

Psychoacoustics of Tinnitus: Lost in Translation

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Tinnitus: What Is It?

Tinnitus is the perception of sound without an external source, often experienced as a constant or frequent ringing, humming, or buzzing. Tinnitus is reported by more than 50 million people in the United States alone (Shargorodsky et al., 2010); conservatively 1 in 10 US adults has tinnitus (Bhatt et al., 2016). It is estimated that 20-25% of patients with tinnitus consider the symptoms to be a significant problem (Seidman and Jacobson, 1996).

Various nomenclature has been applied to describe tinnitus, including terms such as subjective or objective tinnitus and the more recent recommended terms primary and secondary tinnitus (Tunkel et al., 2014). Primary tinnitus refers to tinnitus that is idiopathic and may or may not be associated with sensorineural hearing loss (SNHL; hearing loss (HL) related to dysfunction of the inner ear and auditory nerve). Secondary tinnitus refers to tinnitus that is associated with a specific underlying cause other than SNHL or an identifiable organic condition such as pulsatile tinnitus (heartbeat perception in ear). Our discussion here is focused on primary tinnitus, which is the more common variant.

Causes of Tinnitus

The understanding of the physiological source of primary tinnitus has significantly expanded over the past 30 years. Numerous portions of the auditory pathway and nonauditory neural pathways have been implicated in tinnitus perception and reaction. Still, the exact mechanisms underlying tinnitus remain elusive.

Contemporary research points to both peripheral and central factors that underlie tinnitus. In other words, peripheral changes to the auditory part of the inner ear and auditory neural integrity, most commonly resulting from noise exposure, ototoxic drugs, and age-related factors, result in compensatory changes/neural plasticity

at more central segments of the pathway. These changes include (1) an increase spontaneous neural activity of excitatory neurons/neurotransmitters and a reciprocal decrease in activity of inhibitory neurons/neurotransmitters, resulting in central gain; (2) distortions in frequency representation as input to more central regions is restricted due to peripheral damage; and (3) nonauditory pathway/structure recruitment, suggesting a multisensory and distributed brain network implicated in mediating tinnitus perception and reaction. Simply stated, tinnitus is the attempt of the brain to fill in the reduced peripheral input (Spankovich, 2019).

Perception Versus Reaction to Tinnitus

A critical distinction is the perception of tinnitus versus the reaction to tinnitus. The tinnitus percept or phantom sound itself has minimal repercussions for morbidity or mortality. Conversely, the reaction or emotional response to tinnitus can have a substantial effect on a person's functional status (Jastreboff and Hazell, 1993). Almost everyone with tinnitus, whether bothersome or not, would want the percept eliminated if possible (Tyler, 2012).

Clearly, tinnitus is not perceived as a positive experience. The onset of tinnitus perception does not generally evoke a feeling of improved health or well-being. For example, if you hear a grinding noise in your car engine one day, your first reaction is not positive in nature. The reaction to tinnitus may further be influenced by events related to its onset, where the tinnitus becomes a reminder of that experience (Fagelson, 2007). For example, a person with an acoustic neuroma (tumor of the auditory-vestibular nerve) and its associated tinnitus may experience an enhanced awareness to tinnitus changes and an exacerbated reaction due to concern that it is a sign the tumor is growing larger or more invasive. A soldier who has experienced tinnitus during or following an active engagement may be

reminded of that experience by the presence of the tinnitus, reinforcing in their mind that they cannot escape the tinnitus nor escape or leave the past behind them.

Is There a Cure for Tinnitus?

Despite decades of research there is no “cure” for tinnitus. Indeed, no medication or surgery can remove the tinnitus perception from the brain. In the absence of a cure, medical interventions focus on mitigating the tinnitus reaction. Treatment options generally include some form of counseling (e.g., education on the neuroscience of tinnitus) and use of sound enrichment (e.g., hearing aids) to help diminish the tinnitus perception and reaction (Tunkel et al., 2014).

The most common side effects of tinnitus are sleep disturbances, concentration issues, loss of quiet/feeling of inability to escape the tinnitus, and emotional/stress-based issues (Tyler and Baker, 1983). Although rare, tinnitus can result in suicidal ideation and suicide (Szibor et al., 2019). It is also common for persons with tinnitus to attribute their hearing difficulties to their tinnitus perception (Henry et al., 2015). This is in general unsupported; tinnitus does not cause HL, but, rather, HL causes tinnitus. Nonetheless, tinnitus can affect concentration that can impact listening (Burns-O’Connell et al., 2019) and speech understanding with competing noise (Oosterloo et al., 2020).

