Chapter 94
Similarities Between Treatments of Tinnitus and Central Pain

Dirk De Ridder and Aage R. Møller

Keypoints

1. Neurobiology, pathophysiology, neuroimaging, and clinical presentation share many common aspects between neuropathic pain and tinnitus.
2. Similar treatments for pain and tinnitus exist, but pharmacological methods are more successful for treatment of pain than for treatment of tinnitus.
3. Peripheral and intracranial ablative neurosurgical treatments yield common results and complications for pain and tinnitus.
4. The most promising analogous treatments for pain and tinnitus are non-invasive and invasive methods for neuromodulation, such as various forms of brain stimulation using transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).
5. TENS, for stimulation of peripheral nerves, and neurofeedback, have beneficial effects on both pain and tinnitus.
6. Invasive neuromodulatory treatments such as cochlear implants, dorsal column stimulation/auditory brainstem implant, subthalamic nucleus stimulation, and sensory cortex stimulation are beneficial for both tinnitus and pain.

Keywords Tinnitus • Central pain • Treatment • Cortical stimulation • Peripheral nerve stimulation • Transcranial magnetic stimulation • Transcranial direct current stimulation

Abbreviations

ABI	Auditory brainstem implant
CI	Cochlear implant
DBS	Deep brain stimulation
DCN	Dorsal cochlear nucleus
DCSCS	Dorsal column spinal cord stimulation
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
fMRI	Functional MRI
MRI	Magnetic resonance imaging
MSI	Magnetic source imaging
MVD	Microvascular decompression
PET	Positron emission tomography
rTMS	Repetitive TMS
STN	Subthalamic nucleus
tDCS	Transcranial direct current stimulation
TENS	Transderm electric nerve stimulation
TMS	Transcranial magnetic stimulation
TMS	Trans cranial magnetic stimulation
VTA	Ventral tegmental area

Introduction

Similarities between pain and tinnitus were discussed in Chap. 14. Similarities Between Tinnitus and Pain. In this chapter, we will discuss similarities in treatment of neuropathic pain and some forms of tinnitus. Apart from the developmental and reorganizational analogy, a clear clinical analogy exists between phantom pain and tinnitus [1–4]. Both symptoms are wholly subjective sensations, events that may change in character and quality. Both can be masked and relieved by electrical stimulation with a residual inhibition. Transection

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of an afferent nerve usually does not help relieve tinnitus or chronic pain. In both systems, the ascending system is modified by a descending counterpart. This leads to similar characteristic symptoms in both tinnitus and phantom pain [2–4].

A normal stimulus to the skin in individuals with phantom pain can create a painful sensation (allodynia) in the same way tinnitus patients can perceive a sound as unpleasant or painful. A painful stimulus often generates an explosive and prolonged reaction to the stimulus (hyperpathia) in individuals with phantom pain similar to the hyperacusis seen in tinnitus patients [5]. The wind-up phenomenon, a worsening of pain sensation with repeated stimuli of the same intensity, is also present in some individuals with tinnitus, where it is described as an increasingly unpleasant sensation on repeating the same sound [2, 3]. Furthermore, a feeling of anxiety, nausea, and a clear stress response is often encountered both in individuals with phantom pain and tinnitus [2, 3] (see also Chap. 14).

There are at least two distinct forms of pain: normal physiological pain, by activation of nociceptors in a normally functioning somatosensory system, and neuropathic pain, which is the result of deafferentation and activation of a hereby pathologically functioning somatosensory system. There is no physiological tinnitus that is analogous to physiological pain, and therefore there are no similarities for the treatment of tinnitus to the common analgesics that are quite efficient for acute physiological body pain. Many different kinds of medications for physiological pain are readily available and have few side effects. There are also medications for neuropathic pain. Medications such as gabapentin and pregabalin are effective in treatment of central neuropathic pain. Similar medication that has a generally beneficial effect on central tinnitus does not exist either. Several other treatments are used for neuropathic pain with varying results including other pharmacological treatments [6], epidural treatments [7], regional nerve blocks [7], destructive lesions [8], treatment with calcitonin [7], transcutaneous electrical nerve stimulation [7], motor cortex stimulation (MCS) [9–11], and thalamic stimulation [12–14]. Existing treatments for various forms of pain are far more efficient than treatment of tinnitus. So even between the pathophysiology of neuropathic deafferentation pain and deafferentation tinnitus, there have to be some fundamental differences.

