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The Neural Mechanisms of Tinnitus and Tinnitus Distress

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Introduction

Approximately 15% of people in the United States experience some type of tinnitus, or the perception of sound in the absence of an external stimulus (Center for Disease Control, 2013). Tinnitus can be perceived as different sensations: a high pitched tonal noise, crickets chirping, buzzing, whooshing, etc. The presence of this inescapable sound can have a profound impact on people who suffer from tinnitus that can be manifested in the form of anxiety, depression, and social withdrawal. Understanding tinnitus and the neural mechanisms that cause tinnitus will increase knowledge of the disorder and its effects, while fostering opportunities for future research.

Tinnitus has many known etiologies. In some cases, it can be caused by damage to the outer ear. The outer ear is composed of the pinna, which is the cartilaginous portion of the ear extending from the skull, and the external auditory meatus (or ear canal). The pinna collects sound waves from the environment and transmits those waves through the external auditory meatus to the tympanic membrane (or ear drum) of the middle ear, which then transmits the waves through the ossicles to the inner ear (Emanuel & Letowski, 2009). Tinnitus can be caused by the outer ear when there is an excess of cerumen (or ear wax). It is believed that this type of tinnitus is the result of the cerumen creating an occlusion effect, causing the person to have a heightened perception of internal bodily sounds that they believe to be tinnitus (Tyler, 2016). Other times, overgrowth of hair in the ear canal or excessive cerumen has been known to touch the tympanic membrane, causing a crackling tinnitus sound in the ear (Tyler, 2016). Fortunately, these causes of tinnitus can be easily addressed by cleaning out the external auditory meatus, thereby removing the debris and eliminating the perception of tinnitus.

Tinnitus can also be caused by damage to the middle ear. The middle ear consists of the tympanic membrane and the ossicles or the three small bones in the ear: the malleus, incus, and stapes. The malleus is the largest of the ossicles and articulates with the tympanic membrane. When the tympanic membrane is set into motion by the acoustic force of sound waves, its movement causes the malleus to move. The malleus articulates with the incus, so the movement of the malleus sets the incus into motion. The movement of the incus then sets the stapes into motion. The stapes is the smallest bone of the middle ear and articulates with the oval window of the cochlea. Because of this point of articulation, the motion of the stapes sets the fluid of the cochlea into motion (Emanuel & Letowski, 2009).

The middle ear is often the cause of pulsatile tinnitus that is related to vascular pathology. Pulsatile tinnitus is the sensation of hearing one's heartbeat in one's ears. Pulsatile tinnitus can be caused various conditions, such as hypertension, or other problems related to the vascular system (Tyler, 2016). This type of "objective" tinnitus differs from other types because others are able to hear a patient's tinnitus through the use of a stethoscope (Tyler, 2016). Middle ear tinnitus can also be caused by infections in the middle ear that are thought to be associated with fluid blockages causing occlusion, thereby causing patients to be more aware of internal bodily noises. Middle ear tinnitus caused by infections is easily treated, and often goes away once the infection is gone (Tyler, 2016).

Tinnitus of the middle ear can also be caused by contractions of the middle ear muscles that falsely set the ossicles into motion and transmit a sound that was not actually heard. The muscle typically associated with this kind of tinnitus is the stapedius muscle that controls the motion of the stapes. If this muscle spasms, the movement of the stapes is no longer indicative of an external stimulus, and therefore, presents a sound that should not be perceived (Tyler, 2016).

Finally, other potential causes of middle ear tinnitus are otosclerosis that occurs when the stapes is fixated into the oval window, causing a conductive hearing loss information (Tyler, 2016), and palatal myoclonus that is thought to be caused by a palatal muscle spasm (Tyler, 2016).

The most common type of tinnitus is caused by damage to the inner ear, termed sensorineural tinnitus. The primary structure of the inner ear is the cochlea. The cochlea is a shell-shaped structure filled with fluid that transduce acoustic sound waves from the ossicles into neurochemical impulses that code for sound in the auditory nervous system. The cochlea also consists of 3,500 inner and 12,000 outer hair cells in the fluid-filled chamber called the cochlear duct. When the fluid is set into motion, the hair cells in the cochlea move and interact with each other to produce action potentials and transmit the auditory signals through the auditory nervous system (Emanuel, & Letowski, 2009).

Sensorineural tinnitus can be caused by noise trauma or sudden hearing loss (e.g., noise trauma, physical trauma, or some immune system processes). It can also be caused by specific ototoxic medications. Any of these influences damage the hair cells of the cochlea, thereby preventing the transmission of information from the cochlea to the auditory nervous system (Tyler, 2016). Tinnitus is also often associated with Meniere's disease, a disease that causes a progressive sensorineural hearing loss and episodic vertigo (Tyler, 2016). Other causes of tinnitus include aging, tumors of the brainstem or cerebellopontine angle, a vascular loop in the brainstem, hypertension, thyroid problems, or fibromyalgia (Tyler, 2016).

