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OPINION

Tinnitus: perspectives from human neuroimaging

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Abstract | Tinnitus is the perception of phantom sound in the absence of a corresponding external source. It is a highly prevalent disorder, and most cases are caused by cochlear injury that leads to peripheral deafferentation, which results in adaptive changes in the CNS. In this article we critically assess the recent neuroimaging studies in individuals with tinnitus that suggest that the disorder is accompanied by functional and structural brain abnormalities in distributed auditory and non-auditory brain regions. Moreover, we consider how the identification of the neuronal mechanisms underlying the different forms of tinnitus would benefit from larger studies, replication and comprehensive clinical assessment of patients.

Tinnitus, often referred to as 'ringing in the ears', is a prevalent disorder that can have many forms, including objective tinnitus and subjective tinnitus. Objective tinnitus is the perception of somatosounds (for example, owing to turbulent blood flow or muscle contraction[1]) that can usually be detected by an observer and corrected, whereas the vast majority of individuals with tinnitus experience subjective tinnitus: the perception of sound in the absence of a corresponding sound source[1,2]. This is an auditory 'phantom' phenomenon that is sometimes considered to be analogous to phantom limb awareness (a feeling that a missing limb is still present after amputation or deafferentation)[3]. Moreover, tinnitus takes the form of abstract sounds and thus differs from musical and auditory hallucinations.

In most cases (more than 80% of people with tinnitus), tinnitus is accompanied by hearing loss, and the frequency spectrum of the tinnitus 'sound' corresponds to the frequency range of hearing loss[4]. For example, a patient who suffers from a unilateral noise-trauma-induced hearing loss of frequencies around 4 kHz typically perceives the tinnitus as a 4-kHz tone on the same side as the hearing loss. This correspondence of laterality and frequency between hearing loss and tinnitus indicates the relevance of a deprivation of auditory input for tinnitus generation, and qualifies tinnitus as a phantom sound.

The rates of prevalence of tinnitus indicate that the disorder is a global burden[5]. Approximately 10–20% of the world population experiences tinnitus[6,7]. Tinnitus prevalence augments with age[8] and is expected to increase in the future owing to increasing noise exposure. In addition, tinnitus is a common disability resulting from warfare[9] (see Further information). Although most patients can cope adequately with their tinnitus, severe tinnitus can be accompanied by frustration, annoyance, anxiety, depression, cognitive dysfunction, insomnia and stress, all of which lead to a substantial decrease in quality of life[10,11], and this is experienced by approximately 20% of individuals with tinnitus (that is, 2–3% of the total population)[6].

Tinnitus as a phantom sound has been compared to phantom pain, clinically[12], pathophysiologically[13,14] and in terms of treatment[14,15]. However, meta-analytic studies of various clinical approaches — including hearing aids[16], sound maskers[17], medication (for example, anti-convulsants, antidepressants and nootropics)[18–20], hyperbaric oxygen therapy[21], acupuncture[22], neuromodulation[23] and cognitive behavioural therapy[24] — have failed to show clear evidence of an unequivocal treatment effect on tinnitus loudness. In the case of cognitive behavioural therapy, there is meta-analytic evidence available for a beneficial effect on the quality of life of patients with tinnitus[24], indicating that the effects of interventions targeting tinnitus loudness and those targeting its impact on quality of life are, at least in part, dissociable.

Approximately 25% of all patients with tinnitus have normal hearing thresholds in the standard audiogram (that is, in the 125 Hz–8 kHz range)[25]. However, even patients with tinnitus who have apparently normal hearing thresholds might have cochlear damage that cannot be detected using conventional audiometry[26,27]. Besides hearing loss, hyperacusis (an increased sensitivity to perceived sounds) is also commonly experienced by people with tinnitus.

Indeed, although tinnitus has traditionally been considered an inner-ear problem, an increasing body of evidence from animal models and human brain-imaging studies has shown that it is accompanied by changes in the CNS. Tinnitus has thus moved from being considered to be a singularly cochlear pathology, to being a disorder or pathology that involves plasticity at different relays in the auditory pathway all the way to the auditory cortex and, most recently, to being a more complex pathology that also involves a wide array of non-auditory brain areas and networks[2,14,28]. In the past few years, tinnitus research has increasingly focused on these areas and networks, and the changes among these areas and networks associated with tinnitus are the main focus of this Opinion article.

Our understanding of the pathophysiology of tinnitus is still incomplete. Although several pathophysiological models have been proposed[14,29–31], none of these models can integrate all of the experimental and clinical findings. In the past decade, the number of animal and human neuroimaging and electrophysiology studies has substantially increased, and their methodologies continuously refined. Even so, many of these studies have thus far provided non-conclusive data. In this Opinion, we critically examine the results derived from such studies to provide an overview of what we currently know about

