Tinnitus and Brain Stimulation

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Abstract The pathophysiological mechanisms that underlie the generation and maintenance of tinnitus are being unraveled progressively. Based on this knowledge, a large variety of different neuromodulatory interventions have been developed and are still being designed, adapting to the progressive mechanistic insights in the pathophysiology of tinnitus. rTMS targeting the temporal, temporoparietal, and the frontal cortex has been the mainstay of non-invasive neuromodulation. Yet, the evidence is still unclear, and therefore systematic meta-analyses are needed for drawing conclusions on the effectiveness of rTMS in chronic tinnitus. Different forms of transcranial electrical stimulation (tDCS, tACS, tRNS), applied over the frontal and temporal cortex, have been investigated in tinnitus patients, also without robust evidence for universal efficacy. Cortex and deep brain stimulation with implanted electrodes have shown benefit, yet there is insufficient data to support their routine clinical use. Recently, bimodal stimulation approaches have revealed promising results and it appears that targeting different sensory modalities in temporally combined manners may be more promising than single target approaches.

While most neuromodulatory approaches seem promising, further research is required to help translating the scientific outcomes into routine clinical practice.

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1 Introduction

Tinnitus can be defined as the conscious awareness of a non-complex sound for which there is no identifiable corresponding external sound source (Jastreboff 1990). Tinnitus occurs in 5–15% of the population (Axelsson and Ringdahl 1989; Heller 2003). Whereas most patients (80%) can habituate to this sound, quality of life is severely disrupted in about 20–25% of the patients who cannot cope with the tinnitus (Axelsson and Ringdahl 1989; Vanneste et al. 2014). In these patients, tinnitus is frequently associated with anxiety, depression, cognitive impairment, and sleep disturbances (Bhatt et al. 2017; Vanneste et al. 2016; Y. Wang et al. 2018b), and tinnitus becomes a mental disorder. Tinnitus disorder can therefore be diagnosed in cases of tinnitus with tinnitus-associated suffering.

Although many treatments have been proposed, both pharmacological and non-pharmacological, some of which are commercially available, evidence for a successful therapy that benefits everybody with tinnitus is lacking (Dobie 1999; Langguth et al. 2013). The lack of efficacious treatments for tinnitus likely originates from the heterogeneity of tinnitus and an incomplete understanding of the pathophysiology of the different forms of tinnitus (Elgoyhen et al. 2015).

Since 2011 pharmaceutical interest in developing neuropharmacological products for neurological or psychiatric indications has dramatically declined. Big Pharma has invested 50% less for brain related disorders (Yokley et al. 2017), because it is too expensive and too risky. Developing medication for brain disorders has 50% less chance of making it to the market (6.2% vs 13.3%) (Gribkoff and Kaczmarek 2017), takes 30% longer to develop (19.3 vs 14.7 months) (Gribkoff and Kaczmarek 2017), and costs 30% more than heart medication (Gribkoff and Kaczmarek 2017). Eighty percent of medications fail phase III trials (Kesselheim et al. 2015), predominantly because they do not outperform placebo (46%) (Kesselheim et al. 2015). Thus, notwithstanding repurposing of existing medication (Pushpakom et al. 2019), the likelihood of a pharmaceutical solution for tinnitus and tinnitus disorder is therefore limited. As such, other treatment options need to be investigated, one of which is brain stimulation. The history and evolution of the understanding of the pathophysiology of tinnitus goes hand in hand with the development of brain stimulation approaches.

2 History and Evolution of the Pathophysiology of Tinnitus

Tinnitus is an enigmatic symptom. Even the earliest historic reference, dating back to the 19th CBC, in the Ebers papyrus, in which tinnitus was considered the consequence of a bewitched ear, is controversial (Dietrich 2004) (Fig. 1). Tinnitus as a

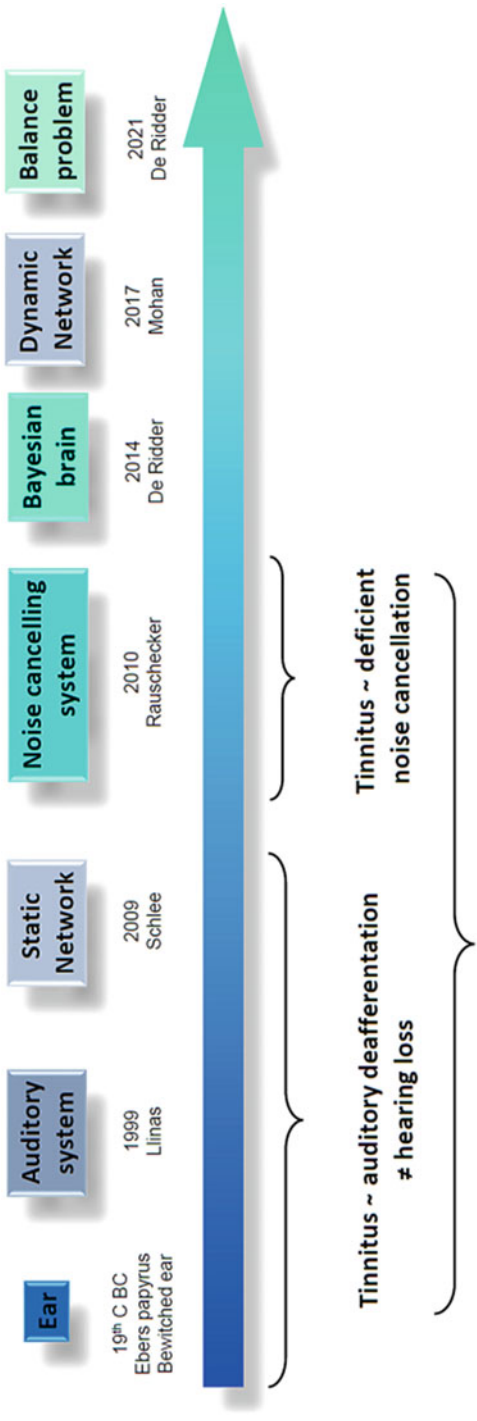

Fig. 1 History of the pathophysiological models for tinnitus

problem of the ear, caused by hearing loss, predominated until the 1990s, and consequently treatment focused on improving hearing function and masking of sound. In 1990 Jastreboff developed a theoretical neurophysiological model implying that the phantom sound was the consequence of classical conditioning (Jastreboff 1990). The neurophysiological model focused on the distress associated with tinnitus, and lead to the development of Tinnitus Retraining Therapy (TRT). TRT comprises directive counselling and potential use of hearing aids and sound therapy, not with the goal of complete masking, but to facilitate habituation of tinnitus reaction and possibly perception. But Jastreboff did not specify which neuroanatomical structures were involved in this conditioning, so the brain components involved remained inside a black box. In 1999 Rodolfo Llinas published the first paper that specifically proposed a pathophysiological model implying the interaction between the auditory cortex and thalamus as the generator of tinnitus, called thalamocortical dysrhythmia (R. R. Llinas et al. 1999). It is based on the clinical evidence that tinnitus, in most cases, is associated with hearing loss or abnormalities in the inner ear or the peripheral auditory pathway, which results in neuroplastic changes in auditory and non-auditory brain networks (De Ridder et al. 2014d). However, some forms of tinnitus exist in which tinnitus is unrelated to hearing loss, and this seems to be associated with a different underlying pathophysiological mechanism (Vanneste et al. 2019; Vanneste and De Ridder 2015), possibly requiring different neuromodulation targeting. Whether tinnitus without hearing loss is fundamentally different or a variation of the same underlying pathophysiology still remains to be proven, as tinnitus without audiometric hearing loss does not imply that there is no auditory deafferentation (Weisz et al. 2006). The thalamocortical dysrhythmia model of Llinas states that in the deafferented state, the dominant resting-state alpha rhythm (8–12 Hz) slows down to theta (4–7 Hz) (R. R. Llinas et al. 1999) band frequencies. Even though it is called theta, from an electrophysiological point of view it should be considered slowed alpha activity, as the neural generators of true theta activity are different from the generators of alpha and slowed alpha activity (Tsanov 2015; Whittington et al. 2018). In the awake state, the thalamocortical loops within the brain idle around 10 Hz (8–12 Hz), called the alpha frequency, generated by the thalamus. During light sleep, theta band activity is predominant, generated by the septal nuclei and hippocampus, and in deep sleep delta activity (1–3 Hz) predominates (G Buzsaki 2006). The theta that emerges in thalamocortical dysrhythmia is thalamically generated and therefore more likely represents alpha activity that is slowed down to the theta frequency range. Conceptually, this can be explained as a decrease of the firing rate when less information needs to be processed (Borst and Theunissen 1999) due to the deafferentation, and that firing and oscillation rate are coupled at the thalamocortical level (Crunelli et al. 2018; R. Llinas et al. 2005). As a consequence, $GABA_A$ mediated lateral inhibition weakens (R. Llinas et al. 2005), inducing gamma (>30 Hz) band activity (R. R. Llinas et al. 1999) surrounding the deafferented theta area, also known as the edge effect (R. Llinas et al. 2005). Confirming the initial studies by Llinas (R. Llinas et al. 2005; R. R. Llinas et al. 1999) a decrease in alpha power is associated with an increase in gamma power (Lorenz et al. 2009), and gamma is

coupled to theta activity (Weisz et al. 2007). Other studies have since demonstrated the presence of both low (delta or theta) and high frequency activity in the auditory cortex of tinnitus patients (Adamchic et al. 2012, 2014; Adjamian et al. 2012; Ramirez et al. 2009), and the theta-gamma cross-frequency coupling has also been identified on electrode recordings of implanted patients (De Ridder et al. 2011b), confirming the MEG data.

