Viewpoints

The Neural Bases of Tinnitus: Lessons from Deafness and Cochlear Implants

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Subjective tinnitus is the conscious perception of sound in the absence of any acoustic source. The literature suggests various tinnitus mechanisms, most of which invoke changes in spontaneous firing rates of central auditory neurons resulting from modification of neural gain. Here, we present an alternative model based on evidence that tinnitus is: (1) rare in people who are congenitally deaf, (2) common in people with acquired deafness, and (3) potentially suppressed by active cochlear implants used for hearing restoration. We propose that tinnitus can only develop after fast auditory fiber activity has stimulated the synapse formation between fast-spiking parvalbumin positive (PV^+) interneurons and projecting neurons in the ascending auditory path and coactivated frontostriatal networks after hearing onset. Thereafter, fast auditory fiber activity promotes feedforward and feedback inhibition mediated by PV^+ interneuron activity in auditory-specific circuits. This inhibitory network enables enhanced stimulus resolution, attention-driven contrast improvement, and augmentation of auditory responses in central auditory pathways (neural gain) after damage of slow auditory fibers. When fast auditory fiber activity is lost, tonic PV^+ interneuron activity is diminished, resulting in the prolonged response latencies, sudden hyperexcitability, enhanced cortical synchrony, elevated spontaneous γ oscillations, and impaired attention/stress-control that have been described in previous tinnitus models. Moreover, because fast processing is gained through sensory experience, tinnitus would not exist in congenital deafness. Electrical cochlear stimulation may have the potential to reestablish tonic inhibitory networks and thus suppress tinnitus. The proposed framework unites many ideas of tinnitus pathophysiology and may catalyze cooperative efforts to develop tinnitus therapies.

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Introduction

Chronic, subjective tinnitus, an auditory phantom sensation, affects approximately one-sixth of the general population (Shargorodsky et al., 2010). Tinnitus can be triggered by a variety of causes that may act synergistically (Tyler et al., 2008a; Henry et al., 2014; Moller et al., 2015), but hearing loss is the biggest risk factor for tinnitus (Roberts et al., 2010; Knipper et al., 2013; Lanting et al., 2014; Bauer, 2018). The majority of tinnitus researchers assume that tinnitus is linked to damage or dysfunction in the periphery of the auditory system (Demeester et al., 2007). Because tinnitus can occur without hearing threshold elevation (Roberts et al., 2010; Geven et al., 2011; Langers et al., 2012; Lanting et al., 2014) and normal hearing thresholds rely on

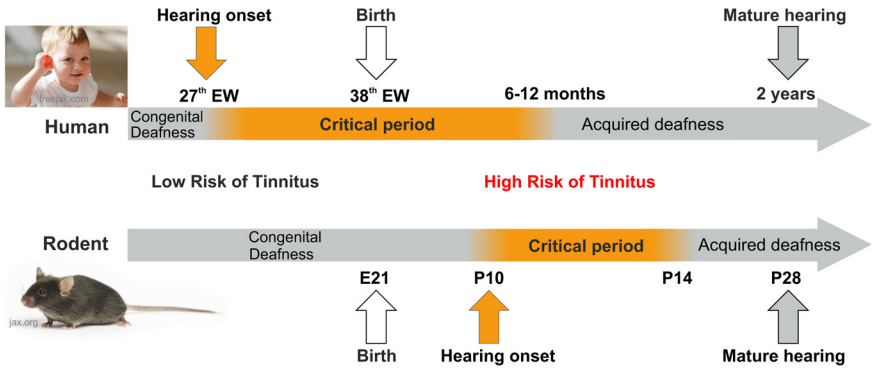

Figure 1. Timing of hearing onset and major maturation steps in the auditory pathway relative to birth. In humans, hearing starts *in utero* at about embryonic week (EW) 27, followed by a critical period with hearing experience. This critical period spans intrauterine and extrauterine periods up to at least 6-12 months. Adult-like, mature hearing is reached 2-3 years after birth. In rodents, hearing starts after birth (embryonal day 21: E21) at postnatal day 10 (P10) followed by at P10 followed by the critical period until ~P14. Mature hearing is reached by ~P28. The risk of tinnitus is high after the critical time period and in acquired deafness.

the proper function of outer hair cells (Dallos, 2008), outer hair cell dysfunction is unlikely to be a primary cause of tinnitus. Instead, deafferentation of inner hair cells by auditory nerve fibers is suggested to be linked to tinnitus in animal models (Müller et al., 2003; Bauer et al., 2007; Roberts et al., 2010; Knipper et al., 2013; Rüttiger et al., 2013; Singer et al., 2013) and in humans (Weisz et al., 2006; Geven et al., 2011; Langers et al., 2012; Boyen et al., 2014; Gilles et al., 2016; Guest et al., 2017; Milloy et al., 2017; Hofmeier et al., 2018). Other risks for tinnitus include anxiety and stress-related disorders (Canlon et al., 2013; Durai and Searchfield, 2016; Mazurek et al., 2017).

From studies on auditory neurons, tinnitus has been linked to hyperexcitability and elevated spontaneous activity in the brain. Such increases in activity are observed, for example, in the cochlear nucleus (Auerbach et al., 2014; Gao et al., 2016), the inferior colliculus (Bauer et al., 2008), the medial geniculate body (Kalappa et al., 2014), and the auditory cortex (AC) (Norena and Farley, 2013; Eggermont and Tass, 2015) after acoustic trauma, ototoxicity, or deafferentation of auditory nerve fibers. There is an ongoing debate about the source of hyperexcitabililty and elevated spontaneous activity, however. Most previous tinnitus literature suggested that tinnitus is the result of homeostatic increases in central neural gain (for review, see Norena, 2011; Schaette and McAlpine, 2011; Schaette and Kempter, 2012; Auerbach et al., 2014; Sedley et al., 2016; Shore et al., 2016; Roberts, 2018; Roberts and Salvi, 2019). In contrast, other studies propose that tinnitus is not related to increased central gain (Zeng, 2013; Möhrle et al., 2019; Sedley, 2019), but instead occurs when auditory input falls short of thresholds for increasing neural gain, so stimulus-evoked responses are diminished in the ascending auditory path (Rüttiger et al., 2013; Singer et al., 2013; Zeng, 2013; Hofmeier et al., 2018; Möhrle et al., 2019). In the present review, we question the previous hypotheses that neural gain is the source of tinnitus, and propose instead that hyperexcitability during tinnitus is the result of a failure to generate central neural gain because of impairment of an inhibitory network that had developed with maturation of fast auditory fibers to enable high stimulus resolution. In this view, a loss of fast auditory fibers would reduce the drive for tonic inhibition in auditory-specific circuits, resulting in the emergence of hyperactivity that underlies tinnitus. Hence, tinnitus may only develop after fast auditory fibers have stimulated the development of tonic inhibition within these auditory-specific circuits and would not develop in persons with congenital deafness. This hypothesis would explain why congenital deafness is rarely associated with tinnitus, whereas acquired deafness is often associated with tinnitus (Eggermont and Kral, 2016). We moreover suggest that fast auditory fibers that mature with sensory experience improve stimulus resolution through brain-derived-neurotrophic factor (BDNF)-dependent synapse formation between fast-spiking parvalbumin-positive (PV^+) inhibitory interneuron complex dendritic networks and pyramidal projection neurons in the ascending auditory path, as shown for the AC (Xu et al., 2010). Thereby the representation of specific auditory stimuli can be integrated in distributed frontostriatal networks that control attention-driven amplification processes. Through the activation of this network, precisely timed, stimulus-driven bottom-up feedforward, and top-down feedback activity can accentuate relevant over irrelevant stimuli by contrast amplification, as we discuss in more detail later in this article. The loss of the critical drive that maintains baseline tonic inhibitory PV^+ network activity may cause an increase in spontaneous firing rates (SFRs) in central auditory circuits and impair input for specific contrast amplification in affected frequency-specific auditory regions, resulting in tinnitus. This view is consistent with various earlier findings that link tinnitus with (1) insufficient gain control, (2) central hyperexcitability, (3) excessive cortical synchrony, elevated γ oscillations and corrupted noise-cancellation, (4) increased spontaneous neural activity generated through stochastic resonance, (5) disrupted functional connectivity between auditory-specific and frontostriatal microcircuits, or (6) amplification of a tinnitus precursor through attention or stress. This view is also consistent with previous findings that suggest that tinnitus can be suppressed by cochlear implant (CI) stimulation or by hearing aids (Punte et al., 2013; Knopke et al., 2017). By bringing together the single parts in this review, we trust that new synergies and mutual scientific exchange will help to develop a cure for tinnitus.

