CHAPTER 1

Tinnitus and neural plasticity of the brain

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Abstract

Objective
Describe the current ideas about the manifestations of neural plasticity in generating tinnitus.

Study selection
Review articles and controlled trials were particularly selected.
Data were selected systematically, scaled on validity and comparability.

Conclusions
An altered afferent input to the auditory pathway may be the initiator of a complex sequence of events, finally resulting in the generation of tinnitus at the central level of the auditory nervous system. The effects of neural plasticity can generally be divided into early modifications and modifications with a later onset. The unmasking of dormant synapses, diminishing of (surround) inhibition and initiation the generation of new connections through axonal sprouting are early manifestations of neural plasticity, resulting in lateral spread of neural activity and development of hyperexcitability regions in the CNS. The remodeling process of tonotopic receptive fields within auditory pathway structures (DCN, IC and the auditory cortex) are late manifestations of neural plasticity. The modulation of tinnitus by stimulating somatosensory or visual systems in some tinnitus sufferers might be explained by the generation of tinnitus following the nonclassical pathway. The similarities between the pathophysiological processes of phantom pain sensations and tinnitus have stimulated the theory that chronic tinnitus is an auditory phantom perception.
Introduction

Approximately 10 to 15% of the general population complains of continuously perceiving tinnitus, and 4-5% is severely affected by this intrusive symptom (1;2). The perception of tinnitus causes tinnitus sufferers to experience problems like anxiety, depression, problems falling asleep and reduced ability to concentrate and relax. Consequently, tinnitus may have great negative implications on the perceived quality of life and frequently causes a great amount of psychological distress.

Whether tinnitus is generated in the cochlea or in higher structures of the auditory pathways has been a frequently discussed topic over the last decennia. The heterogeneity observed in a population of tinnitus sufferers indicates that several different mechanisms may be responsible for the generation of tinnitus. The precise origin of tinnitus generation and associated mechanisms are only partially understood and we may assume that no single theory explains all forms of tinnitus. Several different mechanisms may be responsible for tinnitus in the same person, as well.

The auditory system

The auditory system is characterized by several feedback loops between the different structures of the auditory pathways, a tonotopic frequency selectivity within receptive fields and a differentiation between classical and nonclassical pathways. The different structures and pathways of the auditory system are shaped by GABAergic and glutamergic modulations, as mentioned in figure 1.

The classical or lemniscal pathway (figure 1) is defined as strictly auditory, narrowly tuned to frequency, processing the auditory information from the cochlea to the primary auditory cortical areas, via the ventral cochlear nucleus, the central part of the inferior colliculus and the ventral nucleus of the thalamus (3;4). Several feedback loops characterize the auditory system connecting the cochlea to the superior olivary complex, the lower brain stem nuclei to the inferior colliculus, and the inferior colliculus to the thalamocortical system (3;5).

Inhibitory activity can be differentiated into infield inhibition and surround inhibition. GABAergic infield inhibition arises from and remains at the same receptor area as (glutamergic) excitation to the neurons, whereas GABAergic surround inhibition is the inhibition surrounding excitatory receptive fields (10-12). The tonotopic organization of the cochlea is represented in several structures of the auditory pathway: in the auditory nerve, the dorsal cochlear nucleus (DCN), the inferior colliculus (IC) and auditory cortex (9;13-15). The tonotopic organization is characterized by a neuronal frequency selectivity; this indicates that a neuron is capable of responding to a limited range of frequencies and responds most sensitively to a single frequency, called the characteristic frequency (16).

The nonclassical or extralemniscal pathway (figure 1) processes information parallel to the classical pathway (4). The nonclassical pathway is believed to branch off from the classical pathway at the level of the inferior
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colliculus (3;4;7); it projects to the medial and dorsal portions of the thalamus and the association cortices, which in turn have connections to the amygdala and other limbic system structures (3;17). The nonclassical pathway is more broadly tuned, more diffusely organized and is considered as being more plastic compared to the classical pathway. Since the nuclei of the nonclassical pathway perform less specific analysis of sounds than those of the classical pathway (18), the nonclassical pathway is normally not involved in hearing (17). The nonclassical pathway receives information not only from the ear, but also from other sensory organs of other sensory systems, such as the somatosensory system and the visual system (19).