Theta activity is associated with negative symptoms such as hearing loss (and hypoesthesia in the somatosensory system), and gamma activity reflects the positive symptoms, tinnitus (pain in the somatosensory system) in diseases characterized by thalamocortical dysrhythmia (R. Llinas et al. 2005; R. R. Llinas and Steriade 2006). Thus negative symptoms (e.g., hearing loss, hypoesthesia) are linked to decreased information processing and therefore slowed alpha activity, as if the deafferented thalamocortical columns are "as asleep"(R. Llinas et al. 2005). It has been proposed that this theta could then act as a long range carrier wave (Freeman 2003, 2005; Freeman and Rogers 2002) on which the tinnitus information can be nested by means of high frequency oscillatory activity (De Ridder et al. 2015b; De Ridder et al. 2014d). If this model is universal, then that would imply that all tinnitus patients could be treated by auditory cortex stimulation, whether non-invasively or invasively. The first attempts to test this theory were performed with transcranial magnetic stimulation and brain implants (De Ridder et al. 2004; Eichhammer et al. 2003a; Plewnia et al. 2003).

However, early research of TMS and implants demonstrated that not every person suffering from tinnitus could be helped with auditory cortex stimulation. Different explanations were postulated for this including the duration of the tinnitus (De Ridder et al. 2005; Kleinjung et al. 2007), the gender of the tinnitus patients (De Ridder et al. 2007d), the amount of hearing loss (Kleinjung et al. 2007), the tinnitus pitch (De Ridder et al. 2007d), the perceived laterality, left or right side, of the tinnitus (De Ridder et al. 2007d), laterality of the tinnitus generator in the brain (De Ridder 2010; Langguth et al. 2006), and also TMS related aspects such as the delivered dose (Plewnia et al. 2007). The failure in obtaining predictable and clinically satisfying results prompted the proposal of a novel pathophysiological model, in which the tinnitus percept would not be phrenologically limited to the auditory cortex but to a tinnitus-associated network (Schlee et al. 2009a, b). Even though that network dynamically changes, adapting to externally and internally generated triggers, on average it remains fairly stable, so that it could be averaged over 5–20 min recording intervals, with the current MEG and EEG technology (De Ridder et al. 2011a; Schlee et al. 2009a, b). Translating theoretical concepts from network science (Albert et al. 2000) to brain stimulation, it was hypothesized that directing stimulation at more than one target could disrupt the tinnitus network more effectively than one single target. As the frontal cortex was already a somewhat successful target for transcranial direct current stimulation (tDCS) (De Ridder and Vanneste 2012; Frank et al. 2011; Song et al. 2012; To et al. 2017; Vanneste and De Ridder 2011; Vanneste et al. 2011) and TMS (De Ridder et al. 2012a, c; Vanneste and De Ridder 2012a), the first multitarget stimulations selected the frontal cortex and temporoparietal junction (auditory cortex) (Kreuzer et al. 2011), but later attempts

also used auditory cortex and high cervical C2 area (De Ridder and Vanneste 2015), using the same reasoning. Because the success rate was not high, these network science based models were modified for tinnitus to employ both random and targeted modulation on the tinnitus network (Mohan et al. 2017). The restricted benefits of neurostimulation based on the distributed network model led to investigation of an alternative model, in which tinnitus was the result of a deficient noise cancelling mechanism (Leaver et al. 2011; Rauschecker et al. 2010), analogous to pain (Fields 2004; Kong et al. 2010). However, according to this model the subgenual anterior cingulate cortex was critically involved in tinnitus generation, a difficult neuroanatomical target for current brain stimulation technologies. Furthermore, other groups failed to replicate the imaging data on which the model was based. A further model was proposed that tinnitus could actually be the result of a Bayesian prediction error (De Ridder et al. 2014a, c). According to this model tinnitus can be understood as the result of a mismatch between the predicted sound percept and the actual neural input from the ear, which is reduced because of hearing loss. It was hoped that the underlying anatomical and oscillatory correlates could be targeted with brain stimulation. It also theorized that neuroplastic changes involved in tinnitus were multiphasic, suggesting a theoretical difference between the neural generators of tinnitus in tinnitus with and without deafferentation. As such, the model attempted to combine and integrate both the deafferentation based theories and the noise cancelling theories (De Ridder et al. 2014a, c, d).

Using a sliding window analysis method combined with graph theoretical analyses permitted the development of a dynamical tinnitus network, in which the tinnitus sound is the consequence of the auditory cortex constantly looking for missing information, in keeping with the Bayesian tinnitus concept. Distress is associated with the loss of temporal flexibility (Mohan et al. 2018a, b). This model has not yet led to novel therapeutic approaches.

In a further attempt to integrate both the deafferentation based and noise cancelling models it has recently been proposed that tinnitus could be the result of an imbalance between bottom-up and top-down influences (Vanneste et al. 2019), which would make very clear predictions on what targets to apply which kind of brain stimulation (Fig. 1).

3 A Theory of Symptom Generation in the Brain

The brain can be seen as a complex adaptive system (Freeman et al. 2001; Sporns et al. 2004), similar to the world wide web, the climate, the economy, or an ant society (Holland 2014). In order to qualify as a complex adaptive system, a system has to fulfill two criteria (Amaral et al. 2004): (1) its structure follows a small world topology and (2) the system has to embed noise (Amaral et al. 2004). The reason for these criteria relates to the adaptiveness of the system. Network systems can be topologically structured in three ways (Bullmore and Sporns 2012). At one extreme, the network can have a lattice or regular topology, which means that every stimulus

will always result in exactly the same processing, which is both predictive and efficient but not adaptive whatsoever (Catania 2009). At the other extreme, a system can be completely random, which is inefficient and disadvantageous because every stimulus will always have a completely random response. An intermediate structure between regular and random has a small world topology, which permits flexibility and adaptiveness to changing environments through variability. As such, such a system can learn (Bassett et al. 2006; Karuza et al. 2016). The brain has a small world structure and thus fulfills the first criterion (Achard et al. 2006; Bassett et al. 2006; Bullmore and Sporns 2009; Eguiluz et al. 2005). The brain is also noisy, fulfilling the second criterion, but the noise is structured, generally following a power law distribution (G. Buzsaki and Mizuseki 2014), i.e. a pink (1/f) or brown ($1/f^2$) noise structure. This structured noise has an advantage that it has memory and can carry information, in contrast to white noise which is an unstructured completely random noise (Keshner 1982). Thus, such a system can learn, is flexible, while still maintaining stability. Since small worlds are adaptive, implanting electrodes in an adaptive system such as the brain makes intuitive sense as a means to modify its structure and thus its function. In a regular network or completely random system, the same concept would make little to no sense: a regular system would respond identical with or without stimulation and a random system would respond differently to every stimulus. One of the most important fundamental characteristics of every complex adaptive system is emergence: the whole is more than the sum of its components and cannot be predicted from its constituent parts. The whole has new properties that depend on the very specific connectivity between the parts. A collection of car parts is not a car. Only when all parts are put together (i.e., connected) in a very specific way does a functional car emerge. Yet, a simple car is complex but non-adaptive. It doesn't reconfigure itself based on a changing environment. Bees do, ants do, our brain does and so does the internet. Emergentism in the philosophy of mind supports the belief that consciousness is an emergent property of brain function, and by extension, that every thought, feeling, action is the consequence of specific connectivity patterns resulting from adaptive neuroplasticity, and every symptom or disease is the result of maladaptive plasticity (Fornito and Bullmore 2014). Thus, using TMS or transcranial electrical stimulation (tES), or implanting electrodes on the cortex should change or use the brain's connectivity in order to create a change in symptoms (De Ridder et al. 2017).