Tinnitus occurs with low prevalence in congenital deafness but with high prevalence in acquired deafness

Rodents are unable to hear when they are born on embryonic day 21, and hearing onset is delayed until postnatal day 10 (P10) (Fig. 1, rodent). This is different from the human fetus, in which hearing starts during embryonic week 27 (Fig. 1, human). After hearing onset, there is a critical period during which hearing experience shapes the acuity and fidelity of hearing (Fig. 1, critical period). In rodents, the critical period extends from P10 to P14 (de Villers-Sidani et al., 2007) and in humans, it likely occurs between the 27th embryonic week and the sixth to 12th month after birth (Sharma et al., 2016).

Auditory experience has been suggested as a possible prerequisite for tinnitus because tinnitus has been reported to be absent in congenital deafness (Eggermont and Kral, 2016). Several studies have surveyed the prevalence of tinnitus in hearing-impaired young adults, and tinnitus does not seem to be problematic in younger children (Baguley and McFerran, 2002; Rosing et al., 2016). In responses to direct questioning, reports of tinnitus are higher in moderately or severely hearing-impaired youth than in

those with profound loss. In addition, those with acquired loss are significantly more likely to report tinnitus (Fig. 1, high risk of tinnitus) than those with congenital hearing loss (Graham, 1987) (Fig. 1, low risk of tinnitus). However, limited data are available on this topic; and in existing studies, it is not always possible to determine when congenital hearing loss occurred. For example, a mid- to late-pregnancy infection, or a peripartum event, such as anoxia or the administration of aminoglycoside antibiotics, may cause early deafening after some weeks or months of intrauterine auditory experience. Two clinical studies, however, indicated that tinnitus may indeed be absent in the population that has had no auditory experience. In children with a Gap junction beta-2 protein (GJB2) mutation, for whom a complete lack of auditory experience can be surmised, there was a near absence of tinnitus (Tsukada et al., 2010). Moreover, a recent study found a relationship between deafness and the absence of tinnitus, even for congenital single-sided deafness (S. Y. Lee et al., 2017). In that study, strikingly, none of the 20 subjects with congenital deafness perceived tinnitus on the affected side (Fig. 1, congenital deafness), whereas 30 of 44 subjects with acquired single-sided deafness did experience tinnitus on the affected side (S. Y. Lee et al., 2017) (Fig. 1, acquired deafness). In contrast to congenitally deaf patients, patients with normal maturation who acquire sudden sensorineural hearing loss often experience tinnitus, with a prevalence of 60%-90%, often on the deaf side (Fig. 1, high risk of tinnitus) (Van de Heyning et al., 2008; Chadha et al., 2009; Eggermont and Kral, 2016).

Based on the findings described above, it was concluded that the development of tinnitus needs to be preceded by auditory experience (Eggermont and Kral, 2016; S. Y. Lee et al., 2017). Specifically, it was suggested that the emergence of tinnitus requires the preexistence of a tonotopic map as a reference for the integration of sensory input to "somatic memory" (Eggermont and Kral, 2016). But the proper topographically ordered connections are established in the auditory pathway well before hearing actually functions (Friauf and Lohmann, 1999; Clause et al., 2014). Additionally, tonotopic maps in the brain persist in mice with profound deafness, independently of whether the hearing loss is acquired or congenital (Babola et al., 2018). Therefore, tonotopy, per se, is unlikely to cause tinnitus. Instead, a sensory experience-dependent maturation step must be required for the emergence of tinnitus.

Maturation steps that require auditory experience

Because hearing appears to be essential for the development of tinnitus, properties that arise after the onset of hearing are more likely to contribute to tinnitus than properties that emerge before hearing onset. One property that develops after hearing onset is the brain's SFR. The developing brain is hyperexcitable because neurons that release γ-aminobutyric acid (GABAergic neurons) are excitatory at this time. The effects of GABA depend on the chloride gradient across the plasma membrane, which in developing neurons favors chloride efflux and depolarization. A maturational shift in chloride transporters is required to reverse the chloride gradient so that GABA becomes inhibitory (Marin and Rubenstein, 2001; Ben-Ari, 2002) (Fig. 2*A*,*B*, green plus signs). This process is predicted to be dependent on BDNF, which has been shown to facilitate the expression of potassium chloride cotransporter 2 (KCC2) (Wardle and Poo, 2003), which contributes to this switch (De Koninck, 2007). This excitatory-to-inhibitory switch in GABAergic signaling occurs after tangentially migrating inhibitory neurons have successfully reached their destinations in higher brain regions, a process accomplished in rodents around birth (Marin and Rubenstein, 2001). In the auditory system, the switch occurs in a region-specific pattern after hearing onset (Kandler and Friauf, 1995; Friauf et al., 2011), possibly driven by sensory experience (Shibata et al., 2004) (Fig. 2*A*,*C*, orange minus signs).