Once the hair cells of the cochlea are stimulated, the auditory information in the form of an electrical impulse is sent to the brain. This electrical impulse is driven by chemical reactions between neurons. Neurons consists of several parts including a) a cell body (gray matter), b) an axon (white matter) that extends from the cell body, and c) often several dendrites that collect

neurotransmitters from a preceding axon. The connection from one neuron to the next is termed a synapse and the electrical impulse is generated through the release of neurotransmitters, or specific chemical compounds designed to polarize and depolarize neurons to convey chemical messages through the nervous system. Once the neurotransmitters have depolarized a neuron, the chemical balance within the neuron is temporarily disturbed. Because the neuron wants to reach a point of homeostasis (equilibrium), the neuron achieves an action potential which sets off an impulse to another neuron. This action potential sparks a series of chemical reactions down a neural pathway, from neuron to neuron, through the auditory nervous system to send a message to specific cortical areas conveying the sensory information initially received (Bhatnagar, 2013). After the neuron has generated an action potential, it returns to a resting state of equilibrium until another message is sent. These action potentials occur hundreds of millions of times as we code sensory information, execute a motor movement, or perform an autonomic process like breathing (Bhatnagar, 2013).

These action potentials convey information through the auditory nervous system pathway beginning with the vestibulocochlear nerve (cranial nerve VIII) that transmits auditory information from the hair cells to the next structure in the pathway, the cochlear nucleus. The cochlear nucleus is divided into the dorsal cochlear nucleus (DCN) and the ventral cochlear nucleus (VCN). These nuclei contain different cell types that are specialized for different functions (Emanuel & Letowski, 2009). These cells take in information and transmit it to the superior olivary complex. The superior olivary complex then transmits the information to the lateral lemniscus. The lateral lemniscus sends the information to the inferior colliculus located in the brainstem. This contralateralization allows for cohesive neural interaction in response to a stimulus (Emanuel & Letowski, 2009). The inferior colliculus then sends information to the

medial geniculate nucleus housed in the thalamus, which transmits information to the auditory cortex. The auditory cortex is primarily housed in the temporal lobe of the brain. The temporal lobe houses Heschl's gyrus and Wernicke's area which are both essential cortical areas to sound processing (Emanuel & Letowski, 2009).

As mentioned previously, sound is transmitted along this neural pathway through the constant firing of nerves via action potentials. When you hear a sound, the sound wave is transduced into an electrochemical pulse via the stimulation of the hair cells of the cochlea. This electrochemical pulse is transmitted via action potentials along the auditory nerve, up the auditory nervous system pathway. Sometimes though, the nerves fire spontaneously. This is often a normal process, and does not negatively affect our hearing abilities. However, when this spontaneous firing becomes excessive, people hear sounds that are not caused by an external stimulus. It is believed that most cases of sensorineural tinnitus are caused by a misfiring of the auditory nervous system (Tyler, 2016).

Research has discovered several specific neural correlates that account for the presence of sensorineural tinnitus. Furthermore, these neural correlates indicate other affected brain areas that may be indicative of some of the emotional and cognitive effects associated with tinnitus. Tinnitus is often associated with depression, anxiety, and attention deficit disorder, but the emotional harm that is often experienced by tinnitus sufferers, may be due to physiological processes in the brain causing negative reactions.

The purpose of this paper is to investigate the neural mechanisms of tinnitus by answering the following research questions:

- 1) *What neurophysiological changes in the hearing mechanism contribute to tinnitus?*
- 2) *How do different neurological models of tinnitus explain the presence of tinnitus?*

3) How do these neural mechanisms of tinnitus relate to one's emotional/physiological reactions to tinnitus?

Summary of Findings

Neurophysiological Changes Related to Tinnitus

Sensorineural tinnitus is thought to be caused by neurophysiological irregularities in the hearing mechanism. Considering the neurophysiological changes that contribute to tinnitus is essential to understanding the clinical applications for treating tinnitus. Overall, research concerning neurophysiological changes implicated in tinnitus is limited by the various studies' small sample size, and differing experimental designs. These factors have prevented researchers from being able to determine, with statistical certainty, that sensorineural tinnitus is caused by a specific neural mechanism, connection, or activity. Furthermore, patients with tinnitus tend to be a heterogeneous group. This factor makes it difficult to assert overarching generalizations about the mechanisms that contribute to tinnitus. However, despite these experimental limitations, research has shown two basic theories for neurophysiological changes that contribute to tinnitus, including changes involved in the a) the auditory network and b) the auditory cortices.

