Neural plasticity and its initiating conditions in tinnitus

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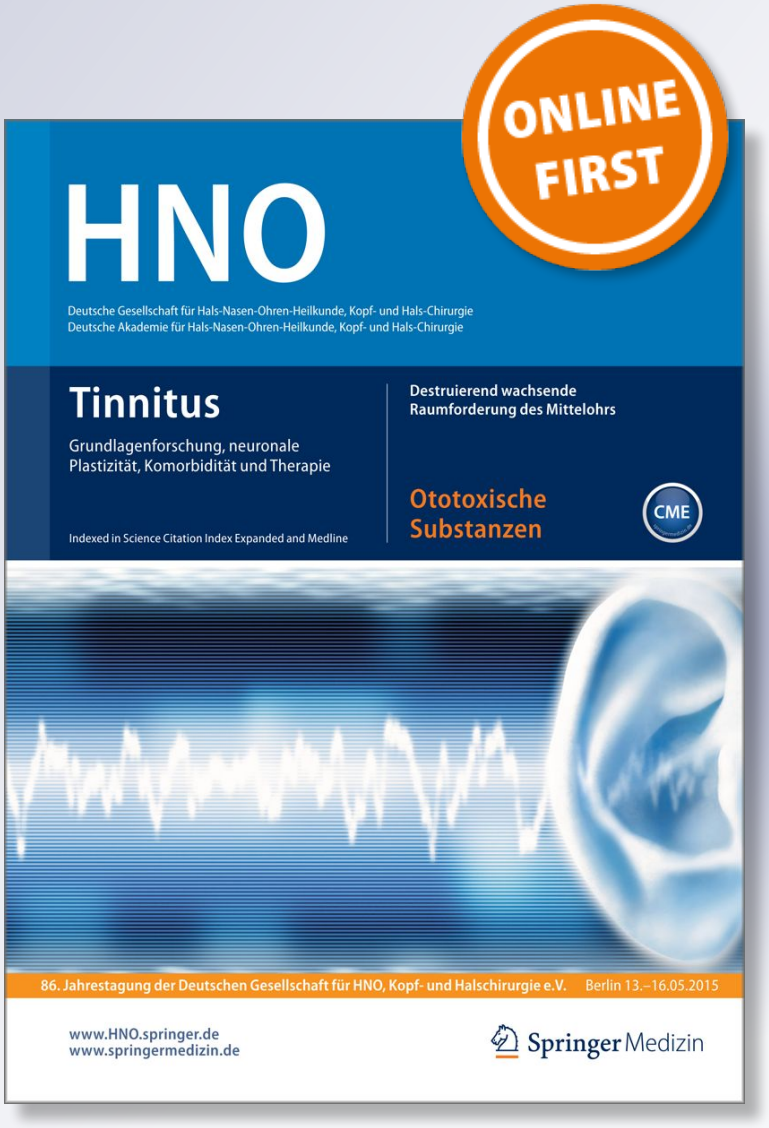

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Background

It has often been observed that tinnitus percepts and the circumstances associated with their onset are to some degree variable between individuals. While it is important to acknowledge this variability and memorable unique cases that may be related to medical disease, it is nonetheless true that most chronic tinnitus sufferers describe their tinnitus as a continuous tonal, ringing, or hissing sound, and that hearing impairment measured by the clinical audiogram up to 8 kHz is present in up to 90% of cases [15]. Nonetheless, tinnitus without audiometric hearing loss needs to be explained, as does the absence of tinnitus in many individuals where such hearing loss is present. Recent research findings suggest that some if not many of these cases could reflect cochlear changes that are not detected by threshold measurements. Deafferentation resulting from cochlear pathology is known to activate forms of neural plasticity in auditory pathways that appear to underlie tinnitus percepts and associated conditions including hyperacusis and impaired auditory temporal processing. In this article, I give a brief overview of these lines of evidence and suggest how research on the mechanisms underlying tinnitus may provide insight into normal auditory information processing.