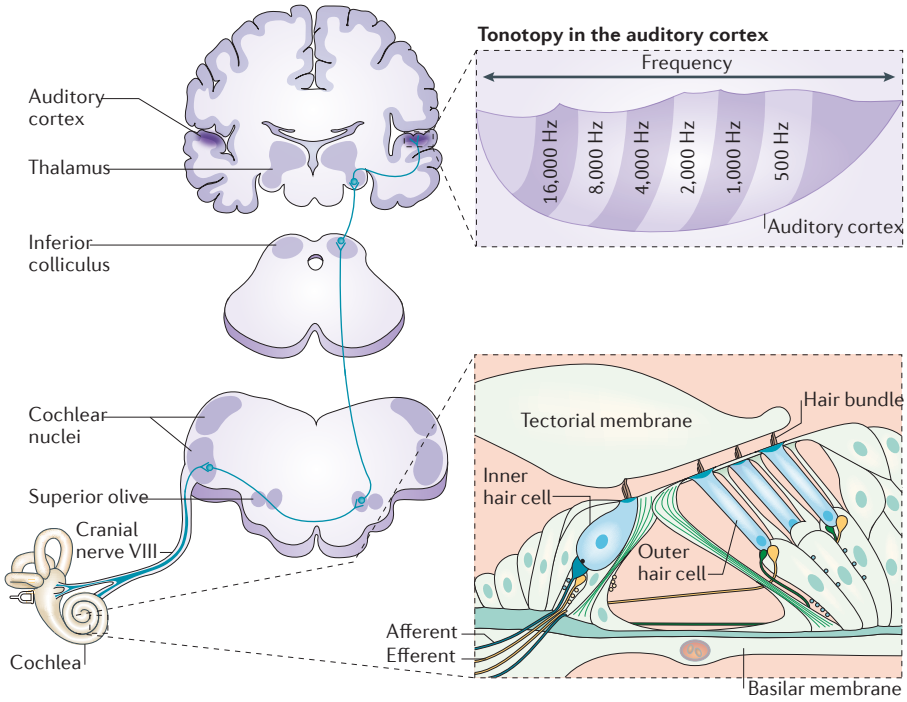

Figure 1 | **The human auditory pathway.** Sound is detected in the sensory epithelia of the cochlea within the inner ear (bottom right panel). Sensory cells of the organ of Corti (which extends along the length of the spiral cochlea) called inner hair cells transform sound vibrations into receptor potentials and release the neurotransmitter glutamate, which activates the dendrites of type I spiral ganglion neurons. The axons of these neurons form part of cranial nerve VIII (the cochleo-vestibular nerve). Cochlear outer hair cells are involved in sound amplification[169]. The first relay of the primary auditory pathway is in the cochlear nuclei in the brainstem, which receive type I spiral ganglion inputs. The majority of auditory fibres cross the midline here and synapse in the superior olivary complex, the second relay of the primary auditory pathway. The third relay is at the level of the mesencephalon in the inferior colliculus. The last relay in the lemniscal pathway occurs in the median geniculate body of the thalamus, before signals are transmitted to the auditory cortex[170]. The lemniscal pathway is tonotopically arranged — that is, each hair cell within the cochlea responds to one characteristic frequency — and this is mirrored in brainstem relays and in the primary auditory cortex (top right panel), which is in the temporal cortex[169,170]. The non-primary auditory pathway (also known as the extra-lemniscal pathway; not shown in the diagram) is not tonotopically arranged: from the cochlear nuclei, small fibres connect with the reticular formation, where the auditory signal joins signals concerning all of the other sensory modalities. From the reticular formation, neurons project to the non-modality-specific thalamic nuclei before terminating in the polysensory (associative) cortex[171].

tinnitus pathophysiology. In addition, we propose strategies to overcome the current limitations of research into tinnitus.

Animal studies

Subcortical changes in the auditory pathway. Tinnitus can arise from damage at any level of the auditory pathway (FIG. 1), but most cases are caused by cochlear damage. Thus, acoustic trauma in animals (BOX 1) has been used extensively as a model to study tinnitus, and observed changes at different relays of the auditory pathway have been proposed to represent neural correlates of tinnitus (reviewed elsewhere[28,32]). In short, these studies have shown that peripheral deafferentation owing to cochlear damage leads to increased spontaneous neuronal activity at various auditory pathway relays (except in the auditory nerve) all the way to the auditory cortex (FIG. 2). This increase in spontaneous relay activity is reflected by a decrease in neuronal inhibition and an increase in excitation, owing to alterations in GABAergic, glycinergic and glutamatergic neurotransmission[33].

An explanation for this increased excitability can be provided by a computational model that is based on the assumption that mean neuronal firing rates are stabilized by homeostatic plasticity[34]. According to this proposed model, central auditory structures react to the reduction in cochlear input by upregulating neuronal excitability, to compensate and therefore maintain a stable mean firing rate. In turn, this upregulation is also proposed to amplify 'neural noise', thus resulting in the generation of tinnitus[35].

In addition to the increased neuronal firing rate, an increase in the synchrony of neuronal firing has been observed in the auditory cortex of animals after the induction of hearing loss (FIG. 2). The increased synchrony occurs mostly in the part of the primary auditory cortex that codes for the frequency or range of frequencies of the hearing loss[35]. As the frequency of hearing loss matches the frequency of the tinnitus percept in tinnitus patients[4], the increased cortical synchrony observed in animal models of tinnitus has been proposed to be a neural correlate of tinnitus[28].

Mechanisms of auditory–somatosensory information integration at the dorsal cochlear nucleus may also be relevant for tinnitus generation. Inputs from the dorsal roots and the trigeminal ganglia that carry somatosensory information terminate in the cochlear nuclei, and somatosensory stimulation produces immediate and long-term facilitation or suppression of responses to sound in the cochlear nucleus[36]. In addition, the integration of auditory–somatosensory information, leading to modulation of neuronal activity in the central auditory pathways, has also been described to take place in primary auditory cortex[36]. This finding may explain the occurrence of tinnitus following neck trauma[37] or with temporomandibular joint disorders[38].

Auditory cortex reorganization. After cochlear damage (for instance, due to noise trauma), loss of inner hair cells that usually each transduce a certain frequency of sound in the cochlea leads to peripheral deafferentation. Animal studies have shown that if hair cell loss extends over a large frequency range, it is followed by tonotopic rearrangement of the primary auditory cortex, where the normally orderly representation of spectral frequencies is consequently altered[28] (FIG. 2). Noise trauma experiments in animals have shown that sensitivity to high frequencies is lost and that cortical neurons that usually respond selectively to frequencies in the frequency range of the hearing loss no longer respond to their designated frequency, but instead shift their tuning to respond to frequencies at the edge of the lesion; that is, to frequencies slightly lower than the lowest of the lost frequencies[39]. This over-representation of so-called edge frequencies has previously been assumed to increase spontaneous activity and synchronicity, which together could lead to the

Box 1 | **Animal models of tinnitus**

There are two major challenges in the development of animal models of tinnitus. The first is the induction of tinnitus and the second is its assessment. Two different methods have been developed to generate tinnitus: first, systemic treatment with ototoxic drugs such as salicylate or quinine, and second, exposure to traumatizing noise levels. Of these two different methods, exposure to traumatizing noise levels is probably more reflective of the clinical situation. Animals are trained to respond to silence, and errorful responses (or lack of a correct response) in silent trials are ascribed to perception of an internally generated phantom sound[161]. The first description of an animal model for tinnitus[162] was based on a conditioned-response paradigm. Water-deprived rats were given water while listening to a continuous background noise that was interrupted by brief silent intervals that were paired with a mild foot shock. With time, animals learned to stop drinking during silent periods; however, if salicylate was applied to the rats after the training, they continued to lick more often when the noise was turned off than did control animals. The interpretation of this result is that salicylate-treated rats still perceive a sound during the silent interval: the sound of their tinnitus.

