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Tinnitus: Does Gain Explain?

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Abstract—Many, or most, tinnitus models rely on increased central gain in the auditory pathway as all or part of the explanation, in that central auditory neurones deprived of their usual sensory input maintain homeostasis by increasing the rate at which they fire in response to any given strength of input, including amplifying spontaneous firing which forms the basis of tinnitus. However, dramatic gain changes occur in response to damage to the auditory periphery, irrespective of whether tinnitus occurs. This article considers gain in its broadest sense, summarizes its contributory processes, neural manifestations, behavioral effects, techniques for its measurement, pitfalls in attributing gain changes to tinnitus, a discussion of the minimum evidential requirements to implicate gain as a necessary and/or sufficient basis to explain tinnitus, and the extent of existing evidence in this regard. Overall there is compelling evidence that peripheral auditory insults induce changes in neuronal firing rates, synchrony and neurochemistry and thus increase gain, but specific attribution of these changes to tinnitus is generally hampered by the absence of hearing-matched human control groups or insult-exposed non-tinnitus animals. A few studies show changes specifically attributable to tinnitus at group level, but the limited attempts so far to classify individual subjects based on gain metrics have not proven successful. If gain turns out to be unnecessary or insufficient to cause tinnitus, candidate additional mechanisms include focused attention, resetting of sensory predictions, failure of sensory gating, altered sensory predictions, formation of pervasive memory traces and/or entry into global perceptual networks.

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Key words: tinnitus, gain, neurophysiology, electroencephalography, functional imaging, psychophysics.

INTRODUCTION

The term ‘tinnitus’ refers to sound heard in the ears in the absence of an external physical source for that sound, and in most cases, including in this article, it refers specifically to ‘subjective tinnitus’, in which there is no internal sound source either, such as turbulent blood flow. Typically the sound is a high-frequency tone and/or hiss, but various percepts are reported. Almost everybody experiences short periods of transient tinnitus in their lifetime, and over half of healthy adults with no known hearing abnormality report a very quiet ongoing tinnitus-like percept if placed in a silent environment and asked to pay attention to what they are hearing (Levine et al., 2003; Tucker et al., 2005). Furthermore, many others are able to elicit a tinnitus-like percept transiently through forced contraction of jaw, facial or neck muscles (Levine et al., 2003). Up to 15% of people will experience permanent or long-term tinnitus in their lifetime (Shargorodsky et al., 2010) that is sufficiently loud to be heard in real-world environments (i.e. clinically significant). The main risk factor is hearing loss, and an abnormal audiogram is found in around 90% of people with tinnitus. However, the majority of people with hearing loss do not experience clinically significant tinnitus, irrespective of the severity of hearing loss. Studies on people with tinnitus and a normal audiogram usually find more subtle evidence of peripheral auditory damage (Roberts et al., 2006; Weisz et al., 2006; Schaette and McAlpine, 2011). Tinnitus can also be reversibly induced by simulating hearing loss through the chronic placement of an ear plug (Schaette et al., 2012).

A popular and intuitive explanation for the causation of tinnitus is that reduction in auditory input (usually through hearing loss) leads to increased *gain* in the central auditory pathway; that is, the neurons receiving reduced input restore their usual activity level by responding more strongly for any given strength of input. It is thought that the action of gain on spontaneous activity in the auditory pathway (a normal and ubiquitous phenomenon to some extent) amplifies that spontaneous activity, leading to the perception of tinnitus (Schaette and Kempter, 2006).

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This article considers gain in the broadest sense, encompassing all mechanisms by which a single neuron, or ensemble of neurons, increases the ratio of the response it elicits in its onward targets to the combined ascending inputs it receives. Its principal consideration is evidence linking gain changes to the emergence of tinnitus, including whether gain is sufficient to explain tinnitus and, if not, what additional evidence is required, or what alternative/additional processes might explain tinnitus.

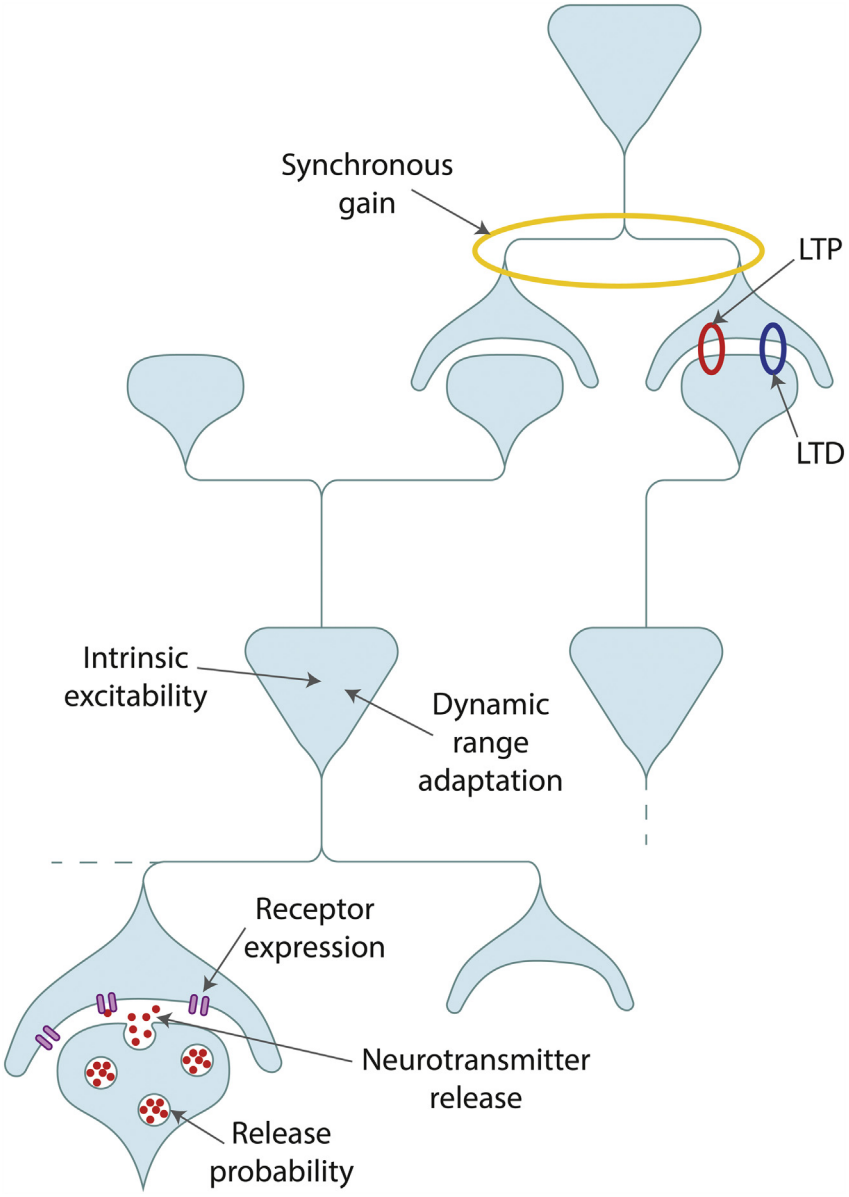

Fig. 1. Neuronal mechanisms of gain. Schematic of excitatory neurons and synaptic connections between them. At the synapse, release probability controls the chance of a depolarization causing excitatory neurotransmitter release. Along with neurotransmitter concentration and receptor expression, this influences depolarization of the postsynaptic neuron. At the level of whole neurons, intrinsic excitability influences the input-output function, in terms of firing rate for a given strength of input. Dynamic range adaptation provides a finer control over this function to constrain firing rates over time to within a desired physiological range. Multiple simultaneous dendritic inputs to the same neuron constitute synchronous gain, whereby the additive effect of the inputs increases the probability of depolarizing the target neuron. Synchronous gain is promoted by coherent neuronal oscillations whereby large numbers of neurons increase and suppress their firing rates in a common rhythm. These oscillations occur due to the interaction of excitatory cells and inhibitory interneurons. Hebbian plasticity comprises long-term potentiation (LTP) and long-term depression (LTD) whereby, depending on the precise relative timing of neuronal firing of pre-synaptic and post-synaptic neurons, synaptic connection strengths are increased or reduced respectively.

