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Exploring the Neural Basis of Tinnitus

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Declaration of authorship

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The above noted work is submitted to the School of Bioscience at the University of Skövde, as a final year Bachelor project toward the degree of Bachelor of Science (B.Sc.) in Cognitive Neuroscience. The project has been supervised by Anders Milton.

I, Nicole Salinas Thunell hereby declare that:

1. The above noted work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any other degree.

2. The above noted work is the result of my own investigations, except where otherwise stated. Where corrections services have been used, the extent and nature of the corrections have been clearly marked.

Nicole Salinas Thunell	2015.06.02
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Abstract

Tinnitus is a phantom auditory perception characterized by a ringing sound in either one or both ears. It is a common disorder most often associated with hearing loss and can have a severe impact on a persons quality of life. There is currently no cure and no efficient therapeutic options. There is little known about the neural mechanisms underlying the generation of tinnitus but a better understanding of its neural basis could greatly benefit the development of efficient treatment methods. This literature study aims to explore the neural mechanims of tinnitus in terms of generation, perpetuation and perception. Cochlear dysfunction, changes in neuronal firing rates and oscillatory properties, hyperactivity, lack of inhibitory activity and plasticity in auditory-limbic structures have been associated with tinnitus and may be a part of a crossmodal network involved in generating, perpetuating and perceiving tinnitus, through maladaptive CNS plasticity. New developing treatment methods aim to modulate and re-route tinnitus-related plasticity, however this leads to treatment difficulties due to the crossmodal nature of the tinnitus pathophysiology. These difficulties will be further examined in the discussion.

Keywords: tinnitus, auditory-limbic interactions, maladaptive plasticity, salicylate, therapeutic options

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Introduction

The word tinnitus stems from the Latin word *tinnire* which means "to ring". Different ideas about this phenomenon have been proposed throughout history. For example, in ancient oriental texts, tinnitus was once regarded as a sensitivity towards the divine. Roman medicine associated it with seizures and depressive disorders and in the Babylonian Talmud, it was mentioned to be a gnat buzzing in the brain (Dan, 2005). Today, tinnitus is believed to be a phantom auditory perception originating from the brain. It is generally characterized as a "ringing" sound in either one or both ears that arises in the head, is involuntary and may be heard without any external stimulus present. (Eggermont & Roberts, 2004). Heller (2003) argues that across the general population, 5-15% suffer from chronic tinnitus. Only in the United States 50 million people have reported to experience tinnitus. 16 million of those people seek medical attention and two million patients are suffering from tinnitus so severe that they cannot function in their normal day-to-day life (2011-2012 National Health and Nutrition Examination Survey). As a result of the focus on and preoccupation with one's tinnitus, it can produce a vicious cycle of distress such as mood changes, annoyance, stress, anxiety, fear and ultimately depression, all affecting the quality of life. Therapeutic treatment have shown to be relatively inefficient (Chrbolka, Paluch, & Alsuik, 2015) as it doesn't cancel any perceived noise, rather makes it less annoying.

Despite the high prevalence of tinnitus and its effect on the individual's quality of life, there is still little understanding of the neurophysiology of tinnitus. It is already well established that tinnitus must originate within the brain (Eggermont & Roberts, 2004). Animal models are frequently used in tinnitus research to better understand structural, neural and molecular changes (Jastreboff, 1990; Knipper, Zimmermann, & Müller, 2010; Leaver et al., 2011) and functional magnetic imaging (fMRI), magnetoenchephalography (MEG) and positron emission tomography (PET) are used to study tinnitus in human subjects (Landgrebe et al. 2009; Lanting, Kleine, & Dijk, 2009). With such techniques,

changes in neuronal activity and firing rates, hyperactivity, oscillatory synchronization, and gray matter can be observed and correlated with tinnitus.

It is commonly agreed (Jastreboff, 1990; Kraus & Canlon, 2012; Lanting et al. 2009; Mahoney et al., 2011; Roberts et al., 2010; Schlee et al., 2009) that a neural understanding of tinnitus is important not only for the understanding of neural mechanisms related to hearing, but also for the development of efficient treatment of tinnitus. Therefore the aim of this essay is to explore the underlying neural mechanisms of tinnitus, from generation to perpetuation and its perception. Focus will be on abnormal auditory, limbic and central nervous system (CNS) functions, as well as abnormal activity and interaction between these systems that is proposed to be involved in tinnitus. Closer consideration will be given to cochlear dysfunction (specifically hair cell damage) and aberrant activity within auditory, hippocampal, amygdalar and thalamic structures. Additionally, a brief evaluation of treatment methods in contrast to the neural basis of tinnitus is to be made.

This essay will begin with a short presentation of possible causes of tinnitus and available therapeutic options. Then moving forward to what mechanisms in the brain that may generate tinnitus. This will be done by firstly discussing cochlear dysfunction in the form of hair cell damage, then narrowing it down further, to the effect calcium has on various parts of the cochlea and how this may cause hyperactivity within the auditory system. Research will be presented on auditory, limbic and CNS connectivity, structural and functional changes, and their part in generating tinnitus. Secondly, oscillatory properties of the CNS and thalamocortical dysrhythmia will be mentioned. Following this, research will be presented on the effects of salicylate on cochlear, auditory, and limbic structures. After that new developing treatments will be shortly mentioned. The discussion will contain a summary of the central findings regarding the neural mechanisms of tinnitus. Furthermore therapeutic options will be discussed in contrast to the neural findings in this essay, to finally suggest future directions for the neuroscience of tinnitus.

Due to the many causes of tinnitus (see section: Causes and therapeutic options), the data collected in this essay have been limited to what is considered the most relevant for tinnitus in general. For example anomalies in the vascularture of the head or multiple sclerosis is known to cause tinnitus but may have very different neural mechanisms compared to other types of tinnitus (McFadden, 1982) and can therefore be inappropriate to consider in this essay. This leaves three types of tinnitus that are relevant: Tinnitus caused by age-related hearing loss, damage to auditory pathways, and temporarily induced by either exposure to drugs or noise. Not only are these three types understood to share similar neural mechanisms, but are also the most common amongst the population (McFadden, 1982).

Causes and therapeutic options

Tinnitus as suggested by McFadden (1982), is the consequence of a variety of different causes. All of these causes are traceable to the brain and the musculature and vasculature around it. However, the diversity of causes raises a problematic issue regarding the treatment of tinnitus. Different causes may have different pathophysiology. Therefore it is of significant importance to understand the neural mechanisms that may account for the generation of tinnitus (De Ridder et al., 2014; Eggermont & Roberts, 2004; Jastreboff, 1990; Henry, 2005; Landgrebe et al., 2012).

Causes

The causes of tinnitus may be relevant for a number of aspects such as avoidance or care for possible causes, therapeutic options as well as locating generative mechanisms. The causes of tinnitus is in this sense not the source of tinnitus, but what has been observed to correlate with its beginnings. The source is rather the neural events that may generate tinnitus after irregularities or damage to the head and brain, which will throughout this essay be considered as causes themselves. The cause has throughout time been established by either one of three factors (McFadden, 1982): 1.) There is a sudden occurrence of both the cause and the tinnitus. 2.) There is frequent associations between the cause and tinnitus. 3.) There is disappearance of the tinnitus following removal or treatment of the

cause. The source is rather the changes on a neuronal level which is to be discussed in further detail later.