Since that study, models have been developed in different rodent species and with different behavioural paradigms, using positive- or negative-reinforcement techniques. These behavioural tests require months to train the animals, and rely substantially on the learning capabilities, memory and motivation of the animals. To circumvent these problems, another animal model of tinnitus exploits the acoustic startle response[161]. The magnitude of the startle reflex in response to, for example, a loud sound, is reduced when the startling stimulus is preceded by a silent gap in an otherwise continuous acoustic background. Noise-traumatized or salicylate-treated animals show a smaller reduction in their startle reflex after the silent gap than do control animals, and this is interpreted as an indication of tinnitus.

One main criticism of these animal models is that they analyse only the perception of tinnitus, and not the emotional aspects that are very often observed in patients. Moreover, as the inhibition of the startle response occurs subconsciously, the second model does not inform as to whether the phantom sound is consciously perceived. Furthermore, the available models are not suitable for assessing chronic tinnitus, owing to behavioural habituation and low reliability over time.

perception of tinnitus. Thus, tinnitus has been viewed as a case of cortical maladaptive plasticity analogous to phantom limb sensation and pain, in which changes in the architecture of the primary somatosensory cortex are observed in humans following amputation and deafferentation[3]. Moreover, a recent study in mice showed that noxious noise (noise that can damage hair cells) may be transduced by type II afferents and can induce brainstem responses, leading to a form of 'auditory nociception' (REF. 40). This finding might be relevant in some patients who describe their tinnitus as painful.

However, several findings challenge the analogy of phantom pain for tinnitus in humans. First, the tinnitus pitch matches that of the hearing loss rather than the edge frequencies that have been proposed to become over-represented by cortical reorganization[4]. Second, tinnitus can develop with little or no hearing loss (approximately 25% of individuals with tinnitus have a normal audiogram[25]) and, in animals, hair cell loss limited to a small frequency range, or small shifts in hearing threshold induced by noise exposure, do not lead to cortical reorganization[41]. Moreover, two recent high-resolution functional MRI (fMRI) studies in people with tinnitus showed that tinnitus can occur without macroscopic cortical tonotopic reorganization[42,43]. Therefore, the distortion of cortical tonotopic maps is now increasingly thought to be a compensatory response to hearing-loss-induced deafferentation, and not necessarily the cause of tinnitus[44,45]. As both map changes and most cases of tinnitus depend on deafferentation, map changes may reflect this shared underlying cause, rather than directly inducing the tinnitus. Similarly, the maladaptive cortical reorganization theory of phantom pain after limb amputation has been recently questioned: a loss of sensory input causes structural and functional degeneration in the deprived sensorimotor cortex, whereas chronic phantom pain is associated with the preservation of the structural and functional organization of this region[46].

Limitations of animal models. In spite of the development of behavioural tests for assessing tinnitus in animals (BOX 1), whether such studies are modelling hearing loss, hyperacusis or tinnitus is still debated[32]. The fact that the cortical map reorganization observed in animal models of tinnitus is now viewed as a compensatory response to hearing loss rather than directly related to tinnitus generation reflects one of the difficulties of interpreting findings from animal models. An additional challenge to the use of tinnitus animal models is that, in humans, the phantom sound is frequently accompanied by emotional and cognitive symptoms[2,5]. To date, research on tinnitus-related emotional or cognitive symptoms in the available animal models is still preliminary and inconclusive[47,48].

Currently, available animal models are only of limited value for predicting efficacy of novel treatments in humans. For example, a recent treatment approach that paired brief tones above and below the tinnitus frequency with vagus nerve stimulation in order to reverse tinnitus-related cortical reorganization[49,50] was shown to be highly effective in eliminating physiological and behavioural signs of tinnitus in a rat model of noise-induced tinnitus[49], but had only relatively small effects in humans[50]. Similarly, carbamazepine seems to be efficacious in rats[51] but not in humans[20] (apart from in people with a rare subform of tinnitus[52]), and the same is true of *Ginkgo biloba*[19]. An enriched acoustic environment seems to ameliorate tinnitus in animals[53] but to a lesser extent in humans[54]. The reported discrepancies between the results from animal models and human treatment studies do not necessarily mean that animal models of tinnitus have no predictive value, as inconsistencies may also be related to methodological limitations in both animal and human studies. As with every other pathology of the CNS, caution is warranted in the direct translation of animal research on tinnitus to humans, especially research into novel treatments. The limitations of the interpretation and translation of animal studies mean that there is a great need for analysing tinnitus-related brain changes in human studies.

Human imaging studies

It has long been proposed that tinnitus pathology involves auditory and non-auditory brain regions[2]. Specifically, it was suggested that whereas tinnitus perception is related to abnormal neural activity in the auditory pathway, tinnitus distress is associated with increased co-activation of frontal, limbic, memory and autonomic brain areas[2]. In recent years, however, central non-auditory areas have been proposed to participate not only in tinnitus-associated distress but also in the generation of the phantom sound[29]. The participation of the CNS in tinnitus has been explored using a number of different neuroimaging techniques (see Supplementary information S1 (table)). In spite of technical limitations, imaging techniques have also been used to investigate the participation of subcortical areas to tinnitus pathophysiology; findings from these studies are summarized in BOX 2.