MECHANISMS OF GAIN

Gain refers to a change in the input-output function of a system such that a given input results in a stronger output, or a given output can be elicited by a weaker input. Here, I refer mainly to gain, but in reality consider increased gain as functionally equivalent to reduced *inhibition,* and vice versa. In broad terms, gain control is a major part of achieving *homeostasis*, the maintenance of a dynamic system within a preferred and relatively stable range of states, which is essential for the survival and optimal functioning of all organisms. Fig. 1 illustrates major mechanisms of gain, which are discussed in the remainder of this section. Neurons, specifically, need to constrain both their mean firing rates, and the *dynamic range* of their firing rates (Dean et al., 2005; Watkins and Barbour, 2008; Wen et al., 2009). *Homeostatic plasticity* (Turrigiano, 2012) encompasses the neural changes that maintain homeostasis, including intrinsic neuronal excitability, receptor expression, volume and probability of neurotransmitter release.

The converse type of plasticity to homeostatic plasticity is *Hebbian plasticity* (Gütig et al., 2003), which is elicited via the coherent firing of the neuron's pre-synaptic inputs and post-synaptic targets, and modifies the connection strengths between the neurons involved. Thus, the colloquial description of Hebbian plasticity is that "Neurons that fire together wire together". However, this is an oversimplification, and in reality the effect on the synaptic connections depends on the order and the precise timing (i.e. exact delay over a timescale of milliseconds) of the coherent firing of the neurons involved: In *long-term potentiation* (LTP), synaptic connections are strengthened, while in *long-term depression* (LTD), synaptic connections are weakened. In isolation, both LTP and LTD are unstable, as in they are self-reinforcing. Homeostatic plasticity counterbalances these, and thus maintains overall homeostasis of the system.

Both Hebbian and homeostatic plasticity involve local neurochemical changes, but gain can also be influenced by wider or extrinsic changes in neurotransmitters and neuromodulators. Changes in the production, release or receptor number of excitatory neurotransmitters, principally glutamate and glutamine, affects gain, as do equivalent changes with respect to inhibitory neurotransmitters such as GABA and glycine. Furthermore, both of these sides of the excitation-inhibition balance can be affected by changes in glutamic acid decarboxylase (GAD), an enzyme which regulates the conversion of excitatory glutamate to inhibitory GABA. Acetylcholine is a prevalent neuromodulator which acts to increase postsynaptic gain (Hasselmo, 2006), which is discussed in a subsequent section on the role of attention.

Subcortical gating (McCormick and Bal, 1994) refers to the attenuation or enhancement of particular signals via the action of subcortical neural pathways external to the sensory pathway conveying those signals. For instance, the thalamic reticular nucleus (TRN) has tonically active inhibitory projections to ascending sensory pathways as they pass through the thalamus, and thus activation of the TRN acts to suppress sensory input, while inhibition of the TRN facilitates its propagation to cortex. The TRN is under descending control from cortical areas, via the nucleus accumbens. Although its mechanism is different to any of the gain mechanisms described above, it can nonetheless be considered a type of gain control, as its sole effect is to modify the input-output functions of ascending sensory pathways.

Cross-modal connections are rich in the brainstem, and are necessary for allowing different sensory and motor systems to act in a coordinated fashion, and for predicting and minimizing the effect of one system on another (e.g. suppression the perception of self-generated sounds). Somatosensory inputs are abundant in the dorsal cochlear nucleus (DCN) (Zhou and Shore, 2004), and can exert modulatory effects on auditory responsive neurons (Marks et al., 2018), including via Hebbian plasticity, which again constitutes a form of gain control.

In addition to the response properties of individual neurons, as discussed so far, coordinated activity across neurons is of fundamental importance in gain control. The chance of causing depolarization of a targeted neuron is dependent on the summed dendritic activity at a given moment in time, and therefore the more neurons simultaneously send input to a given neuron, the more likely that neuron is to generate an action potential. This phenomenon is termed *synchronous gain* (Chawla et al., 1999), and its major determinants are the number of neurons simultaneously projecting to a common target, and the synchrony with which those neurons fire. Coordinated rhythms of neuronal firing depend heavily on the interaction of inhibitory interneurons with excitatory neurons. In the auditory system, tonotopic map plasticity (Pienkowski and Eggermont, 2009) (whereby neurons shift their frequency response to over-represent some acoustic frequencies at the expense of others) can be thought of as a contributor to synchronous gain. Map plasticity is closely related to *lateral inhibition,* which is the phenomenon whereby stimulation of a particular frequency channel leads to suppression of activity in neighboring channels.

NEURAL MANIFESTATIONS OF GAIN

The common, and potentially synergistic, effect of gain from all such sources is increased postsynaptic depolarization on the neuronal population's downstream targets, hence a greater impact on the activity in those areas. In tinnitus, these mechanisms are relevant at all levels of the auditory pathway, with gain in hierarchically lower levels affecting the input to higher levels, and thus the neural activity and responses in those higher levels. Auditory cortex (primary and non-primary areas) is the top level of the auditory hierarchy itself, and the level at which neural activity is most closely related to what is consciously perceived.

While it is possible to observe the contributory mechanisms to gain themselves, most research has focused on the consequences of gain. Interrogating neural responses to stimulation is one commonly-used approach, and can range from comparing responses to a single stimulus intensity to delineating response functions. The other approach is investigating spontaneous activity, in light of the spontaneous and ongoing nature of tinnitus. The most commonly used measures are the following:

- At the level of individual neurons, typically it is firing rate that is measured, either spontaneously (SFR), or driven by stimulation. The synchrony of firing can also be examined. With single cell recordings, this can be assessed by cross-correlating the firing patterns of two or more neurons.
- Rhythmic firing patterns across very large numbers of neurons can be observed as *oscillations*, either in the *local field potential* (LFP) recorded invasively, or the electrical potential (or magnetic field) recorded at the scalp. These are a composite measure influenced by both firing rate and synchrony, which cannot easily be disambiguated. They are typically categorized by the frequency with which they oscillate, ranging from delta (1-3 Hz) to gamma (>30 Hz).
- Large-scale stimulus driven responses that are time-locked to the stimulus are referred to *event-related* or *evoked* potentials. These represent synchronous activity in similarly large neuronal ensembles to oscillations, and are expressed as the size or latency of the peak response.
- Functional imaging techniques, such as fMRI or PET, are indirect indicators of net neuronal activity. Of the above metrics, they most closely correlate with the magnitude of gamma oscillations (Mukamel et al., 2005).

BEHAVIORAL/PERCEPTUAL MANIFESTATIONS OF GAIN:

From a clinical, or perceptual, perspective, the manifestations of gain all relate to changes in the perceived intensity of a particular sensory signal, with common examples in the auditory system comprising the following:

- *Loudness recruitment* (Moore and Glasberg, 2004): in the cochlea, the usual response to hearing loss is to increase gain by steepening the response functions of inner hair cells at affected frequencies. This correction is inherently

sub-optimal, as the rightward shift cannot be corrected, but only the slope of the function. At sound intensities close to hearing threshold, this provides only limited compensation, while at moderate intensities sound loudness is approximately restored, and higher intensities there can be overcompensation. Loudness recruitment has been extensively studied, and can be predicted from an individual's audiogram and cochlear dead regions. It is important to consider loudness recruitment in studies of sound-driven responses in the context of hearing loss, as it can make the oft-used method of subtracting hearing threshold from sound intensity (i.e. dB *sensation level*; SL) grossly inaccurate, and in some cases less accurate than simply using constant sound pressure level (SPL) and not taking into account hearing at all.

- *Loudness growth curves* can be plotted, which delineate the function of delivered sound intensity to perceived sound loudness.
- *Uncomfortable loudness levels* (ULLs) can be thought of as a quicker and less detailed form of loudness growth curve, and measure the quietest sound that is perceived as uncomfortable.
- *Hyperacusis* refers to an intolerance of sound loudness, i.e. the perception as uncomfortable (on account of their loudness) sounds that would be comfortable to most listeners. This is typically quantified by scores on questionnaires such as the Hyperacusis Questionnaire (HQ). It can be considered a manifestation of excessive gain, though correspondence with ULLs is typically low.