Many studies have found evidence for neurophysiological changes in the auditory nervous system pathway rather than specific auditory cortical structures. The auditory nervous system pathway consists of nervous system fibers that transmit information from the ear to the auditory cortex where sound is processed. Disruptions in this pathway could result in auditory deprivation (e.g., Schaette & McAlpine, 2011). When the auditory cortex experiences auditory deprivation, it becomes hypersensitive to nerve impulses. Furthermore, the neurons that previously transmitted sounds become hyperexcited. These hyperexcited neurons increase their spontaneous rate of firing, causing them to transmit sounds without the influence of an external auditory stimulus, consequently transmitting sounds an individual perceives as tinnitus.

Davies, Gander, Andrews, and Hall (2014) studied these neuronal networks during rest using functional magnetic resonance imaging (fMRI), and termed these structures *resting state networks* (RSNs). When studying these RSNs, using independent component analysis and partial correlational analysis, they found evidence of a neural pathway between bilateral auditory cortical areas in 12 individuals with tinnitus. Researchers termed this neural pathway a location of *functional connectivity* that could be defined as “the mathematical quantification of simultaneous interactions between different brain areas” (Davies, Gander, Andrews, & Hall, 2014, p. 194). By mathematically quantifying interactions between brain areas, researchers were able to effectively determine specific networks that exist in patients with tinnitus that do not exist in individuals without tinnitus. Specifically, they found increased functional connectivity between the right supramarginal gyrus and left posterior middle temporal gyrus in the tinnitus group. These findings differed from previous research indicating a reduction in bilateral auditory cortical functional connectivity, but these differences could be due to differences in hearing acuity among the participants.

Leaver et al. (2016) conducted a similar study of 21 patients with tinnitus using fMRI to examine functional connectivity in a resting state. They also found significant evidence for an auditory neuronal network connecting specific cortical areas. Some of these areas are typically implicated in actions of auditory processing (such as Heschl’s gyrus and the inferior colliculus), and some of them are more related to other cortical functions (such as the striatum and mediodorsal nucleus). This network (Leaver et al., 2016) was found to connect medial Heschl’s gyrus, the inferior colliculus, the mediodorsal nucleus, the striatum, the orbitofrontal cortex, and the lateral prefrontal cortex. This network was evident through fMRI in patients with tinnitus as these structures did not indicate increased neural activity in patients without tinnitus. Therefore,

the presence of this network would account for the neural connectivity underlying tinnitus perception. Although this study's results contradict the previous fMRI study of RSNs, this further provides support that there are differences in the cortical connections of the brain in people with tinnitus compared to those without tinnitus. Furthermore, this study indicates a network that connects limbic system structures in people with tinnitus that does not exist in people without tinnitus. The limbic system is a cortical area responsible for the regulation of emotion, motivation, learning, and memory. The primary structures of the limbic system include the amygdala, hippocampus, septal nuclei, and cingulate gyrus. These brain areas are also highly connected to the prefrontal and insular cortex (Bhatnagar, 2013, p. 425). These limbic system connections are evident in our examination of auditory cortices implicated in the perception of tinnitus.

Besides finding these complex networks implicated in the perception of tinnitus, some researchers have examined the individual nerve pathways that may cause tinnitus. Schaette and McAlpine (2011) investigated irregularities in the auditory nerve (i.e., vestibulocochlear nerve, cranial nerve VIII) that could result in tinnitus. The vestibulocochlear nerve transmits information from the cochlea to the brain. In that study, auditory brainstem responses (ABRs) were obtained in humans to find differences in the physiology of the auditory nerve. ABRs were measured by determining the mean amplitude of wave I auditory brainstem responses. ABRs were used so that researchers could test what was termed "hidden hearing loss."

By using ABRs, the potential effect of cochlear damage on tinnitus is observed, but also the effect of neural mechanisms largely attributed to the auditory nerve and brainstem is measured. In fact, results revealed that in patients with tinnitus, the mean amplitude of wave I auditory brainstem responses were lower than controls with statistical significance (Schaette &

McAlpine, 2011). This evidence indicates that there is a de-afferentation of the auditory nerve. These findings are consistent with findings from animal model studies proving de-afferentation of the auditory nerve. This reduced function of the auditory nerve is implicated in the neural plasticity of the brain. Damage to the auditory nerve results in less sensory information conveyed throughout the auditory nervous system, depriving it of sensory information. When the auditory nervous system experiences sensory deprivation, the brain adapts (due to its plastic nature), and the other nerve cells become hyperexcited. This increases normal spontaneous nerve firing, and causes the nerves to fire at incorrect times, therefore, resulting in the perception of tinnitus.