Neuroplasticity can operationally be defined as the brain's capacity to modify its structure and function in order to adjust to a changing environment. However, these adaptive brain changes can be both adaptive and maladaptive, i.e. can lead to learning how to adjust to a changing environment but can also lead to symptoms. Any changes in the external or internal environment lead to neuroplasticity, i.e. both deprivation of input or increased environmental stimulation. These adaptive changes can be modulated by adrenal and gonadal hormones, neurotransmitters, growth factors, certain drugs, and aging (Fuchs and Flugge 2014). This results in adaptive changes at multiple scales: molecular and neurobiochemical changes, synaptic adjustments, neurogenesis, connectivity, and network changes (Fuchs and Flugge 2014). From a clinical perspective, neuroplasticity can be visualized by structural

and functional brain imaging as changes in structure, activity, and connectivity. Changes in connectivity can be differentiated in structural, functional, and effective connectivity (Bassett et al. 2006; Lewis et al. 2009). Structural connectivity refers to anatomical changes in the brain (Hagmann et al. 2008), functional connectivity refers to co-activation of different brain areas (Friston 2011), and effective connectivity identifies from where to where the information flows in the brain, and can thus be seen as a form of directional functional connectivity (Friston 2011). This reorganization facilitates stability in constantly changing functional and effective connectivity networks, which results in changing emergent properties, like altered percepts, thoughts, emotions, actions, symptoms, etc.

3.1 Neuromodulation as Targeted Neuroplasticity

Neuromodulation and neurostimulation or brain stimulation are being used interchangeably. Yet, neuromodulation is becoming the preferred term because it doesn't carry the connotation of activation, which seems to be inherently implied with neurostimulation. Indeed, if the electrical or magnetic stimuli reach a brain area in which GABA receptors predominate, the clinical effect can be inhibitory. And neuromodulation means influencing brain activity (and connectivity), without suggesting the influence is excitatory.

Neuromodulation can be operationally defined as the induction of neuroplastic changes via targeted application of electrical, magnetic, sound (including ultrasound), optical or pharmacological stimuli. This is a broader definition than the one used by the International Neuromodulation Society: "Neuromodulation is technology that acts directly upon nerves. It is the alteration – or modulation – of nerve activity by delivering electrical or pharmaceutical agents directly to a target area" (http://www.neuromodulation.com/about-neuromodulation).

Neuromodulation can be performed on any part of the nervous system, from the peripheral nerve field, to specific peripheral or autonomic nerves, to the dorsal root ganglion (DRG), the spinal cord, the brainstem, or the brain. In brain stimulation, a distinction can be made between cortex stimulation and deep brain stimulation, but even here the terminology is not always uniform (De Ridder et al. 2017). For example, wire electrodes have been implanted inside the anterior cingulate gyrus and this procedure was called deep brain stimulation (DBS) of the anterior cingulate (Boccard et al. 2014), whereas paddle electrodes have been implanted onto the same target (De Ridder et al. 2016a, b; Leong et al. 2020) and this qualifies as cortex stimulation. The same can be said for deep brain stimulation of the subgenual anterior cingulate cortex (Brodmann area 25) for major depressive disorder. In essence, it is intracortical stimulation (with wire electrodes) of the subgenual anterior cingulate cortex, in which the electrodes are inserted inside the cortex rather than onto the cortex (Mayberg et al. 2005). The same terminological confusion exists for tinnitus. Whereas in most studies the electrodes are implanted extradurally or intradurally overlying the primary or secondary auditory cortex, respectively

(De Ridder et al. 2004, 2006a, 2007a, b, 2008, 2010, 2011b; Friedland et al. 2007; Litre et al. 2009), some patients have been treated with wire electrodes implanted inside the auditory cortex (Seidman et al. 2008). We will consider any form of cortical stimulation, whether intracortical or onto the cortex, as cortex stimulation, and deep brain stimulation as specifically targeting deep nuclei, rather than cortical structures.

3.2 Mechanism of Action of Cortex Stimulation

A better understanding of how cortex stimulation exerts its beneficial effect is essential; this requires a better understanding of the pathophysiological mechanisms involved in tinnitus generation. Symptoms are emergent properties resulting from maladaptive network activity, and not phrenological activity of one area in the brain (Barabasi et al. 2011; Fornito and Bullmore 2014; Fornito et al. 2015). Indeed, when patients in vegetative state, who have no conscious awareness, are presented with a sound, their auditory cortex is functionally and metabolically activated, yet there is no conscious sound perception (Boly et al. 2005). This suggests that activity in the auditory cortex per se is insufficient for conscious awareness, as has been discussed and demonstrated in the visual cortex (Crick and Koch 1995; Melloni et al. 2007). Only if the auditory cortex is functionally connected to a consciousness supporting network do auditory stimuli become accessible for conscious perception, analogous to what has been shown for painful stimuli (Demertzi et al. 2012; Laureys et al. 2000, 2002). These consciousness supporting networks consist of the self-representational default mode network and the attentional frontal parietal network (Akeju et al. 2014). Therefore it is plausible that the auditory cortex has to be functionally connected to the default mode network and frontoparietal attention network to permit conscious awareness of the presented stimulus.

It has been proposed that the presence of functional connections might be an essential requirement for transmitting the cortically applied stimulus into a wider network associated with the emergent property, i.e. tinnitus, that requires treatment (De Ridder et al. 2016a; Fox et al. 2014). When comparing success and failures to auditory cortex stimulation via implanted electrodes, the functional connectivity between the auditory cortex and the parahippocampus was critical for obtaining a beneficial result (De Ridder and Vanneste 2014). The importance of functional connectivity is similar to what was suggested for anterior cingulate implants (De Ridder et al. 2016a) and is in keeping with what has been shown for non-invasive brain stimulation in multiple neurological and psychiatric disorders (Fox et al. 2014). Indeed, it was shown that a lack of functional connectivity identified sites where stimulation was ineffective, and the sign of the correlation related to whether excitatory or inhibitory non-invasive stimulation was found to be clinically effective. These results suggested that resting-state functional connectivity may be useful for both optimizing treatment and identifying new stimulation targets (Fox et al. 2014).

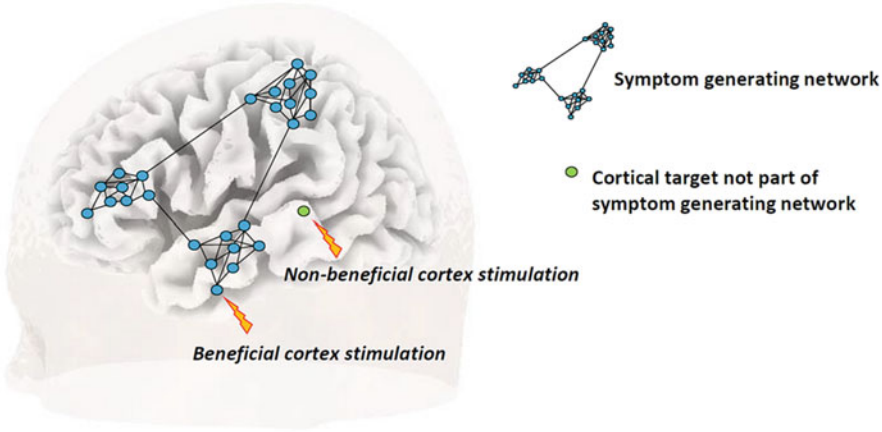

Fig. 2 The hypothesized mechanism of action of cortex stimulation (De Ridder et al. 2017). The electrode or non-invasive stimulation device has to be positioned at a cortical target where the symptom generating network reaches the brain surface. The stimulation is thought to change the functional connectivity of the network, thereby changing its topology and its related emergent property, i.e. the symptom

In summary, if the cortical target is part of a symptom generating network, the stimulation might be beneficial, whereas stimulation of a cortical target that is not functionally connected to the symptom generating network might not be beneficial (De Ridder et al. 2017) (Fig. 2).

3.2.1 Brain Stimulation Techniques in the Treatment of Tinnitus

Brain stimulation can be performed in two ways, non-invasively and invasively, in other words with or without surgery involved. Non-invasive brain stimulation encompasses transcranial magnetic stimulation (Barker 1999; Barker et al. 1985) and transcranial electrical stimulation (Moreno-Duarte et al. 2014; Paulus 2011; Vanneste et al. 2013a).

3.2.2 TMS for Treating Tinnitus

In 1985 it was demonstrated that it is possible to depolarize neurons in the brain using external magnetic stimulation (Barker et al. 1985). Unlike electrical stimuli, magnetic stimuli are not attenuated by the bone of the skull. The skull has 8–15 times the resistivity of soft tissues (Barker et al. 1985). Indeed, for electrical stimuli it has been calculated that 75% of the applied current is blocked by the skull (Voroslakos et al. 2018). Magnetic stimulation of the cortex is particularly effective because of the ability of the magnetic field to pass through high-resistance structures. TMS

produces a magnetic field of the same size as that of an MRI scanner, i.e. 1–3 Tesla, but that only lasts for about a millisecond (Walsh and Rushworth 1999). Because the magnetic field changes very rapidly (from zero to a very high value, then back to zero again in 1 ms), based on Faraday's law, it induces electrical currents in the area of the brain beneath the coil. Effectively, the magnetic field "carries" the electrical stimulus across the barrier of the skull and scalp into the brain (Ridding and Rothwell 2007). The induced current pulse lasts for about 200 μs and is similar in amplitude to that produced by a conventional stimulator applied directly to the surface of the brain (Ridding and Rothwell 2007). It is thought to activate the axons of neurons in the cortex and subcortical white matter, rather than the cell bodies of cortical neurons (which have a much higher threshold) (Ridding and Rothwell 2007) a longer pulse width (>1,000 μs) is required (Ranck 1975).