McFadden (1982) constituted that there are causes of tinnitus than can be reasonably confirmed by these three factors. Hearing loss is a common cause, however it is important to stress the fact that tinnitus can occur without any form of hearing deficit. Either way tinnitus is most prevalent in age-related hearing loss but may occur in most types of hearing loss (Heller, 2003). Exposure to intense noise is well established as a cause (McKinny, Hazell, & Graham, 1999) and many animal studies regarding tinnitus is either on drug or noise induced tinnitus. Severe blows to the head may occasionally cause transient, long-term, or even permanent tinnitus. McFadden (1982) says that the source would in such an instance suggestively depend on the localization of the head injury, within the range of the neural mechanisms of tinnitus. Overdoses of drugs and general anaesthetics, as McFadden (1982) further mentions, has frequently been reported to cause tinnitus and may initiate as well as heighten the experienced noise. Furthermore McFadden states that anemia, hypertension, hypothyroidism, migraine, multiple sclerosis, Meinere's disease, tumors on the eight nerve and immobilization of the inner ear structures have been associated with tinnitus.

All the above mentioned types of tinnitus (as determined by their cause) are what is referred to as subjective tinnitus (Henry, 2005). Subjective tinnitus is the noise perceived internally, by whoever is experiencing it. Objective tinnitus is instead the actual noise that can be heard not only by the one experiencing but by others as well and may be correlated with anomalies of the vasculature and musculature of the head, neck and jaw. The noise heard in tinnitus originating from anomalies in the musculature is in McFadden (1982) believed to be involuntary, rhythmic contractions of the soft palate.

Tinnitus can have many underlying mechanisms as which can be understood from its many possible causes. However as mentioned earlier, tinnitus may sometimes be observed in severe illnesses as Meiner's disease, Multiple Sclerosis or of a tumor. Henry (2005) therefore stresses the importance of

taking tinnitus as a potentially serious symptom.

Therapeutic options

The severity of tinnitus in a clinical sense refers not to the level of noise but to what extent the quality of life is affected. There are many degrees of tinnitus. Some people may experience an occasional high pitched tone in the ear whereas others may experience a constant loud noise, some may even experience both. It can be debilitating for concentration as well as preventing adequate sleep (Heller, 2003). Focus and preoccupation with one's tinnitus may seriously impact the quality of life causing stress, annoyance and depression. There is no currently universal therapeutic strategy for treating tinnitus (Chrbolka et al, 2015) and no therapeutic options available which substantially reduces the experience of the noise (Smit et al., 2015).

Therapy is used to treat a number of disorders such as anxiety, personality and eating disorders as well as depression and addiction. It may also be used to try to alleviate tinnitus. There are many types of tinnitus therapies ranging from counseling to a diversity of cognitive behavior therapy styles (Gans, 2010; Jasper et al., 2014), acceptance and commitment therapy to tinnitus retraining therapy (Zetterqvist Westin et al., 2011). Even though therapy in its many varieties are widely used in tinnitus treatments, its efficacy remains unsatisfactory (Chrbolka et al, 2015; Smit et al., 2015).

Chinese herbal treatment accompanied by classical tinnitus therapy is suggested to enhance therapy efficacy by diminishing the psychological sensation of tinnitus and improving sleep quality (Lin et al., 2015). Reduction of caffeine consumption is sometimes also used as treatment, however Rodrigues Figueiredo et al. (2014) claim that there is no justification for the effects of this reduction in most cases of tinnitus.

Acupuncture, both normal and electrical are well used treatment methods for tinnitus. However, according to Wang, Bugge & Bugge (2010), there is disagreement between researchers on whether it is efficient as a therapeutic option.

Drugs are used to ease sleeping difficulties, mood changes and depression caused by tinnitus. This however does not target the tinnitus but rather alleviate its side effects. Drugs in general have shown to be relatively inefficient as possible treatment. Lidocaine has had subjectively reported relief from tinnitus, however the numbers are few and the effects are brief (Kalcioglu et al., 2005).

In patients with both profound hearing loss and tinnitus, cochlear implants and hearing aids have been used in an attempt to lessen the perception of tinnitus. The cochlear implant (Vallés-Valera et al., 2013) was successful in decreasing the perception of the tinnitus, however, the tinnitus was still present and this type of procedure is only suited for a certain type of tinnitus patient. Moffat et al. (2009) have shown that hearing aids pitch and loudness matched for the patient's tinnitus frequency may in some cases be useful as treatment.

The neural mechanisms underlying tinnitus

The source of tinnitus, or rather the generation of tinnitus is believed to occur at a neural level (Eggermont & Roberts, 2004). As to be seen below, changes in firing patterns can result in hyperactivity in neural networks related to tinnitus which can lead to maladaptive plasticity in the CNS (Leaver et al., 2011). Oscillatory properties of neurons and their networks may strengthen connectivity thereby adding to the maladaption (Llinas, 1988). Furthermore (Mühalu et al., 2006) a lack of inhibitory activity within these networks may be a reason for the plasticity and disynchronization of oscillations. Salicylate can induce temporary hearing loss and tinnitus (Chen et al, 2013) and can influence various areas related to tinnitus.

Cochlear dysfunction

The cochlea is the shell shaped part located in the inner ear. The function of the cochlea is to transform input from its associated structures and vibrations of the cochlear liquids into neural signals that pass through the auditory nerve and are carried onwards to the brain (Irwin, 2006). The cochlea is divided in to three tubes, the scala vestibuli, scala media and scala tympati that are all liquid filled.

Between the scala media and the scala tympati there is a thin membrane called the basilar membrane, on to which the organ of Corti is attached. It is in the movement of the organ of Corti that the transduction of sound happens (Hudspeth, 2014).

The organ of Corti holds the inner and outer hair cells (see Appendix for a picture of the Organ of Corti). These cells are crucial for proper transformation of auditory stimuli to neural signals (Hudspeth, 1985). All hair cells, inner as well as outer, have bundles of stereocilia on their tip. In outer hair cells (OHC) the stereocilia are embedded in the tectorial membrane, or the "roof" of the organ of Corti and acts as inhibitor of afferent activity through efferent nerve fibers and accounts for the fine-tunings of sound frequencies. The inner hair cells (IHC) have no contact with the tectorial membrane but manages the transformation of the vibrations in the cochlear liquids in to electrical signals that are transferred to the brainstem and auditory cortex via the auditory nerve. This process happens through afferent nerve fibers coming from the IHC (Hudspeth, 1982).

Stereocilia located in the same bundle are coupled with one another. This coupling occurs at the ends of each stereocillum. As described in Hudspeth (1985) the so called "filaments" connecting the cilia works as a gating mechanism that opens and closes ion channels. When the tension of the filaments increases there is an increase of ions flowing into the hair cell causing it to depolarize and that results in electrical potentials. These electrical potentials, as mentioned above, is what ultimately leads to neural signaling to the auditory nerve.

Damage, either transient or permanent to the organ of Corti in any way, should alter our perception of sound (Jastreboff, 1990). As to be suggested and further explained in the following sections is how these neural changes may result in tinnitus.

Inner and outer hair cell damage. Exposure to ototoxic drugs or intense sound may cause damage to the structures within the cochlea, starting at the basilar membrane affecting inner and outer hair cells. Extensive exposure to ototoxic agents (Abrashkin et al., 2006) can cause scars and ultimately

death of hair cells. Extensive exposure to intense sound can cause the hair cell stereocilia to bend, either temporarily or permanently (Jastreboff, 1990). This may result in a necrotic process where the hair cells start to decay within hours after exposure (Murai et al, 2008).

Drug-induced as well as sound-induced damage may result in either complete or partial destruction of hair cells throughout the basilar membrane. Complete destruction of OHC and IHC throughout the entire basilar membrane would result in heavy hearing loss or even deafness. Damage to only a portion of the basilar membrane will affect proper functioning of the organ of Corti. On a partially damaged basilar membrane, there may be areas with total destruction of both OHC and IHC as well as areas with damaged OHC while reasonably intact IHC remains (Jastreboff, 1990).

