Aud Vest Res (2016);25(2):89-97.

REVIEW ARTICLE

Noninvasive neuromodulation of tinnitus with transcranial current stimulation techniques with insight into neurobiology and neuroimaging

Abdollah Moossavi[1], Samer Mohsen[2,3*]

[1]- Department of Otolaryngology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

[2]- Department of Audiology, School of Rehabilitation Sciences, Iran University of Medical Sciences, Tehran, Iran

[3]- Department of Otolaryngology, School of Medicine, Damascus University, Damascus, Syria

Received: 29 Mar 2016, Revised: 18 Apr 2016, Accepted: 23 Apr 2016, Published: 18 May 2016

Abstract

Background and Aim: Tinnitus is an auditory phantom percept in the absence of any objective physical sound source. Although advances have been made in its treatment, there is very low percent of patients that report an elimination of their tinnitus. A novel approach using noninvasive neuromodulation has emerged as an interesting and promising modality for tinnitus relief. Our aim in this review is to investigate the efficacy and the specific parameters of some types of noninvasive neuromodulation using transcranial electrical stimulation (TES) namely transcranial direct current stimulation (tDCS), transcranial alternative current stimulation (tACS), transcranial random noise stimulation (tRNS). Then we will correlate the outcomes with the findings of the most newly neurobiologic and neuroimaging researches.

Recent Findings: Up to now, the optimal use of tDCS was to apply a current of 2 mA for 20 minute over both auditory cortex or dorsolateral prefrontal cortex. The results were somewhat good but still need more optimization. While there is no effects of tACS; tRNS is shown to have the more suppressive effects among the three types of TES, so it would be a promising therapeutic tool for modulating tinnitus. In addition, recently many researches on tinnitus have shed light on the tinnitus generating network and it's correlation to another functional brain networks. This article show how can the neuromodulation be optimized by using these new concepts.

Conclusion: Although the different techniques introduced revealed promising results, further research is needed to better understand how they work and how the brain responds to neuromodulation.

Keywords: Tinnitus; neuromodulation; transcranial direct current stimulation; transcranial random noise stimulation; transcranial alternative current stimulation; neuroimaging

[*] **Corresponding author:** Department of Audiology, School of Rehabilitation Sciences, Iran University of Medical Sciences, Shahid Shahnazari St., Madar Square, Mirdamad Blvd., Tehran, 15459-13487, Iran.
Tel: 009821-22221577 ext. 266,
E-mail: mohsen.s@tak.iums.ac.ir

Introduction

Tinnitus is an auditory phantom percept with a tone, hissing, or buzzing sound in the absence of any objective physical sound source [1]. It has been generally recognized that tinnitus is clinically heterogeneous, with respect to its etiology, its perceptual characteristics and its accompanying symptoms. The constant awareness of