Measuring Tinnitus in Humans

There is currently no widely accepted or validated method to identify the presence of primary tinnitus and quantification of its perceptual characteristics other than what is reported by the patient. An objective measure of primary tinnitus by the clinician, a long-held goal, is complicated by the relationship among tinnitus, HL, and hyperacusis (sound sensitivity related to increased central neural activity compensating for reduced peripheral input) and a lack of sensitivity and specificity from electrophysiological measures or imaging studies. Developing objective measures of tinnitus has been challenging in studies in both human and animal.

Then again, perhaps an objective measure to rule-in or rule-out the presence of tinnitus is not necessary. For example, the gold standard for assessment of hearing sensitivity is the pure-tone audiogram (Figure 1), which indicates the lowest sound level a human or animal can detect at different frequencies. The audiogram is, however, a psychophysical measure that is nonobjective in nature. Of course, a method

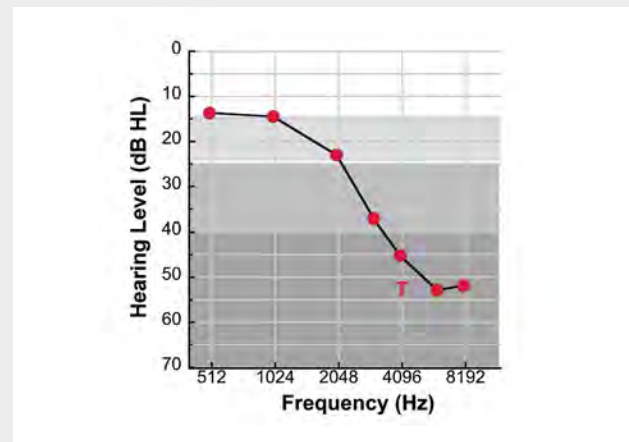


Figure 1. Audiogram and tinnitus match. An audiogram is a graphical representation of hearing thresholds at different frequencies. The frequency of the signal is plotted against the level required for the patient to detect the sound stimulus. Gray bars, variable levels of hearing loss (HL). Levels less than 15 dB HL are considered normal hearing and greater than 15 dB HL corresponds to escalating levels of HL severity. This tinnitus patient (right ear only) has normal low-frequency hearing, sloping to a high-frequency HL or a moderate level. Red T represents the pitch and loudness match for the patient. In brief, this patient matched their tinnitus pitch at 4,000 Hz and loudness at 55 dB HL or 10 dB sensation level to their threshold (45 dB HL).

to measure tinnitus that has translation between animal models and humans would be most efficacious to empower development of diagnostic and treatment approaches.

Recommendations for the psychophysical assessment of tinnitus were postulated over 20 years ago by the Ciba Foundation and the National Academy of Sciences. Methods for administering the psychoacoustic battery for tinnitus assessment have been reviewed (Henry, 2016). To date, standardization of these procedures is still not recognized; however, generalized clinical methods are briefly described here.

Pitch match (PM) measures the patient’s perceived tinnitus pitch (perception of sound frequency) by matching the tinnitus to a specific frequency or range of frequencies. PM is typically measured, although crudely, using an audiometer where two sounds are played, and the person with tinnitus chooses the pitch closer to their tinnitus percept. Most patients with peripheral hearing deficits match their tinnitus pitch at frequencies respective to their HL.

Loudness match (LM) measures the perceived loudness level of the tinnitus and is typically reported in sensation level (SL), that is, the level relative to the individual's auditory threshold. LM is measured by presenting a tone or noise and asking the patient to indicate if the tone is softer or louder than their tinnitus. The intensity of the tone is then adjusted until the patient reports the tone is a comparable loudness to their tinnitus.

To determine the ability of external sounds as a means of tinnitus suppression (i.e., masking), the minimum masking level (MML) is often assessed. The MML is the minimum level of external acoustic stimulation, typically a noise, needed to cover up the patient's tinnitus perception. In this assessment, a low-level broadband noise (BBN) is presented to the patient via an audiometer. The intensity of the noise is slowly raised until the patient reports they can no longer hear their tinnitus. This measure can be useful in prescribing sound therapy-based recommendations to patients.