Medication

Some medications are used for both neuropathic pain and tinnitus, for example, clonazepam [15, 16] and gabapentin (and this only in acoustic trauma related tinnitus) [17]; however, most pain medication will not benefit tinnitus patients. For a detailed analysis of pharmacological approaches to tinnitus, the reader is referred to Chap. 78.

Destructive Procedures

Nerve Sections

The auditory information is brought to the brain via the auditory or cochlear nerve, and feedback from the cortex to the cochlea is mediated via the vestibular nerve [18, 19]. The inferior vestibular nerve connects to the auditory nerve via a small nerve fiber bundle [20]: Oort's bundle which contains about 360 myelinated and 1,000 unmyelinated axons [21]. As always, there is some variability, but vestibulocochlear anastomoses can be found in 80% of the population [22]. Based on this anatomical knowledge, both cochlear and vestibular nerve sections have been performed in an attempt to cure tinnitus.

In a recent review paper on vestibular nerve section performed for tinnitus [23], the proportion of patients in whom tinnitus was exacerbated postoperatively ranged from 0 to 60%, with a mean of 16.4% (standard deviation 14.0). The proportion of patients in whom tinnitus was unchanged was 17–72% (mean 38.5%, standard deviation 15.6), and in whom tinnitus was improved was 6–61% (mean 37.2%, standard deviation 15.2). In the majority of patients undergoing vestibular nerve section, ablation of auditory efferent input (and thus total efferent dysfunction) to the cochlea was not associated with an exacerbation of tinnitus [23]. Therefore, if a nerve section is elected, vestibular nerve section is to be preferred to cochlear nerve section in which the success rate in abolishing tinnitus is disappointing and the results generally unpredictable [24]; an important part of the patients (55%) report no effect or a worsening of their tinnitus [25]. Only one paper reports good results with cochlear nerve section for tinnitus [26]: two-thirds

completely relieved, 28% improved, and only 5% non-responders, without a single patient worsening (see Chap. 39).

Section of the auditory nerve is controversial and now regarded contraindicated because it involves causing deprivation of signals to the auditory system, which is known to promote plastic changes. Despite a long history of ablative procedures in neurosurgery for pain control, the evidence supporting destructive procedures for benign pain conditions remains limited to class III evidence (retrospective studies) [8]. The fact that nerve lesioning is worse than non-destructive treatments [e.g., microvascular decompression (MVD)] in pain is demonstrated in trigeminal neuralgia where MVDs are better than destructive treatments such as rhizotomies or gamma knife surgery. MVD has the highest rate of long-term patient satisfaction with the lowest rate of pain recurrence [27, 28].

After surgical removal of vestibular schwannoma with resection of the auditory nerve, most patients have a small improvement of their tinnitus, but 50% of the people who do not present with tinnitus develop it after the surgery [29].