Although significant evidence exists to corroborate the existence of specific neural networks implicated in the presentation of tinnitus, research also indicates that specific cortical areas are integrally related to the perception of tinnitus. To correctly identify areas implicated in the perception of tinnitus, voxel-based morphology has been used to identify specific cortical areas that are active when people hear tinnitus. Muhlau, Rauschecker and Oestreichner (2006) found that there were differences in the activation of the subcallosal region and the thalamus during the perception of tinnitus. The subcallosal region is typically associated with individual's unpleasant emotions caused by musical dissonance (Muhlau, Rauschecker, & Oestreichner, 2006, p. 1286). Researchers found evidence of decreased gray matter in this region, as well as increased gray matter volume in the thalamus. The increased gray matter concentration was the result of hyperactivity of neuronal cells. Because of the plastic nature of the cerebrum, this resulted in a higher volume of gray matter in the thalamus, correlating to a tinnitus sensation.

Landgrebe et al. (2009) attempted to replicate Muhlau's findings using the same experimental design, but with a larger sample size. Unfortunately, different cortical areas were found in the presentation of tinnitus in the replicated study by Landgrebe et al. (2009).

Specifically, gray matter differences were found in auditory cortical areas (such as the inferior colliculus), that contradicted evidence to support Muhlau's assertion that the subcallosal region was implicated in the perception of tinnitus. Landgrebe et al. (2009) also found evidence to support limbic system connections in the perception of tinnitus (especially in the hippocampus). Although these two studies yielded different findings, they agree that the limbic system is somehow implicated in the presentation of tinnitus. Together these structures mediate our emotional responses to stimuli. Therefore, these structures play an integral role in people's responses to tinnitus. These limbic system connections to the presentation of tinnitus could potentially explain the negative emotional reactions to tinnitus, such as depression and anxiety.

Another technique used to identify brain regions implicated in specific perceptions is positron emission tomography (PET). PET measures cerebral blood flow to different cortical areas to determine the activation of specific brain areas during different neural tasks. Many PET studies have been done to identify structures involved in the presentation of tinnitus. Schecklmann et al. (2013) studied differences in cerebral blood flow using PET to determine areas implicated in the presentation of tinnitus. Researchers found that tinnitus is associated with activity of the right inferior frontal cortex and the right ventro-medial prefrontal cortex (Schecklmann et al., 2013). The inferior frontal cortex houses Broca's Area for speech/motor planning (left hemisphere) and risk aversion/impulse control (right hemisphere). A similar study conducted by Lockwood et al. (1998) found that the temporal lobe was implicated in tinnitus perception. The temporal lobe is considered the primary area for sound processing in the brain. Evidence from these studies indicates that tinnitus could be the result of damage/abnormalities of various cortical structures.

Because of limitations to sample size, differences in experimental design, and variability among research subjects, studies indicate different neurophysiological mechanisms involved in tinnitus perception. However, most of the research regarding these neural mechanisms suggests that there are two general neurophysiological changes that cause the hearing disorder: a) changes in the auditory network and b) changes in the auditory cortices (specifically in the auditory cortex and limbic system). Changes in the auditory network are found through increased functional connectivity between the right supramarginal gyrus and left posterior middle temporal gyrus. Other structures such as the medial Heschl's gyrus, the inferior colliculus, the mediodorsal nucleus, the striatum, the orbitofrontal cortex, and the lateral prefrontal cortex have been implicated in tinnitus. Although studies of cortical regions implicated in the presentation of tinnitus were contradictory, research confirms auditory cortical areas (especially in the temporal lobe) and limbic lobe connections relevant to the presentation of tinnitus. Conclusively, examining any and all of these changes gives us a neurophysiological basis for understanding tinnitus.

Neurological Models of Tinnitus

Understanding the differences in the neural anatomy and physiology that cause tinnitus contributes to a better understanding of the mechanisms involved, and consequently improves the models used to describe tinnitus. These tinnitus models are largely theoretical, and though grounded in research, they involve many conflicting theories about the mechanisms involving tinnitus. As mentioned in the previous chapter, tinnitus research is difficult to replicate due to small sample sizes and large variability among tinnitus patients that prevents the literature from presenting conclusive results. Essentially, there are two different types of models: a) peripheral models of tinnitus and b) central models of tinnitus.

Peripheral models of tinnitus refer to tinnitus as a mechanism of the cochlea or auditory nerve. In the past, researchers believed that tinnitus was caused by a dysfunction of the cochlea, supporting a peripheral model of the disorder, but recent findings challenge that model for several reasons. First of all, tinnitus is known to persist even after severing the vestibulocochlear nerve (Muhlau et al., 2006). The fact that tinnitus is able to persist despite the loss of the vestibulocochlear nerve is indicative of structures more central than the peripheral auditory system that contribute to tinnitus. Furthermore, tinnitus is not present in all people who have hearing loss, and conversely, it is present in individuals with normal hearing. If tinnitus was solely caused by damage to the cochlea, it would be present throughout the hearing impaired population. Also, people can experience acute forms of tinnitus in specific situations, where they might hear tinnitus in their ear for a short period of time, but it goes away (e.g., after a rock concert, after working out really hard, etc.; Muhlau et al., 2006). Despite these recent findings refuting peripheral models of tinnitus, the role of the cochlea should not be overlooked. Research on central and peripheral models shows how these models are integrally related. Therefore, the most effective model of tinnitus integrates peripheral and central models to present a holistic understanding of the neural mechanisms that induce tinnitus.