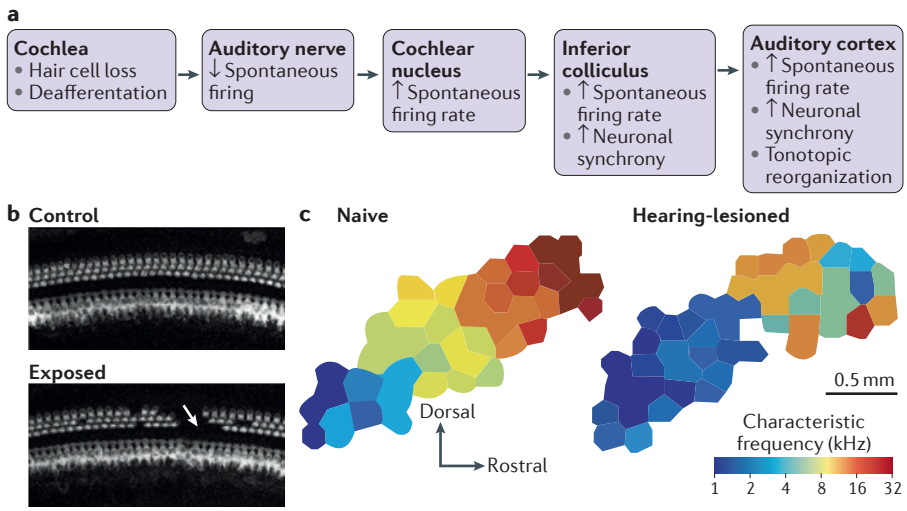

Figure 2 | **Noise-trauma-associated changes in the auditory pathway of animals. a** | In animals, noise exposure (one of the main causes of tinnitus) results in damage to the organ of Corti. The degree of damage depends on sound intensity and duration of exposure, ranging from deafferentation (a loss of afferents innervating hair cells)[26] to hair cell loss and deafferentation[172]. As a consequence, spontaneous activity of auditory nerve fibres is reduced[28]. In addition, increased spontaneous firing rates are observed in the cochlear nucleus, inferior colliculus and auditory cortex[28]. Increased neuronal synchrony has been described in the inferior colliculus[173] and the primary auditory cortex[35] after exposure to loud sounds in animals. **b** | Outer hair cells are more vulnerable than inner hair cells to noise-induced damage[172]. **c** | In animals, noise exposure usually leads to hearing loss in the high-frequency range and to cortical tonotopic rearrangement, whereby the regions corresponding to the lost high frequencies respond to the neighbouring low frequencies at the edge of the lesion[32]. In this example, mice were exposed to a 4-kHZ tone at 123 dB for 7 hours. Changes in tonotopy can be observed immediately after peripheral damage[35]. However, such cortical rearrangement has not been confirmed to be a neural correlate of tinnitus in humans. Part **b** is reproduced with permission from REF. 172, Elsevier. Part **c** is adapted with permission from REF. 44, Proceedings of the National Academy of Sciences.

In about 85% of all cases of chronic tinnitus[55], the tinnitus sound is perceived constantly; thus, resting-state functional measurements seem well suited to identify the neuronal correlates of tinnitus. Resting-state networks are based on spontaneous fluctuations in widely separated (although functionally related) brain regions and are evident in the human brain during the awake resting state, in the absence of goal-directed neuronal action and in the absence of external input[56]. These fluctuations can be measured by tracking blood oxygenation level-dependent (BOLD) signals with fMRI, and such recordings are being increasingly used to understand neurological and psychiatric diseases, many of which have been shown to be associated with alterations in resting-state activity[57]. In addition, rhythmic synchronous resting-state activity of large neuronal assemblies can be assessed using magnetoencephalography (MEG) or electroencephalography (EEG).

These various brain-imaging methods have revealed functional and structural abnormalities across distributed auditory and non-auditory brain regions, including the dorsolateral prefrontal cortex[54,58–60], cingulate cortex[58–76], parietal cortex[77,78], temporoparietal junction[79], parahippocampus[60,67,70,72,73,75,80–85], amygdala[64,86] and insula[62,63,73,75,79,80,87–89] (as discussed below; FIG. 3). This has led to the view that tinnitus is a complex brain disorder that involves alterations in brain networks mediating perception, distress, salience, memory and attention[14]. Different models for the generation of the phantom sound and its associated distress have also been proposed[2,29,31,90]. Here, we depict the limitations of studies in individuals with tinnitus, before summarizing the information that can be drawn from them.

Limitations of human studies. Tinnitus is a very heterogeneous condition with respect to the characteristics of the perceived sound, its various degrees of associated awareness and distress, its duration and its comorbidities[91,92]. As the variability in the clinical presentation of the disorder is expected to be reflected by a similar variability among the structure and function of neuronal correlates, identifying the underlying neuronal mechanisms of tinnitus is extremely challenging. Supplementary information S1 (table) summarizes findings from functional and structural imaging studies in humans with tinnitus. Notably, the findings from these studies are highly inconsistent in some cases.

This can be illustrated by comparing the results of the MRI studies that aimed to identify structural brain changes associated with tinnitus (Supplementary information S1 (table)). Findings differ from study to study and there seems to be almost no area that consistently shows the same changes in the available cross-sectional studies. One study revealed reduced primary auditory cortex volume in individuals with tinnitus[93], whereas another study demonstrated increased auditory cortex volume[94] and many other studies found no such structural alterations in this region[61,88,95–100].

To some extent, the observed inconsistencies can be explained by methodological aspects, such as small sample sizes, heterogeneity in the selection and characterization of patient and control samples, differences in the applied neuroimaging techniques, and differences in the method of analysis. Moreover, there are important differences among study designs. These designs can include, for instance, cross-sectional comparisons between individuals with or without tinnitus, studies correlating specific tinnitus parameters with neuroimaging findings, or longitudinal studies investigating the effects of specific interventions.

A critical aspect in the design of cross-sectional studies is the choice of the control group. As tinnitus is often comorbid with other disorders, such as hearing loss, hyperacusis or depression, the choice of the best control group is challenging. Earlier studies only matched control groups to tinnitus groups for age and sex, and observed that structural and functional differences were attributed to tinnitus even if the groups also differed in hearing loss, hyperacusis or affective state. More-recent studies have involved control groups matched for hearing loss, hyperacusis and depressive symptoms[95], so that any group differences can be unequivocally assigned to tinnitus. For example, a study comparing a group of individuals with tinnitus with two control groups — one group with and one group without hearing loss — showed that hearing loss is accompanied by a decrease in grey-matter density in the auditory cortex, and that this reduction is less pronounced in people with hearing loss plus tinnitus. This finding suggests that tinnitus may represent a compensatory mechanism that results from a tendency to normalize hearing-loss-induced changes

in auditory cortex structure[101]. However, like many of the findings described in Supplementary information S1 (table), these results still need replication. Another study comparing individuals with tinnitus with control participants who were matched for age, sex, handedness and hearing thresholds in the standard clinically analysed frequencies (125 Hz–8 kHz) showed that grey-matter changes were not related to tinnitus but instead negatively correlated with hearing thresholds at frequencies above 8 kHz[102]. It remains unknown which variables must be matched between tinnitus and control groups.