NECESSARY FEATURES OF A PUTATIVE CORRELATE OF TINNITUS

In order for a given neural process or metric to be a convincing correlate of tinnitus, it is far from sufficient to simply demonstrate that is different, at group level, between a tinnitus and non-tinnitus group. Here, based simply on face validity, I propose a minimum set of criteria that must be met in order to make a strong case for a basis or invariant correlate of tinnitus. It is not to say that not fulfilling all the criteria, for instance due to lack of evidence, debunks a particular correlate, but rather that further evidence is required to support it as a basis for tinnitus. Conversely, if reliable evidence emerges that a given correlate breaks one or more of these criteria, then either it is not a true correlate of tinnitus, or it is only part of the pathophysiology of the condition. That said, a partial explanation of tinnitus can still be extremely important, and even provide a valuable biomarker or therapeutic target. It is also not envisaged that all of these points be addressed by individual studies, but rather by whole lines of research aiming to robustly link particular processes to tinnitus generation. The criteria are as follows:

- **Accurately classifies individual subjects or patients in terms of the presence of absence of tinnitus, despite equal predisposition** (i.e. same level of hearing loss, or same auditory insult applied) and close matching in other key respects (e.g. age, and task or attentional state during recording).
  Simply demonstrating a significant difference in group means is not sufficient, as it does not explain tinnitus at the individual level. While measurement noise might prevent a perfect categorization of subjects, a substantial overlap suggests against a sufficient correlate of tinnitus. Even with perfect distinguishing power, uncertainty still remains over any correlate supported only by studies without close matching for all the factors described above, as it is unclear what combination of tinnitus, the tinnitus-inducing insult, predisposing or consequential factors is responsible for the difference. Fig. 2 illustrates the importance of featuring a matched control group, and the erroneous interpretations that can result from omitting such a group. In human studies this means either recruiting a control group with comparable hearing thresholds, or studying tinnitus patients with normal hearing. The latter approach seems logical, but its robustness to confounds has yet to be proven, particularly as numerous studies have shown evidence of hidden hearing loss in these normal hearing tinnitus groups (Weisz et al., 2006), including damage to high-threshold auditory nerve fibers (Paul et al., 2017), and elevated thresholds above 8 kHz (Roberts et al., 2006).

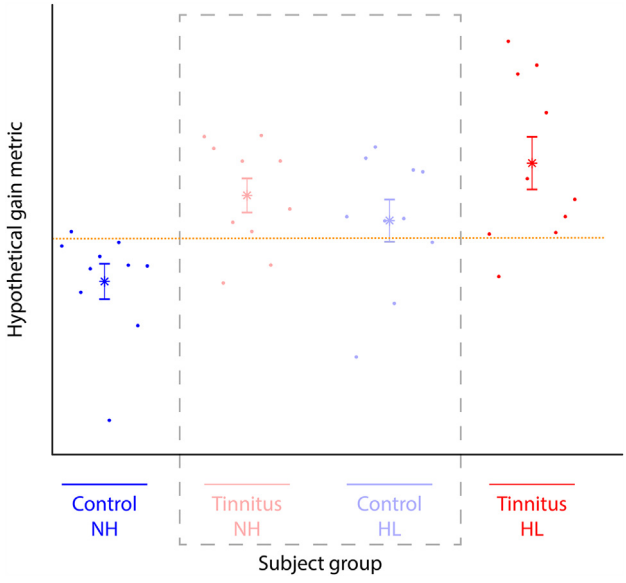

Fig. 2. Classification of tinnitus status at the individual subject level. The figure depicts a hypothetical neural metric or correlate that is postulated to underlie or indicate tinnitus. Four subject groups are indicated, categorized by their tinnitus and hearing status. Dots represent individual subjects, and horizontal separation between dots is only to aid visual clarity. Asterisks and error bars indicate group mean and standard error of the mean respectively. The faded colors (surrounded by the grey dashed box) indicate the groups often not present in research studies, for instance in animal studies where all of the exposed group have tinnitus, or in human studies where the control group is not matched for hearing loss. Without considering these groups, it appears that there is near-perfect ability of the metric to indicate the presence or absence of tinnitus, based on a threshold indicated by the dotted orange line. However, inclusion of these groups makes it clear that both tinnitus and hearing loss are associated with a group-level increase in the metric, with an additive interaction between the two, and that the metric does not differentiate hearing loss from tinnitus. The most likely interpretation, therefore, is that the neural metric relates to a process that is contributory towards tinnitus but not a sufficient sole cause.

Ideally studies should feature a factorial group design, with each of *tinnitus* and *non-tinnitus* groups being divided into *normal hearing* and *hearing loss/damaged* groups. The reason is that there might be a neural process or metric that is increased (or decreased) by hearing damage, but also in association with the presence of tinnitus; values of the metric might therefore turn out to be higher or equal in hearing damaged controls compared to normal hearing tinnitus subjects. In this instance, while relevant to tinnitus, this metric would not constitute a sufficient basis for the condition. This is especially the case for human studies (where tinnitus patients with normal audiograms are frequently encountered), while for animal studies a three-group design (omitting the normal-hearing tinnitus group) will typically suffice.

Numerous studies aim to strengthen their claims of a link to tinnitus rather than hearing by demonstrating a significant linear correlation between a particular neural metric and tinnitus behavior. While this is a worthwhile factor to examine, two important caveats are generally overlooked; firstly, such a correlation is not necessary to demonstrate a causal role in tinnitus, as the mechanisms of tinnitus causation and tinnitus loudness or distress are not necessarily the same; secondly, when performing these correlations, ideally correlations within the tinnitus group should be presented, as well as within the subject group as a whole, because the latter analysis in isolation can potentially give a misleading impression, as explained in Fig. 3.

- **Increases in response to auditory or other insults that cause tinnitus** (for candidate *causes* of tinnitus only, as opposed to consequences)

  While it might seem sufficient to meet the above criterion, there still needs to be a plausible explanation of how a particular neural process causes tinnitus. If the process is not enhanced (or inhibited) by auditory insults then it is difficult to appreciate how tinnitus can be caused by hearing damage without invoking additional explanations. For instance, if a given neural correlate distinguishes hearing-damaged controls from equally hearing-damaged tinnitus subjects, but the group mean is no different between normal hearing and hearing-damaged controls then it seems perhaps more likely that the correlate relates to a predisposition to tinnitus rather than presence of the condition *per se*. Note that the criterion here is only a difference in group means, and not the stringent individual level discriminability specified in the previous criterion.
- **Common across multiple etiologies of tinnitus**

  Unless there are strong rational grounds to suppose that two particular etiologies of tinnitus are mediated by different mechanisms at every stage (for instance, in subjective tonal tinnitus versus pulsatile vascular tinnitus) then there should at least be a final common pathway, and a necessary and sufficient correlate of tinnitus should be an obligate part of that pathway. In human studies it is possible to contrast patient groups with, for instance, noise induced or age-related hearing loss with patients experiencing tinnitus following ototoxic medication. In animal studies, the main tinnitus inducing methods are noise trauma, noise overexposure and salicylate toxicity.

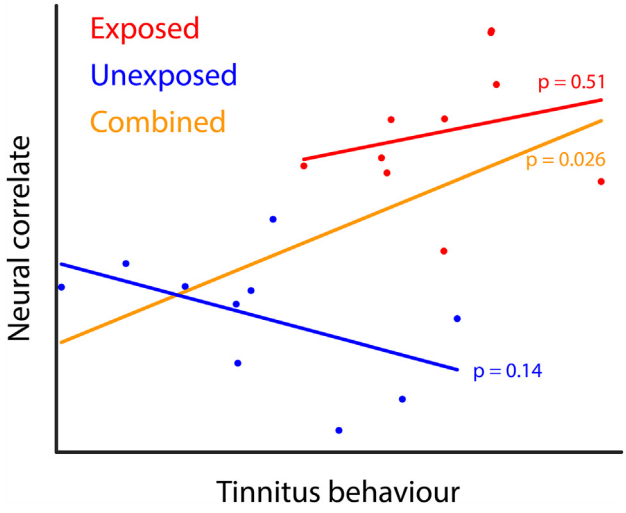

Fig. 3. Spurious correlations between tinnitus behavior and putative neural tinnitus correlate. This figure is particularly applicable to animal studies of tinnitus, as the presence of tinnitus is often inferred from conditioned or innate behavioral responses that exist on a continuum. Only two subject groups are presented, categorized by whether or not they received a damaging auditory insult such as sound overexposure (though the same principle applies even if the control group is matched for the predisposing insult). In this example, all or most of the exposed animals developed 'true' tinnitus, and none or few of the unexposed animals had it. There is also measurement noise leading to dispersion of tinnitus behavior values, which contributes to the degree of overlap between groups. One 'true' effect of exposure is to increase the putative neural correlate. The orange line indicates the regression line for the whole study population, and appears to show a significant correlation between tinnitus behavior and the neural correlate, which might be interpreted as evidence that the neural correlate is specifically one of tinnitus, rather than of exposure to the auditory damage. However, in reality it is only appropriate to consider correlations within the subject groups, rather than pooling the subjects. Once this is done (blue and red lines) is it clearly apparent that there is no significant correlation in either group, and that the non-significant trends towards correlation go in opposite directions. Thus, the correct interpretation is that the neural correlate relates to tinnitus, the auditory insult, or both, and that the present data cannot distinguish which.