There are two important limitations of TMS: (1) the magnetic field falls off rapidly with distance from the coil surface, limiting direct stimulation to the superficial parts of the cerebral cortex immediately under the skull, and (2) the site of stimulation is not as focal as direct electrical stimulation of the brain with inserted electrodes (Ridding and Rothwell 2007), even though a 2 mm precision can be reached when neuronavigation is used (Schonfeldt-Lecuona et al. 2005), improving further to 1.3 mm when robotic neuronavigated positioning is used (Goetz et al. 2019). This reaches the intrinsic resolution of the structural and functional imaging itself: At 3 T, MRI machines can resolve details of the brain as small as 1 mm. That resolution can be as fine as 0.5 mm in a 7-T machine (Nowogrodzki 2018).

Magnetic coils can have different shapes: round, figure of eight, double cone coil, and H-coils. Round coils are relatively powerful but less focal. Figure-eight-shaped coils are more focal with a maximal current at the intersection of the two round components (Rossini et al. 2015). Double cone coils and H-coils penetrate deeper and can, for example, reach the anterior and posterior cingulate cortex (Carmi et al. 2019; Hayward et al. 2007). Due to the strong decline of the magnetic field with increasing distance from the coil, direct stimulation effects are limited to superficial cortical areas. However, stimulation effects can propagate to functionally connect remote areas: low frequency TMS can increase functional connectivity, whereas high frequency TMS can decrease functional connectivity (Fox et al. 2012).

Based on TMS studies of the motor cortex it has been shown through electromyographic recordings of the activated muscles that TMS has a double effect. A single TMS stimulus evokes a burst of activity that can last for 5–10 ms after the pulse (Day et al. 1987), which is followed by a period lasting 100–200 ms during which activity is suppressed (Ridding and Rothwell 2007). The effect of the TMS pulse is brain state dependent, as well as dependent on the position and orientation of the stimulation coil and the exact site of stimulation (Ridding and Rothwell 2007). For example, if a TMS stimulus is given during sleep, anesthesia or coma, the stimulus will only exert a local effect and will not spread through the brain, in contrast to an awake state (Massimini et al. 2005). Furthermore, TMS efficacy seems to be dependent on the stimulated person's genetic polymorphism. Certain genes such as BDNF and 5-HT(1A) influence the sensitivity to non-invasive stimulation, both TMS and tDCS (Cheeran et al. 2008; Malaguti et al. 2011). In view of the

interindividual anatomical variability of the brain, it has been suggested that the efficacy can be improved by using neuronavigated TMS based on the individual's brain structure obtained by structural or functional imaging (Fleming et al. 2012). The interindividual variability between the location of the sylvian sulcus and superior temporal sulcus that borders the auditory cortex is 1.5–2 cm (Steinmetz et al. 1990), suggesting that indeed a navigated approach makes sense. Concomitant intake of medication such as benzodiazepines (Deppe et al. 2020; Hunter et al. 2019), psychostimulants (Hunter et al. 2019), or neuroleptics (Hebel et al. 2020) can influence the effect of rTMS, but other medication such as anti-migraine medication does not seem to influence the treatment effect by TMS (Almaraz et al. 2010). For example, whereas concomitant benzodiazepines decrease the efficacy of TMS as a treatment for depression (Deppe et al. 2020; Hunter et al. 2019), concomitant psychostimulants increase the efficacy (Hunter et al. 2019).

Device related parameters determine the effect and side effects of TMS. The type of coil used also influences the reliability of the TMS (Fleming et al. 2012). Stimulation parameters such as stimulation frequency and amplitude influence the effect of the TMS as well (Speer et al. 2000).

Whereas single magnetic pulses only exert an immediate effect, the application of multiple pulses repetitively, called repetitive transcranial magnetic stimulation (rTMS), can have long-lasting effects that outlast the stimulation period.

In summary, many patient-dependent and device-related factors determine the outcome of transcranial magnetic stimulation (Table 1)

Table 1 Factors influencing TMS and tES effects

	TMS influencing factors	tES influencing factors
Person/patient dependent	Brain structure	Brain structure
	Brain state/function	Brain state/function
	History of activity in the stimulated Area	History of activity in the stimulated area
	Brain area	Brain area
	Genetic polymorphism	Genetic polymorphism
	Medication	Medication
	Skull-cortex distance	Soft tissue and bone structure
Device/protocol dependent	Coil type	Electrodes size
	Coil orientation	Electrodes positions
	Frequency	Frequency in tACS/tRNS
	Intensity	Intensity
	Stimulation pattern (burst/tonic)	Electrode polarity
	Duration	Duration
	Inter-train interval (intermittent/continuous)	
	Number of sessions	Number of sessions
	Interval between sessions	Interval between sessions
	Pulse form	

Table 2 Different effects of high (≥5 Hz) and low (1 Hz) frequency transcranial magnetic stimulation

	High frequency TMS	Low frequency TMS
Frequency	>5 Hz	1 Hz
Excitability	Increased	Decreased
PET metabolism	Increased metabolism	Decreased metabolism
EEG	Upper alpha and beta synchronization	Lower alpha and beta synchronization
Molecular	GABA and glutamate unchanged	GABA and glutamate increased
Plasticity	LTP-like	LTD-like

It is assumed that high frequency stimulation (HFS) and low frequency stimulation (LFS) have opposite effects (Table 2), as demonstrated by functional imaging, with HFS exerting an increased metabolism and LFS a decreased metabolism (Kimbrell et al. 1999; Speer et al. 2000). The effects on excitability and plasticity are opposite as well: whereas HFS seems to exert an increase in excitability (Pascual-Leone et al. 1994) and an LTP-like effect (Wang et al. 1996, 1999), LFS seems to generate a decrease in excitability (R. Chen et al. 1997) and an LTD-like effect (Wang et al. 1996, 1999). Furthermore, the effect on oscillatory activity is different (Brignani et al. 2008; Fuggetta et al. 2008; Paus et al. 2001), as is the effect on neurotransmitter release (Keck et al. 2001, 2002; Yue et al. 2009) (Table 2).

The widespread effect of TMS is beyond the area of stimulation (Kimbrell et al. 2002). This is mediated by transmission of the stimulus via structural connectivity (Momi et al. 2020) thereby influencing functional and effective connectivity (Shen et al. 2015). It has indeed been shown that low and high frequency stimulation exert a different effect on functional connectivity. Furthermore, TMS changes directional functional connectivity, in other words effective connectivity (Grefkes et al. 2010). By altering the functional and effective connectivity TMS can change the emergent property of the stimulated network and thereby exert its clinical effect.

The Regimen, Parameter, and Efficacy of TMS

rTMS has been used in tinnitus research in two different ways: single and repeated sessions.

Single Sessions

Single sessions of rTMS have been used for three reasons: (1) Pathophysiology and anatomy – to evaluate whether cortical areas that are identified on functional imaging are pathophysiologically involved in the generation of tinnitus, or just spurious associations. The assumption is that if rTMS can induce transient reductions in tinnitus perception by targeting the brain areas that are associated with tinnitus,

these areas are causally involved in the tinnitus generation. As such the temporal cortex (De Ridder et al. 2005; Eichhammer et al. 2003a; Plewnia et al. 2003), the frontal cortex (De Ridder et al. 2012; Vanneste and De Ridder 2012a), the parietal cortex (Vanneste et al. 2012), and the anterior cingulate cortex (Vanneste and De Ridder 2012b) have been shown to be implicated in the generation of tinnitus. (2) To verify if TMS could be a prognostic test to select proper candidates for more invasive permanent solutions such as cortical brain implants (De Ridder et al. 2004, 2006a, 2011c, 2016a). (3) To delineate optimal stimulation parameters (De Ridder et al. 2005; Schoisswohl et al. 2019; Kreuzer et al. 2017) that can be employed for multiple rTMS sessions as a possible treatment.

