

# Tinnitus and the Brain

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Moving animals have developed a brain in order to reduce the inherent uncertainty present in an ever changing environment. The auditory system permits to perceive danger, food or a potential partner at a distance, even when it cannot be seen. When the auditory system cannot pick-up certain sounds, eg due to hearing loss, the brain will try to reduce the increased uncertainty associated with the deprived auditory input. This effort to compensate the hearing loss by sounds from memory may be the reason, why humans and also animals develop a tinnitus sound after hearing loss.

## *How does auditory system work?*

When externally generated sound waves hit the eardrum these waves are transmitted via the middle ear bones to the cochlea. Here the information is translated into neural signals which are transferred via the auditory nerve to the brainstem and from there to the auditory cortex. (see fig 1). There are actually at least 2 pathways that bring auditory information from the cochlea to the brain. One pathway, called the extralemiscal system, detects salient (= behaviourally relevant) changes in the auditory environment and the other pathway, the lemniscal system then signals the content of that change to the brain. But there are also 2 descending inhibitory or noise suppressing systems that modulate cochlear activity. How loud you perceive a sound depends not only on how loud the external source is, but also on how much the external sound is modulated by the descending noise suppressing mechanisms.

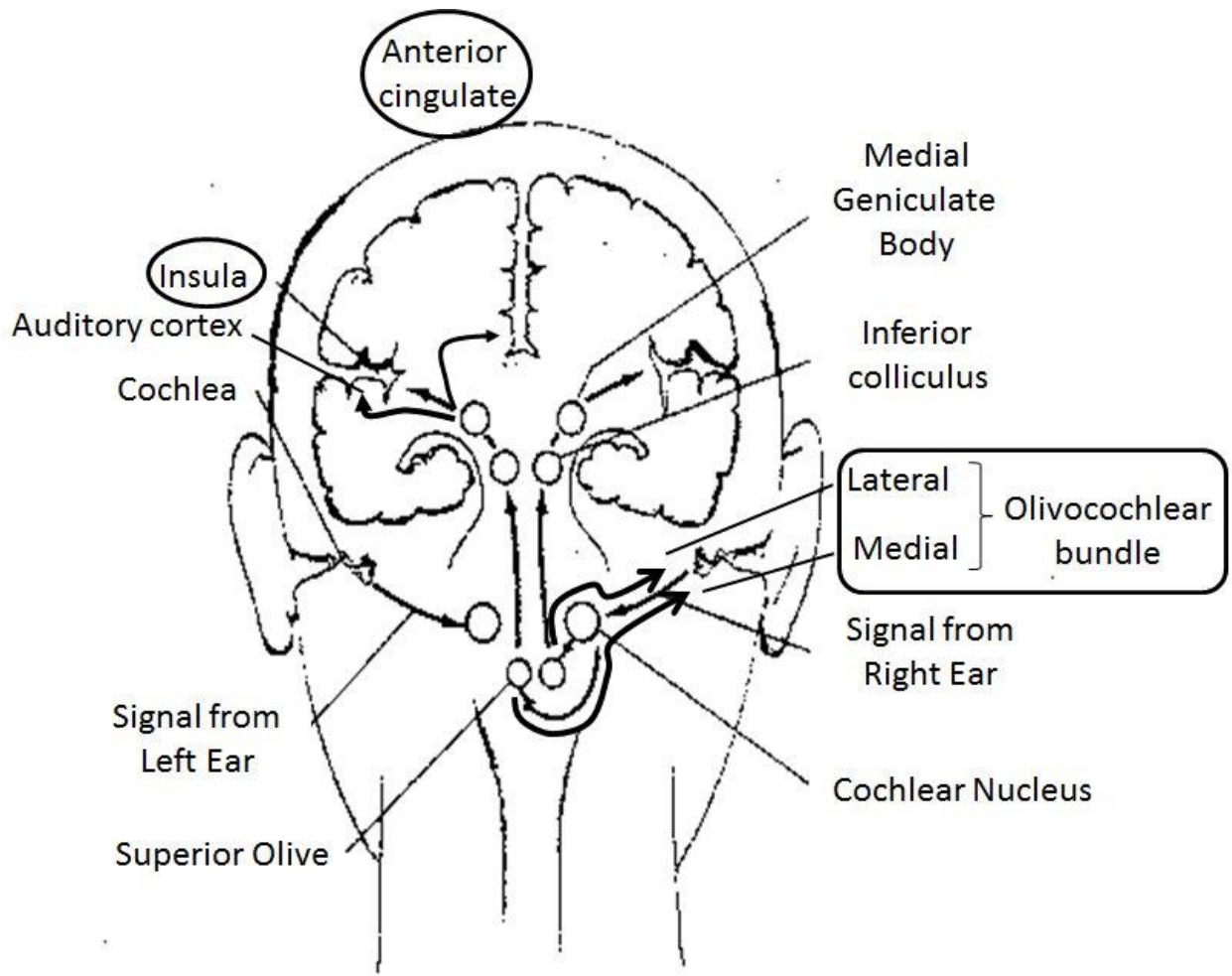
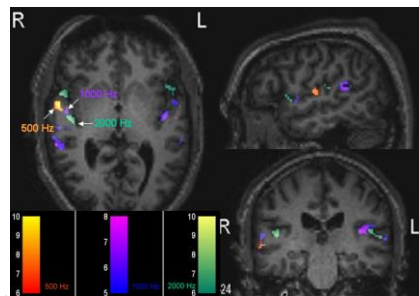