The neurons within the receptive fields of the different structures of the auditory pathways are modulated by excitatory and inhibitory inputs, respectively predominantly glutamergic and GABAergic in character (6-9)

Figure 1. The auditory system
Peripheral input deprivation initiates the central modifications in the generation of tinnitus

Tinnitus has been described in association with nearly every form of ear pathology, and the majority of tinnitus cases are related to cochlear dysfunction (5). Deprivation of input, abnormal input or injury are frequently initiating causes of tinnitus at peripheral level. Peripheral causes of tinnitus can generally be divided into subgroups with an otologic, neurologic, infectious, drug-related, and other origin (20). These peripheral causes alter the afferent input to the central auditory system.

Cochlear damage and loss of auditory receptors, the hair cells, are most frequently described as being the initiating causes of tinnitus, caused by mechanical lesions of the cochlea, biochemical lesions induced by ototoxic drugs, noise exposure, and aging. A diminished afferent input to the CNS can also be caused by dysfunction, injury, compression or irritation of the auditory nerve. Sectioning of the auditory nerve on one hand induces or increases tinnitus in some subjects, indicating a central origin of tinnitus (19;21-23), but on the other hand it diminishes or reduces tinnitus in other subjects (21;23).

In order to compensate for and adapt to an altered peripheral afferent input, and sometimes even a completely diminished input in deaf patients, the function of several central structures of the auditory pathway may consequently alter. This may lead to the generation of tinnitus in central parts of the auditory pathways.

**Pharmacological, animal and neuroimaging studies prove the generation of tinnitus in the central auditory pathways**

Intense sound exposure (13;16;24-26) and the tinnitus-inducing agents salicylate and quinine (5;16;27;28), are described to induce tinnitus by altering the peripheral afferent neural input. Measured alterations of frequency representations in the different structures of the auditory pathway, effects on neuronal firing patterns and increases in spontaneous neural firing rates, have all been described to be neural correlates of tinnitus (13;16;22;25).

Animal studies investigating the processes of neural plasticity in the DCN and the IC support the hypothesis that both structures might be an important site for the
generation and modulation of tinnitus-producing signals (24;29,30). Following an intense tone exposure and pharmacologically decreased GABA-mediated inhibition, an increased spontaneous activity was measured in the DCN and the IC of several species (7;24;26;28-34).

The alterations of the response properties of neurons of the auditory pathways after noise trauma, application of ototoxic drugs and pharmacological distortion of excitation and inhibition, indicate the involvement of several structures of the central auditory pathways in the generation of tinnitus. Central changes are assumed to correspond tonotopically to damaged regions of the cochlea (15). Since the effects of noise trauma and ototoxic drugs have been described to possibly induce tinnitus in tinnitus sufferers, it is reasonable to assume that the mechanisms measured in these studies contribute to the understanding of the pathophysiological processes concerning the generation of tinnitus.

Neuroimaging studies have been used to measure tinnitus-related effects on brain metabolism and cerebral blood flow. Real sounds presented to just one ear produce bilateral auditory cortex activity, whereas tinnitus-associated brain activity is usually unilateral measured by means of neural imaging techniques like PET and fMRI (35;36). Therefore, unilateral measured brain activity associated with tinnitus demonstrates that tinnitus is not directly induced by activity of the cochlea but is generated in higher structures of the auditory pathways. Using fMRI, Melcher (37) compared the neural activity of unilateral tinnitus sufferers with the neural activity of non-tinnitus sufferers during on and off conditions of sound. Tinnitus is associated with an increased basic level of neural activity during off-conditions of sound. When offering sound, the increase in neural activity from basic level to sound-induced neural activity compared between tinnitus subjects and non-tinnitus subjects is smaller, indicating the central origin of tinnitus.