Repeated Sessions

Repeated sessions of low frequency rTMS of the temporal (auditory) cortex have been proposed as a novel treatment approach for tinnitus based on the assumption that tinnitus is related to increased neuronal activity in the auditory cortex (Eichhammer et al. 2003b). A large number of studies have looked at low frequency TMS for treatment of tinnitus, with inconclusive results (Schoisswohl et al. 2019), likely due to the high variability and the fact that women respond better than men to rTMS, as shown in a meta-analysis (Lefebvre-Demers et al. 2020). Whereas most meta-analyses do show an improvement for tinnitus associated suffering (J. J. Chen et al. 2020; Lefebvre-Demers et al. 2020; Liang et al. 2020; Soleimani et al. 2016), other meta-analyses do not (Dong et al. 2020). Comprehensive analyses of the literature therefore identify a possible therapeutic efficacy in terms of reduction of tinnitus suffering, but the effect at clinical level is usually partial and temporary (Lefaucheur et al. 2020), with a THI improvement of about 7–8 points (Liang et al. 2020), which is the minimum for clinical efficacy (Zeman et al. 2011), lasting up to 6 months (Liang et al. 2020). Before the publication of the recent meta-analyses already a level C recommendation (possible efficacy) using evidence-based guidelines was proposed (Lefaucheur et al. 2014), stating that low frequency (1 Hz) rTMS of the left temporoparietal cortex in tinnitus is possibly efficacious for tinnitus (Lefaucheur et al. 2014). A more recent follow-up study confirmed these results (Londero et al. 2018)

Apart from the variability in study design, and the fact that women respond better than men, also different stimulation parameters are being used. A recent systematic analysis of the relationship between stimulation parameters and treatment outcome revealed a higher success rate for lower stimulation intensities (Schoisswohl et al. 2019), confirming the evidence based guidelines (Lefaucheur et al. 2014).

More recently, in an attempt to reduce the individual variability, a personalized approach has been investigated, taking into account the heterogeneity of tinnitus generators in the brain, by performing a stimulation protocol tailored to the individual patient. In a pilot study this concept was explored, by delivering rTMS at various frequencies over the left and right dorsolateral prefrontal (DLPFC) or temporoparietal (TPC) cortex in a preliminary test session to select the type of

protocol subsequently applied for several days (Kreuzer et al. 2017). The personalized protocol yielded a larger benefit than the standard protocol (20 Hz-rTMS over left DLPFC followed by 1 Hz-rTMS over the left TPC). This suggests that a "tailored" rTMS protocol may be clinically more beneficial.

In summary, rTMS likely provides benefit in the treatment of tinnitus. However, if rTMS is to become routine clinical practice, it is essential to look for mechanisms that may boost or potentiate the therapeutic effect. One such way is to enhance the efficacy of rTMS pharmacologically, e.g. by adding psychostimulants or ketamine. It has been shown that psychostimulants improve the benefit of rTMS for depression (Hunter et al. 2019). Another approach could be to test ketamine enhanced rTMS, which in a preliminary trial in the treatment of depression, a frequent co-morbidity in tinnitus, shows it is feasible and exerts long-term (2 years) beneficial effect (Best et al. 2019).

Thus, rTMS may benefit especially those patients who severely suffer from the tinnitus, expressing anxiety or depression.

Reports of side effects were rare. In a meta-analysis of rTMS for tinnitus, side effects consisted of headache, discomfort at the area of stimulation, muscle twitching, neck contractions and worsening of tinnitus (Dong et al. 2020). No seizures were reported. This could be related to the fact that TMS delivered within published guidelines in individuals without risk factors results in fewer than 1 seizure per 60,000 sessions (Lerner et al. 2019).

tES for Treating Tinnitus

Three different versions exist of tES, depending on how the current is delivered to the brain (Fig. 3): transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS), which is a special version of tACS (Paulus 2011; Vanneste et al. 2013a).

3.2.3 Transcranial Direct Current Stimulation (tDCS)

Conventional tDCS

Medical use of direct electric current to the scalp has a long history. In 43–48 A.D., Scribonius Largus (the physician of Roman Emperor Claudius) reported the treatment of pain by placing a live torpedo fish – delivering a strong direct current – over the scalp (Fodstad and Hariz 2007). In the eleventh century, Ibn-Sidah suggested the placement of a live electrical catfish on the frontal bone for the treatment of patients suffering from epilepsy (Kelloway 1946). In the eighteenth century, with the introduction of the electrical battery by Galvani (Galvani 1791, 1797), it was recognized that electrical stimuli of varying duration can evoke different physiological effects (Zago et al. 2008). In honor of Galvani, direct current stimulation is often called Galvanic stimulation. One of the first clinical applications of galvanic currents was in the nineteenth century when Aldini (Aldini 1804) (Galvani's nephew) and other

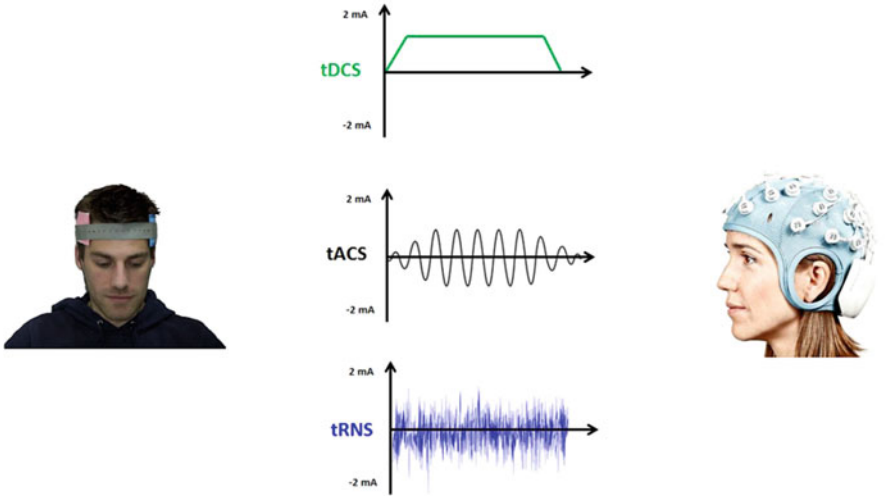

Fig. 3 Different forms of tES: tDCS delivers direct current, tACS and tRNS deliver alternating current. tES can be applied with two electrodes or more. When more electrodes are used it is called high-definition transcranial electrical stimulation (HD-tES)

researchers (Arndt 1869) used transcranial electrical simulation to treat melancholia and depression. In the 1960s and 1970s, this method had a brief comeback (Lippold and Redfearn 1964; Redfearn et al. 1964), with a more sustained revival at the turn of the millennium (Guleyupoglu et al. 2013).

Conventional tDCS uses one anode electrode and one cathode electrode on the scalp to modulate a particular brain area by inducing a controlled electrical current which flows from the anode to the cathode. Due to the high electrical resistance of the skull (Barker et al. 1985), only 25 (to 50%) of the transcranially applied direct current reaches the brain, the rest being shunted through the extracranial soft tissues, as demonstrated by calculations on realistic head models, validated both in animal (Rush and Driscoll 1968; Voroslakos et al. 2018) and human (Dymond et al. 1975; Voroslakos et al. 2018) experiments.

tDCS modulates the cellular membrane potential facilitating or inhibiting spontaneous neuronal activity (Moreno-Duarte et al. 2014; M. A. Nitsche et al. 2008). Anodal stimulation will produce inward current flow, resulting in depolarization of pyramidal cortical neurons and apical dendrite hyperpolarization, while cathodal stimulation will typically produce outward current flow resulting in somatic hyperpolarization of pyramidal cortical neurons and apical dendrite depolarization (Radman et al. 2009; Zaghi et al. 2010a). The depolarization under the anode will result in an increase of firing and excitability under the anode, whereas the firing rate and excitability are decreased under the cathode (Bindman et al. 1964; M. A. Nitsche and Paulus 2001).

However, tDCS often results in a delayed clinical effect (Fujiyama et al. 2014; Stramaccia et al. 2015), which cannot be explained by the immediate effect of tDCS

on pyramidal or interneuron cell firing. Therefore, two other mechanisms have been proposed to be involved in tDCS: glial and stem cell modulation. One type of glial cells, astrocytes are possibly modulated by tDCS (Monai and Hirase 2018; Ruohonen and Karhu 2012). Astrocytes control the formation, maturation, function (and elimination) of synapses through various secreted and contact-mediated signals (Clarke and Barres 2013) and can thereby regulate neural circuit development and function (Clarke and Barres 2013). Furthermore, another type of glial cell, microglia, who prune synapses, might also be involved (Mishima et al. 2019). It has indeed been shown that tDCS activates microglia both under anode and cathode (Rueger et al. 2012). Thus, glial cells might be modulated by tDCS resulting in synapse formation and/or elimination, which takes time and can therefore better explain the delayed effects of tDCS.

Furthermore, microglial and astrocytic activation by tDCS may have a neuroimmunomodulatory effect (Goerigk et al. 2021) by altering the expression of immune-mediating genes (Rabenstein et al. 2019).

But apart from modulating neurons, both pyramidal and interneurons and glial cells, both astrocytes and microglia, tDCS could exert its delayed effects via stem cell activation. Indeed, tDCS seems to recruit proliferating neural stem cell under the cathode (Rueger et al. 2012) thereby opening the possibility of regenerative capacities for tDCS and an even more delayed clinical effect of tDCS. The neurogenesis and improved rehabilitation effects of tDCs have been shown in animal models (Zhang et al. 2020).

