



## Is Tinnitus a Disease of the Ear or a Hiccup of the Brain?

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Tinnitus is the subjective experience of chronic noise in the head that approximately 10–15% of the population in Western societies suffer from. Individuals who are affected often report a permanent ringing, rattling, or rustling that appears to originate either from one or even both ears. This sound is characterized by dynamic changes in that it often varies in frequency and intensity. The vast majority of affected persons adapts to this permanent soundscape relatively quickly, even though it is by all means considered aversive. Only a minority of individuals whose tinnitus has become chronic are not able to cope with this disorder and suffer from serious impairment of life quality in that they demonstrate severe psychopathological symptoms of anxiety disorder, depression, or sleep disorders (Adjajian, Sereda, & Hall, 2009).

My interest in tinnitus is of twofold origin. First, from a scientific point of view, tinnitus is a challenging phenomenon as there is no straightforward causal relationship between a biological, organic generator and an objective auditory experience. Even though it is reasonable to assume that the human auditory system is affected, there is currently mounting evidence provided by neuroscientific research that large-scale networks in the brain also contribute to the consolidation of chronic sound. In this article, I will first sketch out what we know today about the neural circuits that generate tinnitus. More importantly I will explain why these circuits consolidate in the head of some (but not all) individuals who have experienced traumatic or age-related hearing loss (presbycusis). Thus, the generation and consolidation of tinnitus may serve as an impressive example of the human brain's maladjustment to a disorder of the auditory system.

Second, there is no established intervention that is able to *cure* tinnitus. Unfortunately most individuals affected by acute tinnitus learn from their otologist that “there is nothing one can do except to adapt.” This is by no means true. A myriad of interventions are offered to the affected persons. However, only a small number of approaches can be considered really effective. The second part of this contribu-

tion introduces one approach that has turned out to be helpful in that it relieves the distress associated with the chronic ringing in one's head rather than succeeding in annihilating the sound per se.

For a long time tinnitus has been exclusively considered a matter of the ear. Otologists correctly assessed that tinnitus often follows traumatic exposure to noise or presbycusis. Undisputably, peripheral deficits in the inner ear or damage to the auditory pathway may elicit tinnitus but they are not solely responsible for its maintenance. This insight had been established after it has been realized that tinnitus persists even after cutting through the auditory nerve (De Ridder, De Mulder Walsh, Muggleton, Sunaert, & Møller, 2004). In other words, tinnitus should not be primarily considered a pure ear disease. Short-term treatment by means of hydrocortisol to increase blood circulation in the inner ear may occasionally help compensate for hearing loss but does not directly affect the hissing in the ear. The inability of standard medical intervention to terminate patients' suffering has opened the arena for a myriad of esoteric and obscure money-spinners promising complete relief after “magic herbals” have been taken or other opaque and diffuse therapies have been applied (homeopathic drugs, hypnosis, acupuncture, and the like).

Over the last decade tinnitus has steadily become a subject of neuropsychological research and intervention. First, animal studies have shown that tinnitus sensation is usually accompanied by a reorganization of the auditory cortex as a function of sensory deprivation (Eggermont & Roberts, 2004). After irreparable damage to inner hair cells a fraction of auditory signals are not conducted via the auditory pathway and hence do not arrive at the central auditory fields. As a function of this signal loss, neurons in the auditory cortex that are organized tonotopically and that are preferentially driven by specific auditory frequencies encoded by the damaged inner hair cells are rendered idle. In the absence of incoming auditory signals, these neurons do not fire systematically. Within hours and days after partial hearing loss, however, the

subtle balance of lateral inhibition and excitement of adjacent neuronal ensembles changes gradually and slightly. This loss of balance results in increased firing of the deafferented neurons (Llinas, Urbano, Leznik, Ramirez, & van Marle, 2005) that is caused by a dysrhythmia of exciting and inhibiting thalamo-cortical circuits (Llinas, Ribary, Jeanmonod, Kronberg, & Mitra, 1999). It is of utmost importance to note that in this understanding chronic tinnitus can be considered a neurogenic phenomenon comparable to chronic pain. The lateral disinhibition is fostered by a thalamo-cortical loop that simply responds to the dormancy of the deafferented neurons and that begins to “nudge” the idle brain cells to “get back to work”. This unsuccessful attempt of the thalamic nuclei to restore the former organization in the auditory cortex serves as an unfortunate example for a maladjusting process based on the neuroplastic nature of the brain. For this reason tinnitus is often dubbed “the auditory phantom pain” as it results accidentally from the brain’s fatal mistake to fix the “hiccup” of the auditory system.