- **Correlates with short-term and long-term changes in tinnitus** (especially changes in tinnitus loudness, or the presence/absence of tinnitus)

  If a candidate correlate meets the above criteria regarding individual subject discrimination but is not yoked to variations in tinnitus over time then it cannot be the sole basis of those changes. Such correlates not tracking tinnitus over time might constitute predisposing factors (or *trait* as opposed to *state* markers of tinnitus), or alternatively consequential changes such as altered focus of attention during the study.
- **Correlates more strongly with tinnitus than with attention**

  Attention affects the magnitude of both responses to attended/ignored stimuli and ongoing spontaneous neural activity. Furthermore, attention in the presence of tinnitus tends to be directed towards the auditory modality, and towards the tinnitus frequency within that modality. The same has recently been shown in a rodent model of tinnitus also (Brozoski et al., 2018). Therefore, if attention is

not carefully considered then it could cause a significant modulation of spontaneous or driven neural activity that appears to correlate with tinnitus, but in reality is a non-specific marker of focused auditory attention. Accurate standardization of attention between subjects/groups would be ideal, but in reality is very difficult to achieve.

The other way to ensure observed changes are not simply due to attention is to include an explicit modulation of attention in the study that is of larger magnitude than any potential attentional differences due to tinnitus. Thus, if the changes linked to tinnitus are of greater magnitude than those due to attention, it would seem highly unlikely that attention would prove to be responsible for the observed differences.

EVIDENCE LINKING TINNITUS TO GAIN CHANGES

This section discusses selected evidence linking tinnitus to alterations in gain anywhere in the auditory system, and considers how it fares against the criteria laid out in the previous section. It is not in the form of a systematic review, but rather aims to highlight examples that span the wide range of anatomical scales and hierarchical levels in the auditory system, and most strongly support the major contemporary theories of tinnitus generation to which they relate. Fig. 4 (A and Bi) illustrates a simplified auditory pathway, and the main sites at which gain increases relevant to tinnitus might occur.

Mechanisms of Gain – Synaptic Properties

While synaptic properties in the auditory pathway in general have been long-studied, and in tinnitus there has been a body of work looking at these in auditory-somatosensory interactions, their study in unimodal auditory processing in tinnitus has only recently been examined. In the DCN of acoustically over-exposed mice with behavioral evidence of tinnitus, release probability was found to be increased, and LTP increased to the point of saturation (Tagoe et al., 2017). The absence of an exposed non-tinnitus group precludes attribution of these changes to tinnitus or hearing loss specifically.

The literature examining somatosensory-auditory synaptic properties is much more extensive and established. Cross-model connections have long been recognized in MGB (Wepsic, 1966), and DCN (Zhou and Shore, 2004), and also that the DCN shows neuronal responses to trigeminal nerve stimulation (Shore, 2005), which are enhanced in the presence of hearing loss (Shore et al., 2009). More recently, it has become apparent that the presence of tinnitus (vs an exposed non-tinnitus group) is associated, in DCN to bimodal stimulation, with a skewing away from LTD towards LTP, and that this shift in synaptic plasticity positively correlates with firing rates and neuronal synchrony. These changes appear compellingly implicated in mechanisms of tinnitus, though so far there have not been demonstrations of accurate classification of tinnitus status at the individual subject level based on these.

Mechanisms of Gain – Neurochemistry

In rodents, ageing is associated with changes in the IC including reduced GABA concentration (Banay-Schwartz et al., 1989), reduced density of GABA-ergic neurons (Caspary et al., 1990), reduced expression of GAD (Burianova et al., 2009) and reduced stimulus-evoked GABA release (Caspary et al., 1990), and changes in auditory cortex of reduced GAD levels (Ling et al., 2005), and reduced free GABA concentration (Banay-Schwartz et al., 1989). Experimentally-induced hearing loss has been shown to cause similar changes in IC, including reduced GAD levels (Argence et al., 2006), and reduced GABA(A) receptor transcription (Dong et al., 2010). In humans, hearing loss was found to be associated with reduced auditory cortex GABA concentration (Gao et al., 2015). Studies using noise-overexposed animals in which behavioral evidence of tinnitus was confirmed have again showed concordant findings, including excessive magnitude and spread of DCN responses to stimulation mirroring those produced by application of GABA antagonists (Middleton et al., 2011), similar findings in auditory cortex (Llano et al., 2012), reduced GABA concentration in contralateral MGB (Brozoski et al., 2012), and reduced GAD expression in auditory cortex (Yang et al., 2011). Conversely, a study comparing rats with behavioral evidence of tinnitus to exposed non-tinnitus controls found *increased* tonic GABA(A) receptor currents, and associated increases in evoked bursting behavior (Sametsky et al., 2015).

Altered inhibitory glycinergic function has been demonstrated in the DCN in ageing rodents (Caspary et al., 2005), and in an age-related rodent model of tinnitus (Wang et al., 2009).

In summary of animal studies, most studies show an association between various factors indicating reduced inhibitory neurotransmission, at multiple levels of the auditory pathway, and predisposing factors to tinnitus, namely ageing and hearing loss. Exposed animals with behavioral evidence of tinnitus show similar changes, but without evidence specifically linking these to tinnitus itself. However, one study, well controlled for hearing damage, found increased GABA-ergic activity in MGB.

A single human study with hearing-matched controls shows a just-significant group-level auditory cortex GABA decrease specifically attributable to tinnitus itself (Sedley et al., 2015), while one other study has shown increased excitatory glutamine and glutamate in the contralateral, compared to ipsilateral, temporal lobes of patients with unilateral tinnitus but symmetrical hearing thresholds (Wojcik et al., 2017).

Cholinergic neurotransmission is discussed in a separate section on attention.

Mechanisms of Gain – Tonotopic Map Plasticity

Lasting effects of narrowband noise trauma, and of chronic non-traumatic narrowband noise overexposure, include a re-tuning of cat auditory cortex neurons within the noise band to *edge* frequencies immediately adjacent to it (Norena and Eggermont, 2005; Noreña and Eggermont, 2006). In a rat