Deafferentation is an initiating condition

Recent animal studies have shown that noise trauma of an intensity similar to that encountered in some recreational and industrial environments can induce neuropathic injuries in the cochlea that are not expressed in hearing thresholds, but rather exhibit themselves when suprathreshold hearing is tested [9]. In these studies, a level of noise exposure was used that produced a temporary threshold shift but no permanent damage to the cochlear transduction mechanism; inner (IHC) and outer (OHC) hair cells on the basilar membrane of the inner ear and their associated stereocilia were normal, as determined by confocal imaging. However, synapses connecting auditory nerve fibers (ANFs) to the IHCs are more vulnerable to noise trauma as well as to the effects of aging. Especially vulnerable are synapses on ANFs with high thresholds for depolarization (HT ANFs) and high-frequency tuning. This pattern of synaptic loss is relevant to tinnitus without threshold shift, because its presence would not affect the detection of low-level sounds (thus exempting the audiogram) but would affect ANFs tuned to high frequencies, which is where tinnitus percepts lie in these and other tinnitus cases [4]. The presence of hidden hearing loss in tinnitus is supported by two reports that wave I of the auditory brainstem response (ABR) evoked by clicks >80 dB SPL is reduced in tinnitus sufferers with normal audiograms compared with normal-hearing controls [5, 18], although one recent study did not confirm this result. By contrast, the later occurring wave V reflecting processing in the auditory midbrain was either normal or enhanced in the tinnitus subjects of these studies [5, 18], revealing compensatory changes that may underlie decreased sound level tolerance reported in tinnitus sufferers with normal audiograms [6]. Mechanisms of homeostatic and/or Hebbian plasticity are believed to underlie these effects, which reflect increased "central gain" in auditory pathways. Hearing loss arising from HT ANF synaptopathy has been called "hidden hearing loss," because it will not appear in the clinical audiogram [9].

While this evidence suggests that synaptic loss affecting HT ANFs may be present in tinnitus without threshold

Abbreviations

A1	Primary auditory cortex
A2	Nonprimary auditory cortex
ABR	Auditory brainstem response
AM	Amplitude modulation
ANF	Auditory nerve fiber
CN	Cochlear nucleus
DCN	Dorsal cochlear nucleus
EEG	Electroencephalography
EFR	Envelope following response
HSR	High spontaneous rate (ANFs)
IC	Inferior colliculus
HL	Hearing level
HP	Homeostatic plasticity
HT	High threshold (ANFs)
IHC	Inner hair cell
LT	Low threshold (ANFs)
OHC	Outer hair cell
PTS	Permanent threshold shift
SFR	Spontaneous firing rate
SPL	Sound pressure level
STDP	Spike-timing-dependent plasticity
TTS	Temporary threshold shift

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shift, it should be noted that synaptopathy affecting low-threshold (LT) ANFs can also be hidden from the audiogram. This is because hearing thresholds are not elevated as long as at least ~20% of IHCs remain intact. Paul and coworkers [12] applied cochlear modeling using a well-established model of the auditory periphery to investigate the putative contribution of both fiber types to individual differences in temporal processing ability in young adults with and without tinnitus, all of whom had normal audiometric hearing. Subjects were first required to detect the presence of amplitude modulation (AM) in a 5-kHz tone embedded in background noise intended to degrade the contribution of LT fibers, such that AM coding was preferentially reliant on HT fibers. The 5-kHz frequency was chosen because this was in the tinnitus frequency region of the tinnitus subjects. Subsequently, neural coding in the auditory midbrain was measured using the "envelope following response" (EFR), a midbrain response recorded by electroencephalography (EEG) that has been shown to correlate with temporal processing skills in normal-hearing listeners and to be sensitive to ANF synaptopathy induced in animals [20]. EFRs were measured in background noise where HT fibers encoded the AM, and also in quiet where both LT and HT ANFs were expected to contribute to AM coding. Paul et al. found that subjects without tinnitus whose EFRs were comparatively resistant to the addition of background noise had better AM detection thresholds in background noise than subjects whose EFRs were more affected by noise. Simulated auditory nerve responses using the peripheral cochlear model suggested that synaptic losses affecting HT ANFs alone were sufficient to explain the EFR results of non-tinnitus subjects with poor AM coding. Tinnitus subjects had worse AM detection thresholds and exhibited reduced EFRs compared with controls, even though thresholds for the test stimuli averaged <2 dB HL in both groups. Simulated auditory nerve responses found that in addition to severe HT fiber loss, a degree of LT fiber loss that would not be expected to affect audiometric thresholds was needed to explain the results of the tinnitus subjects. Thus, while HT synaptopathy was sufficient to explain degraded temporal coding ability, an additional loss of LT fibers insufficient to affect the audiogram was necessary to explain tinnitus. A key role for LT loss is also implicated by the high prevalence of audiometric threshold shift observed in tinnitus patients.