Much of the evidence supporting peripheral models of tinnitus has used salicylate (aspirin) as the drug to induce tinnitus. Salicylate in large or prolonged doses has been proven to induce tinnitus in human patients, and it is often recommended that patients use salicylate until they begin to experience tinnitus, after which they should lower their doses (Noreña, 2011). Noreña (2011) cited multiple studies that induced tinnitus in animals by administering doses of salicylate that were significantly higher than those necessary to induce tinnitus in human patients. Use of animal models allowed for more invasive neuroimaging techniques. These

salicylate studies confirmed that tinnitus primarily takes place in the cochlear nerve, supporting the peripheral model of tinnitus. However, Noreña (2011) also cites similar experiments using salicylate that indicate tinnitus as a central mechanism. Because tinnitus was induced with an ototoxic drug, it is difficult to generalize these findings to other tinnitus patients. For example, approximately 40% of patients with tinnitus have an idiopathic, or with no known, cause to their tinnitus (Noreña, 2011). Therefore, researchers cannot generalize findings from salicylate-induced tinnitus, to tinnitus caused by other/unknown damage.

Although tinnitus is often not attributed to a specific physical insult, it is frequently comorbid with hearing loss. This comorbidity indicates that in addition to cortical dysfunction, there is subsequent damage to specific peripheral auditory mechanisms such as the cochlea and vestibulocochlear nerve. From a clinical perspective, this comorbidity supports the argument for a tinnitus model reflecting damage to peripheral hearing mechanisms, because hearing aids are a highly successful therapeutic technique for patients with tinnitus. Their ability to successfully treat tinnitus supports the integral role of the cochlea, substantiating a peripheral model of tinnitus.

Henry et al. (2014) report instances in which cochlear damage (i.e., the peripheral model) induces alterations in the central auditory nervous system (i.e., the central model) that may be related to tinnitus. Through multiple studies, it is evident that cochlear damage is implicated in the presentation of tinnitus, however, as research progressed, researchers found that damage is not localized to peripheral mechanisms. For example, certain animal models show reorganization of tonotopic maps in the primary auditory cortex following cochlear damage. Tonotopic maps describe the areas of the brain that process specific frequencies. The brain is typically organized to process specific frequencies independently, but if hearing loss causes auditory deprivation, the

areas of unused cortical space will be reprogrammed for processing other frequencies or for other functions. This progression indicates that cochlear damage may cause reorganization of central auditory nervous system pathways (Henry, Roberts, Caspary, Theodoroff, & Salvi, 2014). This is related to the concept of auditory deprivation discussed in the previous chapter. As peripheral mechanisms are damaged, their ability to transmit sound/impulses to the central areas of the brain are damaged, causing these brain areas to experience sensory deprivation. When these brain areas are not stimulated for a prolonged period of time, they are remapped or reorganized, resulting in tinnitus due to hyperexcited cells with an increased spontaneous firing rate.

Central models of tinnitus suggest tinnitus is a result of a reorganization of the central auditory pathway. Schaette and McAlpine (2011) studied how central auditory structures adjust neural responsiveness to accommodate for reduced sensory input from the auditory nerve. In that study, researchers used ABR responses to determine if there were central auditory mechanisms, rather than peripheral or cochlear loss that contributed to the presence of tinnitus. In doing so, they found that tinnitus could be explained by increased spontaneous firing of neurons in the auditory brainstem. This finding supports a central model of tinnitus.

Similarly, Rauschecker (1999) presents arguments for a central model of tinnitus in a study examining auditory cortical plasticity. Rauschecker cited previous studies lesioning cat retinas for the purpose of studying cortical reorganization. In other words, it was believed that small lesions to the cochlea would result in a similar cortical reorganization such that the tonotopic map of the auditory cortex of the animal would reorganize. Rauschecker (1999) used magnetoencephalography (MEG) and positron emission tomography (PET) to find areas of cortical reorganization in tinnitus patients found evidence of this frequency shift in tinnitus patients (Rauschecker, 1999).