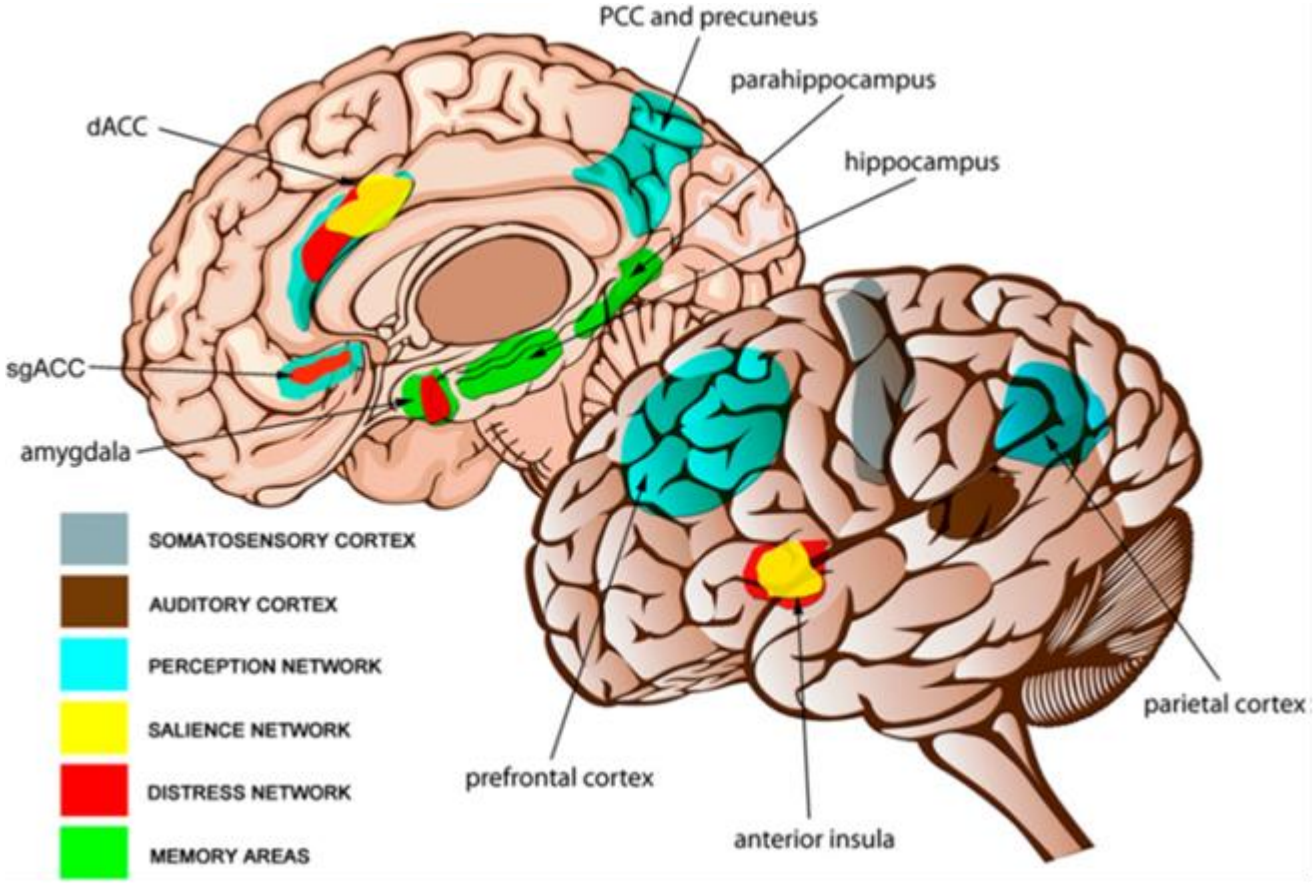

Fig. 1. Brain networks involved in phantom perception. With courtesy from PNAS [6].

this phantom sound often causes a considerable amount of distress. Between 6% and 25% of the affected people report symptoms that are severely debilitating [2,3] and 2-4% of the whole tinnitus population suffers from the worst severity degree, leading to a noticeable decrease in the quality of life in this group [4].

Tinnitus is classified according to whether the perceived noise has its source within the patient's body, known as objective tinnitus, or whether it is perceivable only to the patient and lacks a specific sound source, namely subjective tinnitus. Subjective tinnitus is by far the most common form. Tinnitus mechanisms involve both peripheral and central auditory systems. Damage to the cochlea causes hearing loss and often triggers tinnitus, but the central nervous system is likely to play a key part in chronic tinnitus. There are several theories for the way that tinnitus can be generated; one is the neuroplastic response to sensory deprivation [5]. Whereas other theories containing an increased spontaneous firing rate of neurons in the central auditory system and the neural synchrony [5]. Recently, a proposed model suggests that the tinnitus sensation might reach conscious awareness only when aberrant neuronal activity in the primary sensory cortex is connected to a broader cortical network involving frontal, parietal, and limbic brain regions forming the tinnitus network [6].

Neuroimaging and electroencephalograph (EEG) studies demonstrate that tinnitus generator is such like a network involving different dynamic overlapping brain networks, each representing a specific tinnitus characteristic [6], Fig. 1. The "awareness" and "salience" brain networks consisting of the inferior parietal cortex, the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC),

anterior insula and the posterior cingulate cortex (PCC) [7]. The "distress" brain network consisting of the ACC, anterior insula and amygdala [8], lift and right DLPFC for mood and distress networks respectively [9]. In addition, memory mechanism can play a role in the persistence of the awareness of the phantom percept suggesting that the missing information triggers the brain to "pull it" from the auditory cortical neighborhood or from the parahippocampal memory and integrates it in a self-perceptual network [10,11].

Available treatments for the management of tinnitus are diverse, but all of limited efficacy. These include counseling and cognitive behavioral therapies, sound therapy; methods that attempt to increase input to the auditory system, such as hearing aids and cochlear implants. Pharmacological treatment is another choice with low benefits and recently neurobiofeedback and neuromodulation. The mechanisms of neuromodulation is based on the modification of neuronal activity intimately involved in the neural circuits responsible for tinnitus processing and perception. Researchers believed that stimulation of the cerebral cortex either inhibits or interrupts and interferes with tinnitus signals that originate from the auditory central nervous system and other areas in the tinnitus network of the brain. Brain stimulation techniques can be non-invasive, e.g. transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) or invasive, e.g. epidural or deep brain electrical stimulation.