We hypothesize that not hearing experience, per se, but fast auditory processing resulting from maturation of a distinct auditory fiber type after hearing onset is critical for the BDNF- and sensory experience-dependent maturation of inhibitory GABAergic circuits in the auditory system. Whereas at the beginning of hearing onset, auditory fibers with low SFRs (Fig. 2*B*, low-SR, green fiber) and high activation thresholds (Yates, 1991; Merchan-Perez and Liberman, 1996) dominate, after hearing onset, ~60% of auditory fibers develop high SFRs (Fig. 2*C*, high-SR, orange fiber) and low activation thresholds (Merchan-Perez and Liberman, 1996; Glowatzki and Fuchs, 2002; Grant et al., 2010). These high-SR fibers determine the threshold of the summed auditory-nerve response, measured by the compound action potential (Bourien et al., 2014), and are responsible for the shortest-latency auditory responses at any given characteristic frequency. Therefore, fast (high-SR) auditory fibers are suggested to determine perceptual thresholds (Meddis, 2006; Heil et al., 2008). Hence, high-SR auditory fibers likely contribute to lowered thresholds and shortened latency of cortical auditory responses, which can be measured after the sharpening of cortical receptive fields (Fig. 2*C*, cortical resolution⇑) (de Villers-Sidani et al., 2007) at the end of the critical period after hearing onset: between P10 and P14 in rodents (de Villers-Sidani et al., 2007) and between the 27th embryonic week and sixth to 12th months after birth in humans (Neville and Bavelier, 2002). The sharpening of receptive fields, moreover, leads to narrower bandwidth responses, likely as a result of stimulus-evoked release of BDNF from cortical pyramidal neurons, which is suggested to trigger synaptogenesis in a complex network of fast-spiking PV-expressing GABAergic interneurons (PV^+ interneurons) that provide perisomatic and dendritic inhibition to cortical pyramidal neurons (Fig. 2*C*, cortical resolution⇑, BDNF⇑, PV⇑) (Hong et al., 2008; Xu et al., 2010; Lehmann et al., 2012; Griffen and Maffei, 2014). Fast-spiking, PV^+ interneurons play a key role in several higher microcircuit functions, such as feedforward and feedback inhibition, high-frequency network oscillations, and pattern separation. For all of these functions, the fast signaling properties of these neurons play a critical role (Hu et al., 2014, 2018). Notably, fast-spiking PV^+ interneuron networks develop in auditory subcortical and cortical projections with sensory experience (Lohmann and Friauf, 1996; Chumak et al., 2016), as also described for other sensory systems (Itami et al., 2007; Xu et al., 2010; Lehmann et al., 2012; Kimura and Itami, 2019).

In further support of our hypothesis, fast (high-SR) auditory fiber activity was related to the development of perisomatic PV^+ interneuron inhibition and the enlargement of dynamic range of auditory responses after hearing onset (Chumak et al., 2016). Perisomatic PV^+ interneuron activity contributes to feedforward inhibition that narrows the window for temporal summation of EPSPs and action potential initiation in principle neurons (Pouille and Scanziani, 2001) and thereby promotes both sharpening of receptive fields and pattern separation (Leutgeb et al., 2007). Because maturation of fast (high-SR) auditory fiber activity was also linked to enhanced auditory fidelity, including increased inhibitory strength and shortened latencies (Xu et al., 2010; Chumak et al., 2016), we may predict that fast (high-SR) auditory fiber activity also contributes to PV^+ interneuron-mediated feedback inhibition at principal-cell dendrites (Couey

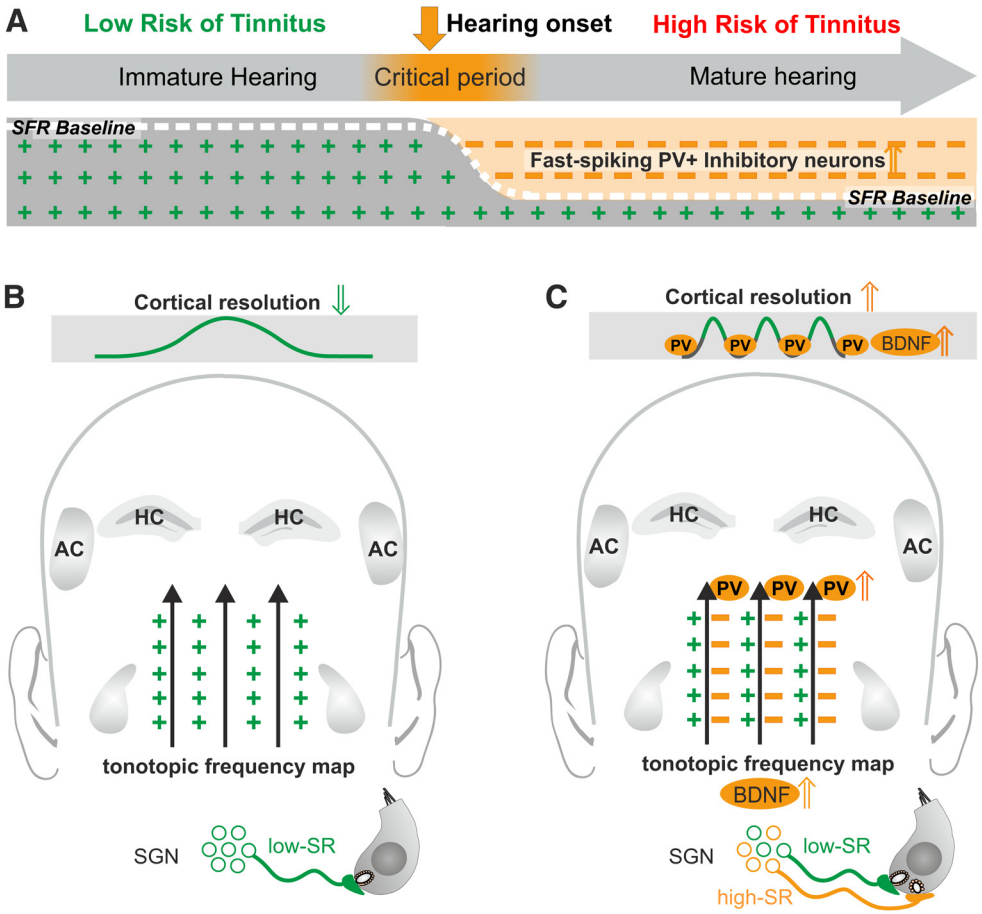

Figure 2. Diagram of auditory excitatory and inhibitory states before (***A***, left, ***B***) and after (***A***, right, ***C***) the critical period. ***A***, Immature hearing and congenital deafness go along with a low risk of tinnitus. In this state, GABAergic neurons still act in an excitatory manner (green +) on the SFR in the brain (white dashed line). When GABA becomes inhibitory after the critical period (orange minus), the lower SFR baseline may initiate a high risk of tinnitus. ***B***, At hearing onset, auditory fibers with low SFRs (low-SR, green) can already be recorded along the tonotopic frequency map (black arrows) when GABAergic neurons in the ascending path are likely still excitatory. At that time, excitation dominates over inhibition (green +) and auditory discrimination capacity is not yet specific for distinct sensory modalities (low cortical resolution, green downward arrow). ***C***, With sensory experience, fast and specific auditory processing evolves with the development of fibers with high-spontaneous rate characteristics (high-SR, orange) and the maturation of inhibitory circuits (fast spiking PV^+ interneuron network, orange minus). The high-SR fibers may drive BDNF secretion from ascending auditory projection neurons up to the AC in a stimulus-dependent way. BDNF regulates perisomatic synaptic contacts between PV-positive interneurons and cortical pyramidal neurons, and sharpens auditory cortical resolution (orange upward arrow), enabling improved task performance. HC, Hippocampus; SGN, spiral ganglion neurons; ↑, increase; ↓, decrease.

et al., 2013), which has been shown to improve stimulus resolution and discrimination above noise in sensory systems (Caraiscos et al., 2004; Hu et al., 2014).