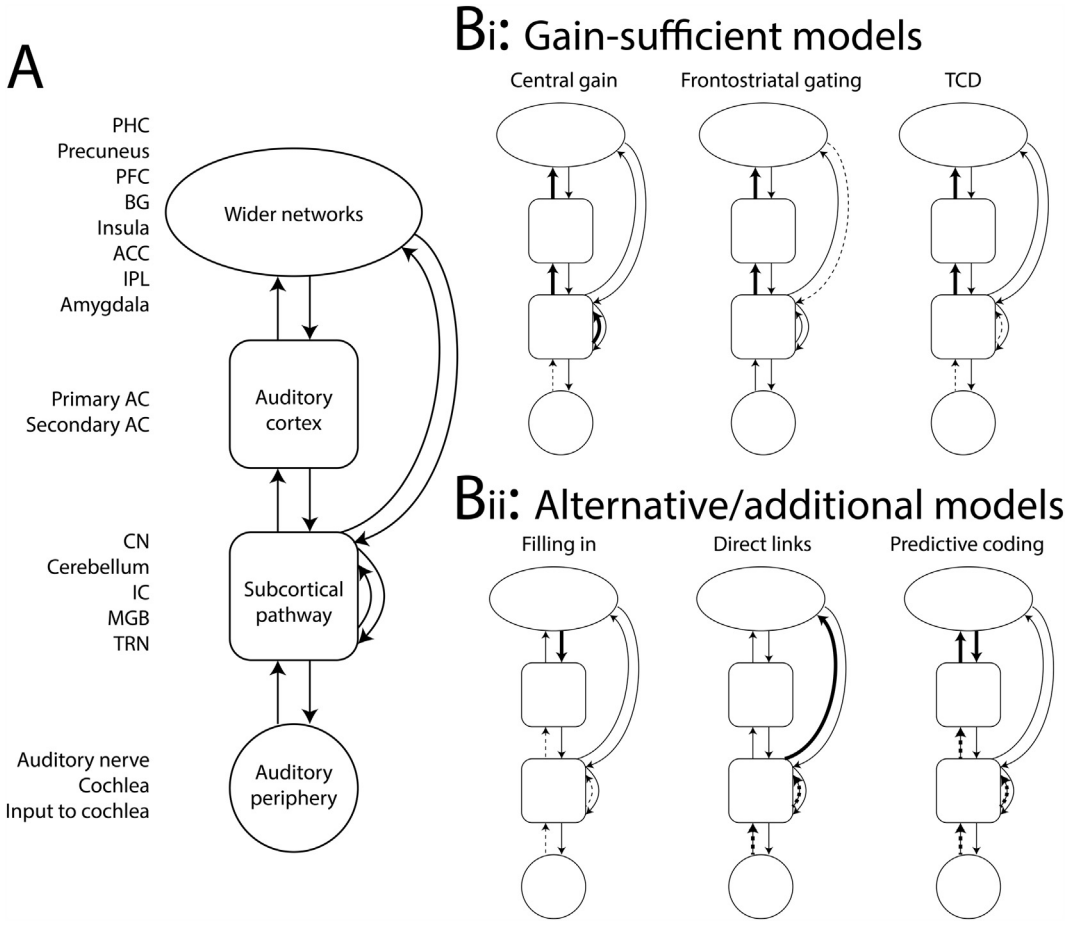

Fig. 4. Simplified schematic of the auditory pathway (A) summarizing major gain models (Bi) and models where gain changes are not required or are insufficient (Bii). A: Illustration of the major neuroanatomical groups considered in the figure, the connections between these, and which parts of the nervous system comprise each. Arrows indicating connections within the subcortical pathway particularly refer to links between CN and IC or between IC and MGB, but could encompass other connections. I consider here, in very basic terms, that conscious perception of sounds (including tinnitus) requires both representation in auditory cortex and propagation to wider brain networks subserving perception. B: Indication of the gross changes in major connections inherent in popular models of tinnitus. Bold arrows indicate stronger connections or increased information flow through connections, while dashed arrows indicate the opposite. Arrows dashed between normal and increased thickness indicate gain increases that are optional to the model in question. Bi: Models where tinnitus can be understood solely as the result of aberrant gain. In the archetypical central gain model, reduced peripheral input leads to central gain from early brainstem nuclei onwards, which is relayed on to auditory cortex and wider perceptual networks. Theoretically the gain changes might start higher in the auditory hierarchy than illustrated here. Frontostriatal gating postulates that inhibitory prefrontal connections, via nucleus accumbens, are deficient, and thus fail to suppress ascending signals from MGB. At the level of auditory cortex, this is equivalent to other central gain models. In TCD, the putative tinnitus driver is increased low-frequency burst firing in MGB which projects to auditory cortex. The only differences from other gain models are the rhythmicity of this firing, and the origin of the firing in thalamic hyperpolarization; i.e. the conversion from understimulation at one level to overactivity at the next occurs higher up the auditory pathway. The common feature to all gain models is that they must require an ongoing spontaneous pattern of excessive activity at the level of auditory cortex. Bii: In filling in models, the deprivation of auditory input due to hearing loss does not result in central gain, but instead leads to chronic understimulation right up to the level of auditory cortex. The deprived region gets activated by adjacent normally-functioning parts of auditory cortex, or from auditory memory, either of which leads to tinnitus. There exist direct links from ascending sensory pathways to multimodal forebrain areas, for instance the amygdala. In principle, such connections could be overactive in a way that orients perception towards a signal represented in auditory cortex, but would not have been consciously perceived without the cue from direct subcortical inputs. In predictive coding models, there may or may not be increased central gain leading to hyperactivity of auditory cortex, as this is not the determinant of whether tinnitus occurs (though it is usually a major contributor). Instead, higher perceptual networks that normally act to disregard spontaneous auditory activity as noise switch to recognizing the signal as an auditory entity. Increased gain increases the chance of this happening. PHC = parahippocampal cortex. PFC = prefrontal cortex. BG = basal ganglia. ACC = anterior cingulate cortex. IPL = inferior parietal lobe. AC = auditory cortex. CN = cochlear nuclei. IC = inferior colliculus. MGB = medial geniculate body. TRN = thalamic reticular nucleus. TCD = thalamocortical dysrhythmia.

study of noise-induced tinnitus, behavioral evidence of tinnitus correlated with the degree of tonotopic map plasticity in auditory cortex (Engineer et al., 2011), though differential levels of damage due to the noise stimulus could not be ruled out as a common determinant of both.

In humans, tinnitus patients with hearing loss were found to have altered source location of evoked electromagnetic auditory responses compared to normal-hearing controls (Mühlnickel et al., 1998; Wienbruch et al., 2006). However, subsequent human work using relatively normal-hearing tinnitus patients and hearing-matched controls, this time using fMRI, found no evidence of such tonotopic map reorganization attributable to tinnitus (Langers et al., 2012), at least at a macroscopic scale.

Mechanisms of Gain – Gating

The existence of an underactive gain control mechanism, acting via the TRN, has long been speculated to underlie tinnitus, particularly in the presence of normal hearing (Rauschecker et al., 2010, 2015), based initially on the finding of reduced grey matter, in human tinnitus groups with tinnitus compared to normal-hearing controls, in ventromedial prefrontal cortex, which is thought to regulate sensory gating via the nucleus

accumbens and TRN (Mühlau et al., 2006; Leaver et al., 2011). However, other groups have not been able to replicate the structural brain changes as a function of either hearing loss or tinnitus (Husain et al., 2011). Resting-state EEG in humans has found that the strength of ongoing low to middle frequency oscillations in ventromedial prefrontal cortex, and adjacent anterior cingulate cortex, correlates with the percentage of time subjects are aware of their tinnitus, suggesting perhaps a more dynamic role in gating relating to moment-to-moment awareness (Song et al., 2015).

As discussed previously, if deficient gating via the TRN is the mechanisms of tinnitus in general, then this should be manifest as some sort of increased pattern of spontaneous activity at the level of MGB and auditory cortex, and evidence for such activity is considered in a subsequent section.

A widely-studied marker of gating is suppression of the P50 cortical evoked potential, i.e. reduction in amplitude from the first to the second stimulus in a pair presented in quick succession. Intact gating is indicated by significant P50 suppression. Recently, young normal-hearing tinnitus patients were found to have smaller P50 responses than controls (to low-frequency tones far from the tinnitus frequency) to the first stimulus in the pair, and similarly-sized responses to the second (Campbell et al., 2018). Contrary to the authors' interpretation, I would take this as possible evidence of persistently active gating in tinnitus patients, compared to controls who activate gating mechanisms dynamically after the first stimulus in each pair.

Behavioral/Perceptual Manifestations of Gain

It has long been recognized that symptoms of hyperacusis are more common and more pronounced in patients with tinnitus compared to controls, though the two conditions are not inextricably linked, as only 30-40% of tinnitus patients have symptomatic hyperacusis, and somewhat different audiometric profiles have been seen in tinnitus and hyperacusis patients (Sheldrake et al., 2015). Noise-exposed animals with behavioral evidence of tinnitus show exaggerated acoustic startle responses compared to controls with equal hearing thresholds, which is taken as evidence of hyperacusis (Sun et al., 2012; Chen et al., 2013). In human tinnitus patients, increased loudness growth has been observed in tinnitus ears in tinnitus patients (Hébert et al., 2013), while other work has found reduced uncomfortable loudness levels (ULLs) in both tinnitus and non-tinnitus ears of tinnitus patients versus controls (Shim et al., 2017). Reduced ULLs have been found in volunteers without permanent tinnitus audible in normal listening environments, but who experienced tinnitus in a soundproof room (Sanchez et al., 2016).