Last, many patients report that tinnitus suppression may persist after the masker has been turned off, a phenomenon known as residual inhibition (RI). RI is a measure of the duration of patient-reported tinnitus suppression after a patient has been presented with masking noise. Noise is presented at 10 dB above MML for 60 s. After the procedure, the patient is asked if they experience any difference in their tinnitus. If their tinnitus is suppressed, the duration of suppression is timed; this often only lasts for seconds to minutes. Use of this procedure is cautioned, however, because it can exacerbate tinnitus in some patients.

The use of these subjective tinnitus measurements is not ubiquitous among audiologists. The reliability of such measurements is often questioned, as is their purpose, and none of these measurements are recommended in the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (Tunkel et al., 2014) nor the US Department of Veterans Affairs (Henry and Manning, 2019) clinical guidelines. At best, the tinnitus assessment serves to provide a quantification of a person's tinnitus perception, which, in turn, may provide a tool in counseling and considerations of sound-based therapy. Nonetheless, the tinnitus assessment does not necessarily differentiate persons with tinnitus and those feigning a tinnitus perception. Furthermore, the results of the tinnitus assessment described have limited correlation with tinnitus reaction (Manning et al., 2019).

Tinnitus or No Tinnitus?

In 2006, Jim Henry and colleagues at the National Center for Rehabilitative Auditory Research (NCRAR) in Portland, OR, described an automated system for the psychoacoustic assessment of tinnitus. The system was a self-assessment tool using on-screen instructions that allowed the individual with tinnitus to alter frequency and intensity parameters to match the psychoacoustic attributes of their tinnitus percept.

In an interesting twist, the study design included a group of participants with comparable hearing status but that did not report tinnitus, rather they were instructed to feign a tinnitus percept. Henry et al. (2006) reported significant differences in outcomes between the tinnitus and the no-tinnitus group. First, the loudness matches for the tinnitus group were two to four times greater than the no-tinnitus group. Second, the PM was nearly an octave higher for the tinnitus group relative to the no-tinnitus group. Reliability between sessions was not different for the LM, but the no-tinnitus group showed greater variance for PM. The authors proposed developing a statistical method to determine the probability an individual has tinnitus based on variance of the measures.

Perception Versus Reaction

An additional limitation of the psychophysical assessment of tinnitus is the lack of correlation to tinnitus reaction or functional impact (Manning et al., 2019). Numerous scales exist to measure tinnitus reaction (Meikle et al., 2012). Although the relationship between measures of tinnitus perception and reaction is weak, this does not eliminate their relative potential for determining the presence of tinnitus and identifying the affective and functional impact, respectively. Finally, visual numeric rating scales (NRS) and visual analog scales (VAS) to assess tinnitus loudness are additional methods to quantify tinnitus perception. However, studies suggest that rather than correlating to loudness, these measures are more reflective of the tinnitus reaction (Hall et al., 2017).

Measuring Tinnitus in Animals

Animal models of tinnitus are important for more invasive measures to determine physiological changes related to tinnitus perception and development of potential therapeutics. Early animal studies (Jastreboff et al., 1988) used high doses of sodium salicylate, the active ingredient in aspirin, to induce transient tinnitus. Aspirin at

high doses has been shown to reliably induce tinnitus in humans but is also usually reversible and again limited to high doses; a baby aspirin is unlikely to cause tinnitus.

Given that tinnitus is a phantom auditory perception, how can it be measured in animals? The simple answer is that patients cannot perceive quiet while tinnitus is present, and neither can animals. Across studies, animals are trained to exhibit one set of behaviors (e.g., pressing levers, moving from one side of the chamber to another, climbing a pole) when there is no sound in the environment and another set of behaviors when sound is on in order to obtain food or avoid punishment. Among the animal models (Brozoski and Bauer, 2016), the most common approach is to have animals (usually rodents) detect a gap in a continuous sound. When tinnitus is present, animals make more errors detecting gaps in continuous sound, especially if the frequency of the continuous sound is similar in pitch to their tinnitus.