» Cochlear changes hidden from the audiogram may explain cases of tinnitus without audiometric hearing loss

These observations do not rule out a role for extracochlear mechanisms in cases of tinnitus and hyperacusis without audiometric hearing loss. However, they suggest that cochlear changes hidden from the audiogram could be sufficient to explain many such cases. Hearing loss without tinnitus might also be explained if such loss was related primarily to age-related changes in outer hair cell function and not to LT synaptopathy. LT fiber synaptopathy may be important, in part because loss of these fibers is likely accompanied by damage to the more vulnerable HT fibers. However, an important functional difference between LT and HT fibers is that LT ANFs exhibit much higher rates of spontaneous activity in quiet than do HT fibers. Accordingly, LT fibers are typically referred to as high-spontaneous rate (HSR) fibers in the literature. The results of cochlear modeling just reviewed suggest that hidden injury to HSR/LT fibers appears to add a tinnitus deficit to impaired temporal processing in individuals where hearing thresholds are clinically normal. Why this may be so is addressed in the next section, which overviews the neural changes seen in tinnitus and the neuroplastic mechanisms believed to generate them.

Role of neural plasticity in tinnitus

Neural changes associated with tinnitus have been studied experimentally by exposing animals to putative tinnitus-inducing procedures such as salicylate administration or to noise trauma that can be scaled to give temporary (TTS) or permanent (PTS) threshold shifts. The presence of tinnitus has subsequently been evaluated by methods such as gap detection (a silent gap inserted in a sound delivered prior to an acoustic startle stimulus will suppress a startle response, unless tinnitus fills the gap) or by making a tinnitus-like sound a cue for a behavioral response (responding in quiet after a tinnitus-inducing manipulation signals tinnitus). Animal models are important because they allow for the comparison of neural changes between animals that express behavioral evidence of tinnitus and animals that do not, when their preceding experience has been the same. Two neural correlates of tinnitus identified by this approach are

(1) an increase in the *spontaneous activity* of neurons in central auditory pathways, and
(2) an increase in cross-correlated or *synchronous* activity among the affected neurons.

Homeostatic plasticity (HP) and spike-timing-dependent plasticity (STDP), respectively, are thought to underlie these two neural correlates, although as will be noted later, these mechanisms may interact to produce tinnitus behavior. These forms of plasticity are also believed to underlie increased *sound-driven* neural and behavioral responses that have been observed in noise-exposed animals, suggesting hyperacusis, which is reported subjectively by about 40% of tinnitus patients.

Homeostatic plasticity and central gain

It has long been known that noise trauma sufficient to damage the cochlear transduction mechanism or auditory nerve synapses reduces the spontaneous and driven activity of the auditory nerve [4]. In response to reduced input from the cochlea, neurons in central auditory structures increase their input/output functions (gain) in order to maintain neuron firing rates within their dynamic ranges in different acoustic environ-

Abstract · Zusammenfassung

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Abstract

Background and objective. Deafferentation caused by cochlear pathology (which can be hidden from the audiogram) activates forms of neural plasticity in auditory pathways, generating tinnitus and its associated conditions including hyperacusis. This article discusses tinnitus mechanisms and suggests how these mechanisms may relate to those involved in normal auditory information processing.