Figure 1 : the auditory system. The ascending lemniscal and extralemniscal system run in parallel to the inferior colliculus. From there the lemniscal system continues to the primary auditory cortex, the extralemniscal (oval) to the anterior cingulate, insula (and secondary auditory cortex). The descending system is depicted from the superior olive to the cochlea (rectangular).

*Tonotopic organisation of the auditory system* The lemniscal auditory system is organized in such a way that in the cochlea specific hair cells are activated by specific frequencies, leading to what is called a tonotopic representation. More precisely, at the base of the cochlea, the hair cells are sensitive to high frequencies, whereas at the apex of the cochlea, hair cells are sensitive to low frequencies. Because the auditory centers are massively organized in parallel, this tonotopic organization is found all through the auditory system. As such, in the cortex also specific areas process the auditory information of specific frequencies, the low frequencies being processed more laterally (outside) than the high frequencies. This can be seen with functional imaging, also known as fMRI. (see fig. 2)

(figure 2)



The extralemniscal system is not or less tonotopically structured, as to detect changes in the auditory environment, no or less tonotopy is required. On the contrary, it can be beneficial to have little tonotopic structure so that any change can be detected, and not only frequency-specific changes. Both descending pathways seem to be tonotopically structured.

### *Information processing in the brain*

The brain is one big information processing machine, made up of 100 billion cells, each connected to about 10.000 other brain cells. Information between brain cells is transmitted by

trains of action potentials. Information theory, which is a mathematical framework for quantifying information transmission can calculate the cumulative information rate related to the spike frequency. Information theory has shown that the higher the firing rate is, the more information is being transmitted up to a certain frequency. The synchronous electrical activity of the brain can be analyzed by electroencephalography (EEG) and its magnetic counterpart by magnetoencephalography (MEG).

Electrical activity in the brain can be evaluated in two ways: either spontaneous oscillations can be analysed or potential changes resulting from an exogenously or endogenously triggered stimulus or task. The frequency of the spontaneous oscillations in the EEG and the level of consciousness are correlated: the higher the frequency and the lower the amplitude of the EEG, the higher the level of consciousness. Using a Fourier analysis one can decompose the complex EEG or MEG data into its composing frequencies. Slow wave frequencies between 0.5 and 4 Hz with large amplitudes are found in deep sleep, anaesthesia and coma and are called delta waves. Somewhat higher frequencies, in between 4 and 8 Hz are noted in light sleep (theta waves). Alpha waves have lower amplitudes but higher frequencies from 8 to 12 Hz and are seen in the parietal and occipital areas (sensory areas) in a resting state with eyes closed. Alpha activity has been suggested to correlate to a scanning mode of the brain and not a mere idling rhythm. Beta waves (13 to 30 Hz) are noted primarily frontally when people attend to something. Data from multiple sensory systems suggest that gamma waves (30-80 Hz) are a prerequisite for conscious perception of a sensory stimulus. Thus auditory consciousness is correlated to gamma band activity in the auditory thalamocortical system. Synchronization of separate gamma-band activities, present in different thalamocortical columns, is proposed to bind distributed neural gamma activity into one coherent auditory percept. Coherent gamma band activity in the cortex in general, and auditory cortex specifically, is normally present in locally restricted areas for