Neural Manifestations of Gain – Neuronal Firing Rates

There is overwhelming and consistent evidence that noise trauma and overexposure sufficient to produce tinnitus causes lasting increases in SFR at all levels of the central auditory pathway studies, including DCN (Brozoski et al., 2002; Kaltenbach et al., 2004; Brozoski and Bauer, 2005; Zhang et al., 2006; Finlayson and Kaltenbach, 2009), IC (Ma et al., 2006; Bauer et al., 2008; Mulders and Robertson, 2009), MGB (Kalappa et al., 2014) and AC (Noreña and Eggermont, 2006; Engineer et al., 2011). Studies specifically designed to distinguish SFR correlates of tinnitus from hearing loss have been much less numerous, but in DCN have shown increased SFR in equally exposed tinnitus vs non-tinnitus groups (Wu et al., 2016), and that treating tinnitus via cross-modal Hebbian plasticity reduced SFR (Marks et al., 2018). However, there are some observations from these and other studies that cast doubt over the viability of SFR as a mechanism or biomarker for tinnitus. These include that a plasticity-based intervention successful in eliminating tinnitus behavior further increased auditory cortex SFR rather than normalizing it (Engineer et al., 2011), that the increase in SFR following noise trauma occurs after a delay of hours, unlike tinnitus which begins rapidly (Norena and Eggermont, 2003), and that neither SFR nor low-frequency burst firing in IC proved discriminatory for the presence of absence of behavioral evidence of tinnitus following noise trauma at the individual subject level (Longenecker and Galazyuk, 2016).

Regarding drug-induced tinnitus, while it has been shown that 'platin' chemotherapy agents produce similar changes in IC to noise trauma (Bauer et al., 2008), neural consequences of salicylate exposure show a largely different pattern, including SFR that is reduced in the cochlear nerve (Stolzberg et al., 2011), DCN (Wei et al., 2010), IC (Ma et al., 2006) and auditory cortex (Sun et al., 2009; Yang et al., 2011). Conversely, increased SFR has been found in recordings from extra-lemniscal parts of IC (Chen and Jastreboff, 1995; Manabe et al., 1997), and non-primary auditory cortex (Eggermont and Kenmochi, 1998).

Driven firing rates behave similarly to SFR in some ways. Immediately after noise trauma stimulus-evoked responses were found to decrease in IC, but differed in that there was an immediate increase in evoked responses in auditory cortex (Sun et al., 2012). Salicylate toxicity has likewise been shown to cause a rapid increase in driven firing rates in rat auditory cortex (Yang et al., 2007).

To summarize, in most of the auditory pathway SFR is increased by noise trauma or platin chemotherapy, and reduced by salicylate, while salicylate increases SFR in extra-lemniscal IC and non-primary auditory cortex. Instances of specific attribution of these changes to tinnitus are limited, applying only to DCN in noise-induced tinnitus. The different directions of change with different methods of inducing tinnitus render SFR in most locations unlikely to prove a neural basis for tinnitus. Extra-lemniscal IC and non-primary auditory cortex remain as theoretically potential sites of common mechanisms of tinnitus across different etiologies, but there is little evidence so far to support this.

Neural Manifestations of Gain – Local Neural Synchrony

Local neural synchrony has been shown to be a more reliable indicator of acoustic stimulation than neuronal firing rates (Eggermont, 2000). In DCN, increased synchrony and bursting (correlated to enhanced cross-model LTP (Marks et al.,

2018)) have been found to be significantly elevated, at group level, between animals overexposed to noise with vs without behavioral evidence of tinnitus (Wu et al., 2016). Thus, a persuasive case is made that these changes appear specifically attributable to tinnitus. However, so far, these measures have not been shown to discriminate individual subjects as to their tinnitus status. Though they did show a correlation with the degree of tinnitus behavior, this appeared to be driven by between-group rather than within-group differences. In IC, animals with noise-induced and platin-induced tinnitus exhibited similarly increased neural synchrony compared to unexposed controls (Bauer et al., 2008). In auditory cortex, neural synchrony increases rapidly following noise trauma, in line with the timescale of emergence of tinnitus perception (Noreña and Eggermont, 2003), and chronic similar changes persist (Norena et al., 2006). Non-traumatic noise overexposure likewise increases neural synchrony in the whole central auditory pathway (Noreña and Eggermont, 2006; Pienkowski and Eggermont, 2009), particularly in tonotopic divisions above the frequency of the noise. In the auditory cortex of rats with behavioral evidence of noise induced tinnitus, neural synchrony was increased, and a plasticity-based intervention successful in behaviorally eliminating tinnitus reversed this excess synchrony (Engineer et al., 2011).

To summarize findings relating to local neural synchrony, this appears ubiquitously increased at multiple levels of the auditory pathway in noise-induced tinnitus. Evidence specifically linking to this change to tinnitus is much more limited, and includes a clear difference between equally exposed tinnitus and non-tinnitus groups, in DCN, and common reversal of excess synchrony in auditory cortex and tinnitus behavior with a single intervention. Neural synchrony thus appears a plausible neural correlate of tinnitus, though additional complementary evidence would make a stronger case, such as demonstration of accurate single-subject classification of equally exposed animals into tinnitus-and non-tinnitus groups based on such a metric of neural synchrony.

Neural Manifestations of Gain – Cortical Oscillations

Most human research on neural synchrony is limited to the extracranial measurement of large-scale oscillations. Low-frequency oscillations encompass delta (1-3 Hz) and theta (3-8 Hz) frequencies (considered as a single frequency band here for clarity), which likely relate to thalamocortical drive, and organize the firing patterns of higher frequency oscillations the amplitude of which is coupled to their phase (Canolty et al., 2006). Demonstration of the putative drive comes from direct thalamic recordings in human neurosurgical patients with tinnitus and other neurological or psychiatric pathologies (Jeanmonod et al., 1996). More recent work in rodents with noise-induced tinnitus (Kalappa et al., 2014) has demonstrated similar burst firing, but at a lower frequency. Hearing-matched controls or exposed animals without tinnitus were not featured in these studies. Human studies have demonstrated increased amplitude of low-frequency oscillations in auditory cortex of patients with tinnitus compared to normal hearing controls (Llinás et al., 1999; Weisz et al., 2005, 2007; Moazami-Goudarzi et al., 2010), leading to the popular theory of *thalamocortical dysrhythmia* (Llinás et al., 1999; De Ridder et al., 2015), which proposes that these low-frequency oscillations trigger high-frequency oscillations that are the basis of the tinnitus percept. However, a similar study using tinnitus patients and controls with and without hearing loss found only a just-significant difference in low-frequency oscillation amplitude between tinnitus with hearing loss and control with normal hearing groups, and not between others (Adjamian et al., 2012). Transient suppression of tinnitus via residual inhibition (RI) following, or masking during, a prolonged loud auditory stimulus has been associated with reduced low-frequency oscillation amplitude in auditory cortex (Kahlbrock and Weisz, 2008; Adjamian et al., 2012; Sedley et al., 2012, 2015). An auditory plasticity-based intervention produced greater and longer-lasting short-term low-frequency suppression than an acoustically matched sham stimulus (Adamchic et al., 2017) and, when successful, was associated with long-term reductions of low-frequency amplitude in and around auditory cortex (Tass et al., 2012). In a model of salicylate induced tinnitus, exposed animals had reduced low frequency oscillation amplitude compared to unexposed controls (Stolzberg et al., 2013).

Mid-range oscillations in the alpha (8-12 Hz) and beta (12-30 Hz) ranges do not have a clear enough relationship to gain to be suitable for consideration in the present review, though these may still have important roles in determining various aspects of tinnitus phenomenology.