Several of these animal studies have shown that the pattern of results supports the presence of tinnitus after high doses of sodium salicylate, quinine (an antimalarial drug known to induce tinnitus in humans), and noise exposure. Importantly, the pitch of the tinnitus is consistent with the adjusted frequency range (relative to peripheral HL) reported in humans.

To effectively test animals for the presence of tinnitus, several fundamental features are necessary for rigorous investigation. These include the use of well-established behavioral response paradigms for determining the phantom sound of tinnitus, known and reliable inducers of tinnitus, and/or reliable physiological responses consistent with the presence of tinnitus. Psychophysical assessment of tinnitus is typically categorized either as an interrogative model, which evaluates changes in behavioral outcomes as a function of tinnitus, or as a reflexive model, which assesses changes in automatic, lower-order processing responses consistent with the perception of a phantom sound.

Interrogative models require that the animal voluntarily respond to the acoustic environment indicating the presence of silence or the presence of an auditory stimulus. Early preclinical behavioral measures of tinnitus used interrogative methods, operant conditioning, and response suppression to detect and characterize the presence of tinnitus (Jastreboff et al., 1988). In the first animal model,

rats were conditioned to associate a mild but unavoidable foot shock that occurred after a continuous sound was turned off. This resulted in suppressed licking from a water spout in preparation of the imminent shock. Following conditioning, rats in the experimental group were given a high dose of sodium salicylate, whereas the control group received a placebo. During this phase, the foot shock was eliminated but the sound conditions remained. Rats in the control group continued to suppress licking when the sound was turned off because the lack of sound was associated with foot shock. In contrast, rats treated with sodium salicylate continued to lick even when the sound was turned off. Simply put, the animals could not tell that the sound was turned off (presumably due to presence of tinnitus) and continued to lick from the waterspout.

A number of subsequent animal models have shown results consistent with the presence of tinnitus and consistent with Jastreboff's lick suppression model (Eggermont and Roberts 2015). Other models have used either avoidable shock or positive reinforcement with food whereby animals have to differentiate between trials with sound and trials with no sound. Although interrogative assessments in animal models are crucial for investigating perceptual correlates of tinnitus, it is important to note the considerable challenges in interrogative models because behavioral conditioning requires lengthy and consistent training schedules (Brozoski and Bauer, 2016), and even then, some animals may not respond as expected due to inability to do the task or lack of motivation.

Given the challenges associated with interrogative models, reflexive models for tinnitus assessment have been widely used for determining the presence of tinnitus. The acoustic startle reflex (ASR) is a large-motor response akin to a jumping/jolt-like response that can be readily elicited in rodents using a loud startling acoustic stimulus. The ASR can be easily measured in rodents using pressure sensitive platforms to record the amplitude and duration of the reflex (Turner et al., 2006).

Interestingly, the ASR can be attenuated by presenting an acoustic cue before the startling acoustic stimulus. For example, a 50-ms tone before the loud startling stimulus will result in a reduction in the ASR. Because of the compressed time frame, the changes in the ASR are believed to involve rapid lower level auditory processing before the startle elicitor; in other words, the animal did not

need to think it over before startling. For the purposes of assessing tinnitus, a continuous sound is played in the background and a brief gap is presented before the loud startling stimulus, called gap prepulse inhibition of an acoustic startle (GPIAS). However, if tinnitus is present and the background continuous sound is similar in pitch to the tinnitus, the animals will be unable to reliably detect the gap and there will be no reduction or smaller reductions in the ASR. This paradigm can be used to assess both the presence of tinnitus as well as the frequency range of the tinnitus. For example, Lobarinas et al. (2015) demonstrated that rats with evidence of noise-related tinnitus based on the ASR showed an improved startle response (i.e., less tinnitus filling gap) when treated with the drug cyclobenzaprine (a tricyclic antidepressant).

Reflexive models such as the GPIAS have the main advantage of precluding overt and long behavioral training. However, these models are not without their limitations, such as habituation of the ASR (Lobarinas et al., 2013a) and loss of reactivity to loud startling stimuli following unilateral HL. Although these drawbacks have called the widespread use of the GPIAS into question, it remains the most popular paradigm used in preclinical models of tinnitus. One way to overcome one of the limitations of the GPIAS is to elicit the startling response with a tactile stimulus. Thus, an acoustic stimulus can be used to cue the imminent startling stimulus without concerns of the efficacy of an acoustic startle elicitor. Lobarinas et al. (2013a) demonstrated success using an air puff to the animal's back to elicit a robust startle response. Cuing the air puff with an acoustic stimulus reduced the startle response to the air puff. Using a tactile stimulus such as the air puff has allowed the model to be used to study unilateral and bilateral tinnitus as well as other auditory phenomena such as hearing in noise and suprathreshold deficits associated with subclinical HL (Lobarinas et al., 2017).