short periods of time. This temporal coherence has been proposed to establish feature specification and cognitive binding through synchronization. Thus gamma activity per se is not synonymous with auditory conscious perception, but it most likely is an essential requirement for an auditory stimulus to be heard. Based on this concept it has been proposed that tinnitus, a spontaneous auditory percept is related to persistent gamma band activity.

### *How does tinnitus arise?*

For a long time it has been assumed that tinnitus is caused by increased activity in the cochlea, which is transmitted via the auditory nerve to the brain and results there in the perception of tinnitus. Consequently in some patients with severe tinnitus transections of the auditory nerve have been performed in order to reduce tinnitus. However this treatment did not bring any relief, in contrary in most cases tinnitus was increased after the transection of the auditory nerve.

In recent years new techniques allowed to investigate in more detail the changes in neuronal functions in tinnitus. First animal models of tinnitus have been developed and second new functional imaging techniques enable to observe the brain at work. This makes it possible to investigate changes of neuronal function in tinnitus patients.

This research has demonstrated that tinnitus arises when the activity in the auditory nerve is reduced. This reduction of activity in the auditory nerve can have different causes, but in most cases it is caused by hearing loss in the higher frequencies. In most cases of hearing loss hair cells in the cochlea are damaged. This results in reduced activity in those nerve fibers that convey information of these damaged hair cells to the auditory centers in the brain. This reduced incoming signal is further processed in the brain stem, then transmitted to the thalamus, the main relay station in the brain, before it reaches the auditory cortex. Normally there is a fine tuned balance between inhibitory and excitatory mechanisms at all these processing levels. However

the reduced input signal causes changes in this balance. In detail the reduced input signal results in reduction of the inhibitory functions. In other words this means that the brain tries to compensate for the reduced input by amplifying the incoming signal. This “amplification” in turn causes increased activity in the auditory system, which then results in increased nerve activity in the auditory cortex (fig 3). This increased activity is then perceived as an ongoing sound, even if there is no incoming signal from the ear.

### *Brain changes induced by deafferentation*

Hearing loss can be total or pertaining only to a couple of frequencies. For example presbycusis is characterized by hearing loss at high frequencies, noise trauma usually induces a hearing loss which is fairly specific for 4000 Hz. Damage to these frequency-specific hair cells has the consequence that the related neurons do not receive any information, which is called deafferentation. Deafferentation is not the same as hearing loss. Part of the auditory nerve can be cut without hearing loss, due to overlapping tuning curves (fig 3). This means that you can have deafferentation without hearing loss.

