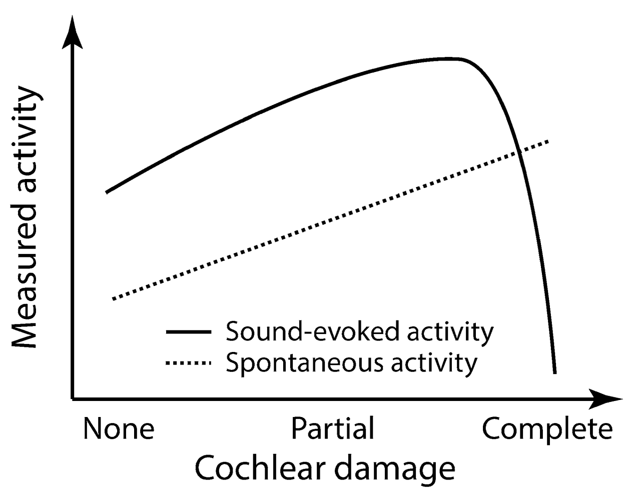

Fig. 6 Hypothetical depiction of auditory cortical activity as a function cochlear damage. The solid line reflects cortical activity measured indirectly using sound stimulation. The dashed line reflects cortical activity measured directly via spontaneous neuronal activity or indirectly via electric stimulation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

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 hyperactivity in auditory cortex persists following complete auditory deprivation is also unclear. Based on research on other biological tissue (Cannon and Rosenblueth 1949), hyperactivity 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, 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 hyperactivity nor of a loss of inhibition. 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 hyperactivity more directly from human listeners is an important first step towards understanding how hyperactivity is shaped by the degree of hearing loss.

Open question 4: how do experimental design choices impact measures of hyperactivity?

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, hyperactive 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 hyperactivity, 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, 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 hyperactivity and neural recovery times, and may come to different conclusions.

This short list of examples is not exhaustive—it simply serves as a reminder that a loss of inhibition and increased activity 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, hyperactivity, and perception.

Summary

In this section, we reviewed open questions in the study of hyperactivity, 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 excitation and Hebbian mechanisms that support the formation of new connections between neurons to hyperactivity 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, hyperactivity, and hyperresponsivity to sound and between experimental factors and hyperresponsivity to sound. These non-linearities pose a challenge for investigations of how hyperactivity interacts with the degree of hearing loss in humans, where hyperactivity 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 activity levels of downstream brain regions in the auditory pathway. In this paper, we have (a) reviewed the causes and neurophysiological mechanisms underlying hyperactivity, showing that hyperactivity does not arise from cochlear damage per se, but rather results from decreased input to the system occurring subsequent to that damage; (b) suggested that hyperactivity 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 hyperactivity, and outlined some of the open questions in the study of hyperactivity in humans. Our hope is that this review provides a foundation from which researchers can develop targeted approaches for investigating hyperactivity in humans.

Author contributions BH had the idea for the article. BH and BEB performed the literature search. BH drafted the manuscript. BH and BEB critically revised the manuscript.

Funding BH was supported by the Canada Research Chair program.

Declarations

Conflict of interest The authors have no conflict of interest/competing interests.

Consent for publication BH and BEB consent to the publication.

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