High-frequency oscillations in the gamma range (>30 Hz) have a fairly ubiquitous role in local processing (Merker, 2013), are increased or elicited by attention (Bauer et al., 2006) and are a major contributor to synchronous gain, as previously reviewed (Sedley and Cunningham, 2013). There is a clear quantitative link between gamma oscillation magnitude and *prediction error* (unexpectedness of a sensory signal), which is discussed separately later (Arnal et al., 2011; Sedley et al., 2016). Increased resting-state gamma oscillation magnitude in auditory cortex has been reported in tinnitus patients compared to young, normal hearing controls (Weisz et al., 2007), but this finding was not replicated in a similar study with age and hearing matched controls (Adjamian et al., 2012). Correlation between resting-state gamma amplitude and subjective tinnitus intensity has been reported (van der Loo et al., 2009; Balkenhol et al., 2013), but only one of two subsequent studies on much larger cohorts replicated this finding, as a just-significant effect (Vanneste et al., 2015; De Ridder et al., 2015). Transient reduction in gamma oscillation amplitude can accompany transient acoustic suppression of tinnitus (Sedley et al., 2012; Adamchic et al., 2017) and suppression by cortical electrical stimulation (De Ridder et al., 2011), though gamma *increases* have also accompanied transient tinnitus suppression in a small number of subjects (Sedley et al., 2012, 2015). More unexpectedly, transient tinnitus *increases* following acoustic stimulation were also associated with *suppression* of gamma oscillations (Sedley et al., 2012). In the longer term, tinnitus exacerbation by failed acoustic therapy has correlated with gamma amplitude increases (Vanneste et al.,

2013), while successful acoustically based tinnitus therapy has been accompanied by gamma decreases (Tass et al., 2012). However, successful psychological treatment of tinnitus leading to reduced distress, but not decreased intensity, has been linked to the same pattern of low- and high-frequency oscillation suppression in auditory cortex (Song et al., 2017), raising the possibility of the pertinent correlation being with secondary consequences of tinnitus, such as attention, rather than the tinnitus itself.

To summarize findings relating to human oscillations, both low-frequency and high frequency oscillations in auditory cortex appear important in tinnitus, but neither has been demonstrated to significantly differ in the resting state between tinnitus patients and matched controls, even at group level, let alone the additional requirements for a putative neural correlate. Therefore they are unlikely in themselves a sufficient basis for the condition. Furthermore, there are some instances of inverse correlation between gamma oscillations and tinnitus intensity, casting doubt over their candidacy as a sufficient correlate of tinnitus, even in the presence of additional evidence.

Neural Manifestations of Gain – Evoked Potentials

The earliest auditory evoked potential is the auditory brainstem response (ABR), which features 7 characteristic peaks in its waveform, representing stages of processing from auditory nerve (wave I) to cortex (wave VII). Waves I and V are of most interest in tinnitus, and an elevated ratio of wave V/I amplitude is seen as evidence of central gain. Initial reports found evidence of reduced wave I amplitude and increased V/I ratio (Schaette and McAlpine, 2011; Gu et al., 2012) in tinnitus patients with normal audiograms compared to controls, interpreted as evidence of hidden hearing loss with a compensatory increase in central gain. Subsequent studies aiming to replicate these findings have variably reproduced them (Chen et al., 2017) or yielded negative results (Shim et al., 2017).

Periodic acoustic stimuli, most typically sinusoidally amplitude modulated tones, elicit periodic oscillations in the evoked potential at the same rate as the stimulus, termed the auditory steady state response (ASSR) (Galambos et al., 1981). The modulation rate determines the level of the auditory pathway predominantly represented, with the commonest frequency of 40 Hz highlighting the level of input to primary auditory cortex and initial cortical processing. The ASSR is involuntary and pre-attentive, but is increased by auditory-focused attention (Gander et al., 2010), except at the tinnitus frequency in tinnitus patients (Paul et al., 2014), taken as evidence of a pre-existing excess of focused attention in tinnitus. Initial observations in tinnitus research were increased ASSR amplitudes, in high frequencies close to the tinnitus frequency, which increased in proportion to subjective level of tinnitus distress (Diesch et al., 2004). Increased magnitude and displaced location was also reported, at tinnitus and non-tinnitus frequencies (Wienbruch et al., 2006), in patients versus normal hearing controls. Subsequent work using hearing-matched controls showed no tinnitus-related ASSR amplitude changes at any of a range of frequencies (Paul et al., 2014), or a specific decrease in magnitude at the tinnitus frequency (Roberts et al., 2015), with a transient increase in magnitude during residual inhibition of tinnitus, while a different pattern, of enhancements in different frequencies, was seen in the control group. This study, along with another showing differential patterns of interference or enhancement between multiple simultaneous AM tones (Diesch et al., 2010), suggests that within-subject manipulations relevant to the tinnitus frequency may be much more revealing of tinnitus than simple response magnitudes, which may be overshadowed by other factors. More recent work has examined rapid homeostatic responses in ASSRs pertinent to dynamic range adaptation (Diesch and Hassel-Adwan, 2017), by having long stimuli with upward and downward ramps in intensity. The finding was that ASSRs in tinnitus patients, compared to matched controls, had reduced overshoot in upward ramps and decreased undershoot in downward ramps.

The N1(m), or N100(m), is the dominant auditory evoked potential, and is generated across primary and non-primary auditory cortex. It is pre-attentive, but heavily modulated by attention and other aspects of current brain state. It increases in amplitude with louder stimuli, but not necessarily linearly. Changes in N1 amplitude have been reported in many studies, without any apparent consistency. For stimuli below the tinnitus frequency, tinnitus patients (usually against non-hearing matched controls) have been found to show increased (Hoke, 1990; Hoke et al., 1998; Norena et al., 1999; Delb et al., 2008), reduced (Attias et al., 1993; Jacobson and McCaslin, 2003) or unchanged (Jacobson et al., 1991; Colding-Jørgensen et al., 1992) N1 amplitudes. At the tinnitus frequency, N1 amplitudes have been found to show steeper loudness growth functions (Kadner et al., 2002; Pineda et al., 2008), to be unchanged compared to controls (Weisz et al., 2005), or show reduced amplitude in a pattern of results correlating with hearing loss rather than tinnitus (Sereda et al., 2013). Recent work has found that N1 amplitudes in the tinnitus vs non-tinnitus ear of unilateral patients decrease more in the presence of band-eliminated noise, indicating broader frequency tuning of the N1 response (Sekiya et al., 2017).

Mismatch negativity (MMN) and P300 responses are not primarily manifestations of gain, and are beyond the scope of this article.

In summary, there is not compelling evidence to suggest that alteration in the amplitude of any particular early auditory evoked potential is a reliable indicator of tinnitus, even at group level.

Neural Manifestations of Gain – Functional Imaging

The major current functional brain imaging is functional magnetic resonance imaging (fMRI), which uses the overshoot in local perfusion, hence oxygenation (the BOLD response), that transiently follows local activation to infer and localize brain activity. The BOLD response most closely relates to gamma oscillation magnitude (Mukamel et al., 2005). Changes in blood oxygenation are relative to baseline, and therefore there is no meaningful interpretation of resting-

state BOLD in terms simply of its magnitude. Resting state BOLD correlations between areas are a separate area of study that do not directly relate to gain, and are beyond the scope of this article. Positron emission tomography (PET) measures local glucose uptake as a surrogate marker of neural activity, and single-photon emission computed tomography (SPECT) measures local blood flow. These radioisotope-based methods are much less often used nowadays for functional brain imaging, but do have interpretable resting state magnitude.

Three resting-state PET (Geven et al., 2014) and SPECT (Laureano et al., 2014; Ueyama et al., 2015) studies, one of which featured age and hearing equivalent patient and control groups, all found no differences in any part of auditory cortex between groups, though differences were seen in non-auditory areas. Tinnitus modulations have been studied with PET, and found decreases in tinnitus with orofacial muscle contraction (Lockwood et al., 1998) and intravenous lidocaine (Reyes et al., 2002) in auditory cortex of tinnitus patients compared to the same interventions in controls.