The effects of tDCS depend on a lot of factors, both patient-related and device-related factors (Table 1). Some factors cannot be controlled, such as the resistance of several cephalic structures including the skin, skull, blood vessels, and brain tissue (Brunoni et al. 2012; Medeiros et al. 2012; Moreno-Duarte et al. 2014; Wagner et al. 2007). Device related factors include (1) polarity of the electrodes, (2) size of the electrodes, (3) the position of the electrodes, (4) the intensity of stimulation or the amount of current delivered (in mA), and (5) the duration of the stimulation (varies between 20–40 min in most studies) (Brunoni et al. 2012; Moreno-Duarte et al. 2014; Nitsche et al. 2015; Wagner et al. 2007). By varying these tDCS parameters, stimulation protocols can be customized to a certain extent to achieve the desired direction, strength, focality, and duration of effects on cortical activity and excitability (Brunoni et al. 2012; Nitsche et al. 2015).

In general, no serious adverse events are seen by tDCS application, as evaluated in more than 10,000 subjects investigated in the contemporary tDCS literature (1998–2014) (A. R. Brunoni et al. 2011; Fregni et al. 2015). The safety of tDCS depends on the strength of current, the size of the electrodes, the contact media and the duration of the stimulation (Iyer et al. 2005; Poreisz et al. 2007).

There have been no reports of a serious adverse effect or irreversible injury across over 33,200 sessions and 1,000 subjects with repeated sessions protocols in human trials ($\leq$40 min, $\leq$4 mA, $\leq$7.2 C). tDCS has not produced any severe side effects (Bikson et al. 2016). The threshold for adverse events has been investigated in a safety study in rats, where the current density needed to induce brain damage in rats was found to be at least 100-times higher than the current density used in tDCS trials

(Liebetanz et al. 2009). The most frequent side effects include a tingling sensation during stimulation, predominantly under the anode (A. R. Brunoni et al. 2011; Poreisz et al. 2007), an itching sensation (A. R. Brunoni et al. 2011; Fertonani et al. 2015; Poreisz et al. 2007) right under the electrodes, headache (A. R. Brunoni et al. 2011; Poreisz et al. 2007), moderate fatigue (Poreisz et al. 2007) and burning sensation (A. R. Brunoni et al. 2011; Fertonani et al. 2015; Poreisz et al. 2007).

tDCS has been shown to modulate not only the areas underlying anodal and cathodal stimulation (Antal et al. 2004; Brunoni et al. 2012; Dieckhofer et al. 2006; Matsunaga et al. 2004; Zaehle et al. 2011), but also functional and effective connectivity (Alon et al. 2011; Chib et al. 2013; Keeser et al. 2011a, b; Meinzer et al. 2012, 2013; Pena-Gomez et al. 2012; Polania et al. 2011, 2012b; Stagg et al. 2013; Vanneste and De Ridder 2011; Weber et al. 2014), thereby possibly changing the emergent property of the symptom-generating network (Luft et al. 2014). These functional and effective connectivity changes permit modulation of areas beyond the effects of tDCS under the stimulation electrodes (Lang et al. 2005).

The effect of tDCS has been investigated on the physiology of the motor cortex (Brunoni et al. 2012), the visual cortex (Antal et al. 2004), the somatosensory cortex (Dieckhofer et al. 2006; Matsunaga et al. 2004), and the auditory cortex (Zaehle et al. 2011).

Single sessions of tDCS, tACS, and tRNS have been used for elucidating the involvement of specific brain networks in tinnitus pathophysiology and repeated sessions have been investigated as a potential therapeutic approach for tinnitus patients. In comparison with the large number of studies performed by rTMS, tES has been investigated less frequently and most of these studies focused on the effects of single sessions of tDCS. The targets for stimulation have been either the auditory cortex, the temporoparietal cortex or the dorsolateral prefrontal cortex.

Initial studies demonstrated transient tinnitus reduction for anodal, but not cathodal tDCS over the temporoparietal cortex, but this effect could not be consistently replicated by further studies (Yuan et al. 2018). Thus, the most promising approaches in single session studies over the auditory cortex were left anodal tDCS and bilateral tRNS. Both approaches were tested as a potential treatment in controlled studies, in which repeated sessions were applied, but unfortunately the results were disappointing, as there was no superiority of tDCS over sham stimulation (Lefaucheur et al. 2017) or a control treatment (Kreuzer et al. 2019) respectively.

In addition to the studies focusing on temporal and temporoparietal areas, several studies have targeted the DLPFC, mostly by using a bifrontal electrode montage. A single session of bifrontal anode right/cathode left tDCS reduced tinnitus intensity or distress in about one third of the patients, whereas anode left/cathode right tDCS had no effect (Vanneste et al. 2010). In a further study, the same group investigated whether the efficacy of bifrontal tDCS can be increased, if the electrode polarity is informed by gamma connectivity in EEG measurements (De Ridder and Vanneste 2012), but this was not the case. The bifrontal tDCS protocol with anode right and cathode left was also investigated as therapeutic approach with repeated sessions in

uncontrolled pilot studies, which revealed preliminary promising effects (Frank et al. 2012; Shekhawat and Vanneste 2018).

A meta-analysis demonstrates that tDCS can improve tinnitus distress, but not loudness perception in tinnitus patients (Wang et al. 2018a), confirming an earlier meta-analytic study (Song et al. 2012). Yet, another meta-analysis found no benefit (Lefebvre-Demers et al. 2020). In stark contrast, a recent network meta-analysis revealed that from all non-invasive neuromodulatory approaches, cathodal tDCS over the left DLPFC combined with tRNS over the bilateral auditory cortex was associated with the greatest improvement in tinnitus severity and quality of life compared with the controls (J. J. Chen et al. 2020)

tDCS has also been combined with different forms of auditory stimulation (Lee et al. 2017; Shekhawat et al. 2014; Teismann et al. 2014). However tDCS could enhance neither the therapeutic effects of hearing aids on tinnitus complaints (Shekhawat et al. 2014) nor the effects of notched music training, a specific form of individualized auditory stimulation (Teismann et al. 2014).

In summary, tDCS effects on tinnitus are promising but also variable, analogous to what is seen in rTMS. Due to the many influencing factors this is not surprising, and further development of the more promising tDCS approaches is mandatory.

High-Definition tDCS

HD-tDCS has been recently introduced to improve the spatial accuracy, by using arrays of smaller "high-definition" electrodes, instead of the two large pad electrodes of conventional tDCS (Datta et al. 2009; Dmochowski et al. 2011; Guleyupoglu et al. 2013; Heimrath et al. 2015; Shekhawat et al. 2015; Villamar et al. 2013) (Fig. 3, right image). For high-definition tDCS, studies using 4 × 1 ring configuration with intensities up to 2 mA for up to 20 min have demonstrated its tolerability in both healthy (Borckardt et al. 2012; Kuo et al. 2013; Nikolin et al. 2015) and patient populations (Donnell et al. 2015; Villamar et al. 2013). No significant differences were found between 2 and 3 mA, suggesting the safety limits can be extended to 3 mA (Reckow et al. 2018). High-definition tDCS has a higher spatial resolution which allows more focal targeting (Borckardt et al. 2012). Furthermore, HD-tDCS permits simultaneous multifocal stimulation, permitting to develop network stimulation (Ruffini et al. 2014).

HD-tDCS has been used in tinnitus, with higher benefit associated with longer stimulation duration and higher stimulation intensities (Shekhawat et al. 2015), but no clinical difference has been noted between the benefit of conventional and HD-tDCS (Jacquemin et al. 2018).

3.2.4 Transcranial Alternating Current Stimulation (tACS)

The main mechanisms by which tACS influences brain physiology have been attributed to frequency-specific entrainment, i.e. phase alignment of endogenous

brain oscillations to externally applied oscillating electric currents (Thut et al. 2011; Witkowski et al. 2015; Zaehle et al. 2010), and modulation of spike-timing dependent plasticity (Polania et al. 2012a; Vossen et al. 2015). It has been shown that alpha-tACS enhances the individual alpha frequency (Zaehle et al. 2010), but the functional effect depends on background activity (Kanai et al. 2008). tACS boosts motor excitability at 140 Hz (Moliadze et al. 2010) and decreases excitability at 15 Hz (Zaghi et al. 2010b). It has been demonstrated that tACS can influence perception (Kanai et al. 2008), memory (Marshall et al. 2006), motor function (Brignani et al. 2013), and higher-order cognition (Santarnecchi et al. 2013).

tACS of the auditory cortex does not seem to improve tinnitus (Vanneste et al. 2013a, b), neither in single nor in multiple sessions (Claes et al. 2014).

3.2.5 Transcranial Random Noise Stimulation (tRNS)

tRNS is a modification of tACS (see Fig. 3). The tRNS device generates alternating current, which follows a white noise structure, i.e. all frequencies (0.1–640 Hz) have equal power, with a Gaussian amplitude structure. Low frequency tRNS is defined as 0.1–100 Hz random noise stimulation, whereas high frequency tRNS is limited to frequencies between 100 and 640 Hz. tRNS has a higher perception threshold than tDCS (1,200 μA vs 400 μA) (Ambrus et al. 2010).