Materials and methods. Research findings from animal models of tinnitus and from electromagnetic imaging of tinnitus patients are reviewed which pertain to the role of deafferentation and neural plasticity in tinnitus and hyperacusis.

Results. Auditory neurons compensate for deafferentation by increasing their input/output functions (gain) at multiple levels of the auditory system. Forms of homeostatic plasticity are believed to be responsible for this neural change, which increases the spontaneous and driven activity of neurons in central auditory structures in animals expressing behavioral evidence of tinnitus. Another tinnitus correlate, increased neural synchrony among the affected neurons, is forged by spike-timing-dependent neural plasticity in auditory pathways. Slow oscillations generated by bursting thalamic neurons verified in tinnitus animals appear to modulate neural plasticity in the cortex, integrating tinnitus neural activity with information in brain regions supporting memory, emotion, and consciousness which exhibit increased metabolic activity in tinnitus patients.

Discussion and conclusion. The latter process may be induced by transient auditory events in normal processing but it persists in tinnitus, driven by phantom signals from the auditory pathway. Several tinnitus therapies attempt to suppress tinnitus through plasticity, but repeated sessions will likely be needed to prevent tinnitus activity from returning owing to deafferentation as its initiating condition.

Keywords

Tinnitus · Neural plasticity · Hyperacusis · Hidden hearing loss · Oscillations

Neuronale Plastizität und ihre auslösenden Bedingungen bei Tinnitus

Zusammenfassung

Hintergrund und Ziel. Über eine Deafferenzierung durch pathologische Veränderungen der Cochlea (die sich im Audiogramm nicht zeigen muss) werden Formen der neuronalen Plastizität in auditorischen Signalwegen aktiviert, die Tinnitus und damit einhergehende Erkrankungen einschließlich Hyperakusis verursachen. In dem vorliegenden Beitrag werden Tinnitusmechanismen erörtert und Konzepte vorgestellt, wie diese Mechanismen mit denen normaler auditorischer Informationsverarbeitung in Zusammenhang stehen können.

Material und Methoden. Dargelegt werden Forschungsergebnisse aus Tiermodellen des Tinnitus und von elektromagnetischen Untersuchungen mit Bildgebung an Tinnituspatienten, die die Bedeutung der Deafferenzierung und der neuronalen Plastizität bei Tinnitus und Hyperakusis unterstreichen.

Ergebnisse. Auditorische Neuronen kompensieren eine Deafferenzierung durch Erhöhung ihrer Eingangs-Ausgangs-Funktionen (Verstärkung, „gain") auf mehreren Ebenen des auditorischen Systems. Formen der homöostatischen Plastizität sollen für diese neuronalen Veränderungen verantwortlich sein, so dass die spontane und gesteuerte Aktivität von Neuronen in zentralen auditorischen Strukturen bei solchen Tieren erhöht wird, deren Verhalten Hinweise auf das Vorliegen eines Tinnitus gibt. Ein weiteres Tinnituskorrelat ist die erhöhte neuronale Synchronizität unter den betroffenen Neuronen. Diese entsteht durch Erregungszeitmuster-(„spike-timing")abhängige neuronale Plastizität in den auditorischen Signalwegen, d. h. die Verstärkung einer synaptischen Verbindung erfolgt in Abhängigkeit von der relativen zeitlichen Differenz der Erregung von Neuronen zueinander. Langsame Oszillationen, die durch wiederholte Aktionspotenziale („bursts") thalamischer Neuronen erzeugt werden und die bei Tieren mit Tinnitus in Zusammenhang gebracht wurden, scheinen die neuronale Plastizität im Kortex zu modulieren. Dabei wird die neuronale Tinnitusaktivität mit Informationen aus Hirnarealen verflochten, die Gedächtnis, Gefühle und Bewusstsein unterstützen und bei Tinnituspatienten eine erhöhte metabolische Aktivität aufweisen.