Here, we will review the principles and mechanisms of noninvasive neuromodulation using TES namely: transcranial direct current stimulation (tDCS), transcranial alternative current stimulation (tACS), transcranial random (electrical) noise stimulation (tRNS), targeting auditory cortex stimulation and dorsolateral prefrontal cortex (DLPFC) stimulation. This article will discuss the efficacy of each one of these methods; we will correlate the outcomes with the many previous researches, which had used repetitive transcranial magnetic stimulation (rTMS) and tDCS. Furthermore, our aim is to focus on the different parameters for each technique and then, we will try to correlate the findings to the results of the more recent neurobiological and neuroimaging researches.

Transcranial electric stimulation (TES) consist of a) transcranial direct current stimulation (tDCS); b) transcranial alternative current stimulation (tACS); c) transcranial random (electrical) noise stimulation (tRNS).

a) The transcranial direct current stimulation (tDCS)

The transcranial direct current stimulation is a noninvasive method of brain stimulation usually applied through two surface electrodes, one serving as the anode and the other as the cathode Fig. 2. When tDCS is applied in humans, a relatively weak constant current (between 0.5 and 2mA) is passed through the cerebral cortex via scalp electrodes. The tDCS can increase or decrease cortical excitability in the brain regions to which it is applied depending on the polarity of the stimulation [13]. Anodal tDCS typically has an excitatory effect on the underlying cerebral cortex by depolarizing neurons, while the opposite occurs under the cathode due to induced hyperpolarization. This effect of tDCS typically outlasts the stimulation by an hour or longer after a single treatment session of sufficiently long stimulation duration [14-15]. Some of the applied current is shunted through scalp tissue and only a part of it passes through the brain.

b) The transcranial alternative current stimulation (tACS)

The transcranial alternative current stimulation is potentially capable of interacting with rhythmic neuronal activity and has perceptual and behavioral consequences [16]. This method relies on application of alternating currents through an electrode and is not sensitive to the direction of current flow. Electrical currents are applied constantly at low intensities over a period and allow manipulation of intrinsic cortical oscillations with externally applied electrical frequencies. As such, tACS is better suited to modulate functions that are closely related to brain oscillations at specific frequencies [17]. For example,