Importantly, both for tACS and tRNS low and high amplitudes seem to have an opposite effect. Both tACS and HF-tRNS at 0.4 mA are inhibitory but switch to excitatory modulation at 1 mA (Moliadze et al. 2012).

High frequency tRNS seems to increase excitability (Terney et al. 2008), and its mechanisms of action are still unknown. It could theoretically increase excitability by a stochastic resonance effect mediated through repeated subthreshold stimulations (Terney et al. 2008) that prevent homeostasis of the system (Fertonani et al. 2011). Another possible working mechanism is through desynchronization of (pathological) rhythms (Paulus 2011), but none of the abovementioned mechanisms of action have been proven. tRNS modulates perception (Romanska et al. 2015), memory (Mulquiney et al. 2011), learning (Herpich et al. 2015; S. Tyler et al. 2015), and other cognitive functions (Cappelletti et al. 2013) possibly by NMDA-receptor independent but sodium-channel blocker and benzodiazepines sensitive plasticity (Chaieb et al. 2015).

Low and high frequency tRNS have been clinically used for tinnitus, both with beneficial results on loudness perception and distress (Joos et al. 2015; Vanneste et al. 2013a). In a head to head comparison of tDCS, tACS, and tRNS, it was shown that tRNS was the only efficacious transcranial electrical stimulation for tinnitus suppression (Vanneste et al. 2013a). Interestingly, both low and high frequency tRNS were beneficial but the combined low + high frequency tRNS was inefficacious for tinnitus suppression (Joos et al. 2015). In a further pilot study tACS and tRNS, respectively, were applied bilaterally over the temporal cortices. This study revealed transient suppression of tinnitus for tRNS, but not for tACS. Furthermore, repeated sessions were more beneficial than single sessions (Claes et al. 2014).

Yet, when performing daily sessions of HF-tRNS, in contrast to the more traditional 2–3 weekly sessions, no benefit was obtained (Kreuzer et al. 2019), suggesting that too much stimulation may be counterproductive. Adding bifrontal DLPFC tDCS to auditory cortex tRNS was superior to only auditory cortex tRNS (To et al. 2017). And this multisite tRNS approach has indeed shown promise by confirmatory studies (Mohsen et al. 2018, 2019).

3.2.6 Vagus Nerve Stimulation (VNS) and Transcutaneous Vagal Nerve Stimulation (tVNS)

The combination of auditory stimulation with vagal stimulation via implanted electrodes has demonstrated highly impressive results in an animal model of tinnitus (Engineer et al. 2011). Based on the rationale that vagal stimulation renders the simultaneously presented sounds more salient, the combined treatment almost completely reversed neurophysiological and behavioral signs of tinnitus, which was not the case with auditory stimulation alone. In subsequent human pilot studies the efficacy of the invasive VNS + auditory stimulation treatment was confirmed (De Ridder et al. 2014b, 2015a; R. Tyler et al. 2017) albeit the effects were clearly less pronounced than in animals. Furthermore, a study in which VNS stimulation was performed via implanted electrodes to treat epilepsy found equally good tinnitus attenuating results (Wichova et al. 2018). But since these patients did not receive the paired auditory stimulation, the relevance of the paired auditory stimulation is yet unclear.

In these abovementioned studies, vagus nerve stimulation has been performed by the implantation of a neurostimulation device connected to an electrode located along the cervical branch of the vagus nerve. However, recently a non-invasive approach for stimulating the vagus nerve has been developed. This so-called transcutaneous vagus nerve stimulation (tVNS) takes advantage of the fact that the vagus nerve has an afferent branch that is located medially to the tragus at the entry of the acoustic meatus and that innervates the external ear canal. For reliable stimulation of the auricular branch of the vagal nerve specific devices have been developed that provide electrical stimulation. Analogous to invasive VNS, stimulation of the vagus with tVNS is typically performed on the left side to minimize potential effects on cardiac rhythm (Kreuzer et al. 2012). In a pilot study the feasibility and safety of 6 months of tVNS were investigated in patients with tinnitus. The stimulation was well tolerated, but did not lead to a relevant improvement of tinnitus complaints (Kreuzer et al. 2014). However, there was a trend towards a reduction of depressive symptoms in treated patients (Kreuzer et al. 2014). Further support for a tVNS induced stress attenuation comes from another study (Ylikoski et al. 2017). In this study the effect of tVNS on heart rate activity was investigated in 173 tinnitus patients and it was found that tVNS can attenuate the sympathetic activation of tinnitus patients

In two small pilot studies tVNS was combined with auditory stimulation, and these studies showed promising effects on tinnitus (Lehtimaki et al. 2012; Shim et al. 2015).

These findings are in line with the animal data (Engineer et al. 2011), where the pairing of vagus nerve stimulation with tones excluding the tinnitus frequency was critical for the reduction of tinnitus, whereas vagal nerve stimulation alone had no effect on tinnitus related behavior.

But tVNS has also been performed without auditory pairing, also demonstrating some benefit (Suk et al. 2018), again questioning the relevance of the paired sound presentation.

3.2.7 Bimodal (Auditory and Sensory) Stimulation

Central auditory circuits are influenced by the somatosensory system, a relationship that may underlie tinnitus generation (Basura et al. 2015; Dehmel et al. 2008; Dehmel et al. 2012; Shore 2005; Shore et al. 2008; Stefanescu et al. 2015).

Bi- or multimodal stimulation is presumably more effective for the induction of neuroplastic effects than unimodal stimulation, as synchronicity of events is an important criterion for the induction of neuroplastic effects. This was first expressed by Donald Hebb many decades ago: "Neurons that fire together, wire together" (Hebb 1949). Unimodal stimulation can induce activity-dependent neuroplastic changes such as long-term potentiation or long-term depression, whereas bimodal stimulation provides the additional opportunity to induce alterations of neuronal activity by the mechanisms of spike-timing dependent plasticity (Basura et al. 2015). However, the experimental investigation of bimodal stimulation is more challenging, because of the much larger parameter space.

In recent years different approaches of bi- or multimodal stimulation have been proposed for the treatment of tinnitus. Apart from the combination of vagal stimulation, tDCS and rTMS with auditory stimulation, the combination of auditory stimulation and somatosensory stimulation has been investigated. The somatosensory stimulation was either performed via the trigeminal nerve or via C2 afferents. The combined auditory and somatosensory modulation is motivated by an increasing understanding of the relevance of the somatosensory system for tinnitus pathophysiology (Shore et al. 2016). The clinical phenomenon, that many patients can modulate their tinnitus by face or neck movements, can be explained by the interaction between somatosensory and auditory afferents on the level of the dorsal cochlear nucleus (Levine 1999). This knowledge in turn motivated two different approaches of combined somatosensory and auditory stimulation.

One approach aims at the modulation of activity in the central auditory pathway by exerting an inhibitory effect on the level of the dorsal cochlear nucleus. The somatosensory and auditory stimuli were presented at specific intervals, derived from basic neurophysiological studies in animals describing stimulus timing dependent plasticity in the dorsal cochlear nucleus (Marks et al. 2018). These findings were translated into a clinical pilot trial with 20 patients, in which the combination of sounds with transcutaneous electrical stimulation of the C2 nerve at the level of the neck was applied over 28 days. The bimodal treatment reduced tinnitus loudness and intrusiveness, whereas the control condition (auditory stimulation alone) did not

deliver benefit (Marks et al. 2018). Yet, the effect was short-lasting, especially for loudness perception, which did not outlast the 3-week bimodal stimulation period, and the distress improvement only lasted for 3 weeks.

In another approach, sounds are simultaneously applied in combination with electrical stimulation of the trigeminal nerve at the level of the tongue (Conlon et al. 2019; D'Arcy et al. 2017). This approach is based on the idea that tinnitus is caused by auditory deafferentation and that bimodal stimulation might compensate the auditory deafferentation by providing stimuli over the somatosensory system. The combined application of sounds and electrical stimulation of the tongue, for a period of 3 months, was investigated in two large trials (with more than 500 patients) (Conlon et al. 2020). Similar to other studies the bimodal stimulation resulted in a clinical benefit for tinnitus distress, but data for loudness improvement were not provided. In contrast to the C2-auditory bimodal stimulation study, long-lasting results (1 year) were obtained (Conlon et al. 2020).