Several neuroimaging studies have been performed during tinnitus modulation by voluntary movements or pharmacological manipulation: tinnitus influenced by voluntary jaw movement (36); evoked by lateral gaze (38;39); modified by oral-facial movements (40); influenced by cutaneous stimulation (41); and modulated with pharmacologic agents like lidocaine or tinnitus masking procedures (42;43). In other neuroimaging studies, those tinnitus sufferers who are able to modulate their tinnitus sensation by a voluntary act, proved to be particularly useful for determination of tinnitus-related neural activity. By measuring the distinction between brain activity during tinnitus perception and during tinnitus suppression, tinnitus-related brain activity can be determined. Activity measured within structures of the limbic system and sympathetic nervous system (44-47) might indicate the central origin of tinnitus-related symptoms, like anxiety, depression, negative attention, emotion and memory.
Neural plasticity in the generation of tinnitus

The general role of neural plasticity of the central nervous system is adaptation to altered peripheral input and compensation for the effects induced by injury or diseases (17). Neural plasticity occurs in all parts of the central nervous system as a normal consequence of a deprivation of peripheral input, an abnormal peripheral input or injury, learning, adaptation, and even behavioral training (12;17;48-50).

Injury and use related plasticity of cortical receptive fields in somatosensory, visual and auditory cortices have been described (51-54). The mechanisms of plasticity are assumed to be similar across all cortical regions (54), and may reflect an accumulation of both cortical and subcortical changes.

Many studies support the hypothesis that neural plasticity plays an important role in the generation of tinnitus (16;17;19;36;49;51;55-57). Because of close loop interaction between the different structures of auditory system, the strong GABAergic and glutamergic influence and the crossmodal interactions along the nonclassical pathway, a substantial part of the brain must somehow be involved in the sensation and generation of tinnitus. Disturbances in one part of the auditory system are reflected in changed functional properties in other parts of the central auditory pathways (15). Since several processes seem to work synergistically, the distinction between peripheral or central origin of tinnitus does not seem very relevant. The effects of neural plasticity following peripheral receptor organ damage can be divided into modifications with an early or later onset.

Legends figure 2

Section II: The early modifications of neural plasticity in the generation of tinnitus. A disturbed peripheral afferent (auditory) input initially causes a disruption of the balance between the inhibitory and excitatory influences. A reduced GABAergic inhibition unmasks dormant synapses and creates new connections through axonal sprouting. This results in a ‘lateral spread’ of neural activity and hyperactivity in the different structures of the auditory pathways that may result in the generation of tinnitus.

Section III: The reorganization process of tonotopic receptive fields is a late manifestation of neural plasticity in the generation of tinnitus. Since the excitatory fields of the auditory system are shaped by (surround) inhibition, the reorganization of the excitatory receptive fields arises from the loss of surround inhibition in the auditory system. These reorganization processes and new axonal connections contribute to an excess of tonotopical cells representing a very restricted tonotopical area of the cochlea, perceived as tinnitus.
Figure 2. The effects of neural plasticity after disturbed afferent input

**I. Normal afferent input to the neurons of the tonotopic receptive fields in the central nervous system.**

**II. Early consequences of neural plasticity**
Disturbed afferent input to the neurons of the central nervous system resulting in reduced GABAergic surround inhibition, unmasking of dormant synapses and initiation of axonal sprouting.

**III. Late consequences of neural plasticity**
Reorganization within the tonotopic receptive fields and creation of new connections through axonal sprouting; adjacent neurons of receptive fields take over the disturbed part of the tonotopic organization.

**Legends**
- **neurons with open synapses**
- **neurons with dormant synapses**
  - high synaptic thresholds
  - inhibition
  - low rate or no input
- **GABAergic (surround) inhibition**
- **disturbed afferent input to the central nervous system**
The early consequences of neural plasticity (figure section II)
During the initial response to peripheral input deprivation, neural plasticity induces the unmasking dormant synapses (17;58) and downregulation of intracortical surround inhibition (13;59;60) and initiates the creation of new connections through axonal sprouting (17;49).

Dormant synapses are synaptic connections that exist anatomically but normally not function as a result of high synaptic thresholds, inhibition or very low rate of input (17;58). Downregulation of intracortical surround inhibition might unmask dormant or suppressed interneuron connections and synapses in the CNS (13). These interneuron connections normally preexist, but are suppressed by the interneuron GABAergic (surround) inhibition (59;60). If these previous inactive synapses become conducting nerve impulses, it is called the unmasking of dormant synapses (58;61).