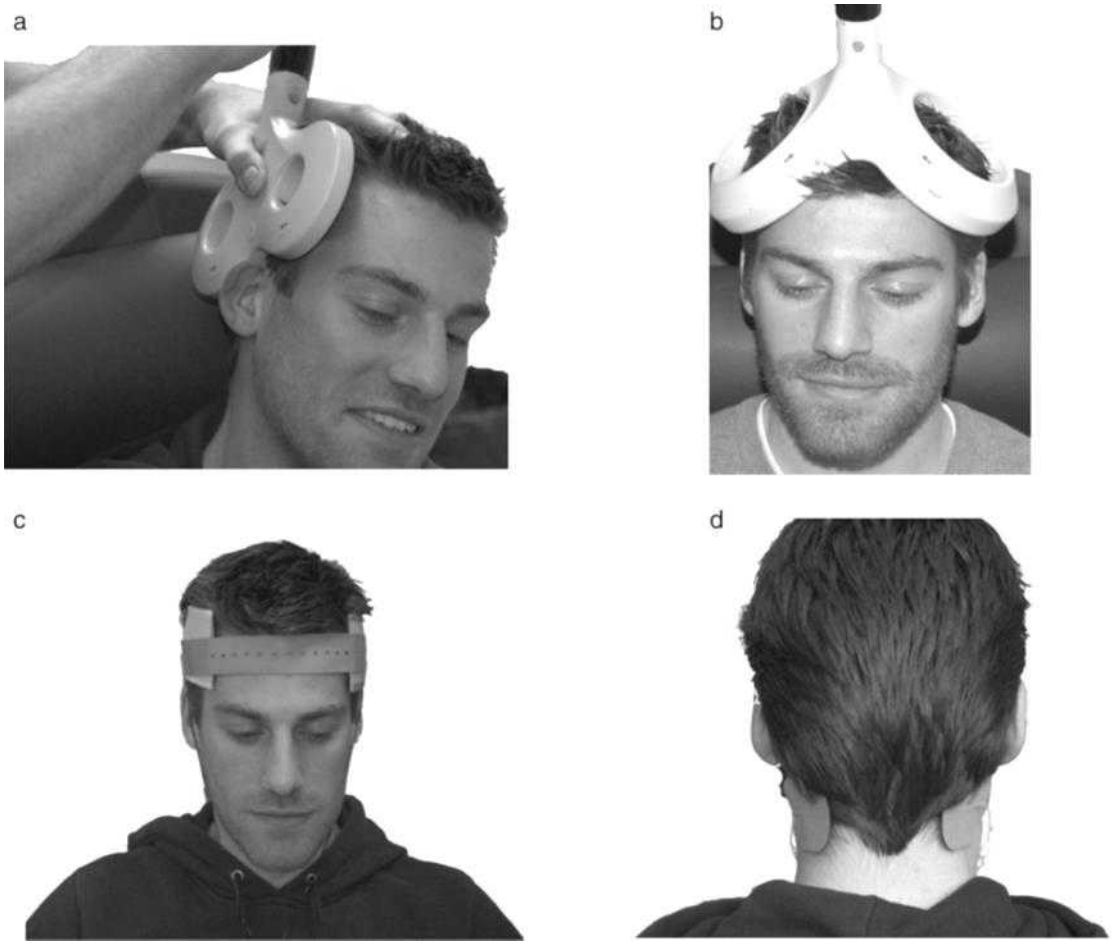

Fig. 2. Noninvasive neuromodulation techniques: a. figure eight coil TMS; b. double-cone coil TMS; c. bifrontal tDCS; and d. TENS stimulation of the C2 nerve. With courtesy from Dr. Sven Vanneste [12].

tACS trengthens the individual alpha frequency (IAF) of the stimulated area [17]. In addition, recent computer modeling data has shown that pulsed AC stimulation induces significant electrical fields in subcortical areas [18].

c) The transcranial random (electrical) noise stimulation (tRNS)

This method has also been tested more and includes a normally distributed random level of current generated with a frequency spectrum between 0.1 and 640 Hz at a sampling rate of 1280 samples per second with no overall DC offset. The frequency spectrum looks similar to the "white noise" characteristic. Research showed that tRNS has a consistent excitability increase lasting at least 60 min, both on physiological and behavioral measures [19]. Long-term potentiation may be a likely mechanism underlying these effects [20]. It was furthermore suggested that the mechanism of action of tRNS was based on repeated subthreshold stimulations, which may prevent homeostasis of the system and potentiate task-related neural activity [21].

Non-invasive neuromodulation of tinnitus

In the last two decades several studies have focused on the use of tDCS and compared it`s effects to repetitive transcranial magnetic stimulation (rTMS) effect. Based on the findings that tinnitus patients have an increased neural activity in the auditory cortex, researchers have investigated the suppressive effects of tDCS on tinnitus by applying the current on the auditory cortex (AC) and left temporoarietal area (LTA).

Single session tDCS with the anodal electrode applied over LTA and the cathodal electrode placed contralateral over the supraorbital area; resulted in a transient suppression of tinnitus. Whereas the single session with the cathodal applied over the LTA had no suppressive effects [22].

Soon after that, with the new insights into the neurobiology of tinnitus suggesting the involvement of the non-auditory areas such as dorsolateral prefrontal cortex (DLPFC) in the pathology of tinnitus [23], several studies used the tDCS applied on the DLPFC in order to modulate it`s activity [24-26]. Vanneste et al. study on 418 non-pulsatile tinnitus patients showed that with a single session of stimulation with the anode over the right DLPFC and the cathode over the left DLPFC, the tinnitus was suppressed in 29.9% of the participants [24]. Repeated bifrontal tDCS sessions with the cathode over left DLPFC reduced the tinnitus loudness and discomfort especially in female patients [27].

In order to optimize the use of tDCS, Schekhawat et al. studied the effects of intensity and duration of the current on the suppression of tinnitus; their results showed that current intensity of 2 mA for 20 minute was the more effective stimulus parameters for anodal tDCS of LTA [28]. Then in a later step, they focused on the effect of high definition tDCS using 4x1 electrodes, four cathodal electrodes and a central anodal electrode, over the LTA and the DLPF. They replicated their previous results of intensity and duration and conducted a new technique in applying electrode, yet their results did not have any significant power in supressing tinnitus compared to traditional tDCS. Moreover, they showed that the stimulation of LTA and DLPFC had the same amount of supression in tinnitus loudness and annoyance respectively [29].