Given that fast inhibitory PV^+ interneurons are critical in generating both γ- (feedforward inhibition) and β-frequency oscillations (feedback inhibition) measured with EEG (Cardin et al., 2009; Sohal et al., 2009; Chen et al., 2017), experiments that used optogenetic disruption of inhibitory networks may help to explain changes in oscillations in tinnitus: Through optogenetic suppression of PV^+ interneuron activity, likely including tonic and phasic activity, increased synchronization of spontaneous activity across a broad frequency range was observed, leading to increased baseline spontaneous γ power and occlusion of changes in evoked γ power (Chen et al., 2017). Interestingly, increased baseline spontaneous γ power linked with reduced evoked γ power was observed in children with deficits in fast auditory processing (Mamashli et al., 2017), strengthening the hypothesis that diminished fast (high-SR) auditory fiber processing might also be able to cause enhanced baseline spontaneous γ power and reduced evoked γ power, a predicted correlate of tinnitus (see Proposed neural correlates of tinnitus reflected in the context of fast auditory processing). Elevated activity in fast-spiking PV^+ interneurons is predicted to play a role in improved task performance and attention-driven contrast amplification (Cardin et al., 2009; Kim et al., 2016; Chen et al., 2017). We therefore suggest that diminished fast (high-SR) auditory fiber activity reduces the ability of listeners to properly attend to relevant stimuli while ignoring irrelevant stimuli (Delano et al., 2007; Nunez and Malmierca, 2007; Wittekindt et al., 2014; Dragicevic et al., 2019), which is another neural correlate of tinnitus (see Proposed neural correlates of tinnitus reflected in the context of fast auditory processing).

It remains to be clarified in future studies whether fast (high-SR) auditory fibers stimulate the maturation of this complex PV^+ interneuron network by activating BDNF promoters and synaptogenesis of fast-spiking PV^+ interneuron with projecting neurons, as has been suggested to occur in auditory and other sensory cortices (Itami et al., 2007; Xu et al., 2010; Lehmann et al., 2012; Kimura and Itami, 2019) or if BDNF acts via the facilitation of inhibitory actions by GABA (De Koninck, 2007). Regardless, both the maturation of fast auditory fibers that drive BDNF promoters and BDNF-driven facilitation of GABA-mediated inhibition would lower the baseline SFR in pyramidal neurons in cortical and functionally connected networks with

auditory experience (Fig. 2*A*, SFR baseline, white dashed line ⇓). The initial hyperexcitability in these circuits resulting from GABAergic neurons being excitatory would thereby be reduced and the fidelity and specificity of responses to auditory input would become enhanced, as hypothesized for the auditory system (Chumak et al., 2016; Matt et al., 2018) and cerebellum (Duguid et al., 2012).

Regarding the lower risk of tinnitus in congenital deafness and the prediction that tinnitus requires auditory experience in children (see above), it is interesting to consider when fast (high-SR) auditory fibers and PV^+ interneurons, whose activity is reflected in γ- and β-frequency oscillations (Cardin et al., 2009; Sohal et al., 2009; Gill and Grace, 2014; Chen et al., 2017), might mature in children. γ oscillations develop in humans between the onset of hearing function before birth, approximately between the 27th embryonic week and sixth to 12th months after birth (Neville and Bavelier, 2002), with predictions that increased γ oscillations, associated with feedforward inhibition, precede the development of increased β oscillations (reflecting feedback inhibition) before 6 months after birth (Sowell et al., 2001; Ortiz-Mantilla et al., 2016). From sixth months onwards, the development of functional connectivity in children's brains proceeds, becoming more clustered and specific for sensory modalities (Sowell et al., 2001; Neville and Bavelier, 2002; Ortiz-Mantilla et al., 2016), a process that is paralleled by enhanced speech comprehension in noise (Obleser et al., 2007; Youssofzadeh et al., 2018) and improvement of attention-driven contrast amplification for auditory stimuli, improved auditory discrimination capacity, and improved temporal discrimination (Sowell et al., 2001; Miller and Buschman, 2013) (Fig. 2*C*, cortical resolution). We thus can conclude that maturation of fast (high-SR) auditory fiber processing and inhibitory PV^+ interneuron microcircuits mature in the first months after birth, providing a good rationale for tinnitus occurring with low prevalence in congenital deafness but with high prevalence in acquired deafness (see above).

We conclude that the onset of fast (high-SR) auditory nerve fiber activity with the onset of auditory experience stimulates the development of a feedforward PV^+ interneuron network that is a prerequisite for the development and maintenance of feedback inhibitory PV^+ interneuron networks in auditory-specific circuits. The lack of fast auditory processing distinguishes congenital deafness, with a low risk of tinnitus (Fig. 2*B*), from mature acquired hearing loss, with a high risk of tinnitus (Fig. 2*C*).

Proposed neural correlates of tinnitus reflected in the context of fast auditory processing

We next reflect on the various predicted neural correlates of tinnitus in the context of fast (high-SR) auditory nerve activity and its predicted functions for central auditory processing described above.

Neural gain

Most previous tinnitus literature suggested that tinnitus is the result of homeostatic increases in central neural gain (see Introduction). We argue against the hypothesis that tinnitus results from neural gain-related hyperexcitability, instead suggesting that central neural gain describes a compensating central response to hearing loss that is not related to tinnitus, as explicated in the following. Central neural gain mechanisms typically include memory-dependent homeostatic modifications to restore the overall firing rate to its baseline or "setpoint" (Barnes et al., 2015; Gainey and Feldman, 2017). Considering that tonic PV^+ interneuron activity may set baseline levels for homeostatic modifications, as discussed above, central neural gain would keep tonic PV^+ interneuron network activity, first established with auditory experience, intact. This may be different in the case of tinnitus, as will be discussed later in this review.