One approach to circumvent the difficulty of the selection of control groups is to include only people whose tinnitus loudness can be influenced by eye movements[103], jaw movements[104], injection of intravenous lidocaine[105], transcranial stimulation[106] or epidural stimulation with implanted electrodes[107]. However, such studies have two inherent limitations: first, they include only a specific subgroup that may not be representative of the entire tinnitus spectrum, and second, the intervention under investigation may have neuronal effects unrelated to the effect on tinnitus.

The influences of differential tinnitus variables (such as laterality, severity and duration) on changes in neuronal structure and function observed in brain-imaging studies have been explored using correlational analyses of large samples[66,87] and comparisons of different tinnitus subgroups[108]; for example, patients with tinnitus with high versus low distress levels[85]. A consistent finding from these studies is that both tinnitus severity and tinnitus duration each have a definitive impact on the neuronal correlates of tinnitus, as observed functional changes vary with increased distress and with tinnitus chronification (although the findings concerning the relevant involved brain structures differ, depending on the neuroimaging method used)[59,66,82,87,109].

The explorative value of cross-sectional studies is limited if certain obviously relevant variables — such as laterality, duration and severity — are not taken into account. Thus, cross-sectional studies require large samples that can be stratified according to specific criteria, or into clinically well-characterized subgroups. However, almost all cross-sectional imaging studies to date have involved sample sizes of no more than 25 people per group, and inclusion criteria have been rather broad. This has resulted in a high heterogeneity both within and between samples with respect to relevant aspects such as duration, laterality of tinnitus, frequency composition (tonal (single frequency) versus noise-like (a mix of multiple frequencies)), or recruitment strategy (for instance, patients presenting at a tinnitus clinic or people with tinnitus recruited by announcements), thus limiting the interpretation of results.

A further degree of complexity is added in fMRI studies that depend on the BOLD response during a specific paradigm. In the case of resting-state fMRI, no paradigm is needed. By contrast, findings from fMRI during a non-resting state critically depend on the used paradigm, which, in most tinnitus fMRI studies, has been auditory stimulation. However, the auditory stimulation used varies across studies (for example, some studies use a tinnitus-matched tone, whereas others use white noise), and brain responses to sound may be affected by comorbidities such as hearing loss or hyperacusis. Moreover, techniques to reduce the impact of the scanner noise, such as sparse imaging, interleaved silent steady state imaging or active noise control, vary from study to study.

Variability also arises from the analysis of results: for example, whereas some studies assess connectivity with respect to a priori chosen seed regions, other studies use purely data-driven approaches that first identify involved individual components, and subsequently analyse connectivity among them (see Supplementary information S1 (table)). Finally, methodological limitations have to be considered in the interpretation of results. For example, the spatial resolution of all human imaging studies is not sufficient to detect microscopic changes in the tonotopic representation of the auditory cortex, and EEG and MEG have only a very limited sensitivity with which to detect changes in subcortical neuronal activity.

Given the high heterogeneity with regard to tinnitus subjects, sample selection, imaging methodology and data analysis method, it is not surprising that inconsistencies across studies are encountered. However, in spite of

Box 2 | **Human imaging studies of subcortical brain areas**

Brain-imaging studies in humans have implicated several cortical structures in tinnitus, but the results for subcortical structures are less straightforward. One reason for this relative paucity of findings is that the anatomical characteristics of subcortical brain structures — specifically, their small size and their close vicinity to large arteries and ventricles — challenge neuroimaging analysis. In this regard, study of the brainstem with non-invasive methods such as MRI is difficult, as it places high demands on image acquisition as well as on data analysis. Nevertheless, the field of brainstem functional MRI (fMRI) has advanced considerably in the past few years, largely owing to the development of several new tools, including new sequences such as balanced steady-state free precession MRI and spoiled gradient echo MRI, that facilitate the study of this critical part of the human brain.

Despite the limitations, several studies on the possible involvement of subcortical brain areas in tinnitus have provided some insight. Studies have shown structural and functional changes in the inferior colliculus in tinnitus[95,114,163,164]. Specifically, a significant decrease in grey-matter concentration in the right inferior colliculus has been reported in patients with tinnitus compared with controls[95]. In addition, compared with control subjects, an abnormal asymmetry of fMRI activation produced by sound activation was observed in the inferior colliculi of people with symmetrical hearing thresholds and tinnitus lateralized to one ear[164]. However, an additional study in which patients were better matched for pure-tone threshold, age and emotional status showed increased sound-evoked inferior colliculus activation in patients with tinnitus compared to controls, but no asymmetry, stressing the importance of including better-matched groups in studies[165]. Another recent fMRI study indicated that increased inferior colliculus activity is related to hyperacusis rather than to the perception of the phantom sound[166]. An fMRI study of functional connectivity during sound-evoked activity, in which patients with tinnitus with only mild to moderate hearing loss were analysed and matched to control subjects, showed two clusters of highly functionally connected areas in both groups: one cluster consisting of the brainstem and thalamic nuclei, which showed highly correlated activity patterns, and a second cluster containing thalamic and cortical areas. That the thalamus was part of both clusters is consistent with its function as a relay station between the brainstem and cortex[167]. In patients with tinnitus, the functional connectivity between the cortical and subcortical clusters (specifically, between the auditory cortex and the inferior colliculus) was diminished and this was interpreted as a thalamic dysfunction[131]. These data were supported by an additional sound-evoked fMRI connectivity analysis, which showed reduced connectivity between the auditory cortex and subcortical areas such as the medial geniculate body, the inferior colliculus and the cochlear nucleus[168]. As reported for animal studies, it still remains to be determined whether the changes in activity and connectivity among subcortical brain areas are responsible for the genesis of the phantom sound or related to other symptoms that accompany tinnitus, such as hearing loss and hyperacusis.

