THERAPEUTIC ADVANCES in
Chronic Disease

Review

State of the art: non-invasive electrical stimulation for the treatment of chronic tinnitus

Ther Adv Chronic Dis

2023, Vol. 14: 1–18

DOI: 10.1177/20406223221148061

Shanwen Chen, Maoshan Du, Yang Wang, Yifan Li, Busheng Tong, Jianxin Qiu, Feihu Wu and Yehai Liu

***Abstract*:** Subjective tinnitus is the perception of sound in the absence of external stimulation. Neuromodulation is a novel method with promising properties for application in tinnitus management. This study sought to review the types of non-invasive electrical stimulation in tinnitus to provide the foothold for further research. PubMed, EMBASE, and Cochrane databases were searched for studies on the modulation of tinnitus by non-invasive electrical stimulation. Among the four forms of non-invasive electrical modulation, transcranial direct current stimulation, transcranial random noise stimulation, and transauricular vagus nerve stimulation yielded promising results, whereas the effect of transcranial alternating current stimulation in the treatment of tinnitus has not been confirmed. Non-invasive electrical stimulation can effectively suppress tinnitus perception in some patients. However, the heterogeneity in parameter settings leads to scattered and poorly replicated findings. Further high-quality studies are needed to identify optimal parameters to develop more acceptable protocols for tinnitus modulation.

Keywords: electrical stimulation, non-invasive, tACS, taVNS, tDCS, tinnitus, tRNS

Received: 15 June 2022; revised manuscript accepted: 13 December 2022.

Correspondence to:
Feihu Wu
Department of Otorhinolaryngology–Head and Neck Surgery, The First Affiliated Hospital of Anhui University of Chinese Medicine, 117 Meishan Road, Hefei 230031, Anhui, P.R. China.
369699562@qq.com

Yehai Liu
Department of Otorhinolaryngology–Head and Neck Surgery, The First Affiliated Hospital of Anhui Medical University, 218 Jixi Road, Hefei 230022, Anhui, P.R. China.
liuyehai@ahmu.edu.cn

Shanwen Chen
Maoshan Du
Yang Wang
Yifan Li
Busheng Tong
Jianxin Qiu
Department of Otorhinolaryngology–Head and Neck Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, P.R. China

Introduction

Subjective tinnitus is the perception of sound in the absence of external stimulation, with a reported prevalence of about 10–20% in adults.[1] Severe tinnitus can bring about a range of psychological comorbidities such as depression, anxiety, and insomnia and can seriously affect the quality of life.[2–4] According to a cross-sectional study in the United States, 26.1% and 25.6% of patients with tinnitus had anxiety and depression, respectively, with shorter sleep duration at night.[5] Many approaches have been developed over the years to treat tinnitus encompassing pharmacotherapy, acoustic therapy, cognitive behavioral therapy (CBT), and surgical intervention. However, no consensus has been reached on the optimal therapeutic approach. Ginkgo biloba extract, steroids, and glutamate antagonists are the most applied agents to treat tinnitus. Interestingly, a review that included four randomized controlled trials (RCTs) found no benefit of ginkgo biloba extract in patients with tinnitus.[6] Negative results were also found with steroids and glutamate antagonists.[7,8] Acoustic therapy includes customized and non-customized sound, such as masking therapy, Heidelberg neuromusic therapy, and tailor-made notched music training (TMNMT).[9] Although some patients experienced tinnitus suppression, strong evidence is still lacking.[10,11] CBT has shown promising results in many studies, but due to the heterogeneity between studies, no definitive recommendation can be made at this time.[12–14] Cochlear implants have also shown positive results on tinnitus suppression but limited efficacy for patients with severe hearing loss.[15–17]

Tinnitus is often related to hearing loss. Peripheral hearing loss causes decreased input from the cochlea to the auditory cortex (AC), resulting in increased firing rate and neuron synchronization. Moreover, this leads to changes in the state of excitement and inhibition, which is called thalamic

cortical rhythm disorder. Studies in tinnitus patients without any hearing abnormalities suggest that the non-auditory brain network also plays a specific role in the occurrence and development of tinnitus. These networks include attention, salience, distress, and memory function. The activation of these non-auditory networks also leads to comorbidities, such as sleep disorder, anxiety, and depression. In general, tinnitus occurs due to changes in the neuroplasticity of the auditory and non-auditory systems. Given that functional changes in neuronal activity cause tinnitus, it could theoretically be suppressed through the corresponding neuromodulation mode.