Lost in Translation

Animal and human findings relative to tinnitus often have conflicting results. For example, the idea that tinnitus fills in perception of a silent gap works in animals but is not so clear that it does so in humans. Continued improvements in animal models will make it possible to evaluate physiological correlates and basic mechanisms under controlled tinnitus-inducing conditions as well as to evaluate hypotheses generated from studying human participants.

It is also worth noting that these animal models of tinnitus all focus on the perception; no animal models of the affective/emotional reaction to tinnitus are well accepted. Here we will consider two tinnitus-related phenomena that have been lost in translation between animals and humans: (1) tinnitus filling in a silent gap and (2) how peripheral hearing damage creates tinnitus.

Tinnitus “Filling in the Gap”

The application of gap detection and suppression of a startle reflex has become a common high-throughput model of tinnitus assessment in animals. In simple terms, the paradigm suggests that the presence of tinnitus disrupts the ability of the animal to detect the silent gap, and thus the startle response is less suppressed. Attempts to translate this measure to humans has been less promising.

For example, Fournier and Hebert (2013) used a GPIAS model measuring reflexive eye blink activity in participants with tinnitus compared with controls. They observed that participants with tinnitus had decreased inhibition of eye blink activity when it was preceded by a silent gap in noise compared with control participants. Nonetheless, despite all tinnitus participants reporting high-pitch ringing tinnitus, the decreased inhibition was found for both low- and high-frequency noise stimuli. In other words, the decreased inhibition was not limited to gaps in noise reflective of the tinnitus perception (high frequency). The findings contradicted the assertion that tinnitus is simply filling in the gap and frequency-specific deficits observed in some animal models but did show altered ASR of eye blinking.

In the same year, Campolo et al. (2013) performed a similar study of tinnitus filling in the gap but alternatively focused on perception of a silent gap than on an effect on an ASR. Applying methods comparable to animal experiments (50-ms silent intervals in varying noise bands), they observed no deficits in detecting the silent gap in persons with or without tinnitus. Similar findings were reported by Boyen et al. (2015), including no difference in detecting shorter gap durations.

The difference in findings of these studies may be explained by different neural circuits underlying reflexive responses and behavioral-/perception-based responses. Fournier and Hebert (2013) were relying on a startle reflex (eye blink) compared with a conscious perception of a sound (or silent gap) as in Campolo et al. (2013) and Boyen et al. (2015).

Loss of Tuning

One of the earliest proposed theories of tinnitus initiation was the discordant damage theory. According to this theory (an extension of theories proposed by Tonndorf 1981a,b), the outer hair cells (OHCs) of the mammalian cochlea are more prone to damage than the inner hair cells (IHCs), resulting in imbalanced activity via type I and type II afferent fibers that, respectively, carry signals from the ear to the dorsal cochlear nucleus (DCN), the first auditory center in the brain. The alteration of input to the DCN results in loss of inhibition and compensatory mechanisms at more central sites, including bursting neural activity, mapping reorganization, decreased inhibition, and central gain mentioned in **Tinnitus: What Is It?**.

Kaltenbach and Afman (2000) showed that significant IHC damage can prevent the onset of hyperactivity in the DCN. Tonndorf's (1981) original model suggested a decoupling of stereocilia (the hair-like projections from the cell) between the OHCs and the tectorial membrane (a membrane floating above the hair cells) that leads to loss of energy and increased noise at the level of the hair cell underlying tinnitus generation. Tonndorf's follow-up theory (1987) suggested that tinnitus was equivalent to chronic pain in the somatosensory system and a result of preferential damage to the OHCs and established an analogy of tinnitus to chronic pain.

In contrast to the discordant damage theory, cochlear insults that commonly lead to chronic tinnitus in humans have been found to produce a long-term decrease in the auditory neuronal spontaneous activity (Liberman and Dodds, 1984). Tinnitus is strongly correlated with HL and cochlear damage as a result of ototoxicity or noise exposure. Specifically, IHC/synaptic loss has been speculated to produce tinnitus.