Since the unmasked connections are predominantly excitatory in character, the excitatory response areas broaden, resulting in an expansion of excitatory receptive fields (10;11;62). The unmasking of dormant synapses and axonal sprouting might result in a redirection of neuronal information within the central nervous system, causing neuronal information to be directed to parts of the central nervous system normally not receiving this neuronal information. On one hand it leads to crossmodal interactions between the structures and pathways of different neural circuits, like the auditory system, the somatosensory and the visual system. On the other hand this leads to lateral spread of neural activity, resulting in enlarged regions of neural activity when stimulating the peripheral receptor. We assume that this ‘lateral spread’ of these excitatory response areas, creates conditions of hyperexcitability in the brain, resulting in tinnitus (13;17;49;55).

Late consequences of neural plasticity (figure section III)
The functional organization of tonotopical maps is not statistically fixed, but seems to alter and adapt dynamically in response to processes of neural plasticity (12;51;53;59;63). Following altered, peripheral, afferent input, the neurons in receptive fields initially becomes silent and less or unresponsive to peripheral stimulation (60), within a period of hours and days following peripheral deafferentiation, new axonal connections are created and the tonotopical map of the neuronal pathways becomes reorganized (64). Since the excitatory fields of the auditory system are shaped by (surround) inhibition, the reorganization of the excitatory receptive fields after peripheral damage is hypothesized to arise from the loss of surround inhibition in the auditory system (10-12;59;60).

The tonotopical region in which the lesioned section of peripheral receptor organ is normally represented, becomes occupied by an expanded representation of adjacent, undamaged, perilesion parts and assumably of perilesion characteristics (3;10;12;13;15;16;29;49;50;65-67). This effect of tonotopical reorganization has two major implications. First, there is an excess of tonotopical cells representing a very restricted area of the peripheral receptor function. More neurons will be tuned to the same tonotopical characteristics. In tinnitus this results in a tinnitus pitch
predominantly located at the frequency edge of the hearing loss (3;9). Muhlnickel (66) found a significant association between subjective tinnitus strength and the amount of shift of the tinnitus frequency in the auditory cortex.

Second, the spontaneous and stimulated activity of these neurons is more synchronized than it was before the reorganization, since more neurons are directed to the same function. Increased synchrony of spontaneous neural activity in the regions of these perilesion frequencies might have perceptual consequences and clinical implications, such as tinnitus (3;9).

The role of extralemniscal pathways in the generation, modification and perception of tinnitus

The effects of neural plasticity in reaction to an altered peripheral auditory input, seem to encompass more neuronal structures than only the neurons of the auditory pathways. The existence of crossmodal interactions between the somatosensory, somatomotor and visual pathways along the nonlemniscal pathway, might explain the fact that some patients are able to induce or modulate the perception of their tinnitus by activating one of these pathways (3;19;56). Several studies described tinnitus modulations by changing gaze (38;68;69), oral-facial movements (70), cutaneous stimulation (41), finger movements, craniocervical movements (71), trigeminal interactions or median nerve stimulation (72). The induced changes in tinnitus perception most frequently concern changes in tinnitus loudness instead of changes in tinnitus pitch or location (68). Since sounds cannot be modulated by these voluntary movements, tinnitus-related neural activity may not be transmitted via the same neural pathways that are normally activated by sound (72), indicating the nonlemniscal pathway to be possibly responsible for the generation of some forms of tinnitus.

Tinnitus perception modulations caused by trigeminal ganglion activation are perhaps the clearest demonstration of involvement of the nonlemniscal pathway. Besides its sensory connections to head, oral mucosa, teeth and facial skin, the trigeminal ganglion is also neurally connected to the cochlea, the ventral and dorsal cochlear nucleus (VCN and DCN) and the inferior colliculus (IC) (73;74). Many tinnitus sufferers report to be able to modify their tinnitus perception by manipulating somatosensory regions of the head, neck and jaw, and by changing gaze. Neck injury, whiplash, tooth abscesses and temporomandibular joint dysfunction, have been frequently mentioned to initiate or modulate the tinnitus perception. These modulations or development of the tinnitus perception might be declared by the assumption that manipulation of the trigeminal ganglion influences the firing pattern in the DCN and the IC. Increased firing of these structures of the auditory pathways might have perceptual consequences like tinnitus.