Diskussion und Schlussfolgerung. Letzterer Vorgang könnte durch transiente auditorische Ereignisse auch in der normalen Hörverarbeitung induziert werden, angeregt durch Phantomsignale aus der Hörbahn jedoch bei Tinnitus persistierend. Bei verschiedenen Ansätzen zur Tinnitustherapie wird versucht, den Tinnitus über Anregungen von Plastizitätsveränderungen zu supprimieren. Aber es erscheinen wahrscheinlich wiederholte Behandlungseinheiten notwendig, um zu verhindern, dass die durch Deafferenzierung ausgelöste Tinnitusaktivität wiederkehrt.

Schlüsselwörter

Tinnitus · Neuronale Plastizität · Hyperakusis · Verborgene Schwerhörigkeit · Oszillationen

ments. Increases in central gain are believed to underlie increases in the spontaneous firing rates (SFRs) of the affected neurons and in their sound-driven responses, both of which have been recorded at all levels of the auditory pathway in animals subjected to traumatizing noise or to ototoxic drugs that selectively destroy IHCs.

Forms of HP are believed to be responsible for changes in gain consequent on deafferentation [13]. In one example, Qui et al. [14] recorded the response evoked by a sound in ANFs, the inferior colliculus (IC), and auditory cortex, of chinchillas in which ~30% of IHCs had been destroyed by an ototoxic drug. Input/output functions were reduced for the ANF response (compound action potential) reflecting suprathreshold hearing impairment, but were near-normal in the IC and normal or supranormal in the auditory cortex, revealing an increase in

gain as the recording site ascended the auditory pathway. This phenomenon may explain increased ABR wave V/I ratios that have been reported when tinnitus patients are presented with suprathreshold sounds. In another study [3], steepened rate-level functions were recorded from the dorsal cochlear nucleus (DCN) of guinea pigs 2 weeks after a TTS induced by noise exposure. Slopes were increased over a wide frequency range and were steeper compared with unexposed controls for neurons with center frequencies below as well as in the range where tinnitus behavior was expressed in the animals. This result supports the clinical observation that hyperacusis has a broader frequency profile than do tinnitus percepts [11]. HP mechanisms could amplify central gain by increasing presynaptic neural transmitter release, by modifying receptors in the postsynaptic membrane of the affected neurons, by activating neuromodulators, by modifying the intrinsic response of the neuron to its inputs, or by all of these processes.

In addition to its expression in many levels of the auditory pathway, gain enhancement occurs at different time scales and even in structures outside of classic auditory pathways [1]. Computational studies [18] suggest that a homeostatic mechanism that maintains the average rate of firing in a network of neurons can increase the spontaneous activity of the network as well as restore driven responses of the network. However, supranormal driven responses are needed for hyperacusis. Descending projections from the auditory cortex and other structures are a further factor that could be involved. Feedback from corticocollicular neurons to the IC has been found to scale with sound intensity and increase above baseline after TTS, revealing hyperacusis-like behavior in both structures. Neuromodulators and interactions with glial cells are also involved in HP and might spread the bandwidth of its effects. Overall, one can say that while HP is likely a key process in hyperacusis and tinnitus, many questions remain as to its specific mechanisms and multiple sites of action.

Spike-timing-dependent plasticity and neural synchrony

Other evidence points to a role for STDP in the development of increased synchrony and SFRs following noise-induced TTS and PTS in tinnitus animals. Wu and colleagues [24] observed that while SFR and synchrony were increased in the DCN of their tinnitus animals, changes in synchrony and SFRs were poorly correlated, in part because synchrony between long-distance unit pairs with low cross-correlation strengths was increased specifically in the tinnitus animals and corresponded more closely with their tinnitus frequencies. One factor leading to aberrant synchronous activity could be downregulation of glycinergic inhibition, which has been observed in the DCN of tinnitus animals [23] as well as after cochlear ablation in the guinea pig. In this respect, it may be instructive to consider what the functional role of this inhibition might be in the DCN, and how its decrease following PTS or TTS might generate neural correlates of tinnitus via STDP.