Central neural gain, which aims to restore an overall stable firing rate in neural networks after auditory deprivation (Fig. 3*A*, Neural gain⇑), is predicted to require the strengthening of synapses via a learning-dependent, positive feedback cycle (for review, see Davis and Bezprozvanny, 2001; Rich and Wenner, 2007; Turrigiano, 2012). The occurrence of this in the auditory system can be concluded from the observation of compensating auditory output activity following reduced auditory input after mildly traumatic (100 dB SPL) sound exposure in mice. This neural gain is linked with elevated hippocampal long-term plasticity and with altered PV^+ interneuron labeling and enhanced BDNF promoter activity in auditory and hippocampal pathways (Matt et al., 2018). Such a complex brain response after auditory trauma is indicative of a positive feedback cycle that includes coactivation of auditory and frontostriatal circuits (for review, see Irvine, 2018b). Compensating central neural gain has moreover been observed after traumatic sound exposure in animals that did not exhibit tinnitus (Möhrle et al., 2019). Here, the restored late auditory brainstem response (ABR) ABR wave IV was linked with shortened response latencies (Möhrle et al., 2019), revealing that central neural gain may include shorter response latency and increased population-discharge synchrony, which are characteristics of attention-driven contrast amplification processes (Siegle et al., 2014; Kim et al., 2016; Chen et al., 2017; Galuske et al., 2019). We therefore propose that central neuron gain, and likewise, attention-driven contrast amplification of auditory responses, involves coactivation of auditory and frontostriatal regions, such as the following: (1) basal forebrain, to accentuate particular auditory stimuli (Fig. 3*A*) (Kilgard et al., 2002; Kraus and White-Schwoch, 2015; Irvine, 2018a); (2) inferior frontal gyrus activity (Fig. 3*A*), to distinguish new or deviant signals from previous ones (Schonwiesner et al., 2007; Malmierca et al., 2014); (3) hippocampus, to extract and memorize the behaviorally relevant signal (Kraus and White-Schwoch, 2015; Weinberger, 2015; Irvine, 2018a) and synaptic-adjusted strength (Fig. 3*A*, hippocampus); and (4) dlPFC and mPFC (Fig. 3*A*), to balance attention-driven plasticity responses (de Kloet, 2014; Irvine, 2018a; Viho et al., 2019) by inhibiting or enhancing stress responses (Sullivan and Gratton, 2002). We moreover suggest that only after auditory experience has enabled fast (high-SR) auditory fibers to stimulate the development of PV^+ inhibitory microcircuits, can BDNF promoters that are specifically activated by fast (high-SR) auditory fiber activity (Fig. 3*A*, BDNF⇑) drive the required compensating PV^+ microcircuit changes in the frontostriatal path, leading to restored ABR wave IV responses (neural gain) (Matt et al., 2018). This positive feedback cycle is not sufficient for initiating tinnitus, however, as suggested in previous studies (Knipper et al., 2013; Zeng, 2013; Sedley, 2019). Previous findings that link neural gain to tinnitus (Roberts et al., 2010; Norena, 2011; Schaette and Kempter, 2012; Shore et al., 2016) may be explained by unmatched hearing impairment between participants with and without tinnitus (Adjamian et al., 2009), or by the co-occurrence of tinnitus with decreased sound tolerance (hyperacusis) (Melcher et al., 2009; Hickox and Liberman, 2014; Auerbach et al., 2019; Möhrle et al., 2019).

In conclusion, we suggest that active feedforward and feedback PV^+ interneuron microcircuits, first established with the emergence of fast (high-SR) auditory fiber activity during auditory experience, form the base substrate on which overall firing

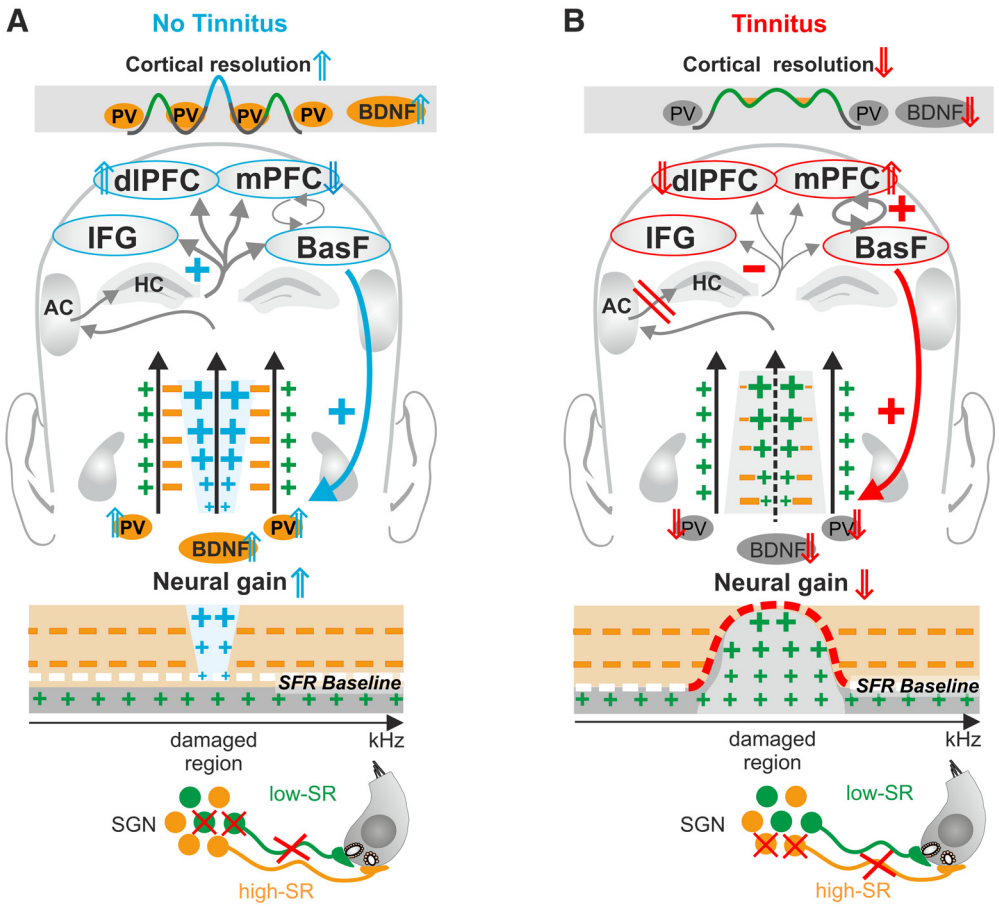

Figure 3. Predicted auditory gating in the absence (***A***) and presence (***B***) of tinnitus. ***A***, Auditory gating may lead to central neural gain, preventing tinnitus after mild acoustic trauma (damaged region). High-SR fiber-driven auditory processing may cause activity-dependent BDNF secretion from auditory-specific synapses. This context-specific signaling can be strengthened (blue +) in a memory-dependent positive feedback cycle requiring activity in the basal forebrain (BasF, blue curved arrow), inferior frontal gyrus (IFG), and dlPFC and mPFC. This may lead to enhanced output activity relative to reduced input (Neural gain). ***B***, Failing central neural gain is predicted to result in tinnitus after severe or stressful acoustic trauma. The lack of high-SR fiber-driven auditory input in the damaged region critically reduces context-specific recruitment of activity-dependent BDNF, possibly essential to maintaining inhibitory, tonic PV-positive interneuron network activity. The baseline levels of spontaneous firing in affected frequency regions is enhanced by hyperexcitability (green + below red dashed line). The prefrontal stress control becomes unbalanced (mPFC up), which leads to uncoupling of auditory-specific and frontostriatal brain regions, resulting in the accentuation of irrelevant hyperexcitability-derived neuronal activity that would otherwise be ignored (tinnitus).

rates can be enhanced after hearing onset in response to hearing loss. However, this memory-dependent positive feedback cycle that leads to enhanced output activity after reduced auditory input (neural gain) is unlikely to be sufficient for tinnitus.