According to Jastreboff (1990), when OHC stereocilia bends or decay, they no longer connect to the tectorial membrane. This decoupling between the tectorial and basilar membrane can give rise to abnormal movement of both membranes or even local collapse of the tectorial membrane. It would decrease the distance between IHC cilia and the tectorial membrane, perhaps to such an extent of physical contact, that the IHC cilia bends and might become depolarized. Damaged OHC will in turn lead to decreased efferent activity as well as decreased inhibition of afferents coming from the IHC hence enhancing the activation of IHC, resulting in abnormal activity within the cochlea. This abnormal spontaneous activity is suggested by Jastreboff (1990) to be an important aspect in the generation of tinnitus.

Age-related hearing loss may be the result of age-related decline in the amount of hair cells within the cochlea (Chen et al., 2009). Like bending of the stereocilia or immediate cell death, this may eventually produce abnormal activity in the cochlea due to unrestricted and spontaneous afferent activity. This follows the hypothesis that tinnitus may be generated by abnormal activity within the brain due to cochlear damage and does explain why individuals with hearing loss tends to be more likely to experience tinnitus (McKinney, Hazell & Graham, 1999).

As to further support this proposal of generation, Thabet (2009) observed abnormal activity of sound stimulated otoacoustic emissions in tinnitus subjects with normal hearing. Otoacoustic emissions are low level sounds that are normally produced by healthy OHC, either spontaneously or following sound stimulation. Thabet suggests that partial damage to the OHC could emit the abnormal otoacoustic activity observed in the tinnitus subjects and that OHC dysfunction may therefore play a vital role in generating tinnitus.

An intriguing aspect regarding hair cells, that also holds a clinical value is the research on the regeneration of hair cells after ototoxic induced death (Kros, 2007). Normally hair cells in the mammalian cochlea do not regenerate. Even so spontaneous hair cell regeneration have been seen to occur in the mouse cochlea 24 weeks after hair cell death (Kawamoto, Izumikawa, Beyer, Atkin, & Raphael, 2009). Kros (2007) stresses the complexity of such a process but that through future research it may be possible to induce regeneration of hair cells. Regeneration of hair cells and its implications for tinnitus however remains limited.

The role of calcium in cochlea dysfunction. Calcium has the potential, through several possible mechanisms, to influence transduction properties within the cochlea. Jastreboff (1990) has proposed that changes in calcium concentration may be responsible for some cochlear dysfunctions in which he includes tinnitus. In his review he describes the following five instances where calcium may influence the cochlea:

Firstly, it may influence the position of the tectorial membrane. This can be understood from increases in intracellular cytosolic Ca^{2+} that holds the possibility to initiate either apoptosis (the process of programmed cell death) or necrosis depending on a lower or higher concentration of Ca^{2+}. Calcium in this sense may act as an intermediary of the necrotic processes of cell death (Zong & Thompson, 2006), and as mentioned earlier (Jastreboff, 1990), when OHC decouples, it may give rise to abnormal movement or even collapse of the tectorial membrane. As further mentioned by Jastreboff

(1990), low concentrations of calcium have shown to result in a decrease of OHC length and increase in OHC diameter, also resulting in a decoupling from the tectorial membrane.

Secondly, it may influence the hair cells calcium-dependent potassium channels. Calcium is essential for the process of transduction, turning acoustic stimuli into electrical potentials. This is mediated by potassium channels (BK channels), specifically the large conductance calcium-activated BK channels that are especially sensitive to electrical changes in membrane potentials as well as increases of Ca2+ (Ghatta, Nimmagadda, Xu, & O'Rourke, 2006).

Thirdly, it may influence transduction properties of the hair cell cilia. Calcium can modify the amplification and adaption transductory properties either strengthening or weakening hair cell cilia coupling. However, according to Rossetto (2003), how these mechanisms work in detail remains poorly understood.

Fourthly, it may influence slow motile properties of OHC. The OHC can change their length when exposed to certain external solutions. An increase of calcium is implicated to slow shortening of the OHC (Ashmore, 2008). Calcium is therefore crucial for slow OHC movement. It is suggested by LePage (1987) to be involved in adjusting the position of the basilar membrane to reassure efficient sound transduction in a broad spectrum of intensities.

Lastly, it may influence the release of neurotransmitters from hair cells. BK channels may be considered as "emergency brakes" (Ghatta et al., 2006) and are controlling the excitability of neurons by limiting firing frequency. These channels play a vital role in inhibition of afferent activity within the cochlea. However, when BK channels are activated due to excessive intracellular calcium release, production of spontaneous bursting activity is decreased and efferent activity (evoked activity) is increased. In contrast to this, low concentrations of calcium causes spontaneous activity to increase and evoked activity to decrease and reduced inhibition of afferent activity (Jastreboff, 1990).

From this it is possible to summarize a dynamic sequence of events when calcium levels

decrease within the cochlea. The tectorial membrane would become weakened by the increase of distance between the membrane and the OHC, causing partial decoupling. And as previously discussed, this decoupling would enhance the afferent cochlear activity. Cilia may through its transductory properties adapt to decreases in calcium by becoming more flexible in their attachment. This flexibility would result in a decrease of coupling between the OHC cilia, which inevitably would decrease the coupling of the tectorial membrane and the OHC with the same outcome as mentioned before (Jastreboff, 1990). Slowing the mobility of the OHC will reduce the inhibitory efferent activity allowing afferent activity to roam more freely and prevents efficient sound transduction. Neourtransmitter release will be affected by the above mentioned dilemmas causing spontaneous cochlear activity to increase and evoked auditory activity to decrease (Jastreboff, 1990).

Both exposure to intense sound, either momentarily or over a longer duration can lead to acoustic overstimulation of the OHC. Normally, when OHC are stimulated by general noise, there is an immediate increase of $Ca2+$, that subsides shortly after (Zong & Thompson, 2006). Acoustic overstimulation however (Fridberg, Flock, Ulfendahl, & Flock, 1998) causes a sustained increase of $Ca2+$ as well as contractions of the cochlea. As seen in Zong and Thompson (2006), increases in $Ca2+$ may initiate the decay of OHC.

Low levels of calcium in the cochlea as well as excessive amounts of calcium concentrations within hair cells greatly affects the status of the cochlea. Changes like all the above mentioned may cause continuous depolarization of IHC leading to continuous spontaneous firing of partially inhibited afferent activity. This hyperactivity within the IHC projects to the auditory nerve and further into the brain and may account for tinnitus related hyperactivity and plastic changes seen in auditory cortex and its neighboring areas (Cacace, 2003). Even so, both Cacace (2003) and Kaltenback (2011) agrees that tinnitus can still persist without afferent input from the cochlea and its IHC which is to be further discussed in the following sections.

Crossmodal networks in the generation of tinnitus

The above described instances of cochlear dysfunction provides insight to what might have initially caused observed tinnitus-related hyperactivity and plastic changes in several brain areas. As stated above, tinnitus itself can persist without continuous activity from the cochlea (Cacace, 2003; Kaltenback, 2011). However Jastreboff (1990) stresses the issue that tinnitus in some cases still needs to be initiated by the IHC hyperactivity regardless of whether this hyperactivity is temporary or not. Cochlea dysfunction is therefore an important aspect in the generation of tinnitus.