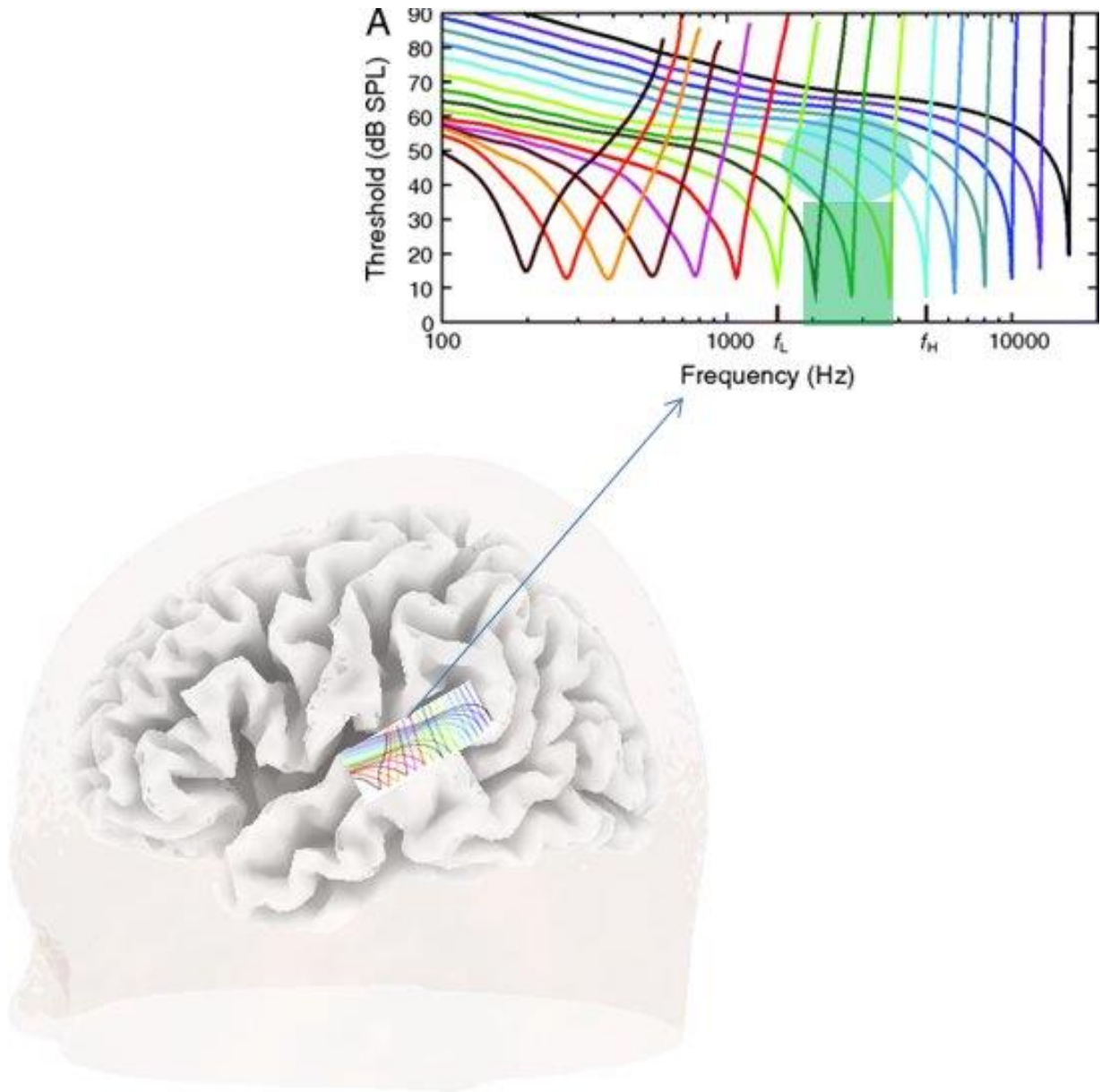


Figure 3: overlapping tuning curves. The frequency structured (=tonotopic) organization is characterized by overlapping tuning curves. This means that when some frequency-coded hair cells are not processing information anymore (green square), the adjacent frequencies can still provide the missing information if the missing information is presented loud enough (eg >40 dB)(blue oval).

Thus if the deafferentation is not too large, deafferentation does not have to always result in hearing loss.

Depending on the amount of deafferentation (bandwidth) it is assumed the brain uses different mechanisms to find the missing information. In simplified terms, when the deafferentation is limited to a small frequency range, the missing information can be found in the neighborhood in the auditory cortex, due to the overlapping tuning curves, but when the deafferentation extends to a larger frequency range, the missing information cannot be retrieved from the adjacent areas in the auditory cortex. An alternative for the brain to replace the missing information is to pull it from memory,

### *Tinnitus without hearing loss*

Tinnitus can arise without audiometrical hearing loss. This can still be caused by deafferentation as deafferentation does not always cause loss, so the same mechanisms as described above can explain the tinnitus. However a second mechanism might be involved. A deficiency in the top down noise suppressing mechanism can cause the perception of a sound. Probably some forms of tinnitus are the result of an imbalance between the bottom up ascending auditory pathways and the noise suppressing descending pathways. The top down noise suppressing system is not well described but likely involves the pregenual anterior cingulate cortex and the tectal longitudinal column and further connecting to the superior olive from where the medial and lateral olivocochlear bundle modulate cochlear function (see fig 1). Finally a third possible mechanism is abnormal input from the somatosensory system, particularly from somatosensory afferents of



the trigeminal nerve and the neck area. These somatosensory afferent converge with the central auditory pathways in the dorsal cochlear nucleus and it has been shown that abnormal somatosensory input can alter neuronal activity in the central auditory system. This mechanism explains the clinical observation that tinnitus can be frequently modulated by neck or face movements.