Furthermore, many studies have found that tinnitus presentation has connections to the limbic lobe of the cerebrum, supporting a central model of tinnitus (Muhlau et al., 2005; Henry et al., 2014). Muhlau et al. (2005) found evidence to support changes in the limbic system in patients with tinnitus. Researchers found that the medial geniculate nucleus (MGN) of the thalamus was reorganized following a dysfunction in the peripheral hearing mechanisms. This reorganization of the MGN generates an increase in spontaneous neuronal activity in the central nervous system, causing tinnitus. Researchers concluded that this altered neuronal activity resulted in an increase in gray matter concentration in the thalamus. The plastic nature of the limbic system structures (thalamus and MGN) are evidenced through these alterations in gray matter concentration and tonotopic reorganization. The alterations of these central structures also provide evidence for central models of tinnitus, because the limbic system is known to be responsible for emotional responses. Therefore, these limbic system connections also shed light on the negative emotional reactions and distress typically associated with tinnitus (Muhlau et al., 2005; Henry et al., 2014).

Some studies have supported the idea of a neuronal model of tinnitus; specifically that dysfunction occurs at the level of the neuron that coincides with central models of tinnitus. Gu, Herrmann, Levine, and Melcher (2012) tested ABRs in people with tinnitus to examine specific areas of the cochlear nucleus. Because the cochlear nucleus is the first point of transmission of auditory information in the auditory nervous system, its role in the perception of tinnitus shows a strong connection to dysfunction of the cochlea, as well as a strong connection to the dysfunction of the auditory nervous system. Researchers found heightened activity of the ABR, indicating activity from the spherical bushy cells of the ventral cochlear nucleus (VCN). The VCN's influence in the presentation of tinnitus from hyperexcitation of its spherical bushy cells is

indicative of central model's explanation of the presentation of tinnitus (Gu, Herrmann, Levine, & Melcher, 2012).

Kaltenbach et al. (1998) found similar research supporting the involvement of the cochlear nucleus in the presentation of tinnitus, however, they found evidence to support the role of the dorsal cochlear nucleus (DCN). They sought to prove the DCN's role in tinnitus in hamsters by exposing the animals to damaging auditory stimuli. After inducing tinnitus in the hamsters, spontaneous activity of the auditory cortex by recording activity of the DCN surface (Kaltenbach et al., 1998). Results revealed that most thresholds of spontaneous activity were shifted 30 days after sound exposure meant to induce tinnitus, but were not shifted two days after exposure. This delay in the threshold shift indicates the plastic characteristic of the DCN. After a peripheral injury has taken place, the DCN will reorganize as a result of a deprivation of auditory stimuli. Through this reorganization, spontaneous firing rates of nerve cells will increase, causing a patient to perceive tinnitus.

Through this body of research, patterns have emerged indicating that peripheral and central models alone cannot explain the neural presentation of tinnitus. However, like there are many causes to tinnitus, these models account for these various clinical symptoms in different ways. Damage to the peripheral system influences the central system in a profound way, and the neural plastic characteristics of the cortex shows how it reorganizes following a peripheral injury. Through peripheral injury and consequential tonotopic reorganization, the existence of hyperexcited neurons causes the perception of tinnitus in the absence of an external stimulus. This interaction between the peripheral and central models, therefore, allows us to understand the neurophysiological etiologies of tinnitus.

Neural Correlates to Tinnitus Distress

Tinnitus is often comorbid with psychological disorders such as depression, anxiety, attentional deficits, and cognitive deficits. These negative emotional and cognitive difficulties greatly affect those who suffer from the disorder. Tyler and Baker (1983) used self-report measures on a sample of 97 patients with tinnitus to determine the percentage of tinnitus patients who experienced various difficulties comorbid with tinnitus. Their findings are shown in Table 1 with the associated difficulties listed from most to least prevalent.

Table 1. *Percentage of Patients Reporting Difficulties Associated with Tinnitus*

Percentage of Respondents	Difficulties Associated with Tinnitus
36%	Depression
35.5%	Worsened Speech Comprehension
34%	Irritation
33%	Worsened Concentration
16%	Feelings of Insecurity
14%	Embarrassment
6%	Nervous Strain
5%	Loneliness
4.2%	Interference with Work
2%	Loss of Confidence

These findings indicate that more than one in three people who suffer from tinnitus experience depression, worsened speech comprehension, irritation and worsened concentration (Tyler & Baker, 1983). Many individuals who suffer from tinnitus also experience feelings of insecurity and embarrassment. These negative emotional reactions to tinnitus reflect a generally worsened quality of life for those who suffer from the disorder. Understanding the true causes of these negative side effects helps to find appropriate therapeutic approaches to treating the disorder, and comorbid psychological disorders. For many years, it was believed that these characteristics of tinnitus distress and depression reflected a learned response between tinnitus and their negative emotional reactions. Many tinnitus therapies still operate under this theory,

postulating that the constant presence of sound caused negative emotional responses. However, recent neurological studies have found neural correlates for tinnitus distress, indicating that tinnitus distress may not be a learned response, but may instead be caused by cortical reorganization.