Even so, there is growing evidence and it is commonly agreed (De Ridder et al., 2014; Eggermont, & Roberts, 2004; Mühlnickel, Elbert, Taub, & Flor, 1998) that tinnitus may be generated and perpetuated at different locations within the brain rather than just at its initial origin. It most likely involves a crossmodal network of areas in addition to the already established cochlea and the auditory system (Cacace, 2003). This can be understood from plastic changes seen in cortical areas that are not generally associated with tinnitus. These areas have hypothesized to be able to modulate the tinnitus perception. Interactions between neural networks subserving such things as attention, emotion and cognition may therefore all be a part of a broad crossmodal neuronal network for sustaining tinnitus (Cacace, 2003).

The auditory system. It has been suggested in Noreña and Farley (2013) that tinnitus progresses over time to become "centralized ", meaning that it becomes less and less dependent on the outer auditory and the low-level auditory structures and more dependent on higher auditory systems and surrounding structures. Noreña and Farley hypothesize that tinnitus eventually could be solemnly generated by its centralization, it follows a bottom-up approach. As to be seen below is how the manner of neural activity and plasticity in the auditory system in tinnitus is suggested to underlie generative, perpetuating and perceptual properties.

Irregularities in the auditory system is believed to be a key factor for the generation of tinnitus

(Laundrie, & Sun, 2014; Leaver et al., 2011). Afferent activity coming from the IHC first travels through different parts of the auditory system in to the primary auditory cortex. It is in the primary auditory cortex the sensation of basic sounds such as a pitch or a rhythm would be processed as well as the characteristic sounds reported to be experienced in tinnitus. Overstimulation of the lower-level auditory systems as well as a lack of inhibitory efferent activity may cause hyperactivity within the auditory system that could potentially lead to structural and functional plasticity (Robertson, Bester, Volger, & Mulders, 2013).

Structural as well as functional changes have been observed in the auditory system in tinnitus and it is proposed by Eggermont and Roberts (2004) that tinnitus can be seen as a course of maladaptive plasticity. According to Llinas (1988) spontaneous firing of neurons arises from a combination of specific intrinsic membrane currents that are expressed by spontaneously active neurons (Llinas, 1988) and may play an important part in neural plasticity. In animal studies, increases of spontaneous firing rates (SFR) have been seen to occur after noise induced trauma in the primary auditory cortex (Seki & Eggermont, 2013). To Adjamian, Sereda and Hall (2009) this is of particular interest because increases of what otherwise appears to be a completely random firing patterns of neurons now have a higher probability of synchronizing their firing and strengthening their connectivity. This may to some extent account for the tinnitus-related maladaptive plasticity as well as observed hyperactivity in the lower-level auditory system.

Noise induced trauma may cause hyperactivity in the lower levels of the auditory system as seen in Mulders and Robertson from 2009. In the same research paper, silencing or ablation of cochlear activity was observed to eliminate hyperactivity in the inferior colliculus (IC). Similarly, silencing of the cochlea in tinnitus has shown to immediately reduce hyperactivity in the IC (Robertson et al., 2013). Following this it has been suggested that the IC needs neural activity from the cochlea in order to maintain hyperactivity. Kaltenbach and Afman (2000) observed that hyperactivity in the dorsal

cochlear nucleus (DCN) after intense noise exposure resembles tone-evoked activity in the normal DCN. Their result suggests that the DCN becomes altered following intense tonal noise exposure and begins to behave physiologically as if it was responding to a tone, even in the absence of any corresponding acoustic stimulus.

Mühalu et al. (2006) found plastic reorganizations of the auditory system in tinnitus subjects. Using fMRI they found increases of gray-matter in posterior thalamus and the medial geniculate nucleus (MGN) as well as a vast gray-matter decrease in the subcallosal area in their tinnitus subjects compared to controls. They also suggest that the MGN may hold the capacity for the perpetuation of tinnitus-related neuronal activity and that this process would be enhanced by the decrease of subcallosal gray-matter. Subcallosal gray-matter normally holds inhibitory feedback that could help to tune out neuronal activity related to tinnitus, a decrease of gray-matter in this area may then result in a decrease of inhibitory feedback (Mühalu et al., 2006).

Tonotopic maps of the auditory cortex are structural arrangements within the auditory pathways where different tone frequencies are transmitted seperately along specific structural parts. In tinnitus, there appears to be a reorganization of these tonotopic maps (Mühlnickel et al., 1998). The reorganization observed indicated an expansion of the tonotopic maps in tinnitus subjects which may lead to an overrepresentation of the tinnitus frequencies. Mühlnickel et al. (1998), could, in relation to this see a correlation between subjective tinnitus strength and the amount of reorganization of the auditory cortex.

Nonetheless, Eggermont (2015) claims changes in tonotopic maps may not be necessary for the generation of tinnitus. Langers, Kleine and Dijk in 2012 found similar tonotopic map reorganizations in patients with hearing loss as in tinnitus. They suggest that this type of reorganization may not be as usual in tinnitus accompanying mild hearing loss or normal hearing but may still be a relevant aspect of tinnitus generation.

As the generation of tinnitus is suggested to be a bottom-up occurrence, the perception of tinnitus has been suggested to be a top-down influence on the auditory cortex (De Ridder et al., 2014). Activity in the auditory cortex in tinnitus that comes from ventromedial prefrontal and posterior cortices have in Schlee et al. (2009) and Seydell-Greenwald et al. (2012) been correlated with subjectively experienced strength of the tinnitus distress. Schlee et al. (2009) propose that specific aspects of tinnitus (as for example loudness, distress, mood or laterality) may have their own neurophysiological and separable networks. But they also suggest that these networks change through time as a result of continuous functional plasticity, which inevitably could interfere with possible treatment options.

What can be understood about tinnitus from irregularities in the auditory system (Leaver et al., 2011) is that changes in neural activity may influence maladaptive functional plasticity of the structures in the auditory system to such an extent that they may exhibit generative and perpetuating properties. These generative and perpetuating properties are not necessarily fixed at specific locations but may shift as plasticity shifts. The lower-level auditory areas such as IC, and the DCN are easily triggered by afferent activity coming from IHC after noise exposure (Mulders, & Robertson, 2009; Robertson et al., 2013). The MGN is by Mühalu et al. (2006) suggested to hold perpetuating properties. In the same study, gray-matter decrease in the subcallosal area may lead to a reduction of inhibitory activity in the auditory system.

The tinnitus percept may involve other areas than just the auditory system (De Ridder et al., 2014; Schlee et al., 2009; Seydell-Grenwald et al., 2012) but the auditory system is for obvious reasons suggested to be a prerequisite for auditory consciousness hence also the perception of tinnitus (De Ridder et al., 2014).

Auditory-limbic interactions. As previously established, the generation of tinnitus is suggested to initially occur within the auditory system. However, there is common consensus that limbic

structures may play a role in modulating, perpetuating the tinnitus percept (Cacace, 2003; De Ridder et al., 2014; Kraus & Canlon, 2012; Leaver et al., 2011). Of specific interest is the hippocampus, the amygdala and the ventromedial prefrontal cortex (Kraus & Canlon, 2012); Seydell-Greenwald et al., 2012). Kraus and Canlon in 2012 explains that both amygdala and hippocampus are highly interconnected structures that have direct connections with auditory systems as well as connections between each other. They account for the memory of the tinnitus sound and its emotional associations. Further on Kraus and Canlon mention that ventromedial prefrontal cortex may enhance these emotional associations. Tinnitus is more often associated with something unpleasant or anxiety-provoking (McFadden, 1982) suggesting that the limbic structures must be of some importance for tinnitus.

The hippocampus receives both direct and indirect auditory input from auditory association cortices and in turn, the auditory association cortices receive input indirectly from hippocampus via parahippocamapal cortex. This allows for the hippocampal-auditory systems to form long-term auditory memories as well as spatial memories related to sound. It also allows for auditory systems to affect structural and functional plasticity in the hippocampus (Kraus & Canlon, 2012).