However, this calamitous mechanism does not necessarily explain why affected individuals frequently react in a panic-fueled and anxious manner as soon as they notice an initially weak sound that obviously lacks an external source. Even though affected individuals experience the permanent ringing in their head as extremely annoying and bothersome it should be emphasized that tinnitus is not a symptom of severe and life-threatening disease. Notwithstanding this fact many tinnitus patients consider the chronic background noise as an “alarm-clock” or “alarm-siren” warning them that something really threatening is going on. In the absence of solid knowledge about the underlying neuroplastic mechanisms of tinnitus generation, affected individuals typically and unintentionally initiate a vicious circle. A negative evaluation of the “harmless” sound marks the kick-off of a fatal loop that recruits large-scale networks subserving attention, cognition, and emotion (Cacace, 2003; De Ridder et al., 2004). Actually the reorganization and the thalamically triggered backfitting of the auditory cortex is probably initiated one or two days before the intensity of the internally generated sound exceeds the hearing threshold. From the moment the affected individual notices the ringing in his/her ear for the first time, he/she inevitably devotes a steadily increasing quantity of attention that is soon coupled with anxious irritation and

aversive feelings to the disturbing sound. Sooner or later a cortico-subcortical network establishes itself by functionally and densely binding together auditory midbrain (i.e., the inferior colliculi), the subcallosal area (i.e. ventral striatum), several thalamic nuclei, the noradrenergic locus coeruleus, the limbic amygdala, and the auditory as well as the frontal cortex (see Figure 1; cf. Leaver et al., 2011; Rauschecker, Leaver, & Mühlau, 2010). In other words, brain regions that are known to subservise attention-related functions as well as negatively tuned percepts and sensations build a circuit that finally consolidates. Accordingly, the affected individual pays an increasing amount of attention to the irritating sound and becomes — under certain circumstances — obsessed by “listening to the inner ear.” Negative feedback and feelings become gradually associated with the tinnitus sensation, are steadily reinforced and systematically sustained. Sometimes the tinnitus occupies a central position in the life of affected individuals as they feel exposed to the permanent “terrorization” by the tinnitus. In such individuals, this can occasionally lead to symptoms of a major depression that can even become persistent.

One may wonder whether the described neuroplastic changes that finally result in chronic tinnitus are reversible. Of course there is no straightforward answer to this question. Individuals who suffer from chronic tinnitus should not be considered a homogeneous group. The majority of individuals adapt to the chronic background noise and grudgingly accept that tinnitus has become part of their life. Some patients undergo a series of more or less established therapies without experiencing comprehensive relief and finally manage to cope with the annoying companion. In order to help patients who suffer from tinnitus more specifically, one should differentiate between therapeutic approaches that are suited for application during acute and chronic tinnitus. With respect to acute tinnitus it has become immensely helpful to offer affected individuals comprehensive counselling during which they learn that tinnitus does not indicate any serious harm or reflect upcoming neuropsychiatric disease. Usually, patients radically and suddenly change their panic-fueled attitude towards the noise as soon as they have learned about the well-intentioned but maladjusting result of the brain’s misguided attempt to fix a leak of the auditory system. In the acute state, before the tinnitus has become sustained, it is best