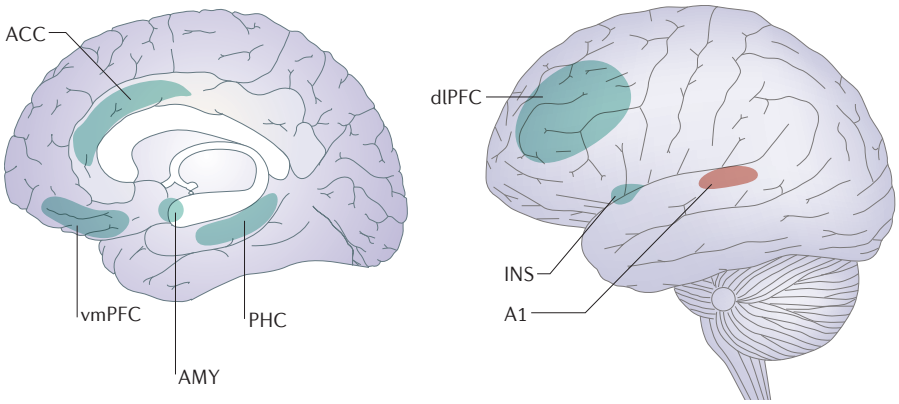

Figure 3 | **Altered activity and connectivity in distributed brain areas.** Imaging studies in patients with tinnitus have shown the involvement of, and increased connectivity among, auditory and non-auditory brain areas. However, inconsistencies between studies exist owing to high heterogeneity with regard to studied groups, sample selection method, imaging methodology and data analysis (Supplementary information S1 (table)). Various brain-imaging methods have revealed functional and structural abnormalities across distributed auditory and non-auditory brain regions, including the dorsolateral prefrontal cortex (dlPFC)[54,58–60], cingulate cortex[58–76], ventromedial prefrontal cortex (vmPFC)[96,97], parahippocampus (PHC)[60,67,70,72,73,75,80–85], amygdala (AMY)[64,86] and insula (INS)[62,63,73,75,79,80,87–89]. Abnormal activity in the primary auditory cortex (A1) has been associated with tinnitus loudness[54,59,70,75,83,84,111,113,125–127] and its increased connectivity with frontal areas to the conscious perception of the phantom sound[132,133]. Reductions in grey-matter volume in the vmPFC of individuals with tinnitus[96,97] have been suggested to indicate a deficiency in a top-down sound-inhibitory system in people with tinnitus[29]. The PHC has been consistently highlighted in functional imaging studies of tinnitus[60,66,74,75,80,81,83,84,90] and has been suggested to participate in the genesis of the phantom sound in response to hearing loss, via the retrieval of the lost auditory information from memory[14,31,90]. Imaging studies have revealed increased activation of the anterior cingulate cortex (ACC)[60,62,64,67,69,73,75,125] and the INS[62,63,69,80]. As both areas are a key part of a 'salience network' that detects the most relevant of all available internal and extrapersonal stimuli[145], increased activation of these areas may be linked to the salience that is attributed to the phantom sound and thereby prevent habituation[14,90]. Increased activity of the AMY[64,80,174] and increased connectivity between the AMY and A1 (REF. 86) have been associated with the emotional component of tinnitus[14,90].

the discussed heterogeneity, all forms of tinnitus have one thing in common: they involve an auditory phantom percept. Because of this shared element, there should be at least some overlap between the neuronal mechanisms that underlie the various tinnitus subtypes. Accordingly, in spite of the mentioned limitations, there are some brain changes that have been consistently implicated in the generation of tinnitus by several imaging studies — including studies using different methods — and these are discussed here (FIG. 3).

Gamma-band activity in the auditory cortex. EEG[110,111], MEG[112,113], fMRI[114] and positron emission tomography (PET)[67] studies have consistently shown auditory cortex hyperactivity in individuals with tinnitus (Supplementary information S1 (table); FIG. 3). Most[110–113] but not all[115] resting-state MEG and EEG measurements from the temporal cortex of individuals with tinnitus reveal a reduction of alpha power (8–12 Hz) and increases in slow-wave power (delta and theta, 1–6 Hz) and gamma power (>30 Hz) in this area. These alterations in oscillatory power are proposed to be generated by thalamocortical dysrhythmia[112]. In thalamocortical dysrhythmia (which occurs in several neuropsychiatric disorders[112]), a reduction of excitatory inputs on to thalamic cells (for instance, resulting from auditory deafferentation) leads to cell membrane hyperpolarization, which causes deinactivation of T-type calcium channels, in turn resulting in the production of low-threshold, low (theta)-frequency calcium spike bursts[116]. As a result, GABA type A receptor-mediated lateral inhibition is reduced, inducing gamma-band activity in the regions surrounding the deafferented area (known as the edge effect)[112,116]. Gamma-band activity in the auditory cortex is necessary for conscious auditory perception[117,118] and so may also contribute to the perception of a phantom sound. In contrast to physiological auditory processing, in which theta–gamma coupling also takes place, but fluctuates[119,120], the thalamocortical dysrhythmia state is characterized by pathologically persistent coupling of theta- and gamma-band activity in the auditory thalamus[121] and auditory cortex[122] contralateral to the ear in which the tinnitus is 'perceived'.

Accordingly, EEG studies have demonstrated that the amount of gamma-band activity in the auditory cortex reflects subjective tinnitus loudness (measured on a visual analogue scale)[111]. Moreover, successful reduction of tinnitus loudness through transcranial magnetic stimulation[123] or acoustic coordinated reset neuromodulation (a specific form of auditory stimulation with the aim to desynchronize hypersynchronous activity in the auditory cortex)[110] is associated with a reduction of gamma power to normal levels. However, in a recent MEG study, transient increases of tinnitus loudness after auditory stimulation were accompanied by a reduction in gamma activity, indicating that the relationship between auditory cortex gamma power and tinnitus intensity may be more complex[124]. Nevertheless, all studies that measured oscillatory patterns in the auditory cortex in tinnitus demonstrate an association of abnormal neural activity in this area with increased tinnitus loudness[54,59,70,75,83,84,111,113,125–127].