Cortical plasticity caused by exposure to intense noise may extend to the hippocampus as seen in Goble, Møller and Thompson (2009). They observed that place cells in the rat hippocampus exhibited alterations in their firing properties after exposure to intense noise that may account for further plasticity of the hippocampus. In another research paper (Carpenter-Thompson, Akrofi, Schmidt, Dolcos, & Husain, 2014), the parahippocampus displayed alterations in emotional processing of novel sounds in tinnitus subjects, which may indicate a lack of habituation to novel sounds. This lack of habituation could possibly help to explain the tinnitus persistence.

Structural changes in the form of gray matter decrease has further been detected in the left hippocampal area in tinnitus subjects compared to healthy controls (Landgrebe et al., 2009). Interestingly so, the same research paper exclaim that there were no signs of decrease of gray matter in

the subcallosal area, as would have been in line with Mühalu et al. (2006). Furthermore they found a

decrease of gray matter in the IC compared to the earlier proposed hyperactivity in the IC reported in

Mulders and Robertson from 2009.

The amygdala is known to mediate general emotional functions in the brain (Kraus and Canlon,

2012). It is highly interconnected with the auditory cortex and hippocampus, either through direct

connections to the auditory system or via thalamic structures. As explained in Kraus and Canlon

(2012), exposure to noise activates the amygdala through the auditory system. Amygdala in response

initiates the release of stress hormones.

Both neuronal activity from auditory-amydalar structures as well as stress hormones can heavily

influence hippocampal alterations such as reducing neuronal activity or modifying synaptic plasticity

and memory (Kraus & Canlon, 2009). The amygdala is also capable of modulating auditory cortex

activity and plasticity (Keuroghlian & Knudsen, 2007) through cholinergic and dopaminergic systems.

Mahlke and Wallhausser-Franke (2004) suggests that because the amygdala is capable of

modulating auditory cortex plasticity and that it is known to have a part in the learning of negative

emotions, it may therefore be responsible for tinnitus-related distress. The amygdala may also aid

tinnitus consolidation by the release of stress hormones to the auditory cortex that coincides with

already aberrant activity in the auditory system causing auditory cortex plasticity. This is of interest to

tinnitus research because of its associations with Pavlovian fear conditioning (Kraus & Canlon, 2012).

In Pavlovian fear conditioning, a neutral stimulus becomes paired with the response network of a

stimulus that is in its nature unpleasant, so that the neutral stimulus eventually, and on its own, trigger

the same response as the unpleasant stimulus. A novel sound as experienced in tinnitus could then be

inappropriately paired with with a stronger reaction to sound as when amygdala responds to intense

noise causing plasticity in the auditory system as well as tying the novel sound to a distressing memory

association (Kraus & Canlon, 2012).

The ventromedial prefrontal cortex has been suggested to be a structure responsible for the perception of tinnitus. Seydell-Greenwald et al. (2012) found that tinnitus-related distress levels in tinnitus subjects could be correlated with the amount of ventromedial prefrontal cortex activity. Further on Seydell-Greenwald et al. propose that the ventromedial prefrontal cortex activity reinforce the emotional aspect of the tinnitus thus interrupting any possible habituation. They also propose that negative emotions on the experience of tinnitus enhances the attention of it which in turn may enhance the perception of it.

As for summarizing the auditory-limbic interactions, they may strengthen connectivity and affect plasticity within auditory as well as hippocampal and amygdalar structures. The interaction between these three structures allows the formation of emotionally significant auditory memories. The involvement of the amygdala may be responsible for experienced tinnitus-distress. Ventromedial prefrontal activity may in turn enhance the perception of the tinnitus noise as well as the accompanying distress.

Similarities with chronic pain. Earlier proposed by Schlee et al. (2009) was that specific aspects of tinnitus may have their own neurophysiological and separable networks. These separable networks are not generally unique to tinnitus and can be seen in other pathologies such as chronic pain. There are many different forms of tinnitus and many different forms of pain, these different forms most likely have differences in their pathologies (McFadden, 1982).

Both tinnitus and chronic pain are subjectively experienced sensations that are continuously perceived and that can change both in quality and character over time. Even so, severe tinnitus has been hypothesized to share some of the same neural features as chronic pain (Cacace, 2003; Jastreboff, 1990; Møller, 2000). Møller in his review from 2000 asserts similarities between severe tinnitus and chronic pain such as that they share similar symptoms, signs and hypotheses regarding their neural mechanisms. He distinguishes between acute pain versus chronic pain and mild/moderate tinnitus

versus severe tinnitus suggesting that acute pain and mild/moderate tinnitus are generated peripherally (where the pain or noise is perceived to be) and that chronic pain and severe tinnitus are generated and sustained centrally (in the CNS) rather than peripherally. This transition from peripheral to a central generation is proposed to be from plastic structural and functional changes of the CNS because of overstimulation of neurons due to lack of inhibitory control.

This follows in line with the previously mentioned aspects of that tinnitus may arise from cochlear deaffarentation to later become centralized (Noreña & Farley, 2013) due to reorganization of tinnitus related structures (Mühlnickel et al., 1998). These similarities between tinnitus and chronic pain could potentially help to further understand both of these disorders and that they may also benefit from similar treatment and therapeutic options (Møller 2000).

Oscillatory properties

As mentioned earlier by Llinas (1988), some neurons are believed to hold intrinsic oscillatory properties that are important for the generation of membrane and action potentials. These neurons display self-generated rhythmic activity that may give rise to spontaneous firing of clusters of neurons as well as spontaneous firing of neurons throughout entire brain structures. These rhythmic firing patterns of single neurons, clusters and brain structures are called oscillations. What Llinas proposes (1988) is that the intrinsic oscillatory properties of thalamocortical neurons and their interconnectivity may through oscillation provide internal context to sensory input.

The oscillations are regulated by inhibitory GABAergic interneurons which are important for normal thalamocortical activity (Mann & Paulsen, 2007) but may also be responsible for the generation of thalamocortical dysrhythmia (Llinas, Urbano, Leznik, Ramirez, & van Marle, 2005).

Thalamocortical disrhythmia has been explained as a source of various neurological and psychiatric disorders such as Parkinson's Disease, epilepsy, depression, migraines and tinnitus (Llinas et al. 2001). The idea behind Thalamocortical disrhythmia (Llinas et al., 2001) is that internally

generated, abnormal oscillations of low frequency will disrupt the normal flow of oscillations in the thalamocortical network. Such alterations in rhythmicity in the thalamocortical networks could result in disturbances of motor performance, sensation and cognition depending on its localization in the thalamocortical network. This abnormal oscillatory behavior would be driven by an overrepresentation of inhibitory activity within the thalamus causing disychronization.

Salicylate as a tinnitus-inducer

Salicylate is a main component of aspirin and is commonly used worldwide as an anti-inflammatory drug (Gong et al., 2008). It is also a substance that in a high dosage, is known to temporarily induce hearing loss and tinnitus (Liu & Chen, 2012; Noreña, Moffat, Blanc, Pezard, & Cazals, 2012 ;Yang et al., 2007) and can have various effects on brain areas that are related to tinnitus (Basta & Ernst, 2004; Chen, Manohar, & Salvi, 2012; Gao et al., 2012; Gong et al., 2008).