The theory that negative responses to tinnitus are learned was supported by a study conducted by Jastreboff (1990). In the study, he lobotomized 20 tinnitus patients (created a surgical incision in the prefrontal cortex). In theory, the damage to the prefrontal lobe caused by the lobotomy should have eliminated learned emotional responses to tinnitus. Although one subject died following the surgery, all 19 of the 20 subjects who survived the lobotomy experienced a decrease in their level of annoyance associated with tinnitus. This study supported the concept that annoyance to tinnitus is a learned response because the learned response was eliminated after damage was inflicted on the prefrontal cortex (Jastreboff, 1990).

Although Jastreboff reported conclusive results based on this surgery, there are downfalls to this theory. The study examined differences in the level of annoyance in patients with tinnitus, but did not examine symptoms of depression, a common condition comorbid with tinnitus. Furthermore, even though people with tinnitus show signs of depression, they do not exhibit the core symptoms of the disorder. For example, although tinnitus patients tend to exhibit characteristics of depression such as fatigue, irritability, insomnia, exhaustion, and difficulty concentrating, people with tinnitus typically do not show signs of the hallmark symptoms of depression such as loss of interest or depressed mood (Langguth, Landgrebe, Kleinjung, Sand, & Ran Hajak, 2011). This finding is indicative of the involvement of other neural mechanisms in the neural correlates of distress and depression associated with tinnitus. If patients do not

typically exhibit crucial symptoms of the disorder, it is purposeful to examine other potential causes of their psychological symptoms.

The previous chapters have provided evidence that tinnitus causes neuroplastic changes in the central nervous system pathway. These changes are indicative of tonotopic reorganization in the auditory cortex, causing related limbic system alterations. Negative emotional responses could be explained by changes to the limbic system that contradict previous theories regarding tinnitus distress as a learned response.

The limbic system is a cortical area responsible for the regulation of emotion, motivation, learning, and memory. The primary structures of the limbic system include the amygdala, hippocampus, septal nuclei, and cingulate gyrus. The amygdala is a limbic structure responsible for aggression, mating, stress-mediated responses, memory, feeding, and drinking. The hippocampus is a limbic structure responsible for memory and learning. The septal nuclei are responsible for hormonal secretion, behavioral reaction, and memory facilitation. The cingulate gyrus is responsible for anxiety and altered behavior such as panic and compulsion. These brain areas are also highly connected to the prefrontal and insular cortex (Bhatnagar, 2013, p. 425). Together, these structures mediate our emotional responses to stimuli and play an integral role in people's responses to tinnitus.

Using neuroimaging techniques, researchers have found evidence of limbic system changes as a result of tinnitus. Leaver et al. (2011) used VBM analyses and found significant anatomical differences between people with and without tinnitus, especially in the ventromedial prefrontal cortex and the subcallosal region. This evidence in limbic system connectivity differences, especially in the prefrontal cortex, can explain the results from Jastreboff's study, by presenting evidence for limbic system connections in the prefrontal cortex. Perhaps patients

exhibited less tinnitus annoyance because the areas of their brain connected to the limbic lobe were severed, alleviating the distress that is associated with that area of the cortex.

This concept was studied further by Leaver et al. (2012). Researchers studied neurological reactions to tinnitus using anatomical MRI. They examined neural correlates of hearing loss, depression, anxiety, and noise sensitivity in 23 tinnitus patients. They found that tinnitus distress was associated with cortical thickness in the anterior insula. They also found that symptoms of anxiety and depression were negatively correlated with cortical thickness in subcallosal anterior cingulate cortex. Furthermore, increased gyrification (more hills and valleys) of dorsomedial prefrontal cortex was severe in patients with tinnitus (Leaver et al., 2012). These findings of structural changes in the anatomical structures of the limbic lobe as a result of tinnitus in the brain, display neurological changes as a result of tinnitus. These neurological changes cause negative emotional reactions at the cortical level.

Electroencephalography (EEG) has also been used to determine specific areas associated with tinnitus distress. Vanneste et al. (2010) used EEG to study neural correlates of tinnitus distress and found that there was significantly more synchronized neuronal activity in various areas of the limbic system in tinnitus patients who were highly distressed. These areas included: a) the subcallosal anterior cingulate cortex (cingulate gyrus), b) the anterior insula cortex (insular cortex), c) the parahippocampal area (hippocampus), and d) the amygdala (Vanneste et al., 2010). Furthermore, researchers found that patients with tinnitus had less synchronized neuronal activity in other areas of the brain such as in the posterior cingulate cortex, precuneus, dorsal lateral prefrontal cortex, and ventrolateral prefrontal cortex. Activation and deactivation of these areas coincides with tinnitus and shows evidence of a network responsible for emotional and

attentional distress in tinnitus patients (Vanneste et al., 2010). These findings of limbic lobe connections to neural correlates of tinnitus are also supported by PET tests (Mirz et al., 1999).