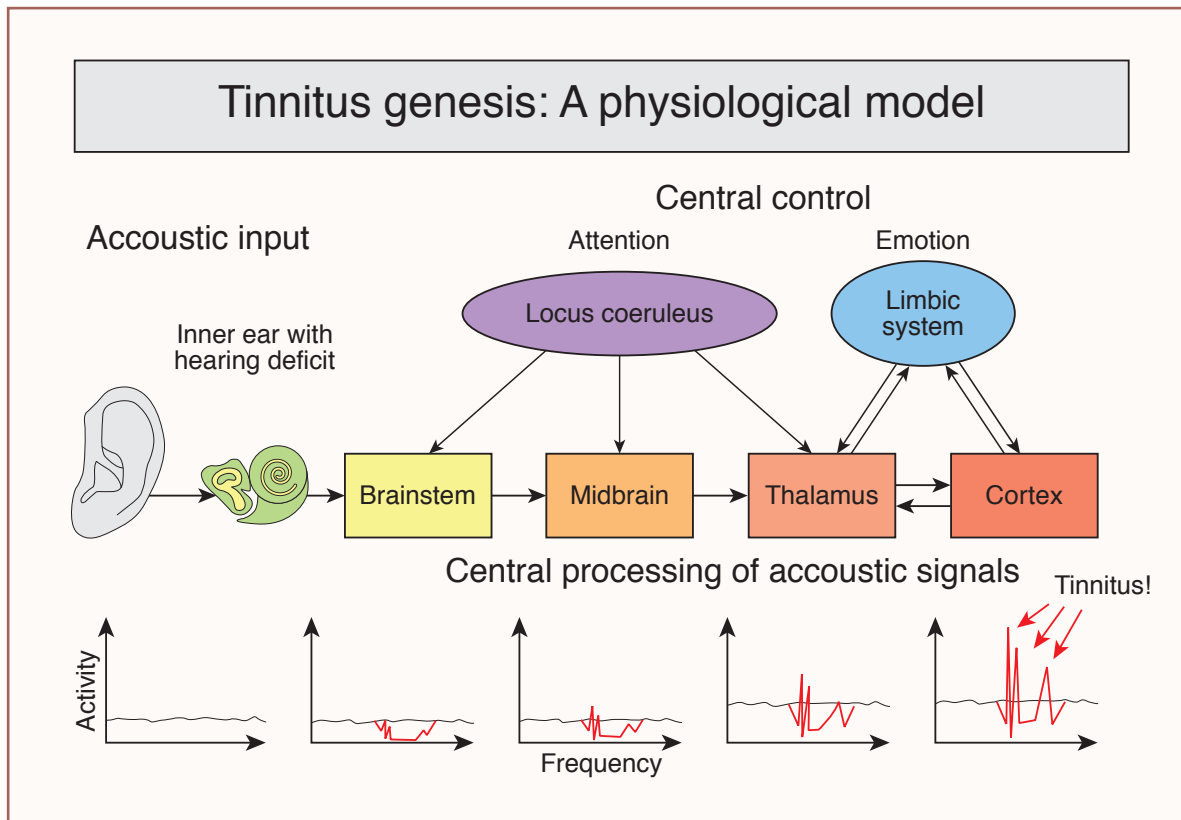


Figure 1. Schematic illustration of the mechanisms of tinnitus development (adapted from Wallhäusser-Franke & Langner, 2001).

to simply ignore the noise and to proceed with normal life — meaning normal exposure to a moderately loud environmental soundscape. In these cases acute tinnitus often vanishes within days or weeks of first occurrence. In other individuals the tinnitus remains persistent but is not experienced as bothersome and does not affect the quality of everyday life. Only in a minority of affected individuals does the presence of tinnitus lead to serious adverse effects.

Several neuroimaging studies have applied functional and structural brain imaging methods to elucidate the neural signature of chronic tinnitus (for a review, see Lanting, de Kleine, & van Dijk, 2009). The results of these studies have shown that tinnitus not only affects the auditory system, but also results in neuroplastic functional and structural alterations in cortical and subcortical non-auditory regions. Hence these studies provide corroborating evidence for the aforementioned models but do not necessarily offer any insight into the temporal dynamics of neural processes that underlie the tinnitus sensation. Neurophysiological techniques, namely EEG and MEG, have turned out to be more suitable as they have a superior temporal resolution at the range of milliseconds. Furthermore, the application of EEG-based source estimation