High concentrations of salicylate can cause ototoxic changes and damage to the cochlea. In Shehata, Brownell and Dieler (1991) salicylate was shown to affect OHC properties. They found temporary changes in OHC shape and motility that caused impairments to cochlear movement, which could account for the salicylate-induced hearing loss mentioned earlier as well as changes in the otoacoustic emissions. Chen et al. (2013) observed a decrease of spiral ganglion neurons in the auditory nerve after long-term exposure to high doses of sodium salicylate. They propose that the degeneration of spiral ganglion neurons occurred by apoptosis that was triggered by the salicylate intrusion. However they did not detect any damage to the OHC which may indicate that salicylate merely alter OHC properties. Even so, decreases of cochlear spiral ganglion neurons results in a decrease of neural output coming from the cochlea.

Salicylate may also affect the auditory system on various levels. According to Liu and Chen (2012), the auditory brainstem show increased electrical activity when exposed to high doses of salicylate. This activity can be measured by auditory brainstem response (ABR) and Liu and Chen

further suggests that ABR may be used as an indicator for salicylate induced tinnitus in animals. Basta and Ernst (2014) observed that neurons in the IC are sensitive to higher doses of salicylate, and that it causes an increase of firing rates within the neurons.

In a more general sense Noreña et al., (2012), in their article suggests that salicylate may change the neural activity within the auditory system in ways such as firing rate, oscillations, local as well as global synchrony and temporal correlations. They hypothesize that the occurence of tinnitus would arise when the salicylate induced neural changes reaches a certain threshold and that these neural changes most likely are proportional to the amount of salicylate that has been induced. Furthermore according to Chen, Manohar, and Salvi, (2012) the amygdala has been seen to show increased excitability when exposed to salicylate which may in turn enhance the effects salicylate may have on the auditory cortex.

Salicylate may also cause hyperactivity in the hippocampus as mentioned in Gong et al. (2008). Salicylate alters GABAergic neurotransmission, leading to a reduced inhibition of activity. Gong and colleagues propose that the hyperactivity observed in the hippocampus is a result of this lack of inhibitory control. The salicylate induced reduction of GABAergic inhibition may explain the increase of activity observed in the auditory system, amygdala and hippocampus (Chen, Manohar, & Salvi, 2012; Gong et al., 2008). Especially so, considering that high doses of salicylate causes a decrease of activity coming from the cochlea (Chen et al., 2013).

Quinine is another substance that is believed to induce tinnitus (Ochi & Eggermont, 1997). Even though salicylate and quinine acts differently on the level of potassium channels, they both have similar effects on the CNS generally and are both ototoxic agents that can cause damage to the cochlear structures (Kenmochi & Eggermont, 1997).

New developing therapeutic options

Now when the underlying mechanisms for tinnitus are slowly beginning to be understood, new

developing treatments are emerging. These treatments target the changes in the brain that are believed to be related to the tinnitus pathophysiology (De Ridder & Vanneste, 2014; Langguth et al, 2008). It still remains a difficult problem to target the tinnitus pathophysiology in every individual, because their pathophysiologies may differ greatly (McFadden, 1982). Even so, there is agreement among many (Landgrebe et al., 2012) that tinnitus research and tinnitus treatment is heading in a positive direction.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method to modulate cortex activity (Langguth et al., 2008). Langguth et al. (2008) furthermore propose that rTMS modulation of auditory cortex activity may result in alterations of the tinnitus sensation. Khedr, Rothwell, Ahmed and El-Atar (2008) suggest that rTMS disrupts the oscillatory hyperactivity involved in the tinnitus generation, thereby aiding the brain in restoring normal activity. Stimulation of the vagus nerve has also shown to modulate auditory cortex activity and plasticity (Engineer, Møller, & Kilgard, 2013). This has however only been shown in animal studies so far but is according to Engineer, Møller, and Kilgard (2013) a promising therapeutic alternative.

Intracranial auditory cortex stimulation by electrode implants is another way to disrupt the synchronized oscillatory hyperactivity which has been successful in some individuals (De Ridder & Vanneste, 2014). However, the responsiveness to this method is difficult to determine and may depend less on the auditory cortex itself and more on its surrounding structures.

A pharmacological approach that targets inhibitory GABA receptors may also be of future interest to tinnitus treatment (Richardson, Brozoski, Ling, Caspary, 2012), knowing that lack of inhibitory activity may give rise to the observed tinnitus related hyperactivity throughout the CNS (Carpenter-Thompson et al., 2014).

Discussion

Although plasticity is fundamentally supposed to be an adaptive mechanism, it may sometimes have its disadvantages. As mentioned previously, Eggermont and Roberts (2004) propose that tinnitus

can be seen as a continuous process of maladaptive plasticity. The difficulty in identifying the neural

mechanisms of tinnitus lies within the fact that it can involve one or multiple brain areas and that some

may or may not be dependent on one another. The dependency of tinnitus-related brain areas may also

shift through time and become more "centralized" as coined by Noreña and Farley in 2013.

Cochlear dysfunction and changes in OHC efficiency as a result of hair cell bending, damage,

death or shift of calcium levels may affect proper sound transduction of certain sound frequencies,

depending on localization of the change along the basilar membrane (Hudspeth, 2014). Such changes

of the OHC Jastreboff says (1990) may result in a decrease of efferent activity and a decrease in

inhibitory control of IHC afferent activity, causing an overstimulation of IHC and abnormal activity in

the cochlea. Møller (2000) suggests that tinnitus can be generated simply by such cochlear

irregularities but that severe chronic tinnitus must rely on its centralization along the CNS.

The auditory system is believed to have a central role in tinnitus pathophysiology (De Ridder et

al., 2014; Laundrie & Sun, 2014; Leaver et al., 2011). First of all, De Ridder et al. (2014) argues that

the auditory system must be involved in tinnitus as it is vital for auditory consciousness. Lower level

structures of the auditory system are sensitive to afferent activity coming from the cochlea (Mulders &

Robertson, 2009) and tinnitus-related hyperactivity within these structures is frequently reported

(Kaltenbach, 2011; Kaltenbach & Afman, 2000; Landgrebe et al., 2009; Laundrie & Sun, 2014). It is in

the higher level auditory system and its associated structures that the centralization of tinnitus is

hypothesized to happen (Noreña & Farley 2013). This has been established by observations of

structural changes and reorganization of the auditory cortex in relation to tinnitus (Langers et al., 2012;

Mühalu e al., 2006; Mühlnickel et al., 1998).

Auditory-limbic interactions modulate and perpetuate tinnitus (Cacace, 2003; Kraus & Canlon,

2012; Keuroghlian & Knudsen, 2007; Mahlke & Wallhausser-Franke 2004; Seydell-Greenwald et al.,

2012). The hippocampus, amygdalar and ventromedial prefrontal cortex connections to the auditory

cortex as well as between each other allow for the formation of emotionally significant auditory memories. It results in the negative and distressing emotions that tinnitus is frequently associated with.

In Carpenter-Thompson et al. (2014) and Globe et al. (2009) the hippocampus has shown alterations of firing properties in sound processing. Furthermore (Carpenter-Tompson et al., 2014), in tinnitus subjects there appears to be a lack of habituation to novel sounds, which may be an explanation to the persistence of tinnitus. The amygdala and the ventromedial prefrontal cortex may modulate the tinnitus sensation. The amygdala may be influenced by auditory cortex activity (Kraus & Canlon, 2015) as well as it can modulate auditory cortex activity and plasticity (Keuroghlian & Knudesen, 2007). The ventromedial prefrontal cortex activity is proposed by Seydell-Greenwald et al. (2012) to reinforce the emotional expression of tinnitus and enhancing the perception of it.