Research has also evaluated the impact of tinnitus on cognitive abilities. Hallam, McKenna and Shurlock (2004) conducted a study where researchers performed multiple cognitive tasks involving attention. They concluded that cognitive deficits associated with tinnitus are integrally related to attentional deficits (Hallam, McKenna & Shurlock, 2004). These findings suggest that tinnitus does not cause cognitive deficits, but rather causes attentional deficits that presents as cognitive deficits.

Further evidence to negate tinnitus's negative impact on cognitive function can be found in a literature review conducted by Andersson and McKenna (2006). They reviewed two studies on the subjects' ability to multitask and their reaction time on a timed task that assessed cognitive ability when presented with different stimuli. Researchers found that even in these demanding auditory conditions, people with tinnitus do not show evidence of cognitive deficits in terms of information processing (Andersson & McKenna, 2006). These studies show that tinnitus does not negatively affect cognition in the way that was previously believed. This new evidence, however, does not negate neurophysiological correlates related to emotional reactions to tinnitus.

Although tinnitus does not seem to be inherently implicated in cognition, it often occurs with psychological disorders. The limbic system's involvement in tinnitus explains these psychological disorders/emotional reactions. However, other research studies showing evidence that these emotional responses are learned neglect to account for certain properties of the brain. These structural differences in the limbic systems of the brains of people with tinnitus are indicative of neural correlates for tinnitus distress that do not reflect a learned response. Rather,

the involvement of the limbic system, where emotional responses are coded, explains the emotional symptoms associated with tinnitus. This understanding has the capability to enhance our treatment of tinnitus distress to make it more effective for those who suffer from tinnitus-related distress.

Conclusion

The ear is a complicated mechanism composed of various structures that transmit mechanical waves into electrical impulses that can be interpreted in the auditory cortex of the brain. When this system sustains damage, many hearing disorders result, including tinnitus. The presence of this inescapable sound can have a profound impact on people who suffer from tinnitus that can be manifested in the form of anxiety, depression, and social withdrawal.

Examining the neural mechanisms that contribute to tinnitus suggests that there are two general neurophysiological changes that cause the hearing disorder: a) changes in the auditory network and b) changes in the cerebrum (specifically in the auditory cortex and limbic system). Changes in the auditory network are found through increased functional connectivity between the right supramarginal gyrus and left posterior middle temporal gyrus. Other structures such as the medial Heschl's gyrus, the inferior colliculus, the mediodorsal nucleus, the striatum, the orbitofrontal cortex, and the lateral prefrontal cortex have been implicated in tinnitus. Although studies of cortical regions implicated in the presentation of tinnitus were contradictory, research confirms auditory cortical areas (in the temporal lobe) and limbic lobe (that regulates emotional reactions) connections relevant to the presentation of tinnitus.

These different structures can be organized into two models of tinnitus etiologies: a) peripheral models of tinnitus and b) central models of tinnitus. Central models refer to tinnitus as a result of a reorganization of the central auditory pathway and peripheral models refer to tinnitus as a mechanism of the cochlea or auditory nerve. Patterns have emerged indicating that peripheral and central models alone cannot explain the neural presentation of tinnitus. However, like there are many causes to tinnitus, these models account for these various clinical symptoms in different ways. Damage to the peripheral system influences the central system in a profound

way, and the neural plastic characteristics of the cortex shows how it reorganizes following a peripheral injury. Through peripheral injury and consequential tonotopic reorganization, the existence of hyperexcited neurons causes the perception of tinnitus.

These models and structures indicate that the limbic system is strongly related to the presence of tinnitus, which could account for tinnitus-related distress. Other research showing evidence that these emotional responses are learned, neglect to account for certain properties of the brain. Structural differences in the limbic systems of the brains of people with tinnitus are indicative of neural correlates for tinnitus distress that do not reflect a learned response. Rather, the involvement of the limbic system, where emotional responses are coded, explains the emotional symptoms associated with tinnitus. This understanding has the capability to enhance our treatment of tinnitus distress to make it more effective for those who suffer from tinnitus-related distress.

Further research should attempt to reconcile contradicting evidence from various studies. This should be done using brain imaging techniques such as PET, VBM, etc., with larger sample sizes of participants. Understanding the mechanisms and models that explain the presence of tinnitus helps us to better serve patients with this disorder. Tinnitus distress can be debilitating, and understanding the neural basis of the disorder and comorbid distress can aid in our ability to lessen their effects. For example, researchers have recently developed a new tinnitus therapy “Neuromonics” that uses neurological concepts of tinnitus to overcome the disorder. With this improved understanding, we can utilize effective evidence-based therapy.

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