Although abnormal activity in the auditory cortex has consistently been demonstrated both in cross-sectional and longitudinal studies, results are less consistent with respect to the laterality of this abnormal activation. Some PET[128], EEG[111] and MEG[113] studies have demonstrated these changes contralateral to the perceived tinnitus laterality, whereas other PET[129] and EEG[75] studies have demonstrated increases in activity on the left side of the brain, and still other PET[64], EEG[59] and MEG[126] studies have shown activation on the right side. Furthermore, some PET[130], fMRI[131] and EEG[74,83] studies have shown activations that are bilateral and independent of the perceived tinnitus laterality, even in unilateral tinnitus[74,83,84]. One EEG study that investigated the neuronal correlates of tinnitus laterality suggested an association between parahippocampal activity and perceived tinnitus laterality[83]. Overall, the issue of whether tinnitus is generated by a left-sided or contralateral auditory cortex activity remains a matter of debate.

Distributed brain areas. A convergent finding from the available imaging literature on tinnitus — irrespective of the study methodology — is the involvement of, and increased connectivity among, auditory and non-auditory brain areas (Supplementary information S1 (table)). In particular, EEG, MEG

and resting-state fMRI studies[54,58–60,81,86,132,133] have robustly shown increased functional connectivity between auditory areas, such as the auditory cortices, and non-auditory brain areas, such as the frontal and dorsolateral prefrontal cortex. Studies of perceptual discrimination in animals[134], dichotic listening studies in humans[135] and data from patients in a vegetative state[136] together suggest that long-range connectivity between auditory and non-auditory areas is key to the conscious perception of sound, including phantom sound[14]. In patients in a constant vegetative state (in which patients are awake but without awareness and without conscious percepts), auditory stimulation increases activity in the primary auditory cortex. However, in contrast to healthy controls, this activity is not functionally associated with activity in the inferior parietal cortex, the hippocampus, the anterior cingulate or the posterior cingulate cortex[136,137], suggesting that activity in these areas may be associated with conscious perception of sound. Similarly, in healthy humans, sounds that are near the hearing threshold — but not consciously detected — induce activity in the primary auditory cortex. By contrast, consciously detected sounds elicit activation of inferior parietal, prefrontal and cingulate brain areas[138]. In addition, several studies in people with tinnitus demonstrated that tinnitus-related distress (as measured by tinnitus severity questionnaires) is associated with increased activity of non-auditory areas and enhanced long-range connectivity between auditory and non-auditory brain areas[14,63,85,87].

Ventromedial prefrontal cortex. Voxel-based morphometry has revealed reductions in grey-matter volume in the ventromedial prefrontal cortex (vmPFC) of individuals with tinnitus[96,97], and an fMRI study has demonstrated that vmPFC activation in individuals with tinnitus in response to a sound in the tinnitus frequency was increased compared with that in age- and sex-matched individuals without tinnitus who were presented with the same sounds[139] (Supplementary information S1 (table)). These alterations are suggested to indicate a deficiency in a top-down sound-inhibitory system in people with tinnitus[29], analogous to the top-down pain-inhibitory system described in pain processing[140,141]. Such a sound-inhibitory system would filter out abnormally increased activity — caused by, for instance, auditory deafferentation — in the ascending auditory pathways. According to this theory, neither an increase in activity in the ascending auditory pathways nor a deficiency in this top-down sound-inhibitory system is alone sufficient to cause tinnitus. However, if both factors occur together, a deficient sound-inhibitory system is unable to suppress the increased activity in the central ascending pathways, which then causes tinnitus[29].

Further support for the relevance of the vmPFC in tinnitus comes from source-analysed resting-state EEG studies that implicate this area in successful coping with tinnitus[142] and associated autonomic control in the disorder[69]. However, many studies could not replicate an abnormality of vmPFC[87] structure or function in patients with tinnitus, and one study suggested that decreases in the volume of grey matter in the vmPFC correlate with hearing loss of high frequencies (>8 kHz) rather than with aspects of tinnitus. Thus, the hypothesis that the vmPFC is involved in the postulated sound-inhibitory system has been brought into question[102]. Moreover, important details of such a system, such as the mechanisms for the detection and selective suppression of the unwanted tinnitus sound, have not yet been confirmed.

The parahippocampal area. Another area that is consistently highlighted in functional imaging studies of tinnitus is the parahippocampal area[60,66,74,75,80,81,83,84,90]. Several resting-state EEG[83,84] and resting-state fMRI[81,143] studies suggest that functional connectivity between the parahippocampal area and the auditory cortex is increased in individuals with tinnitus. Moreover, further support for an involvement of the hippocampal and parahippocampal area comes from a fluorodeoxyglucose (FDG)-PET study that found a positive correlation between the severity of tinnitus distress and the level of metabolic activation of the bilateral posterior parahippocampus–hippocampus interface[66].

Support for a critical role of the parahippocampus in tinnitus networks comes from two interventional studies. In the first, temporary inactivation of the parahippocampal area by selective injection of amobarbital into the anterior choroidal artery resulted in transient suppression of tinnitus in approximately 50% of patients[144]. In the second study, people whose tinnitus improved upon electrical stimulation of the secondary auditory cortex through epidural electrode implants overlying the posterior part of the superior temporal gyrus exhibited higher functional connectivity between the auditory cortex and the parahippocampus before treatment than did non-responders. This suggests that electrical stimulation of the auditory cortex to treat tinnitus relies on auditory cortex–parahippocampus connectivity and might even exert its beneficial effect in the parahippocampus[90]. Following these interventional studies, it has also been suggested that the parahippocampal area may retrieve the phantom sound from memory[90]. According to this notion, the brain of a person with pronounced hearing loss has to deal with a substantial lack of auditory input relative to before the hearing loss started. To compensate for the loss of auditory information, which leads to a disparity between predicted and delivered auditory inputs, sounds may be retrieved from memory by the parahippocampal area and perceived as phantom sound[90]. Recently, it was proposed that the disparity between the predicted and delivered auditory inputs in people with hearing loss may be relevant for both tinnitus perception and salience[31].