Loss of GABAergic inhibition in tinnitus

Numerous studies have suggested that the hyperexcitability linked to tinnitus is associated with acute GABAergic disinhibition in the ascending auditory pathway (Norena, 2011; Schaette and McAlpine, 2011; Schaette and Kempter, 2012; Norena and Farley, 2013; Auerbach et al., 2014; Kalappa et al., 2014; Eggermont and Tass, 2015; Gao et al., 2016; Sedley et al., 2016; Shore et al., 2016; Roberts, 2018; Roberts and Salvi, 2019). From a traditional position, this hyperexcitability has most often been interpreted as resulting from a central neural gain response (see Introduction). We go further in suggesting that the hyperexcitability rather results from critical loss of fast (high-SR) auditory drive that triggers reemergence of GABAergic excitation, instead of GABAergic inhibition (Ben-Ari, 2002).

A notable facet of tinnitus is its rapid onset after acquired deafness. For example, an immediate onset of tinnitus occurred in 60%-90% of cases in children with CIs when the implants were not in use (Van de Heyning et al., 2008; Chadha et al., 2009). Likewise, acquired monaural or binaural sudden sensory hearing loss in rodents has been linked to disinhibition in nearly all ascending auditory nuclei (Abbott et al., 1999; Milbrandt et al., 2000; Mossop et al., 2000). In some cases in rodents, the generation of hyperexcitability was observed in auditory nuclei within a few minutes of deafening or nerve transection (McAlpine et al., 1997; Mossop et al., 2000). Thus, the time frame of hyperexcitability associated with acquired deafness in rodents is congruent with the fast onset of acute tinnitus after CIs are turned off in humans.

Given the rapid time scale (minutes to hours) of activity-dependent functional downregulation or upregulation of KCC2 (Khirug et al., 2010; H. H. Lee et al., 2011; Nardou et al., 2011), a reemergence of GABAergic excitation can occur within the time frame of acute tinnitus. Furthermore, auditory nerve transection has been shown to lead to a decline of KCC2 and a reemergence of depolarizing GABAergic signaling (Tighilet et al., 2016). To date, however, this has only been analyzed 3-30 d after auditory-nerve transection (Tighilet et al., 2016). Considering that, in the auditory system, the GABAergic switch from depolarization to inhibition occurs in a region-specific pattern after hearing onset (Kandler and Friauf, 1995; Friauf et al., 2011) and BDNF-driven facilitation of inhibitory signaling by GABA (De Koninck, 2007) may be maintained through critical fast auditory fiber drive (see

above), future studies are urgently needed to determine whether loss of fast (high-SR) fiber processing causes hyperexcitability in affected frequency regions by inducing reemergence of depolarizing GABAergic signaling, thus leading to tinnitus.

Excessive cortical synchrony and enhanced γ oscillations in tinnitus

Hyperexcitability and a rapidly enhanced SFR during chronic tinnitus have both been linked to neuronal bursting and excessive neuronal synchrony in the AC (Norena and Farley, 2013; Eggermont and Tass, 2015). This abnormal neural synchrony has been suggested to be confined to specific oscillation frequency bands (Eggermont and Tass, 2015), particularly to enhanced spontaneous γ oscillations (30-80 Hz), which were observed in tinnitus patients (Weisz et al., 2007; Ortmann et al., 2011; Vanneste et al., 2019) and in animal models of tinnitus (Tziridis et al., 2015). Currently, the tinnitus theory of thalamocortical dysrhythmia describes enhanced γ oscillations in tinnitus patients as an overactive feedback loop (De Ridder et al., 2015; Sedley, 2019; Vanneste et al., 2019). But we suggest that increased cortical synchrony in tinnitus might result from underactive, rather than overactive feedback inhibition, specifically from underactive tonic PV^+ interneuron activity in auditory microcircuits. We reason that, during tinnitus, a pathologic reduction of tonic (perisomatic) inhibition of cortical pyramidal neurons by monosynaptically coupled PV^+ interneurons in auditory circuits (Fig. 3*B*, PV⇓) might diminish feedback inhibition. Under these conditions, pyramidal neurons would fire synchronously and independently of input. Such a reduction of tonic inhibition mediated by PV^+ interneurons leads to a rapid increase in bursting and a reduced signal-to-noise ratio in neurons in the cerebellum (Duguid et al., 2012) and has been discussed in the context of excessive cortical synchrony shown for epilepsy (Rossignol et al., 2013; Hsieh et al., 2017). Moreover, diminished activity in tonic fast-spiking PV^+ interneuron networks was shown in rodent models (Lodge et al., 2009; Gill and Grace, 2014) and in children with fast auditory processing deficits (Mamashli et al., 2017) linked with enhanced baseline spontaneous γ power and reduced evoked γ power. The same neurobiological deficits that lead to enhanced baseline spontaneous γ power in children with fast auditory processing deficits (Mamashli et al., 2017), as is autism spectrum disorder, is also associated with elevated gap-discrimination thresholds and a diminished ability to detect short gaps (Foss-Feig et al., 2017), an often mentioned phenotypical characteristic of tinnitus (Fournier and Hebert, 2013; Lobarinas et al., 2013; Galazyuk and Hebert, 2015).

We therefore suggest that the excessive cortical synchrony and enhanced spontaneous γ oscillations observed in tinnitus patients and tinnitus animal models (Weisz et al., 2007; Ortmann et al., 2011; Tziridis et al., 2015; Vanneste et al., 2019) may be related to reduced tonic activity in PV^+ interneuron microcircuits resulting from critical diminution of fast (high-SR) auditory fiber drive.

Stochastic resonance as a putative cause of tinnitus

A predicted noise source located within the somatosensory system has been suggested to drive a stochastic resonance mechanism at the level of the dorsal cochlear nucleus during tinnitus (Krauss et al., 2016, 2017). Stochastic resonance is a phenomenon that may occur whenever noise helps to lift a subthreshold input signal above a threshold. This noise source was hypothesized to be upregulated, for example, following reduced cochlear input, and to contribute to central hyperexcitability that on short time scales of milliseconds to seconds could be amplified through neural gain and thereby contribute to a tinnitus percept (Krauss et al., 2016, 2017). Within our proposed framework, we suggest that the noise source that lifts SFR above threshold results from elevated SFRs in dispersed auditory-specific regions as a consequence of critically reduced fast auditory processing and loss of tonic PV^+ interneuron activity in auditory microcircuits. In such cases, the stimulus resolution and specificity for the particular sensory modality would be reduced and stochastic resonance may manipulate the excitability at the level of the dorsal cochlear nucleus.

Disrupted auditory/frontostriatal connectivity and impaired noise cancellation as correlates of tinnitus

Numerous studies have suggested that dysregulation in frontostriatal brain regions and the limbic system is a neural correlate of tinnitus (Muhlau et al., 2006; Vanneste and De Ridder, 2012; Schmidt et al., 2017). More specifically, disruption of a frontostriatal network has been suggested to contribute to tinnitus by impairing "noise cancellation" (Rauschecker et al., 2015).