More recently two innovative techniques of pulsed electrical stimulation namely tACS and tRNS have also shown significant neuromodulatory effects in the cortex. In one study on 111 tinnitus patients, Vanneste et al. had conducted the first head to head comparison of three different types of transcranial stimulation TES that is, tDCS, tACS and tRNS over the auditory cortex and LTA. Their results demonstrated that tRNS has induced the larger amount of transient suppression of tinnitus loudness and tinnitus-related distress as compared to the other two type being used. Furthermore, they did not obtain any suppression on tinnitus loudness by targeting the AC with tACS stimulating at the IAF, individual alpha frequency [30]. The use of multiple sessions of stimulation of tRNS had augmented the suppressive effect on tinnitus loudness but had no additional effect on tinnitus-related distress. In contrast to tRNS, tACS had no suppressive effects neither in one session nor in multiple session [31]. Later studies focused on the differential effects of low frequency (lf-tRNS; 0.1-100 Hz) versus high frequency (hf-tRNS; 100-640 Hz) random noise stimulation in the modulation of tinnitus. There was a significant reduction in tinnitus loudness and tinnitus-related distress when low frequency tRNS had been used, whereas high frequency tRNS had it`s only suppressive effects on tinnitus loudness. Concerning the type of tinnitus, hftRNS was more effective in pure tone tinnitus compared to the narrow band noise type of tinnitus [32].

Discussion

Neuromodulation of tinnitus with noninvasive and invasive electrical stimulation techniques have become one of the most common subjects in tinnitus research studies. Noninvasive techniques such as TMS, rTMS, tDCS, TENS, neurofeedback and more recently tACS and tRNS, have been investigated for the treatment of tinnitus. Many review articles have discussed the effects of magnetic stimulation and compared it to tDCS [33-35]. Our aim in this article was to focus more on the three types of transcranial stimulation and to discuss the different parameters for each technique and then, try to relate the differential effects and individual differences in the various studies to the results of the more recent neurobiological and neuroimaging researches.

Because tDCS is safe and does not cause pain,

there is an increased interest in using it to modulate somatosensory, motor, visual functions and more recently tinnitus [36]. tDCS modulates cortical excitability in a polarity, stimulation intensity and duration dependent way; studies reported that anodal stimulation increases and the cathodal electrode decreases the levels of cortical excitability [37]. About the possible underlying mechanism of these neuroplastic effects, it was shown that the electrical field generated by tDCS is able to increase or reduce the membrane potential of neurons in a linear way [38] so it can increase or decrease the firing rate of the neuron respectively. tDCS also can change the neural plasticity by altering synaptic transmission through long term potentiation (LTP) and long term depression (LTD), modifying intracellular cyclic adenosine monophosphate (cAMP] and calcium levels [36] and modulating the neurotransmitter pathways such as N-Methyl-D-Aspartate (NMDA) [39].

Targeting the auditory cortex has been based on the findings of several neurobiologic, neuroimaging, animal models and neuromodulation studies of tinnitus over the last three decades that have given complementary approaches for identifying the neural correlates of tinnitus. One of these findings is that tinnitus perception correlates to a hyperactivity in the auditory pathway especially in the primary auditory cortex [40]. In addition, tinnitus is related to increased gamma band synchronous activity in the auditory cortex [40]. In a 128- channel EEG study, Paul et al observed that attentional modulation of tinnitus was affected whether primary or non-primary auditory cortex was engaged [41]. Likewise, neurofeedback studies have focused on the auditory cortex and regions in the temporal lobe and have obtained some success in reducing tinnitus loudness [42]. Now it is believed that auditory cortex does not influence tinnitus-related distress by itself; rather it connects to and may influence (or being influenced by) both attention and emotion networks and as such may modulate tinnitus perception [43]. Depending on these findings, several later studies have started to target the DLPFC area and the results came to prove the hypothesis.

In one clinical study, Joos et al. focused on the polarity specific effects of a single tDCS session over the auditory cortex, their statistical analysis revealed that there is a significant main effect for tinnitus loudness regardless of polarity, whereas for tinnitus-related annoyance the anodal stimulation had the more pronounced effect compared to the cathodal stimulation [44]. In order to interpret these findings we can suppose that the suppressive effect of tDCS on tinnitus loudness may be attributed to a disruption of ongoing neural hyperactivity, independent from the inhibitory or excitatory effects [45]. Whereas the reduction of tinnitus –related annoyance is still need the contribution of the adjacent functionally connected brain areas involved in the tinnitus-related distress networks. For instance, the amount of annoyance correlates with an alpha network consisting of the amygdala, anterior cingulate cortex, insula, parahippocampus (PHC) and DLPFC [25].

In contrast to LTA-tDCS, DLPFC-tDCS had polarity specific effects, that is switching the polarity of stimulation was able to suppress tinnitus, with some variations as the left anodal prefrontal tDCS predominately modulates the tinnitus-related depression, while the right anodal prefrontal tDCS improved tinnitus-related anxiety [26]. These findings can be correlated to the lateralization of the prefrontal cortex. In anpther research, data has demonstrated some correlation of current density distribution with distress and depression scores, revealing a lateralization effect of depression versus distress. They indicated that distress is mainly correlated with alpha 2, beta 1 and beta 2 activities of the right frontopolar cortex and orbitofrontal cortex in combination with beta 2 activation of the anterior cingulate cortex. In contrast, the more permanent depressive alterations induced by tinnitus were associated with activity of alpha 2 activities in the left frontopolar and orbitofrontal cortex. These specific neural circuits are embedded in a greater neural network, with the parahippocampal region functioning as a crucial linkage between both tinnitus related pathways [9].