Direct connections from the thalamic nuclei of the nonlemniscal pathway to the amygdala, the hippocampus and other structures of the limbic system, may explain the affective components often accompanying tinnitus (4;17;56). Fear
reactions, phonophobia, hyperacusis, and depression are examples of these affective
symptoms. Unusual connections between the different structures within the CNS
might be established by outgrow of new neural connections (axonal sprouting) or by
increasing the efficacy of normally silent synapses (unmasking of dormant synapses)
(17). The amygdala connects to parts of the endocrine and autonomic systems (19).
This may explain the generation of tinnitus-related symptoms in the sympathetic
nervous system.

**Correlations between tinnitus, phantom sensations and chronic pain**

Manifestations of neural plasticity have been attributed to phantom limb perceptions
and neuropathic, chronic pain (22;54;72;75-77). Phantom limb sensations and
phantom pain are perhaps the clearest demonstrations of disorders in which the
neural activity causes symptoms that do not originate from the peripheral location at
which the symptoms are perceived. Phantom pain is therefore believed to be a pure
form of central pain, generated in the CNS (17).

Phantom limb perceptions can be caused by a reorganization process of the
somatosensory cortex (78-80). Perilesion cortical neurons ‘take over’ the function of
the brain areas corresponding to the amputated limb (81). The induced phantom
perceptions correspond to this reorganized region and spontaneous discharges of
neurons in this region will be misinterpreted as arising from the missing limb
(54;81;82). This can explain the phantom perceptions experienced by individuals
after limb amputation, reporting to feel their phantom limb by touching the face
(76;78). The amount of reorganization of the somatosensory cortex and the amount
of phantom limb pain in upper extremity amputees seems to be significantly
associated (78;80). This indicates similarity of the reorganization processes in
phantom limb perception and tinnitus, since a similar correlation between the
amount of reorganization of the auditory cortex and the perceived tinnitus severity is
found by Muhlnickel (66). Perilesion frequencies take over the frequency
representation of the cochlear lesion, comparable to the processes described after
limb amputation. These parallels would therefore suggest tinnitus to be a phantom
sensation (72;77).

Besides phantom limb perceptions, tinnitus is often compared to the
mechanisms causing chronic pain. Both tinnitus and chronic pain are subjective
sensations, most frequently initiated by peripheral injury, inducing changes at central
level of the nervous system (17;72;75;77). Chronic pain and tinnitus are disorders
with different initiating causes and mechanisms of pathophysiology (72;77). Both
conditions are continuous events that may change in quality and character over time.
The strong psychological component that often accompanies both chronic pain and
 tinnitus might support the hypothesis that limbic brain areas are involved (72).
Conclusions

The characteristics of the auditory system contribute to involvement of the whole auditory system in generating of tinnitus. An altering peripheral input induces dynamical modifiable manifestations of neural plasticity in central parts of the auditory system. Manifestations of neural plasticity result in early and late consequences, finally resulting in a lateral spread of excitatory interneuron connections and the development of hyperactivity within structures of the auditory pathways. Tinnitus may be the perceptual consequence of this hyperactivity in the brain.

The ability of modulation of the tinnitus perception by activating somatosensory or visual systems, may be caused by neural activity along the nonclassical pathways. Since these modulations can create various conditions of tinnitus perception and neural activity, tinnitus-related neural activity can be determined, as used in several neuroimaging studies.

The similarities between the pathophysiological processes of tinnitus, phantom pain and chronic pain perceptions create opportunities for development of new research and treatment modalities. Pharmacological, animal and neuroimaging studies explore the role of the CNS in the generation of tinnitus. Despite the great amount of research performed in the last decennia, much remains unknown about the pathophysiological processes of tinnitus. Further research is needed in order to enlarge our knowledge about tinnitus and for the development of new treatment modalities.
Reference List

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