Invasive and non-invasive neuromodulation techniques have been studied for tinnitus relief.[18,19] Invasive techniques such as deep brain stimulation and epidural stimulation are limited,[20–22] while non-invasive techniques are portable, cost-effective, easy-to-use, and highly acceptable. Transcranial magnetic stimulation (TMS) uses the magnetic field generated by a coil in contact with the scalp to affect the activity of neurons through the skull and resulting in depolarization.[23,24] In recent years, many studies have reviewed the development and application of TMS in tinnitus.[25,26] The remaining non-invasive technologies harness electric current to stimulate the cerebral cortex inducing changes in cortical excitability.[27] Considering the rapid pace at which the research in this field is moving forward, it is important to summarize the state of the art. Several excellent related narrative or systematic reviews have recently been published.[28–33] However, these reviews inevitably lose some information of this theme due to exclusion of unqualified studies or the limited scope. Therefore, this review sought to bring together the continuous work from the literature and summarize the existing types of non-invasive electrical stimulation (NIES) and their application value in tinnitus treatment without excluding studies based on their quality.

Methods

A review was undertaken in September 2021. All studies that fulfill inclusion criteria were included as long as they addressed the topic. The eligibility criteria were as follows: (1) participants: adult patients with subjective chronic tinnitus (>3 months); (2) interventions: NIES; (3) comparison: sham or no treatment or other treatment methods; and (4) outcome: tinnitus distress and loudness measured with validated questionnaires or visual analog scales (VASs). The exclusion criteria included animal studies, non-English articles, case reports or series, and conference and opinion papers.

Our search strategy consisted of two steps. In the first step, we identified relevant studies in PubMed, Embase, and Cochrane (CENTRAL). The retrieval strategy included medical subject headings, keywords, and free words. The search strategy used the following words: 'transcutaneous electric nerve stimulation' OR 'TENS' OR 'non-invasive brain stimulation' OR 'transcranial direct current stimulation' OR 'tDCS' OR 'transcranial alternating current stimulation' OR 'tACS' OR 'transcranial random noise stimulation' OR 'tRNS' OR 'transcutaneous vagal nerve stimulation' OR 'tVNS' AND 'tinnitus'. In the second step, we manually searched the list of references for articles to identify more eligible literature. Two investigators (S.C. and M.D.) independently reviewed the abstracts and the full text of all articles retrieved. They made decisions about including or excluding them. Discrepancies in eligibility were discussed until agreement was achieved. The literature search and flow diagram of study selection are depicted in Supplementary Figure 1.

Results

NIES can be sorted into transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), and transcutaneous auricular vagus nerve stimulation (taVNS). tDCS, tACS, and tRNS involve placing electrodes on the surface of the skull to deliver current for cortical modulation (Figure 1). taVNS stimulates the auricular branch of the vagus nerve (ABVN) for central modulation (Figure 2).[28]

Transcranial direct current stimulation

The tDCS has long been used as a neuromodulation method and is now widely used to treat cognitive, psychiatric, psychological, and other neurological disorders.[34–36] The tDCS involves two electrode pads, one located in the brain area of interest and the other reference electrode at any position on the body surface. A relatively weak and constant current is applied and passed