### *Brain oscillations and tinnitus*

The way tinnitus exactly arises is still a matter of research but recently it has been suggested that tinnitus can be considered an auditory phantom phenomenon similar to the phantom pain which arises for example after amputations. The underlying idea is that auditory deafferentation (=deprivation) results in less information processing going on in a specific thalamocortical column, namely the thalamocortical column that is normally transmitting the missing information. This results in slowing of the firing rate of the neurons of this column with resultant slowing of the oscillations from alpha (8-12 Hz) to delta (0,5-4 Hz) and theta (4-8 Hz). As a consequence the lateral inhibition decreases and the surrounding cells become hyperactive firing and oscillating at gamma (30-80 Hz), also known as the edge or halo effect. (figure 4).

#### Llinas' thalamocortical dysrhythmia

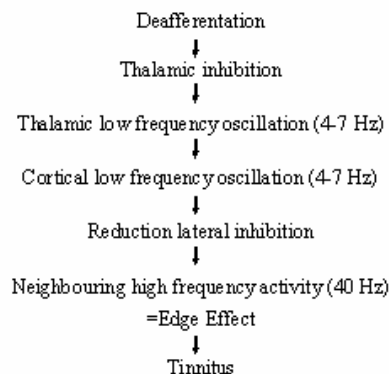


figure4: generation of tinnitus as a consequence of thalamocortical dysrhythmia (according to R. Llinas)

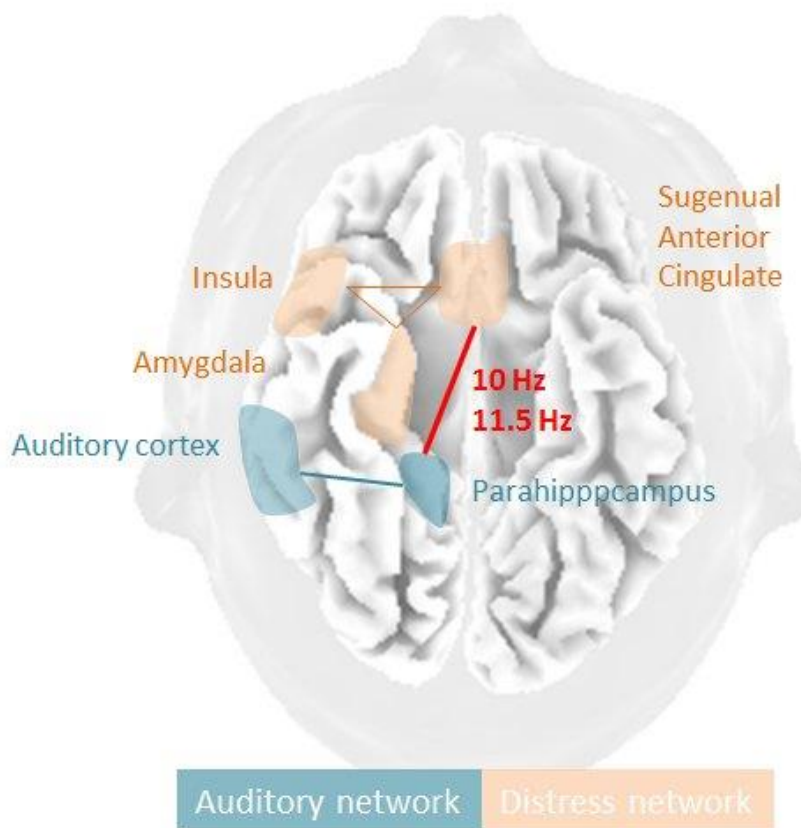
This model has become known as thalamocortical dysrhythmia. Thus gamma band activity is correlated to tinnitus, and present on both sides in the auditory cortex, even in single-sided tinnitus.. However information from studies in the olfactory and visual system suggest that the gamma band activity does not equal the conscious percept of tinnitus. Gamma band activity has to be processed by a consciousness enabling network , and therefore might be nested on theta waves. The theta waves could act as a carrier wave, like the frequency bands on a radio that carry the songs and words. When two or more areas in the brain communicate both the sender and receiver must be tuned in to the same carrier frequency in order for the information to be understood. The tinnitus related information will then be hidden within the gamma band on the theta carrier wave.