Fusiform cells in the DCN are the first site of cross-modal auditory and somatosensory integration in auditory pathways [21]. Inputs from the auditory nerve contact the basal dendrites of fusiform cells, which are then targeted after one synaptic delay by strong feedforward inhibition from glycinergic vertical cells contacted by the same ANF (see **Fig. 1a**). By contrast, somatosensory information from the head and neck region is conveyed by parallel fibers to the apical dendrites of fusiform cells, which are similarly targeted by inhibition from cartwheel cells (not shown in **Fig. 1a**) after one synaptic delay. The excitability of fusiform cells is known to be modified by STDP, depending on the order and time interval between its somatosensory and auditory inputs [21]. This mechanism may integrate somatosensory and auditory information on fusiform cell apical dendrites. In tinnitus animals the timing rules of STDP are changed such that potentiation dominates over suppression for a wider range of intervals on parallel fiber synapses [8]. One mechanism leading to this change could be a loss of feedforward inhibition from ANFs via vertical cells onto fusiform cells, which in the intact brain may gate STDP on the parallel fibers protecting synapses that convey temporally convergent auditory and somatosensory inputs to the neuron from downregulation while other synapses are weakened. If feedforward inhibition driven from the auditory pathway is diminished or lost owing to deafferentation, STDP could be unleashed on parallel fiber synapses, leading to increased synchronous activity among fusiform cells and to tinnitus. If this is one mechanism contributing to hypersynchrony in the DCN, loss of HSR/LT fibers would be especially patholytic. Plasticity unleashed on parallel fibers by such losses may explain why glutamate transporters in somatosensory pathways are upregulated when the auditory nerve is cut and why up to 80% of chronic tinnitus suffers are able to modulate their tinnitus by clenching their jaws and similar movements of the head and neck region [21].

It is recognized, however, that other mechanisms could be at work in the DCN or elsewhere in addition to (or instead of) this process. Downregulation of inhibition by HP could by itself unleash STDP on fusiform apical dendrites. The DCN is targeted by a dense serotonergic input that increases the probability of spikes evoked in fusiform cells by parallel fiber stimulation but not by stimulation of the auditory nerve. Cholinergic neuromodulators are known to modulate STDP plasticity at DCN parallel fiber synapses, affecting SFRs and synchrony [22]. Changes in intrinsic membrane conductance are a further consideration and have been reported in the fusiform cells of mice giving behavioral evidence of tinnitus [10]. Overall, it appears that neural correlates of tinnitus may be generated by a convergence of processes involving reduced inhibition, altered synaptic plasticity, changes in central gain mediated by HP, and alterations in intrinsic ion channels that occur in central auditory structures consequent on deafferentation of auditory pathways.