Nevertheless, the involvement of memory-related brain areas is not supported by all studies (Supplementary information S1 (table)). To confirm the notion of a pathological connection between the auditory and parahippocampal areas, and the role of this connection in the proposed retrieval of auditory information from memory, further studies will be required that include patients with tinnitus with different degrees of hearing loss, to validate whether peripheral deafferentation leads to the memory retrieval of lost information.

Anterior cingulate and insula. Increased activation of the anterior cingulate in individuals with tinnitus has been observed using fMRI[62], PET[64,67] and EEG[60,69,73,75,125]. fMRI[62,63,80] and EEG[69] studies also revealed increased activation of the insula, and one EEG study also indicated increased connectivity between the anterior cingulate and amygdala in people with tinnitus[73] (Supplementary information S1 (table)). As the anterior cingulate cortex and the insula are key parts of the 'salience network', which detects the most relevant stimuli of all available internal and extrapersonal stimuli[145], increased activation of these areas may be linked to the salience that is attributed to the phantom sound and thereby prevents habituation[14]. It is indeed intriguing that tinnitus remains permanently and consciously perceived by many patients, given that typically, unchanging stimuli — for example, the pressure of our clothes — are not salient and are therefore not consciously perceived, except through top-down influences (for instance, when one consciously wants to feel them). Thus, in people who continuously perceive tinnitus, some form of salience has to be attributed to the phantom sound. To test

the prediction that the level of co-activation of the anterior cingulate and the insula is proportional to the level of tinnitus salience, studies are needed that compare individuals with ongoing tinnitus perception with those who perceive tinnitus only by actively focusing their attention on it.

Network alterations. Resting-state network measurements have revealed that tinnitus is associated with alterations in widely distributed brain areas. Tinnitus has been proposed to result from abnormal activity in multiple overlapping networks, and its heterogeneity is suggested to be due to variation in the involvement of individual specific networks[90]. According to these hypotheses, the activation of the auditory cortex may reflect the loudness of the tinnitus, whereas attention to the tinnitus, its conscious perception, its salience and the associated distress are associated with the co-activation of different resting-state networks[146], such as the hippocampal–cortical memory system[147], the frontoparietal control system[148] and the salience network[149], as well as of areas that are activated when emotions are processed[150], including the autonomic nervous system[90]. Although the involvement of each of these brain networks is supported by imaging studies (Supplementary information S1 (table)), the evidence for the attribution of specific aspects of tinnitus to the different networks is still scarce.

Conclusions

Recent neuroimaging data have advanced our knowledge on tinnitus pathophysiology by revealing structural and functional changes of different brain areas (Supplementary information S1 (table)). Available results agree upon the finding that tinnitus-related brain changes are not restricted to the auditory system but instead encompass widely distributed brain regions[14,90]. However, more questions than answers still remain. Neuroimaging results are highly variable, probably owing to differences in sample selection, study design, imaging modality and analysis methods — all factors with inherent limitations[87,151,152]. Even if the interpretation of the relative contributions of each of the different brain areas to the various aspects of tinnitus remains largely speculative, the following model can be proposed on the basis of the available data: tinnitus most commonly follows auditory deafferentation (with or without hearing-threshold shifts) that leads to a lack of sensory information in the tinnitus spectrum. Rather than tonotopic reorganization being the cause of tinnitus generation, the sound percept itself could be the result of increased activity in the auditory pathways (which itself could be induced by homeostatic mechanisms)[30] and permitted[29] or even facilitated[31] by interactions of auditory brain areas with non-auditory brain networks.

Long-range coupling of various distributed brain areas may be important for conscious perception of the phantom sound[14,153], and compensatory efforts of the memory system may 'fill in' the 'missing' auditory information and be mediated by increased functional connectivity between the parahippocampal area and the auditory cortex[90]. Moreover, deficient inhibitory suppression may be involved in the maintenance of tinnitus as well[29]. The co-activation of a salience network that involves the anterior cingulate cortex and the insula gives an added importance to an otherwise non-relevant phantom sound[14]. In tinnitus that is due to cochlear damage, changes in the auditory pathways are likely to be the trigger for the more widespread distributed network alterations that are seen in tinnitus[31,154].

In spite of the advances that neuroimaging data have provided, we are probably still only scratching the surface in terms of our understanding of phantom-sound perception. Investigation of the same participants with different neuroimaging techniques may overcome the limitations of specific techniques. Further imaging studies with better patient stratification, and controlling for hearing loss, hyperacusis, distress, depression and tinnitus perceptual characteristics are needed. Recruitment of study groups that are large enough to achieve this goal will require coordinated efforts from many centres that are willing to collaborate. In addition, large databases containing both clinical and neuroimaging data would enable data-driven identification of tinnitus subtypes[155], which may help to resolve the lasting question: which criteria are most relevant for subtyping tinnitus? If data of such databases were publically available, results could be verified by other groups and the influence of different analysis methods could be assessed systematically.

Innovative ways to approach tinnitus investigation are urgently needed. A recent study with this aim used a novel systems-pharmacology side-effect analysis approach to search for targets that are involved in tinnitus generation[156]. Analysis of a network of 1,313 drug–target pairs identified previously non-associated proteins, such as the angiotensin converting enzyme, as the common targets of 275 compounds that induce tinnitus as a side effect. This approach could be followed by the investigation of drugs that interact with those proteins to elicit an opposite functional effect in people with tinnitus. Imaging techniques for assessing neuronal changes induced by therapeutic interventions in patients with tinnitus have revealed some promising results that may also be useful for disentangling the neuronal underpinnings of the different aspects of tinnitus[110,157,158]. Finally, as for other CNS pathologies[159,160], the use of graph analysis might help to identify brain hubs and alterations in brain topology that are involved in tinnitus development and maintenance. Taken together, better methodological approaches applying different neuroimaging techniques, in addition to innovative ways of looking beyond the obvious, will move the tinnitus field forwards in the quest towards understanding this pathology. Moreover, this will bring a solution to the millions of people for whom tinnitus is a burden.

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Competing interests statement
The authors declare competing interests: see Web version for details.

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