We here suggest that a dysregulation of frontostriatal microcircuits in tinnitus can be well explained through reduced tonic activity in PV^+ interneuron microcircuits that are diminished after critical loss of fast (high-SR) fibers. A critical reduction of fast (high-SR) auditory processing was suggested to be a correlate of tinnitus (Knipper et al., 2013; Hofmeier et al., 2018; Möhrle et al., 2019), as it is expected to impair fast communication between auditory-specific and frontostriatal regions and would therefore diminish memory-dependent adjustment of stimulus-evoked responses following, for example, acoustic trauma. This was verified in tinnitus patients through a reduced and delayed late ABR wave V linked to reduced sound-evoked blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) activity in the AC (Hofmeier et al., 2018; Koops et al., 2020), reduced functional connectivity observed during sound-evoked activity (Boyen et al., 2014; Lanting et al., 2014), and reduced resting-state functional connectivity (r-fc)MRI connectivity between auditory-specific brain regions and frontostriatal regions (Leaver et al., 2016; Hofmeier et al., 2018).

Disrupted functional connectivity between auditory-specific and frontostriatal regions (Fig. 3*B*) is expected to result in a breakdown of contrast amplification, which accentuates relevant over irrelevant stimuli (Delano et al., 2007; Dragicevic et al., 2019). Importantly, contrast amplification relies on an intact temporal, top-down feedback circuit and on intact fast PV^+ interneuron activity (Cardin et al., 2009; Kim et al., 2016; Chen et al., 2017). As a result of critically impaired fast (high-SR) auditory fiber processing and the resulting diminished drive to tonic inhibitory PV^+ interneuron microcircuits (see above), central hyperexcitability in deprived frequency regions may occur. Because this hyperactivity cannot be suppressed through contrast amplification processes, it results in the perception of phantom sounds (tinnitus).

In summary, critical reduction in fast (high-SR) auditory fiber processing after auditory trauma can reduce functional connectivity between auditory-specific regions and frontostriatal microcircuits and thereby impair neural processing that allows one to ignore spurious activity in the deprived auditory regions.

Impaired attention/stress control as a correlate of tinnitus

In tinnitus patients, a tinnitus precursor has been suggested to exist, but it is normally ignored as imprecise evidence against the prevailing percept of "silence" (Sedley et al., 2016). This

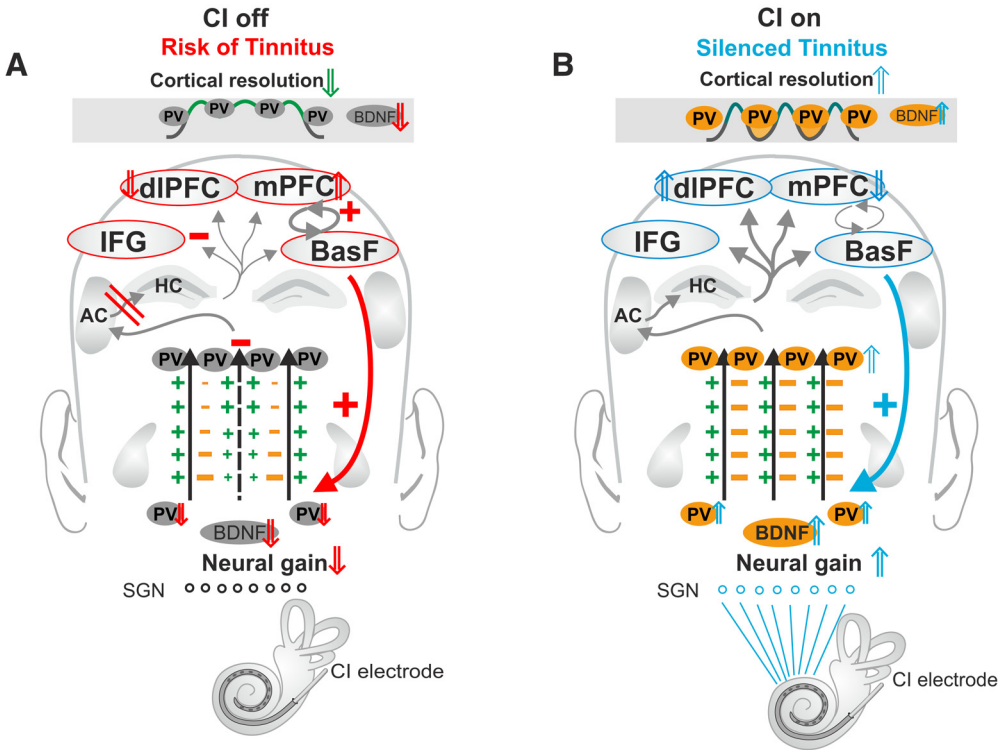

Figure 4. Predicted auditory processing states after cochlear implantation. ***A***, CI off. ***B***, CI on. ***A***, Tinnitus occurs with high prevalence when congenital deafness is treated with a CI and the implant is not in use. Under these conditions, the activity fails to serve as the driving force for context-specific secretion of BDNF. When switching off the implant, initial hyperexcitability would reemerge and on loss of auditory-specific control of frontostriatal coupling would lead to accentuation of irrelevant neural activity in deprived regions basal forebrain (BasF, red curved arrow) leading to Risk of Tinnitus. ***B***, With electrical stimulation, the driving force for context-specific secretion of BDNF may be partially reinstalled. The initial hyperexcitability would be suppressed in deprived regions as irrelevant neuronal information (Silenced Tinnitus).

precursor is amplified (1) through focused attention (Sedley et al., 2016); (2) through fear, anxiety, or stress (Jastreboff et al., 1996); or (3) through a combination of these facilitators that influence individual tinnitus severity, depending on the context of each individual's culture and experience (Searchfield, 2014).

The conscious perception of a tinnitus precursor through focused attention has been discussed in the context of a prediction error in auditory sensation (Sedley et al., 2016; Hullfish et al., 2019). Auditory predictions can only be made, however, after learning about predictable, relevant, auditory signals as distinct from those that are irrelevant. The remembrance of predictable stimuli requires fast (high-SR) auditory fiber activity and maturation of PV^+ interneuron networks that develop only with sensory experience. We hypothesize that a prediction error might be caused by hyperexcitability resulting from impaired tonic PV^+ interneuron activity. This hyperexcitability produces activity that cannot be suppressed by contrast amplification processes, as discussed in the previous section (Fig. 3*B*, impaired SSR baseline, red dashed line).

In the Jastreboff Neurophysiological Model of tinnitus, fear, anxiety, or stress is predicted to be involved in the emergence of "pre-tinnitus activity" that, in subjects without symptoms, is typically ignored (Jastreboff et al., 1996). We suggest that elevated hyperexcitability following the loss of fast (high-SR) auditory fiber processing can lead to imbalanced stress control by disturbing functional connections between auditory-specific regions and the medial prefrontal cortex (mPFC) and dorsolateral prefrontal cortex (dlPFC). While mPFC is assumed to play a role in the activation of stress responses, dlPFC has been found to be linked to inhibition of stress responses (McKlveen et al., 2016). Correspondingly, it was observed that, during tinnitus, resting-state connectivity involving mPFC and dlPFC was disturbed (Schecklmann et al., 2012; Leaver et al., 2016; Hofmeier et al., 2018) (Fig. 3*B*, mPFC⇑, dlPFC⇓).