With regard to sex differences, one study showed that female tinnitus patients differ from

males in the activity of beta1 and beta 2 band of the orbitofrontal cortex (OFC) extending to the frontopolar cortex. The OFC, which has an important role in the emotional processing of sounds, had an increased functional alpha connectivity with the insula, subgenual anterior cingulate cortex (sgACC), PHC and the auditory cortex in female tinnitus patients [46]. This increased functional connectivity between auditory cortex and the auditory emotion-related areas resulted in a more depressive state in females even though they had the same tinnitus intensity and tinnitus-related distress levels compared to the male tinnitus patients [46].

High definition tDCS over LTA does not seem to be more efficient than traditional tDCS, albeit it appears to be safe and more tolerated. It is probable that the distance of 3.5 cm between the anode and cathode electrodes had made the stimulated area more focal and a distance of 7 cm radius might modulate the tinnitus more effectively [29]. These results give power to confirm the hypothetic tinnitus model that correlates various cortical and subcortical networks with the auditory cortex.

Two innovative techniques of stimulation namely tACS and tRNS has been used in noninvasive modulation based on the findings of previous studies on the motor cortex. The clinical outcomes obtained suggest that tRNS might have a different mechanism of action in comparison to tDCS. Chaieb et al. had demonstrated the supposed mechanism underlying tRNS effect; based on the last studies on tDCS mechanism supposing that it can affect the neuroplasticity depending on alterations in neurotransmission especially the NMDA-receptors [39], they showed that the neuroplasticity induced by tRNS is independent of NMDA-receptor but may be sodium channel blocker and benzodiazepines sensitive [47]. However, the neuroplasticity-inducing effects of oscillatory currents may affect ongoing cortical rhythmicity as observed on the behavioural level [21-48].

The tRNS is thought to induce increased excitability in the auditory cortex in healthy participants [49]. In healthy subjects, the resting state electrical activity is predominantly a noise-like signal in the auditory cortex [50]. Since it is proposed that tinnitus patients have a hyper-synchronization in the auditory cortex [51-54], it is possible that adding a noise to the existing hyper-synchronization will disrupt it, whereas it might have no effect in healthy patients [30].

The concept of using tACS for modulating tinnitus is based on the previous findings of association of tinnitus with a decrease of alpha activity in the auditory cortex. Hence, tACS may reduce the tinnitus perception by strengthening the IAF [55]. Though the results showed no suppressive effect, it can be proposed that the intensity of the current was too weak to induce an effect depending on the reports of previous studies on motor cortex, which had used currents of larger intensities [16-17]. Therefore, it can be suggested that tACS at the IAF is not beneficial method for treating tinnitus when applied over neither the AC nor the DPLFC [31]; yet further studies are still needed.

Conclusion

We have had more than two decades of human brain imaging studies for tinnitus and several studies have shed light on various neural networks engaging in tinnitus perception. These studies have demonstrated that tinnitus perception is related to functional alterations in multiple brain structures including auditory cortex, subgenual anterior and posterior cingulate cortex, DLPFC, insula, amygdala and parahippocampus. These findings are compatible with the brain stimulation studies that confirmed the suppressive effect of transcranial stimulation when applied over the auditory cortex and the prefrontal cortex.

The high inter-individual variability of treatment effects suggest that there might be some ambiguity in the pathophysiological models of tinnitus. Hence, when these models can be properly correlated with the neuroimaging and neuropathophysiologic research findings, the efficacy of these modulating methods will reach to the optimal extent. Up to now, the optimal use of tDCS was to apply a current of 2 mA for 20 minute over the LTA or the DLPFC. While the parameters of using tRNS is still need more

study, though we can say that the use of lf-tRNS over the auditory cortex have the more suppressive effects on tinnitus. In addition, tRNS has been shown to have a more suppressive effect among the three types of TES, and having less side effects compared to the sham stimulation [56], so it would be a promising therapeutic tool for modulating tinnitus.

Yet, further development is needed for many of these approaches before they can be considered as an established or standard treatment for clinical use. In addition, new methodologies to analyze brain data might help to further explore the brain and help to target new brain areas or neural networks. For the next steps, we recommend the researchers to conduct new studies that compare the effects of TES especially tRNS and sham stimulations from the point of brain mapping before and after, so we can then find the right correlation of our methods to what have been mentioned about brain activity and tinnitus network.