Frontal Lobotomies

Tinnitus and pain distress have both been linked to a neural network consisting of the anterior cingulate, frontal cortex, and insula [30–33]. These brain areas are also implicated in the distress perceived by people with posttraumatic stress disorder [34, 35], as well as asthma-related dyspnea [36], suggesting that these areas may constitute a "general distress network". In the 1930–1940s frontal lobotomies were performed both for pain [37, 38] and tinnitus [39, 40]. The net results of these treatments were the persistence of the perception of pain and tinnitus, but the affective component related to the pain and tinnitus disappeared. For treatment of pain, the frontal lobotomies have now been refined and restricted to anterior cingulotomies. Except for a decline in focused attention performance [41–43], other neurocognitive functions (including language, memory, motor, visual-constructional, and intellectual functions) remained unaffected after the anterior cingulotomies [43]. The decreased attention modulates (decreases) the emotional experience of pain that was related to self-perceived tension and which was expressed by anger before the treatment, which also improved mood and decreased psychasthenia [44]. Cingulotomy also reduced behavioral spontaneity, expressed as a decrease in self-initiated action [42]. When performing cingulotomies for intractable pain, 72% of patients report improvements in their pain, 55% no longer take narcotics, 67% note improvement in their family life, and 72% note improvement in their social interactions. Fifty-six percent of patients report that the cingulotomy was beneficial and 28% return to their usual activities or work [45]. No reports have been published on the use of cingulotomy for treatment of tinnitus.

Thalamic Lesions

Thalamic lesioning has been used for both pain and tinnitus suppression based on the idea of thalamocortical dysrhythmia [46] as unifying pathophysiological mechanism of tinnitus and pain [47]. However, the experience is very limited up to now; so no definitive conclusions can be drawn of the value of this treatment for tinnitus suppression.

Lesioning of Autonomic Nervous System

It is well known that the sympathetic system influences both pain and tinnitus perception [2, 3]. Both pain and tinnitus tend to worsen under stressful situations. Therefore, interfering with the sympathetic system has been performed both in pain and tinnitus [48–51]. If tinnitus responds to a stellate block, a complete suppression of the tinnitus was possible in 31%, in 50% a partial response, and in 19% no response was obtained by surgical sympathectomy [51]. In Ménière's disease, the patients who did not improve their tinnitus intensity were no more distressed by their tinnitus [51]. The patient should be warned that 24 h after operation the deafness and tinnitus may be slightly worse, possibly as the result of irritation of the sympathetic nerve trunk; it may take a week or 10 days to settle down [51]. It can be expected, however, that cervical sympathectomies for tinnitus relief might only yield a temporary benefit, in a couple of months, similar to what is known for sympathectomies at C2 and C3 for occipital neuralgia [52].

Neuromodulation

Cortex Stimulation

The neurobiological, pathophysiological, and clinical analogies between deafferentation tinnitus and deafferentation pain [1–4, 53] suggest that the resulting phantom symptoms of central pain and central tinnitus are caused by cortical hyperactivity/reorganization. Therefore, it can be assumed that the same basic strategy for treating these two conditions can be applied.

The basic strategy can be summarized as follows:

1. The hyperactivity/reorganization that is associated with central pain and some forms of tinnitus can be demonstrated by functional neuroimaging techniques such as PET scan, fMRI, or MSI (magnetic source imaging).
2. The anatomical area of hyperactivity/reorganization can then be influenced by (neuronavigated) transcranial magnetic stimulation.
3. If successfully suppressed by TMS, an electrode can be permanently implanted extradurally over the anatomical area of cortical hyperactivity/reorganization.

The details of this approach are presented in the chapter on cortex stimulation for tinnitus (Chap. 90). In summary, a selection criterion of more than 50% transient tinnitus improvement, lasting only a few seconds, on two separated placebo-controlled TMS sessions was used for implanting cortical stimulation electrodes.

Deep Brain Stimulation (DBS)

Subthalamic nucleus (STN) stimulation is capable of both improving pain [54, 55] and tinnitus [56] in patients with Parkinson's disease, but the mechanism is unknown. STN stimulation also modulates olfactory [57] and visual [58] function suggesting that the STN has a general modulatory action on sensory processing. Stimulation of the auditory cortex, which does not send direct projections to the subthalamic nucleus, induces only late excitatory responses in the STN via the indirect cortico-striato-pallido-subthalamic pathway [59]. Many cells in the STN respond to both motor and auditory cortex stimulation as well as to frontal cortex stimulation [59]. Therefore, it is possible that DBS of the STN improves tinnitus via its influence on the motor–auditory integration cells in the STN or indirectly via the frontal cortex. Another possibility is that it occurs via an indirect pathway involving the medial forebrain bundle. Activation of connections between the medial (limbic) STN and the medial forebrain bundle has been proposed as a mechanism for the emotional and motivational influences of STN stimulation [60]. The medial forebrain bundle connects the ventral tegmental area (VTA) to the nucleus accumbens, which has been implicated in tinnitus as well [61].