approaches has helped immensely to reveal the neural auditory and non-auditory networks that form the vicious circle keeping chronic tinnitus persistent (Ashton et al., 2007; Kadner et al., 2002; Schlee, Hartmann, Langguth, & Weisz, 2009; van der Loo et al., 2009; Vanneste & De Ridder, 2012; Weisz, Voss, Berg, & Elbert, 2004). Complementarily, recent EEG studies have investigated to what extent chronic tinnitus is characterized by changes in the distribution of distinct oscillatory frequencies in the spontaneous resting state EEG signal (Moazami-Goudarzi, Michels, Weisz, & Jeanmonod, 2010; Schlee et al., 2009; van der Loo et al., 2009). However, the results of these studies are quite inconsistent. Unsystematic increases and decreases in  $\alpha$ -,  $\delta$ -,  $\theta$ -, and  $\gamma$ -bands draw a confusing picture. We surmise that considerable differences between affected individuals account for the heterogeneity of the findings because patients suffering from chronic tinnitus are differently affected by anxiety disorder, emotional distress, and depression. According to Vanneste et al. (2010) the pattern of EEG frequency distribution varies as a function of the individual amount of tinnitus-related distress. Results show more synchronized  $\alpha$ -activity in the tinnitus patients with a serious amount of distress with peaks localized to various emotion-related areas. A comparison between the

tinnitus group with distress and a tinnitus group without distress demonstrated increased synchronized  $\alpha$ - and  $\beta$ -activity and less synchronized  $\delta$ - and  $\theta$ -activity in the dorsal anterior cingulate cortex in tinnitus patients with distress. Thus, it appears that patients who suffer more strongly from chronic tinnitus show some overlap with the emotional component of the pain matrix. Likewise, an unpublished study by our group reveals a relationship between specific patterns in spontaneous resting state EEG activity and psychopathological behavioral measurements (Meyer, Lüthi, Büchi, & Jäncke, 2012). While patients who indicated high strain and distress related to tinnitus demonstrate salient EEG oscillations in the lower  $\beta$ -band, participants who do not feel seriously emotionally affected reveal less prominent oscillations, primarily in the  $\theta$ -band. We consider this study a first step towards a more differentiated assessment and evaluation of the relationship between specific neural signatures and psychopathological indications. Currently, our group is carrying out another EEG study with a large sample of affected individuals that extends the previous project by a more sophisticated collection of psychometric data in combination with structural MRI scans. This comprehensive information will allow us to gain more relevant insight into (more) individual fingerprints of the brain–tinnitus relationship. In the long term, we hope to employ this information to establish innovative neuromodulatory approaches.

Notably, the application of neurofeedback methods is now viewed as a promising approach to help seriously affected individuals to cope with the tinnitus-related distress (Hartmann, Lorenz, & Weisz, 2010). So far, this approach has aimed at unspecifically fixing the dysrhythmia of thalamo-cortical circuits that underlie sustained tinnitus. In the recent past, long-term neurofeedback-based intervention has sought to increase  $\alpha$ -activity, as this frequency band is associated with a moderately relaxed state that is meant to dampen the tinnitus sensation. A more sophisticated approach has been used to enhance  $\tau$ -activity, that is, oscillatory activity produced in perisylvian regions within the alpha frequency range (8–12 Hz) and to reduce concomitant reduction in delta power range (0.5–4 Hz) (Dohrmann, Weisz, Schlee, Hartmann, & Elbert, 2007). According to the authors, the alteration of the  $\tau$ -to- $\delta$  ratio considerably decreases tinnitus intensity. Albeit the beginnings of neurofeedback date back to the 1960s, the technique could still be

developed further. In particular, the combination of source estimation solutions that make it possible to record and feedback neurophysiological signals from and to fairly well constrained cortical regions, namely the auditory cortex, should be considered a promising approach. Akin to other neuropsychological interventions, namely frequency discrimination training (Flor, Hoffmann, Struve, & Diesch, 2004), neurofeedback also plays on the brain's plastic nature. Indeed, neurofeedback, probably due to indirect mechanisms, appears to outperform explicit frequency discrimination training that is meant to help restore the original tonotopic organization (Dohrmann et al., 2007). Presumably, neurofeedback is particularly suitable to alleviate the symptoms of anxiety and distress that accompany chronic tinnitus — more than it can remedy the chronic sound per se.

Even though neuropsychological research on the neural signature of tinnitus and appropriate therapies to reduce patients' chronic strain and suffering has not yet yielded convincing results, we think that this field has a lot of potential. The combination of psychometric, neuroanatomical, and neurophysiological approaches will undoubtedly help gain a better understanding of the brain's auditory hiccup so that this research will inevitably become a burgeoning branch in the realm of applied neuroscience.

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