Considering the different brain areas involved in the generation of tinnitus, Cacace (2003) suggests that tinnitus consists of a large crossmodal network, and as part of the experience of tinnitus, neural networks subserving emotion, attention and cognition must be present. Chronic pain as mentioned by Møller (2000) shares similarities with tinnitus in terms of their crossmodal natures. Møller highlight the fact that both chronic pain and severe tinnitus share some similar neural mechanisms as well as characteristics of centralization.

Thalamocortical disrhythmia is proposed by Llinas et al. (2001) to be the source of tinnitus. Abnormal low frequency oscillations may be internally generated and can influence the normal flow of oscillations in the thalamocortical network. It may strengthen abnormal oscillatory behavior and consequently inflict maladaptive tinnitus-related plasticity.

Salicylate can induce temporary hearing loss and temporary tinnitus and affect the various tinnitus-related brain areas mentioned above. Shehata et al. (1991) found that high concentrations of salicylate temporarily alter OHC motile properties. Decreases in spiral ganglion neurons in the auditory nerve after long-term exposure to salicylate was further observed by Chen et al. (2013). Salicylate on

an auditory system level may increase neuronal firing rates, oscillatory properties, local as well as global synchrony and temporal correlations (Noreña, et al., 2010). Both the hippocampus and amygdala become hyperactive by salicylate (Chen et al, 2010; Gong et al., 2008). The observed hyperactivity and an increase of firing rates may be due to a reduction of inhibitory GABAergic activity. Gong et al. (2008) suggests that salicylate reduce GABAergic inhibition. The hyperactivity would most likely not come from the cochlea considering that salicylate reduce cochlear functioning.

Therapeutic options, such as therapies, drugs, and acupuncture are widely used as treatment for tinnitus, however these methods have not been very successful (Chrbolka et al., 2015). There is a new approach towards tinnitus treatment that targets the tinnitus pathophysiology. Methods as rTMS and intracranial auditory cortex stimulation aims to disrupt the sychronized oscillatory behavior in tinnitus thereby modulate or alter tinnitus-related plasticity (De Ridder & Vanneste, 2014; Engineer et al., 2013; Khedr et al., 2008; Langguth et al., 2008). Pharmacological approaches that target inhibitory GABA receptors are by Richardson et al (2012) promising for tinnitus treatment but require further investigation.

However, there are multiple issues with such target-specific treatment in tinnitus. Firstly, tinnitus is as mentioned earlier by Cacace (2003) a crossmodal network, it is involved with various brain areas that build the entire perception of tinnitus. Connections between the auditory system, amygdala, hippocampus and ventromedial prefrontal cortex may according to Kraus and Canlon (2012) play a vital role in the generation of the emotional aspects of tinnitus. The emotional aspect of tinnitus is what causes experienced distress in tinnitus sufferers (Chrbolka et al. 2015).

Even so, rTMS and intracranial auditory cortex stimulation targets auditory cortex (De Ridder & Vanneste, 2014; Khedr et al., 2008) rather than the surrounding structures suggested to be involved in the generation of tinnitus-distress. But could reversal of tinnitus-related oscillatory behavior and plasticity in the auditory cortex perhaps influence changes in tinnitus-related plasticity in the limbic

structures? In any case, De Ridder and Vanneste (2014) mentioned that the responsiveness to intracranial auditory cortex stimulation depends less on auditory cortex and rather on its surrounding structures, but that it may be an effective method to alter tinnitus-related oscillations.

It is by now well established that tinnitus may involve a rather large network of brain areas. The second issue with target-specific treatment of tinnitus is that even though different types of tinnitus discussed in this essay, in a more general sense share the same neural mechanism tinnitus pathophysiology may still differ from individual to individual (McFadden, 1998). This could perhaps be because of differences in the individuals' stages of tinnitus-centralization, considering that tinnitus progressively centralizes over time (Noreña & Farley, 2013). For the same reasons, the individuals tinnitus pathophysiology may also change over time. This poses difficulties for research regarding tinnitus treatment.

The third issue with target-specific treatment of tinnitus is whether certain structures may be more or less involved in the tinnitus generation. De Ridder et al. (2014) suggests that the auditory system is a prerequisite for auditory consciousness and therefore must play a central role in tinnitus. However it can be argued that the involvement of the limbic structures is vital for tinnitus to be perceived as something distressing and bothersome (Kraus & Canlon, 2012) and it is only when the quality of life is affected that a treatment for tinnitus is needed (Henry, 2005). Khedr et al. (2008) believes that tinnitus-related hyperactivity can be continuously disrupted by rTMS to a point where the brain then could restore normal functioning of the auditory cortex. But there is no evidence so far that tinnitus cannot remain without continuous auditory cortex hyperactivity. After centralization the limbic structures are more involved in the perpetuation and perception of tinnitus and even though hyperactivity within the auditory system could be re-routed, the lack of inhibitory activity still needs to be addressed.

Mühalu et al. (2006) and Carpenter-Thompson et al. (2014) suggests that the CNS hyperactivity

may be caused by a lack of inhibitory control. Salicylate may also reduce inhibition in various tinnitus-related structures (Noreña et al., 2012). Interestingly so, Llinas et al. (2001) propose that the thalamus rather has an overrepresentation of inhibitory activity that causes changes in oscillatory firing patterns. Targeting inhibitory dysfunction in tinnitus with pharmacological treatments may therefore be problematic however not impossible (Richardson et al., 2012). It may also be problematic because of the difficulty of targeting small areas with drugs. Drugs may have a more general effect on broader areas of the brain then the ones one would wish to target in tinnitus. Increasing or decreasing inhibitory activity in areas with normally functioning inhibition may modulate maladaptive plasticity elsewhere.

Therapeutic options such as cognitive behavior therapies, even though rather unsatisfactory on their own may benefit as an addition to newer treatment methods such as rTMS and Intracranial auditory stimulation (Khedr et al., 2008; De Ridder & Vanneste, 2014). Cognitive behavior therapies such as tinnitus retraining therapy or sound therapy are used to change the tinnitus sufferers negative emotion towards his or hers tinnitus. By removing or lessen the negative emotion towards the tinnitus, patients looking for treatment may be more susceptible towards their treatment methods (Smit et al., 2015).

Tinnitus is as mentioned earlier most prevalent in age-related hearing loss (Heller, 2003) and hearing loss in general. Hearing loss related tinnitus must have its origin in cochlea dysfunction (Eggermont and Roberts, 2004) but tinnitus that is not accompanied by any hearing disabilities would more likely originate from for example thalamocortical dysrhythmia (Llinas et al., 2001). Tinnitus that is not accompanied by any hearing loss may still have been temporarily induced by loud noise causing OHC to bend (Jastreboff, 1990) and IHC to influence the lower auditory system.

The tinnitus sound would never reach consciousness if it was classified as a neutral stimulus by the conscious and subconscious brain, it would be continuously blocked from reaching consciousness. Instead the abnormal activity that causes tinnitus becomes perceptualized and spread to other systems

in the brain that react or respond inappropriately (De Ridder et al, 2014). The limbic structures appears to react to the tinnitus sound as something emotionally negative or distressing, especially in cases of severe tinnitus thereby disrupting habituation. The tinnitus may also worsen temporarily when stressed or tired.

Tinnitus and its associations with chronic pain (Møller, 2000) and neurological and psychiatric disorders such as Parkinson's Disease, epilepsy, depression and migraines (Llinas et al., 2001) shows two different approaches to the disorder. Møller (2000) describes severe tinnitus and chronic pain to share many similar neural networks as they are both crossmodal in nature and eventually become centralized. Llinas et al. (2001) however describes tinnitus, as well as Parkinsons's Disease, epilepsy, depression and migraines to occur because of alteration of rhythmic low frequency oscillations that causes disturbances of normal oscillations within the thalamocortical framework. These disorders do not share similar neural networks, but are depending on where in the thalamocortical network the altered oscillations are located. Either way, both Møller (2000) and Llinas et al. (2001) suggest that tinnitus and its associated disorders may benefit from similar treatments.