Transcutaneous Electrical Nerve Stimulation and Cochlear Implants

Neuropathic pain and tinnitus are both related to deprivation of sensory input to the brain (deafferentation symptoms). One way of compensating for the effect of deafferentation is by supplying the missing information through direct electrical activation of the peripheral receptors or the sensory nerves. Electrical stimulation of the peripheral somatosensory nerves, transcutaneous electrical nerve stimulation (TENS), and the auditory nerve [cochlear implants (CI)] has been used to suppress hyperactive clinical states of the respective system, which develop as a result of the deafferentation. Neuropathic pain can be modulated by TENS [62]. The effect on pain from such stimulation of the skin or peripheral nerves is mediated by the inhibitory influence from Aβ fibers on neurons in the spinal cord that receive nocuous input from C and Aδ fibers (see Chap. 14). TENS may also affect central pain, probably through activation of neural plasticity [1].

In the auditory system, peripheral nerve stimulation is performed by CI (see Chap. 77). The use of CI for tinnitus has shown promising results with regards to tinnitus suppression [63–68]. TENS is commonly used in the treatment of pain but has been used in tinnitus as well [69–75]. TENS modulates tinnitus most likely via somatosensory–auditory interactions at the level of the cochlear nuclei [76–78] or the inferior colliculus [79] (see Chap. 9). The DCN has been implicated in the pathophysiology of tinnitus [80, 81] (see Chaps. 9 and 31), and therefore modulating its activity could be useful in some forms of tinnitus (see Chap. 31). Using

c-fos studies, it was recently shown that electrical stimulation of the skin around the ear modulates dorsal cochlear nucleus activity through both direct pathways via the trigeminal system and indirect pathways via the dorsal raphe and the locus coeruleus [82]. When auditory input to the DCN is diminished, an increase in somatosensory influence on auditory neurons occurs, which could be due to cross-modal reinnervation or increased synaptic strength [83]. This favors the use of TENS in auditory deafferentation tinnitus, even though clinical data not always support the use of TENS for tinnitus [84]. Selecting who benefits from TENS and who does not will be important for the future clinical application of this method.

Dorsal Column Stimulation and Auditory Brainstem Implants (ABI)

Electrical stimulation of the second neuron in the somatosensory system is known as dorsal column stimulation (DCS) and is used in the management of chronic, intractable neuropathic pain [85]. The method is based on the "gate–control" theory presented by Melzack and Wall [86], who postulated that activity in large diameter cutaneous fibers (type Aß) inhibits the transmission of noxious information to the brain. Electrical stimulation of these large afferents by an electrode placed dorsomedially in the epidural space elicits a tingling sensation (paresthesia) in the corresponding dermatomes. To obtain successful treatment of chronic, neuropathic pain by DCS, the stimulation-induced paresthesia has to cover the anatomical areas of pain completely [87, 88].

Electrical stimulation of the cochlear nucleus in the auditory brainstem yields suppressive effects on tinnitus in 80% of patients who use their auditory brainstem implants (ABI) daily [89]. This is supportive of the theory that the DCN is critically involved in tinnitus [80, 81] (see Chap. 9).

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) involves stimulation by a weak constant current (between 0.5 and 2 mA) flow through the cerebral cortex via scalp electrodes. Anodal tDCS typically has an excitatory effect on the local cerebral cortex by depolarizing neurons, while the opposite occurs under the cathode electrode through a process of hyperpolarization [90]. This effect of tDCS lasts for an hour or longer after a single 20–30 min treatment session [90–93].