To explore this relationship, a behavioral gap detection task was used to determine the presence of tinnitus in a chinchilla model with selective IHC loss following administration of carboplatin. Carboplatin is an ototoxic anticancer drug known to cause significant IHC loss (>80% loss) while leaving OHCs largely intact (<5% loss) in the chinchilla, an effect unique to the chinchilla model (Lobarinas et al., 2013b). Preliminary data showed overall poorer gap detection performance when tested at lower presentation levels, but the findings were not frequency specific. The absence of frequency-specific deficits suggested that these animals did

not perceive tinnitus even with severe IHC loss. Thus, IHC damage alone does not seem sufficient to generate tinnitus and support the discordant dysfunction theory of tinnitus or a combination of OHC and IHC/synapse injury at play.

Changes to psychophysical tuning curves may offer insight into differentiating OHC vs. IHC/synaptic contributions to the onset of tinnitus but are currently limited to humans in regard to tinnitus effects. A psychophysical tuning curve is a method that can be used to generate comparable data to the physiological frequency threshold curve for a single auditory nerve fiber. A narrowband noise of variable center frequency is used as a masker, and a fixed frequency and fixed-level pure tone at about 20 dB HL is commonly the target. The level of masker is found that just masks the tone for different masker frequencies. With OHC damage, the tuning curve becomes flattened and less sharp due to loss of sensitivity.

For example, Tan et al. (2013) examined psychophysical tuning curves in persons with HL and tinnitus and in persons with HL and no tinnitus. Both groups were compared with a reference group of persons with normal hearing. The normal-hearing group showed expected patterns of low thresholds and sharp tuning curves; these patterns are thought to reflect the nonlinearity of the OHCs. Interestingly, the HL group with tinnitus showed better thresholds, greater residual compression, and better tuning than the no-tinnitus group in the midfrequency range. This was likely reflective of the greater high-frequency HL of the tinnitus group relative to the no-tinnitus group that had a wider array of patterns. Thus, the finding could simply reflect differences in hearing thresholds; however, after matching participants based on HL, the pattern persisted. Tan et al. suggested that the findings may be explained by the tinnitus group having residual OHC function and a preferential loss of IHCs or afferents.

The difference in the animal model of widespread loss of IHCs and lack of tinnitus evidence compared with psychoacoustic tuning curves in humans implicating IHCs/synapse may also be explained by the discordant damage theory. The carboplatin model creates a pure loss of IHCs/synapses without damage to OHCs. Still, humans may still have some level of damage to their OHCs not reflected in their tuning curves. In other words, it would be parsimonious to suggest that there is likely a ratio of damage to both hair cell types involved and necessary

to generate tinnitus perception. Currently, animal-based versions of psychophysical tuning curves are lacking. Development of this paradigm in preclinical models would provide an opportunity to further advance tinnitus research and enhance translation.

Challenge to Psychoacousticians

Psychophysical measures of tinnitus are numerous. In general, these measures have been applied to match attributes of tinnitus, determine the affective impact of tinnitus, and identify the site of lesion and subtyping of tinnitus physiological origin. It is apparent that most psychoacoustic measures such as PM, LM, and MML do not reliably correlate with measures of tinnitus reaction. The use of numerical rating scales, visual analog scales, and questionnaires on affective elements appear to best capture elements of tinnitus reaction.

Tools to assess affective elements have been established in humans but represent a challenge for animal models. The important question is, do animals experience tinnitus related distress? From clinical data, the majority of individuals who experience tinnitus are not disabled by it. It is thus reasonable to expect only a minority of animals will be debilitated by tinnitus. To address this issue, a large number of animals would be needed in studies of tinnitus-related distress, with careful consideration of confounding variables (e.g., housing, animal handling).

The overarching question, given the state of the science, is how can we use principles from psychophysics to identify one or several measures of tinnitus using perceptual attributes of tinnitus that can differentiate individuals who actually experience tinnitus from persons with reported tinnitus but no actual tinnitus perception? Furthermore, how can we use psychophysical experiments to better inform our understanding of the tinnitus neurophysiology. With improved models, further progress can be attained to lead to novel therapeutics for the management of tinnitus.

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