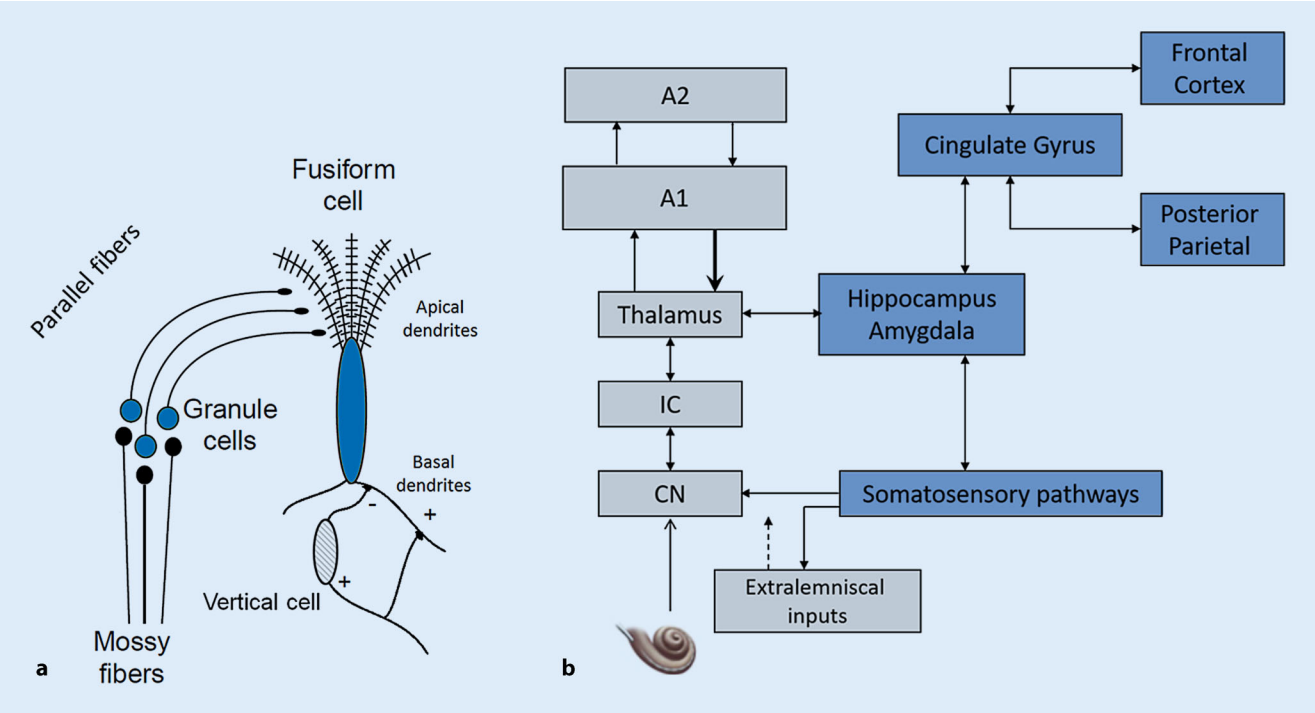

Fig. 1 ▲ Summary of neural structures that appear to be involved in tinnitus. **a** Simplified diagram of one feed-forward pathway in the dorsal cochlear nucleus (DCN, a division of the cochlear nucleus). Input from the auditory nerve excites the basal dendrites of fusiform cells (output cells of the DCN) followed by inhibition conveyed by vertical cells after one synaptic delay. Additional circuits and cell types are not shown. **b** Reduced output from the damaged cochlea unleashes STDP in the cochlear nucleus (*CN*) leading to hypersynchronous tinnitus neural activity conveyed to the medial geniculate nucleus (MGB) of the thalamus. Hyperpolarization of thalamic nuclei switches MGB neurons to a bursting mode. This mechanism may underlie low-frequency oscillations that have been recorded in brain regions involved in memory (hippocampus), emotion (amygdala), attention (cingulate, frontal, parietal cortex), and sensorimotor function (somatosensory structures) where increased metabolic activity has been reported in tinnitus patients. *A1* primary cortex, *A2* nonprimary cortex, *IC* inferior colliculus

Distributed neuroplastic changes in tinnitus

Although one might expect that decreased inhibition in subcortical auditory nuclei in tinnitus-expressing animals would be transmitted to the medial geniculate body (MGB) of the thalamus, Sametsky et al. [17] observed an *increase* in tonic GABAergic inhibition in a subset of thalamic projection neurons that was specific to animals showing behavioral evidence of tinnitus. This effect requires an initiating condition, which could be tinnitus-related neural synchrony inherited from subcortical pathways. Hyperpolarization also switched the affected MGB neurons into a burst firing mode, which is believed to be responsible for generating low-frequency (<4 Hz) delta and theta oscillations that have been recorded from the auditory cortex and several other brain regions from indwelling electrodes [19] or by electromagnetic imaging in tinnitus patients (see **Fig. 1b**). This activity is believed to reflect disinhibited interlaminar processing and synaptic rescaling by STDP in the affected cortical regions [2]. High-frequency gamma oscillations have also been observed in the primary auditory cortex that are nested in slow wave activity and correlate with tinnitus suppression by forward masking (residual inhibition). It was suggested that gamma activity is generated by neural networks as they update current sensory states in accordance with predictive coding models of tinnitus [19]. Oscillatory activity revealed in these studies may reflect integration of the tinnitus signal with information contained in the affected cortical regions, including the primary auditory cortex where neural changes track tinnitus percepts [16].