With the anode electrode placed over the dorsolateral prefrontal cortex, tDCS can modulate both pain [94] and tinnitus (see Chap. 89), possibly via a similar mechanism, most likely a top-down modulation of auditory [95] and somatosensory [96] processing.

For pain, cathodal tDCS stimulation of the somatosensory cortex contralateral to the side to which the pain is referred [97] and left-sided anodal tDCS over the auditory cortex [98] can influence pain and tinnitus, respectively, via a more direct effect than tDCS applied through electrodes placed on the frontal part of the scalp (anode right side, cathode left side).

Transcranial Magnetic Stimulation

TMS is a non-invasive method of inducing electrical current in the brain [99]. It uses a coil placed on the scalp that generates magnetic pulses of very short duration (100–300 μs) at approximately 1.5–2.0 T in strength [100]. Because magnetic fields pass largely undistorted through the scalp and skull, TMS is powerful enough to cause neuronal depolarization in the cortex. TMS originally delivered single impulses. Further development of TMS equipment allowed repetitive magnetic impulses (rTMS) to be delivered, which are more effective than single impulses. The area of the brain that is stimulated and the intensity of the electromagnetic field depend on physical properties and rapidly decrease with the distance to the coil. It was estimated that a "figure of eight coil" stimulates an area of approximately 3×2 cm at cortical surface, but the induced current falls to near zero at a depth of 3 cm [101].

TMS has been used as a putative prognostic tool for cortex implants at the auditory cortex for treatment of tinnitus [102, 104] and for implants on the somatosensory cortex [103, 105] and motor cortex [106] for treatment of neuropathic pain. Details can be found in the chapter on cortex stimulation for tinnitus (Chap. 90).

Repetitive sessions of TMS (rTMS) have also been used as a treatment for pain [107, 108] and tinnitus [101, 109–112]. Details can be found in Chap. 88.

Neurobiofeedback

Tinnitus and pain are associated with abnormally coupled low and high frequency synchronous oscillatory activity in the brain [31, 46, 113–117]. If this abnormal oscillatory activity is related to the auditory and somatosensory phantom percept, a logical attempt to treat these symptoms is by normalizing this abnormal activity. Neurofeedback is a biofeedback technique using electroencephalographic (EEG) or fMRI signals for training individuals to alter their brain activity via operant conditioning. This has been used for both tinnitus [118–119] and fibromyalgia pain [120]. A detailed description of this technique is given in Chap. 87.

A better understanding of the spectral and connectivity changes, as well as alterations in independent components in tinnitus and pain, combined with new software development for source-analyzed neurofeedback training is expected to permit this technique to become a more powerful tool in treatment of both tinnitus and pain.

Conclusion

Tinnitus does not seem to respond to medication used for physiological or neuropathic pain. This means that pharmacological treatment does not seem to benefit from the neurobiological, pathophysiological, neuroimaging, and clinical analogy between tinnitus and pain, and pharmacological treatment [122], in general, has had little success in treatment of tinnitus.

Methods such as ablative neurosurgical approaches consisting of nerve sections or intracranial destructive lesions have found use in treatment of both tinnitus and pain.

Different kinds of invasive and non-invasive neuromodulation seem to be more promising analogous treatments. For invasive stimulation implanted electrodes on the auditory and somatosensory cortex, deep brain stimulation of the subthalamic nucleus and thalamus, TENS/cochlear implants, and dorsal column stimulation/auditory brainstem implants most likely use similar mechanisms to improve pain and tinnitus. Non-invasive neuromodulation techniques such as cortical transcranial magnetic stimulation, transcranial direct current stimulation, transcutaneous electrical nerve stimulation, and neurofeedback appear to be analogous in their effect on pain and tinnitus as well.

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