Thus, in summary it seems that gamma band activity is an essential requirement for tinnitus to be heard but not sufficient. The tinnitus related information should be looked for by analyzing the gamma band activity in various ways.

*Tinnitus distress (figure 5)*

*Tinnitus can be bothersome or not bothersome. Whether or not tinnitus is perceived as being bothersome depends on whether a distress network, consisting of insula, anterior cingulate, parahippocampus and amygdala (orange), in the brain is co-activated with the auditory network (blue), and whether or not the tinnitus network and the distress network are linked to each other via discrete frequencies at 10 and 11.5 Hz(red line). This means that if the distress network, which is non-specific, is activated for whatever other reason causing stress, the tinnitus might be*

*perceived as stressful or bothersome as well if it becomes linked. In stress every stimulus is considered salient, and this might prevent the tinnitus from going away spontaneously.*



*Figure 5: when the auditory network (blue) and the distress network (orange) are linked (red line) tinnitus becomes bothersome.*

### *Neuroplasticity and tinnitus*

Plasticity refers to the capacity of the nervous system to modify its organization to altered input. This change can be brought about by normal or abnormal sensory input, by damage to the nervous system or sensory deprivation. There seems to be a greater potential for plastic changes during development than adulthood, even though similar mechanisms seem to govern developmental plasticity and adulthood plasticity. Another consequence of deafferentation is that

the firing becomes hypersynchronous being activated by the same trigger (deafferented decrease in lateral inhibition). This increased hypersynchronous (all members of the choir sing together) oscillation at gamma frequencies (30-80 Hz) results in the percept of tinnitus. Based on Hebbian plasticity (cells that fire together wire together) this synchronous firing results in cortical reorganization, irrespective of its frequency.

This cortical reorganization is an adaptation to the deafferentation, ie the lack of information. One can also look at this from a Darwinian perspective. Nerves and the brain are not a hardwired computer but seem to be a more a constantly adapting network based on Darwinian principles. Nerve tracts are made up of nerve cells all having a very specific function. Nerve cells that survive are those who fit best for a specific function. This explains why at birth we all have a lot more brain cells than at the age of 3 years. Any change in the environment results in an induced adaptation of our brain to better process the changing incoming information. At birth the auditory system is not completely hardwired and not yet functional. It becomes functional only after it is exposed to environmental sounds. This exposition leads to a refinement of the central tonotopy by dying of synapses and brain cells that are not fit for a specific function. Tonotopy thus arises more or less in a similar way as the sculptor who creates a sculpture out of a big marble block by cutting away all the unnecessary. So out of chaos order is created in such a way that after sound exposure during the neonatal period every brain cell processes a specific sound frequency only connected with those hair cells of the cochlea that process the same sound frequency.

When a lesion of the high frequencies is created, for example by using some antibiotics, or by sound trauma etc, those brain cells that normally process the high frequencies become unemployed. In order to prevent their death those inactive cells will first open dormant synapses by reducing surround inhibition and in a later stage try to grow into the neighboring areas thus

processing for example middle frequency information. But these cells can only generate the percept of high pitched sound, so that the patient hears the sound he is deprived of. A consequence of this Darwinian neuroplasticity principle (survival of the fittest frequency) suggests that any alteration of auditory input during the development of the tonotopy will result in reorganization of the tonotopic map according to the abnormal pattern of incoming neural activity. However when the deafferentation is very large even this mechanism will not work and the brain has to pull the missing information from parahippocampal memory.

In summary, tinnitus is related to synchronous delta/theta-gamma band activity which is associated with neuroplasticity, in other words it is the consequence of the brain trying to solve a lack of auditory input (deafferentation) in order to reduce uncertainty associated with the deafferentation. The deafferentation will also induce auditory tract reorganization. Using sophisticated functional neuroimaging techniques this tinnitus related hyperactivity and deafferentation related reorganization can be demonstrated, giving clinicians better tools to understand tinnitus and thus to develop better tinnitus treatments.