Animal models are frequently used in tinnitus research (Knipper et al., 2010). Animal models opens the possibility to, through invasive methods study neuronal networks as well as individual neurons, which have proven to be of great use for tinnitus research (Von der Behrens, 2014). In animals, tinnitus is generally induced by either ototoxic drugs (generally salicylate as mentioned in Liu & Chen in 2012) or noise trauma. The use of ototoxic drugs may be useful because of its fast uptake but is harder to control, considering it affects various areas of the CNS as well as cochlear functioning. Through noise trauma it is harder to induce tinnitus but the tinnitus can be better controlled and may be induced unilaterally, letting the animal serve as its own healthy control (Von der Behrens, 2014).

In humans, an evaluation of tinnitus is based on self-reports (Henry, 2005). In animal studies behavioral models are used to assess tinnitus (Jatreboff et al., 1988). Jastreboff and colleagues (1988)

used fear conditioning to teach rats to stop drinking water whenever the background noise stopped, by giving them foot shocks. When this behavior was learnt the animals where exposed to salicylate with the intention of inducing tinnitus. The animals once again had to drink until the background noise stopped, however this time there were no foot shocks and whenever the background noise stopped the rats kept drinking. This was taken as an indicator for a presence of tinnitus in the absence of actual noise (Jastreboff et al., 1988). This method have influenced a row of different procedures to more accurately induce tinnitus in animals (Von der Behrens, 2014).

However, Von der Behrens (2014) mentions that animal studies regarding tinnitus are not always easily applied to tinnitus research in human. Rats, that are commonly used in tinnitus animal models have a high-frequency hearing range that is very different from humans. Another disadvantage with animal studies Von der Behrens continues, is the difficulty to study the effects of tinnitus in the auditory system, associated structures and centralization which inevitably seems to be an important aspect for tinnitus treatment in humans. In animal studies tinnitus is generally induced peripherally and studied somewhat immediately (Von der Beherns, 2014), possibly before any centralization may occur. And it is the understanding of that the structural and functional plasticity that may be of use for future treatment options (Khedr et al. 2008). Animal studies do still make it possible to study hyperactivity or other abnormal neuronal behavior in vivo as well as in vitro, giving key information about tinnitus-related neural networks.

The tinnitus pathophysiology is utterly complex but there is a growing understanding of the generation of tinnitus and through that, a growing understanding of possible prevention and management (Eggermont & Roberts, 2004). By looking at tinnitus as a continuous process of maladaptive plasticity through behavioral changes of neurons and their firing patterns it makes sense to target these issues in tinnitus treatment. Tinnitus as a crossmodal disorder, may involve all the above mentioned brain areas however may not be dependent on continuous activity from them in order to be

generated. The tinnitus generation may be more or less dependent on certain structures and locating the core structures could help develop further treatments.

Conclusions and future directions

Tinnitus can be understood as a continuous process of maladaptive plasticity through out CNS caused by changes of firing patters within neural networks. The auditory system may be overstimulated and influenced by cochlear hyperactivity and aberrant oscillatory activity within the thalamocortical networks. The tinnitus sensation is reinforced and given emotional valence by limbic system connectivity which may in turn be modulated by the auditory cortex. The severity of someone's tinnitus is hypothesized to correlate with ventromedial prefrontal cortex activity, Structural and functional plasticity may cause reorganization of tonotopic maps and centralization of tinnitus.

There is no efficient treatment of tinnitus to this day, however promising new approaches to tinnitus treatment have begun to emerge. These new treatment methods aim to modulate and re-route tinnitus-related maladaptive plasticity. Tinnitus centralization, interconnectivity and individual tinnitus pathophysiology poses as potential threats that treatment methods must overcome in order to be more efficient. Pharmacological approaches targeting inhibitory neurotransmitters may also be of interest for future investigation. Cognitive behavior therapy may be a useful addition to these kinds of treatment but is not very useful on its own.

As for future directions, the research regarding the neural mechanisms underlying tinnitus is far from absolute but a better understanding of the generative aspects are beginning to unravel. New developing treatment aim to alter and modulate ongoing maladaptive behavior of neurons and networks in order to restore balance within the CNS. To this day, these treatments are not very efficient and targets very small groups of individuals. There are indeed difficulties to overcome but hopefully a neural approach to tinnitus will continue to guide future research and the future development of more efficient treatment.

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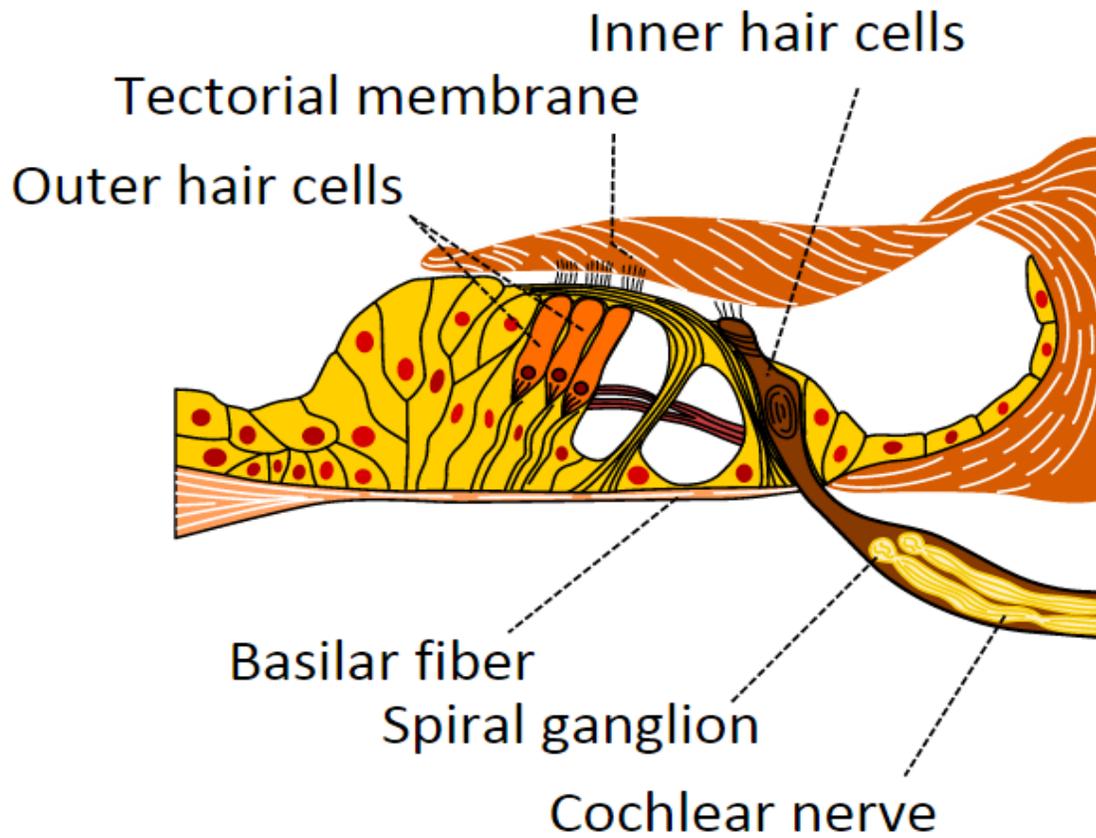
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Appendix

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