REFERENCES

1. Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res. 1990;8(4):221-54.
2. Baguley DM. Mechanisms of tinnitus. Br Med Bull. 2002;63:195-212.
3. Eggermont JJ, Roberts LE. The neuroscience of tinnitus. Trends Neurosci. 2004;27(11):676-82.
4. Axelsson A, Ringdahl A. Tinnitus--a study of its prevalence and characteristics. Br J Audiol. 1989;23(1):53-62.
5. Eggermont JJ. Hearing loss, hyperacusis, or tinnitus: what is modeled in animal research? Hear Res. 2013;295:140-9.
6. De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proceedings of the National Academy of Sciences. Proc Natl Acad Sci U S A. 2011;108(20):8075-80.
7. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007;27(9):2349-56.
8. De Ridder D, Fransen H, Francois O, Sunaert S, Kovacs S, Van De Heyning P. Amygdalohippocampal involvement in tinnitus and auditory memory. Acta Otolaryngol Suppl. 2006;(556):50-3.
9. Joos K, Vanneste S, De Ridder D. Disentangling depression and distress networks in the tinnitus brain. PLoS One. 2012;7(7):e40544.
10. De Ridder D, Vanneste S, Freeman W. The Bayesian brain: phantom percepts resolve sensory uncertainty. Neurosci Biobehav Rev. 2014;44:4-15.
11. De Ridder D, Vanneste S. Targeting the parahippocampal area by auditory cortex stimulation in tinnitus. Brain Stimul. 2014;7(5):709-17.
12. Vanneste S, De Ridder D. Noninvasive and invasive neuromodulation for the treatment of tinnitus: an overview. Neuromodulation. 2012;15(4):350-60.
13. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol. 2006;117(7):1623-9.
14. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527 Pt 3:633-9.
15. Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol. 2003;114(4):600-4.
16. Zaghi S, de Freitas Rezende L, de Oliveira LM, El-Nazer R, Menning S, Tadini L, et al. Inhibition of motor cortex excitability with 15Hz transcranial alternating current stimulation (tACS). Neurosci Lett. 2010;479(3):211-4.
17. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS One. 2010;5(11):e13766.
18. Datta A, Dmochowski JP, Guleyupoglu B, Bikson M, Fregni F. Cranial electrotherapy stimulation and transcranial pulsed current stimulation: a computer based high-resolution modeling study. Neuroimage. 2013;65:280-7.
19. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci. 2008;28(52):14147-55.
20. Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. Exp Neurol. 2009;219(1):14-9.
21. Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci. 2011;31(43):15416-23.
22. Fregni F, Marcondes R, Boggio PS, Marcolin MA, Rigonatti SP, Sanchez TG, et al. Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Eur J Neurol. 2006;13(9):996-1001.
23. Schlee W, Weisz N, Bertrand O, Hartmann T, Elbert T. Using auditory steady state responses to outline the functional connectivity in the tinnitus brain. PLoS One. 2008;3(11):e3720.
24. Vanneste S, Plazier M, Ost J, van der Loo E, Van de Heyning P, De Ridder D. Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. Exp Brain Res. 2010;202(4):779-85.
25. Vanneste S, De Ridder D. Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. Eur J Neurosci. 2011;34(4):605-14.
26. Faber M, Vanneste S, Fregni F, De Ridder D. Top down prefrontal affective modulation of tinnitus with multiple sessions of tDCS of dorsolateral prefrontal cortex. Brain Stimul. 2012;5(4):492-8.
27. Frank E, Schecklmann M, Landgrebe M, Burger J, Kreuzer P, Poeppl TB, et al. Treatment of chronic

tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: outcomes from an open-label pilot study. J Neurol. 2012;259(2):327-33.
28. Shekhawat GS, Stinear CM, Searchfield GD. Transcranial direct current stimulation intensity and duration effects on tinnitus suppression. Neurorehabil Neural Repair. 2013;27(2):164-72.
29. Shekhawat GS, Sundram F, Bikson M, Truong D, De Ridder D, Stinear CM, et al. Intensity, duration, and location of high-definition transcranial direct current stimulation for tinnitus relief. Neurorehabil Neural Repair. 2016;30(4):349-59.
30. Vanneste S, Fregni F, De Ridder D. Head-to-head comparison of transcranial random noise stimulation, transcranial AC stimulation, and transcranial DC stimulation for tinnitus. Front Psychiatry. 2013;4:158.
31. Claes L, Stamberger H, Van de Heyning P, De Ridder D, Vanneste S. Auditory cortex tACS and tRNS for tinnitus: single versus multiple sessions. Neural Plast. 2014;2014:436713.
32. Joos K, De Ridder D, Vanneste S. The differential effect of low- versus high-frequency random noise stimulation in the treatment of tinnitus. Exp Brain Res. 2015;233(5):1433-40.
33. Smit JV, Janssen ML, Schulze H, Jahanshahi A, Van Overbeeke JJ, Temel Y, et al. Deep brain stimulation in tinnitus: current and future perspectives. Brain Res. 2015;1608:51-65.
34. Langguth B, De Ridder D. Tinnitus: therapeutic use of superficial brain stimulation. Handb Clin Neurol. 2013;116:441-67.
35. Langguth B, de Ridder D, Dornhoffer JL, Eichhammer P, Folmer RL, Frank E, et al. Controversy: Does repetitive transcranial magnetic stimulation/transcranial direct current stimulation show efficacy in treating tinnitus patients? Brain Stimul. 2008;1(3):192-205.
36. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimul. 2008;1(3):206-23.
37. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57(10):1899-901.
38. Radman T, Ramos RL, Brumberg JC, Bikson M. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric fieldstimulation in vitro. Brain Stimul. 2009;2(4):215-28, 228.e1-3.
39. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125(Pt 10):2238-47.
40. Husain FT, Akrofi K, Carpenter-Thompson JR3, Schmidt SA. Alterations to the attention system in adults with tinnitus are modality specific. Brain Res. 015;1620:81-97.
41. Paul BT, Bruce IC, Bosnyak DJ, Thompson DC, Roberts LE. Modulation of electrocortical brain activity by attention in individuals with and without tinnitus. Neural Plast. 2014;2014:127824.
42. Hartmann T, Lorenz I, Müller N, Langguth B, Weisz N. The effects of neurofeedback on oscillatory processes related to tinnitus. Brain Topogr. 2014;27(1):149-57.
43. Husain FT. Neural networks of tinnitus in humans: Elucidating severity and habituation. Hear Res. 2016;334:37-48.
44. Joos K, De Ridder D, Van de Heyning P, Vanneste S. Polarity specific suppression effects of transcranial direct current stimulation for tinnitus. Neural Plast. 2014;2014:930860.
45. De Ridder D, Vanneste S, Congedo M. The distressed brain: a group blind source separation analysis on tinnitus. PLoS One. 2011;6(10):e24273.
46. Vanneste S, Joos K, De Ridder D. Prefrontal cortex based sex differences in tinnitus perception: same tinnitus intensity, same tinnitus distress, different mood. PLoS One. 2012;7(2):e31182.
47. Chaieb L, Antal A, Paulus W. Transcranial random noise stimulation-induced plasticity is NMDA-receptor independent but sodium-channel blocker and benzodiazepines sensitive. Front Neurosci. 2015;9:125.
48. Paulus W. Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. Neuropsychol Rehabil. 2011;21(5):602-17.
49. Van Doren J, Langguth B, Schecklmann M. Electroencephalographic effects of transcranial random noise stimulation in the auditory cortex. Brain Stimul. 2014;7(6):807-12.
50. Luczak A, Barthó P, Harris KD. Spontaneous events outline the realm of possible sensory responses in neocortical populations. Neuron. 2009;62(3):413-25.
51. Weisz N, Müller S, Schlee W, Dohrmann K, Hartmann T, Elbert T. The neural code of auditory phantom perception. J Neurosci. 2007;27(6):1479-84.
52. Smits M, Kovacs S, de Ridder D, Peeters RR, van Hecke P, Sunaert S. Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway ofpatients with lateralized tinnitus. Neuroradiology. 2007;49(8):669-79.
53. van der Loo E, Gais S, Congedo M, Vanneste S, Plazier M, Menovsky T, et al. Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS One. 2009;4(10):e7396.
54. Tass PA, Adamchic I, Freund HJ, von Stackelberg T, Hauptmann C. Counteracting tinnitus by acoustic coordinated reset neuromodulation. Restor Neurol Neurosci. 2012;30(2):137-59.
55. Lorenz I, Müller N, Schlee W, Hartmann T, Weisz N. Loss of alpha power is related to increased gamma synchronization-A marker of reduced inhibition intinnitus? Neurosci Lett. 2009;453(3):225-8.
56. Palm U, Chalah MA, Padberg F, Al-Ani T, Abdellaoui M, Sorel M, et al. Effects of transcranial random noise stimulation (tRNS) on affect, pain and attention in multiple sclerosis. Restor Neurol Neurosci. 2016;34(2):189-99.