3.2.8 Invasive Brain Stimulation for Tinnitus

Auditory Cortex Stimulation

The procedure is based on a pathophysiological model that the auditory cortex is involved in a pathologically functioning neuronal network that generates tinnitus and that interference with this network activity by auditory cortex stimulation can alleviate tinnitus and follows a four-step rationale (De Ridder et al. 2012b):

1. Tinnitus is related to increased activity in the auditory and frontal cortex.
2. The anatomical location of the tinnitus generator can be determined by fMRI (De Ridder et al. 2011b).
3. The abnormal neuronal activity can be modulated by neuronavigated TMS resulting in transient tinnitus reduction (De Ridder et al. 2004).
4. If TMS can transiently suppress the tinnitus, electrical stimulation through an electrode implanted on the same area can provide permanent tinnitus suppression (De Ridder et al. 2004, 2006a, 2007a, 2011c).

Multiple small and one larger series of patients with auditory cortex electrodes have been published. A series of 43 patients with severe treatment resistant tinnitus (grade 3 and 4 tinnitus according to the tinnitus questionnaire (Goebel and Hiller 1994)) were implanted with a cortical electrode overlying the secondary auditory cortex (De Ridder et al. 2011c). Surgical eligibility was based on 2 positive TMS sessions. Although all patients reacted to TMS, 1 out of 3 patients did not respond to the cortical stimulation with tonic stimuli after implantation. Among the responders to cortical stimulation there was an average decrease in the perceived tinnitus loudness of 51.3%. There was a significant but weak positive correlation ($r = 0.34$, $p < 0.05$) between the amount of the suppression effect from the test TMS and cortical stimulation after implantation, even though TMS could not predict who would and who would not respond to the implant (De Ridder et al. 2011c).

This may be due to the fact that the mechanism of action of TMS and implanted electrodes is different.

When switching tonic stimulation to burst stimulation (De Ridder et al. 2010) half of the non-responding patients demonstrated change, thereby improving the total response rate from 1 in 3 to 2 out of 3 patients. Burst stimulation was specifically superior to tonic stimulation for suppressing noise-like tinnitus (De Ridder et al. 2011c), analogous to what has been described for TMS (De Ridder et al. 2007c). In contrast to TMS, where the suppression effect decreases with longer tinnitus duration, no correlation was found between the effect of electrical cortical stimulation and tinnitus duration for the same study population, again suggesting that electrical cortical stimulation acts on tinnitus by a different mechanism than TMS.

Treatment effects also depended on tinnitus type. Pure tone tinnitus could be improved more than narrow band noise or the combination of pure tone and narrow band noise, and unilateral tinnitus better than bilateral tinnitus. This surgical neuromodulatory approach of the auditory cortex has been repeated by other centers. A French case study obtained persisting 65% tinnitus reduction in a women using an fMRI based extradural auditory cortex implant (Litre et al. 2009, 2010). Another study of eight patients using a similar technique but different hardware found no permanent tinnitus suppression (Friedland et al. 2007). Temporary effects on tinnitus perception were observed in six out of the eight patients. However, tinnitus distress decreased slowly over time, even without suppression of tinnitus intensity. An electrode with only two contacts was used which limits the way the electrodes can be programmed.

In four patients an intradural electrode on the primary auditory cortex was inserted in the Sylvian fissure, stimulating gray matter of the primary auditory cortex (De Ridder et al. 2004, 2006a). In two patients the purpose was to obtain stabilization of tinnitus suppression, because the stimulus parameters had to be reprogrammed every 2–3 days. In both patients the intradural positioning resulted in a stabilized suppression of their tinnitus.

Another approach has been proposed, inserting a wire electrode in the white matter beneath layer 6 of the primary auditory cortex. This has been performed successfully, using magnetic source imaging for target localization, resulting in tinnitus suppression (Seidman et al. 2008). Interestingly, in patients with tinnitus, intracortical stimulation does not generate a sound percept associated with the delivered current. This is in contrast to patients with epilepsy, in whom intracortical electrical stimulation within Heschl's gyrus does generate sound percepts, the loudness of which correlates with the delivered amplitude (Donovan et al. 2015).

From a mechanistic point of view it was shown that the success of the auditory cortex implant critically depended on activity in the parahippocampal area, which is related to auditory memory (De Ridder et al. 2006b). Responders to the implant were characterized by high beta3 and gamma band activity in the parahippocampal area, even though the electrodes were overlying the auditory cortex. Only those patients who had functional connections between the area of the implant, i.e. the auditory cortex and the parahippocampal area, benefited from the auditory cortex implant (De Ridder and Vanneste 2014).

Multisite stimulation may benefit tinnitus perception, analogous to what is noted in non-invasive neuromodulation. In a partial responder to auditory cortex implantation, complete resolution of the pure tone component of his tinnitus was obtained, without any beneficial effect on the noise-like component of the tinnitus, even after switching to burst stimulation (De Ridder and Vanneste 2015). After an initial successful treatment of his noise-like component with transcutaneus electrical nerve stimulation, a wire electrode was inserted subcutaneously and connected to his internal pulse generator. With the dual stimulation his pure tone tinnitus remains abolished after 5 years of stimulation and his noise-like tinnitus is improved by 50%, from 8/10 to 4/10. This case report suggested that multitarget stimulation might be better than single target implantation (De Ridder and Vanneste 2015).

In some case reports implants were also performed on the dorsolateral prefrontal cortex (De Ridder et al. 2012b), anterior cingulate cortex (De Ridder et al. 2016a) and parahippocampal area (De Ridder et al. 2012b) following the same 4-step approach described above. In the two anterior cingulate implants one patient responded whereas another patient did not benefit from the electrode insertion. The responder also had increased functional connectivity to a tinnitus distress network in contrast to the non-responder (De Ridder et al. 2016a). This suggests that analogous to non-invasive stimulation, brain stimulation via implanted electrodes requires functional connectivity to carry the delivered stimulus throughout the symptom generating network (Fox et al. 2014).

Deep Brain Stimulation

Deep brain stimulation (DBS) has been performed as well, in an attempt to treat tinnitus. This was based on a case report of a woman who became tinnitus-free after a stroke in the locus coeruleus (LC) area of the caudate nucleus while undergoing DBS for Parkinson's disease (Larson and Cheung 2013). Initially, tinnitus was evaluated in patients in whom DBS was performed to alleviate movement disorders. In a first study, tinnitus loudness reductions were found in 4/7 patients, of which most clearly by ventral intermediate nucleus (VIM) stimulation for tremor [256]. In another observational study in six patients with comorbid tinnitus, the concomitant effect on tinnitus perception was evaluated: In five participants where the DBS lead tip traversed area LC, tinnitus loudness in both ears was suppressed to a nadir of level 2 or lower on a 0–10 rating scale. In one subject where the DBS lead was outside area LC, tinnitus was not modulated (Cheung and Larson 2010; Larson and Cheung 2011).

A large multicenter study evaluated the clinical impact of DBS on tinnitus in patients undergoing DBS for movement disorders: the THI tinnitus questionnaire improved only after subthalamic nucleus stimulation [254], suggesting this target may be selected to treat tinnitus related distress. After encouraging results from these observational studies, a phase I study was performed targeting the caudate nucleus as goal to treat severe intractable tinnitus. Tinnitus distress measures improved for three of five patients and one patient had a profound loudness suppression (7.8 points

improvement on NRS). This suggests that the caudate nucleus may be a target worthwhile of further exploration, using different stimulation designs and different electrode configurations. Even though the target space may be narrowed down, the stimulation parameter space for optimal improvement is still large.

4 Conclusion

In the last decades, neuroscientific research has contributed to an increasingly better understanding of the pathophysiological mechanisms that underlie the generation and maintenance of tinnitus. Based on this knowledge, a large variety of different neuromodulatory interventions have been developed.

Most studies for rTMS have targeted the temporal, temporoparietal, and the frontal cortex. Recent meta-analyses have shown that rTMS may be beneficial for tinnitus, improving the suffering, but not the loudness perception. The recent rTMS European guideline (Lefaucheur et al. 2020) recommended that repeated sessions of low frequency-rTMS of the temporoparietal cortex of the left hemisphere or contralateral to the affected ear have a *possible effect* in tinnitus. Many questions remain concerning the use of this technique in everyday practice, such as what could be the optimal treatment target(s) protocol and what could be the role of individual susceptibility to auditory cortex stimulation.

Different forms of transcranial electrical stimulation (tDCS, tACS, tRNS), applied over the frontal and temporal cortex, have been investigated in tinnitus patients. Recent meta-analysis suggests that also tES may be beneficial in chronic tinnitus, and that especially the combination of bifrontal tDCS and auditory cortex tRNS may attenuate tinnitus. Cortex and deep brain stimulation with implanted electrodes have shown benefit but there is insufficient data to support their routine clinical use.

Two decades of research in non-invasive neuromodulatory interventions in tinnitus have yet to result in regular clinical routine use. The most recent meta-analyses do suggest that a transition from experimental to clinical applications of non-invasive stimulation may be in view. Furthermore, research has revealed important insights in the pathophysiology of tinnitus, in particular in the relevance of non-auditory brain areas as well in the heterogeneous nature of tinnitus. Recently, bimodal stimulation approaches have also revealed promising results and it appears that targeting different sensory modalities in temporally combined manners may also be a promising avenue.

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