Conscious percepts of sound may be encoded not only in the AC but also in PFC regions (de Lafuente and Romo, 2005). Unbalanced PFC activity might impact the tinnitus percept itself. According to this view, the observed reduction in selective attention for stimuli outside the tinnitus frequency, but increased vigilance for sounds approximating the tinnitus frequency seen in tinnitus patients (Mazurek et al., 2017; Brozoski et al., 2019) can be considered to be a response to a critically diminished auditory-specific drive after reductions in fast (high-SR) fiber activity and subsequent reduction of PFC-dependent contrast amplification of auditory information (Fig. 3*B*, red curved arrow).

Finally, the individual variability of stress sensitivity might contribute to the observed individually high variability of and susceptibility to tinnitus (Searchfield, 2014; Durai et al., 2017) through, for example, a predicted stress vulnerability for auditory fibers (Singer et al., 2018) or an individual variability in the apparent high metabolic vulnerability of particular PV^+ interneuron synapses (Kann, 2016).

In summary. in tinnitus patients, impaired PFC-triggered attention/stress control following reduced fast (high-SR)-auditory fiber activity may be linked to a reduced ability to habituate to, or ignore, enhanced hyperexcitability in critically deprived frequency regions.

Tinnitus can be suppressed when CIs are turned on but induced when turned off

CIs are the most successful treatment of choice for auditory rehabilitation of patients with severe to profound sensory

deafness (Kral and O'Donoghue, 2010; Wilson, 2017). Electrical stimulation of the auditory nerve via CIs probably reestablishes crucial central functions for fast auditory processing by initiating activity in high-SR fibers. This must be concluded from the success in achieving nearly normal speech and language development in congenitally deaf children (Rajan et al., 2018; Albalawi et al., 2019). This partial implementation of fast auditory processing through CIs may also be reflected in the observed shortened response-onset latencies observed after cochlear electrode implantation in cats (Tillein et al., 2016).

Strikingly, in children implanted between 3 and 15 years, tinnitus occurred most commonly on the implanted side when the implants were not in use (e.g., in bed at night) (Chadha et al., 2009). The incidence of tinnitus is 70%–90% of cases when a CI, implanted following severe bilateral hearing loss, is turned off (Baguley and Atlas, 2007; Ramakers et al., 2015) (Fig. 4*A*, CI Off: Risk of Tinnitus). In contrast, increasing evidence suggests that, on full-electrode stimulation through bilateral CI implants, tinnitus is suppressed (Fig. 4*B*, CI On: Silenced Tinnitus) (Baguley and Atlas, 2007; Tyler et al., 2008b; Punte et al., 2013; Knopke et al., 2017). Also, in patients with unilateral hearing loss, the implantation of a CI suppressed tinnitus (Punte et al., 2013). When tested in their capacity to suppress tinnitus, electric-acoustic stimulation (Mertens et al., 2018; Pillsbury et al., 2018; Li et al., 2019), as well as hearing aids (Searchfield et al., 2010; Shekhawat et al., 2013), have resulted in at least transient tinnitus relief.

We therefore predict that ongoing electrical stimulation of the auditory pathway may be a prerequisite for the suppression of tinnitus. In the future, either persistent stimulation near threshold or stimulation of frequency regions higher than 8 kHz (Levy et al., 2015), which are often not reliably covered in hearing aids or CI, should be investigated as a driving force to maintain or reestablish tonic PV^+ interneuron activity in auditory-specific microcircuits. Thereby appropriate activities for auditory-specific contrast amplification may be reinstated.

In summary, auditory experience through initial CI stimulation is potentially sufficient to drive feedforward and feedback PV^+ interneuron microcircuits in auditory-specific circuits, and this may be a prerequisite for a tinnitus percept to occur in a deaf ear when the CI is turned off. Electrical stimulation of the active CI is however essential to suppress the tinnitus percept.

Conclusion and future perspectives

In conclusion, we consider that congenital deafness (with a low risk of tinnitus) differs from acquired deafness (with high risk of tinnitus). With acquired deafness, the maturation of fast (high-SR) auditory fiber processing and emergence of specific inhibitory PV^+ interneuron microcircuits, essential for accentuation of relevant over irrelevant auditory stimuli, have already taken place. This maturation does not occur in congenital deafness because of the lack of auditory experience. In this view, fast (high-SR) auditory fiber characteristics developing after hearing onset provide the drive to establish feedforward and feedback PV^+ interneuron microcircuits and to maintain feedback PV^+ interneuron microcircuits required for memory-linked reinforcement processes. Upon critical loss of fast (high-SR) auditory fiber processing, hyperexcitability reemerges through loss of tonic PV^+ interneuron activity and reversion to depolarizing GABAergic signaling. Tinnitus sufferers cannot ignore the auditory percepts resulting from this hyperexcitability, and this promotes further alertness to the phantom noise (Figs. 3*B*, 4*A*, red curved arrow, tinnitus).

Fast (high-SR) auditory fiber processing cannot be lost in either congenital bilateral or single-sided deafness because it was never established. Upon cochlear implantation, however, part of the fast auditory processing circuit may develop or be reestablished, albeit with lower resolution (Fig. 4*A*, Risk of Tinnitus). In CI-ON mode, electrical stimulation through CI may be able to install context-specific recruitment of contrast amplification mechanisms, enabling the suppression of tinnitus (Fig. 4*B*, Silenced Tinnitus).

The present article is premised on the hypothesis that various tinnitus subtypes and mechanisms have a final common pathway that acts between the onset of hearing loss and the appearance of the tinnitus percept. Future studies should investigate whether other tinnitus etiologies (Henry et al., 2014; Moller et al., 2015) may be related to the framework suggested here. In this context, (1) the extreme sensitivity and vulnerability of particular inhibitory PV^+ interneuron synapses to any metabolic fatigue or shortfall (Kann, 2016), or (2) the observation that on injury/trauma or glial inflammation a pathologic GABA signaling, that is, excitatory instead of inhibitory (Shih et al., 2017), should be considered as triggers for tinnitus.

In a unified effort across the tinnitus community, tinnitus research (1) could focus on whether a selective loss of one population of auditory nerve fibers (low-SR or high-SR) can explain why some people acquire tinnitus and other do not; (2) may investigate the fragility of fast (high-SR) auditory fiber processing under stress, comorbidities, traumatic, or inflammatory events; (3) should search for pharmaceutical or neuromodulatory tools that enable noninvasive reinstatement of a driving force to maintain feedback fast-inhibitory PV^+ interneuron microcircuits and feedback control of frontostriatal, attentional and stress-controlling circuits; (4) might explicitly analyze the restorative capacity of the identified feedback mechanisms through noninvasive neurostimulation devices, customized sound therapies, CIs, or medications; and (5) explore the relationship between positive effects of CI and cognition (Ramakers et al., 2015; Bruggemann et al., 2017; Knopke et al., 2017) in the context of fast (high-SR) auditory fiber processing and suppression of tinnitus and other comorbidities.

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