In normal auditory processing, low-frequency bursting activity distributed to the brain by thalamic neurons could be a teaching signal that integrates information in sensory pathways with information represented in brain regions underlying memory, emotion, and consciousness in order to support adaptive behavior. In tinnitus, however, these dynamics may persist, although possibly at an adapted level, because they are driven by maladaptive neuroplastic changes that occur in auditory pathways following deafferentation. Consistent with this, brain regions implicated in memory, emotion, and consciousness exhibit increased metabolic and synaptic activity in tinnitus patients ([7, 21]; **Fig. 1b**). If this hypothesis is correct, the oscillatory dynamics and brain network activity seen in tinnitus could be a prolongation of dynamics that occur during normal information processing on a much shorter time scale

Implications for treatment

Evidence that familiar mechanisms of plasticity may be involved in tinnitus and hyperacusis has encouraged approaches that exploit these mechanisms to suppress or renormalize maladaptive changes underlying both conditions. One approach involves extensive exposure to low-level background sounds covering the region of hearing impairment, which could suppress tinnitus by reducing central gain through forms of HP or similar mechanisms [16]. Although to date long-term exposure to such background sound has not been attempted systematically for tinnitus, it has been applied with notable success to hyperacusis [11]. Another approach exploits STDP by delivering paired auditory–somatosensory stimulation choosing an order and timing interval between the bimodal stimuli that has been observed to suppress neural correlates of tinnitus in animal studies. This approach has been found to reduce behavioral evidence of tinnitus in animal models as well as tinnitus loudness assessed by psychoacoustic methods in tinnitus patients [25]. Other sound therapies overviewed elsewhere [21] have reported tinnitus reductions in a noteworthy minority of tinnitus patients, likely drawing on these neural plasticity mechanisms. However, remodeling induced by neural plasticity entails a potential limiting factor, which is hearing impairment leading to maladaptive changes in auditory pathways. Regular repeated treatments are likely to be required to prevent the recurrence of maladaptive plasticity, although looking ahead this could be a small price to be paid to alleviate the suffering endured by many tinnitus patients.

Practical conclusion

- **Evidence that familiar mechanisms of plasticity may be involved in tinnitus and hyperacusis has encouraged approaches that exploit these mechanisms to suppress maladaptive changes underlying both conditions.**
- **A possible approach, already applied to hyperacusis, involves extensive exposure to low-level background sounds covering the region of hearing impairment. This could subdue tinnitus by reducing central gain through forms of HP or similar mechanisms.**
- **Another approach exploits STDP by delivering paired auditory–somatosensory stimulation choosing an order and timing interval between the bimodal stimuli shown to suppress neural hypersynchrony in physiological studies. This approach has been found to reduce behavioral evidence of tinnitus in animal models as well as tinnitus loudness assessed by psychoacoustic methods in tinnitus patients.**
- **Other sound therapies have reported tinnitus reductions in a noteworthy minority of tinnitus patients, likely drawing on these neural plasticity mechanisms. However, remodeling induced by neural plasticity entails a potential limiting factor, which is hearing impairment leading to maladaptive changes in auditory pathways.**
- **Repeated treatments are likely to be required to prevent the recurrence of maladaptive plasticity.**

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Compliance with ethical guidelines

Conflict of interest. L.E. Roberts declares that he has no competing interests.

The research studies reviewed in this article were approved by the ethics committees of the host institutions in accordance with accepted practices and the Declaration of Helsinki.

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