There have been several reports showing elevated BOLD responses to acoustic stimulation in the inferior colliculi (and sometimes cochlear nuclei) of tinnitus patients (Lanting et al., 2008; Melcher et al., 2009; Boyen et al., 2014), including one with age and hearing matched controls (Boyen et al., 2014). The former two studies reported increased activity in MGB and auditory cortex also, while the latter did not find these. One study using healthy hearing-unmatched controls found sound-evoked increases in auditory cortex and nucleus accumbens (Leaver et al., 2011). These studies did not stratify tinnitus patients based on the presence or absence of hyperacusis. One study that performed this stratification found that both tinnitus patient groups showed elevated responses in auditory cortex, while only the hyperacusis group showed increases in IC and MGB (Gu et al., 2010).

To summarize functional imaging findings, tinnitus is not associated with any indication of resting-state hyperactivity in auditory cortex, but short-term tinnitus modulations are accompanied by corresponding activity changes in auditory cortex. On average, tinnitus patients show elevated sound responses throughout the auditory pathway, but one study suggests that below the level of auditory cortex these changes may be indicative of hyperacusis rather than tinnitus *per se*.

Summary of Evidence Linking Tinnitus to Gain Changes

Tinnitus and reduced sound level tolerance show an association, but are not inextricably linked. The relationship has been demonstrated in humans and animals. Auditory pathway GABA decreases are seen in animals with both hearing loss and tinnitus, and specifically associated with tinnitus in one human study. Spontaneous firing rates are generally increased by noise overexposure, decreased by salicylate toxicity, and do not show a convincing relationship to tinnitus. Increased local neuronal synchrony has been demonstrated in many animal studies of hearing loss and tinnitus, and a small number of studies with exposed non-tinnitus animals that can specifically attribute observed changes to tinnitus itself. Oscillations in human brains, indicating large-scale neural synchrony, correlate with tinnitus intensity over short- and long-term changes, but do not differentiate tinnitus from matched control groups. Increased functional imaging responses to auditory stimulation are also seen in tinnitus patients, and may reflect tinnitus and/or hyperacusis depending on the level of the auditory pathway involved. As for oscillations, evoked response magnitudes themselves do not differentiate tinnitus from non-tinnitus groups, but their manipulation by acoustic and other factors may prove a more useful discriminator.

The above evidence combined makes a convincing case that tinnitus is linked to central gain, and the most parsimonious explanation is that increased gain is a causative factor for tinnitus. However, the present evidence does not demonstrate that central gain is sufficient to cause tinnitus. As well as featuring hearing-matched control groups, and presenting correlations within the tinnitus group as well as the whole subject group, studies aiming to implicate gain as a sufficient basis for tinnitus should also examine how accurately their gain metric(s) of interest can classify individual subjects in terms of their tinnitus status. Few studies to date have presented these data, and therefore it remains to be seen whether such an accurate classification exists but has simply not been reported, or whether other factors, such as those discussed below, interact with gain changes to determine the emergence of tinnitus.

ATTENTION AS A CONTRIBUTING FACTOR IN TINNITUS RESEARCH

Attention is a dynamic and flexible tool for cognitive control by selectively enhancing the representation of certain stimuli over others. It is mediated by the basal forebrain cholinergic system, which has finely-tuned topographic projections to diverse cortical regions (Hasselmo and Sarter, 2011). The action of these projections is to enhance the postsynaptic gain of ascending inputs to their target areas (Feldman and Friston, 2010), and thus cholinergic gain control and attention can be considered different ways of thinking about the same process.

A role for attention in the causation and perpetuation of tinnitus has been proposed (Roberts et al., 2013), which has been encompassed into a wider account of tinnitus based on predictive coding (Sedley et al., 2016).

Irrespective of the correctness of attention-based theories of tinnitus, attention is well known to affect the magnitude of several metrics of neural activity and/or central gain widely used to study tinnitus, as discussed in their respective sections previously. This potentially poses a major confound for tinnitus research, if there turns out to be any systematic difference in attentional deployment between tinnitus and control groups. Intuitively, particularly for resting state or task-free studies, one might expect tinnitus patients to spend more time focusing on their tinnitus, whereas controls might direct their attention in a much wider array of directions. Difficulties with cognition and attention are frequently reported by tinnitus

patients, particularly in the context of high levels of tinnitus distress, and recently the cognitive deficit has been characterized as a failure of the ability to switch attention (Trevis et al., 2016). Further evidence of altered auditory attention in tinnitus comes from ERP studies, showing attention-linked changes in early cortical processing (Gander et al., 2010) and high-level processing of unexpected stimuli P300 (Mannarelli et al., 2017; Asadpour et al., 2018). It is not just human volunteers who have altered attention due to tinnitus, but recent rodent work has found increased attention towards tinnitus-like sounds and away from other sounds (Brozoski et al., 2018).

Psychological interventions for tinnitus work largely by disengaging the attentional focus on tinnitus, but do not quiet the tinnitus sound. A recent resting-state EEG study (Song et al., 2017) found correlates of psychological treatment success that looked almost identical to correlates of successful treatment (Tass et al., 2012) to quieten the tinnitus sound itself (which consequently reduced tinnitus-related attention and distress). This raises the possibility that many apparent correlates of tinnitus may, in fact, be correlates of the consequent attentional alteration rather than indicators of the mechanisms of tinnitus generation.

To move forward from this kind of speculation, recent work has begun to directly examine the effect of attention on resting-state EEG in tinnitus (Neff et al., 2019). Comparing a condition with no instructions on attentional focus (as used in most resting-state tinnitus studies) to one with specific instructions to attend to the tinnitus sound, no difference was seen in ongoing brain activity. However, given that the likeliest non-null hypothesis would be excessive auditory attention in tinnitus patients, the more sensitive contrast might be the neutral condition vs attending to another modality (e.g. visual), which future work might examine.

IF GAIN IS NOT A (SUFFICIENT) CAUSE OF TINNITUS

If a given gain mechanism or metric turns out not to reliably discriminate tinnitus status, then some tempting initial arguments can be made to explain this away. It could be claimed that noise in the data causes some overlap between groups, thus preventing highly accurate classification. Alternatively, one could hypothesize that there are multiple origins for tinnitus, and thus only certain subjects/animals might manifest a particular causal mechanism. However, though these may be valid explanations for some individual studies, with direct recordings at least possible in animals, with standardized methods of tinnitus induction it should be possible to achieve accurate single-subject discrimination in at least one study specifically designed to be able to achieve this.

It could also be argued that there are multiple mechanisms and metrics of gain working synergistically, and that what determines tinnitus is the composite action of all of these, hence individual measures do not provide perfect discrimination. However, in this case strong evidence could still be obtained through implementing a computational, but empirically tested, model of gain encompassing all these measures.

Given that large-scale resting-state activity in the human auditory pathway appears unchanged in tinnitus, but short-term tinnitus modulation is associated with significant changes, one might argue that certain gain mechanisms are increased in tinnitus, but over long timescales are compensated for by homeostatic plasticity, leading to unchanged net activity. However, in this scenario the tinnitus-linked gain changes should still be detectable and separable from the compensatory homeostatic factors.

If gain truly is not the cause of tinnitus then then alternative explanations include direct links between the subcortical auditory pathway and higher perceptual networks which bypass auditory cortex, activation of deafferented auditory cortex from adjacent normally functioning areas or from auditory memory (De Ridder et al., 2014), entry of the tinnitus signal into wider perceptual networks (De Ridder et al., 2013), and a predictive coding model in which tinnitus perception is the interplay of spontaneous synchronous activity and the formation of concordant top-down sensory predictions (Sedley et al., 2016). In the latter model, increased gain is a process that is usually, but not always, necessary to cause tinnitus, but not sufficient. These models are summarized in Fig. 4 Bii.

CONCLUDING SUMMARY

Gain control is fundamental to homeostasis, and encompasses a diverse range of contributory mechanisms, neural and behavioral consequences. Peripheral hearing damage causes dramatic, rapid and long-lasting changes in gain and, in some cases, tinnitus. A relatively small number of gain changes have been convincingly linked to tinnitus itself over and above the predisposing hearing damage, though none has been shown to accurately discriminate tinnitus subjects from matched controls at the individual level. The biggest recurring confound in tinnitus research is failure to include hearing matched controls (in human research) or an exposed non-tinnitus group (in animal research), and control of attention is theoretically a major confound which requires much more attention in future.

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