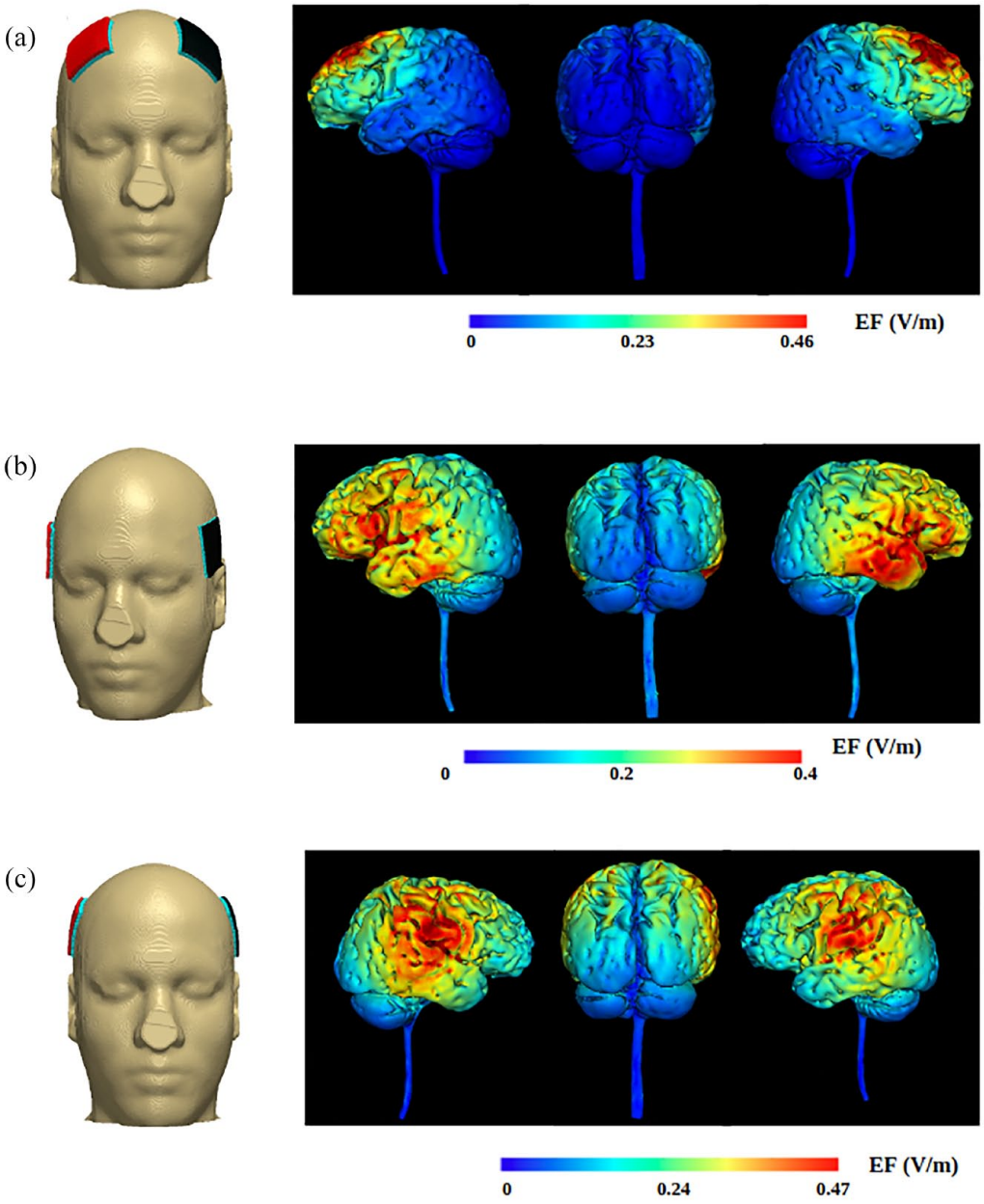

Figure 1. Simulation of electrode positioning and current flow of tDCS with Soterix HD-Explor (Soterix Medical): (a) dorsolateral prefrontal cortex (DLPFC), (b) auditory cortex (AC), and (c) left temporoparietal area (LTA). Each montage used 2 mA current and 5×5 cm electrode pads. Copyright © Soterix, Inc. used with permission.

through the cerebral cortex under the electrodes. The classical view is that the anode induces neural depolarization, which produces an excitation effect on the cerebral cortex, while the cathodal stimulation results in inhibitory effects by hyperpolarization.[37] However, this cannot be regarded as a general rule because the conclusion was drawn from motor cortex stimulation. Subsequent studies have confirmed that in addition to the stimulation polarity, intensity, geometry and electric properties of electrode pads, the distance to the electrode also affects the spatial distribution of the electric field.[38,39] The effect of the electric field on the excitability of local neurons depends on the direction of the axon or somatic dendritic axis with respect to the electric field.[40] Finally, in

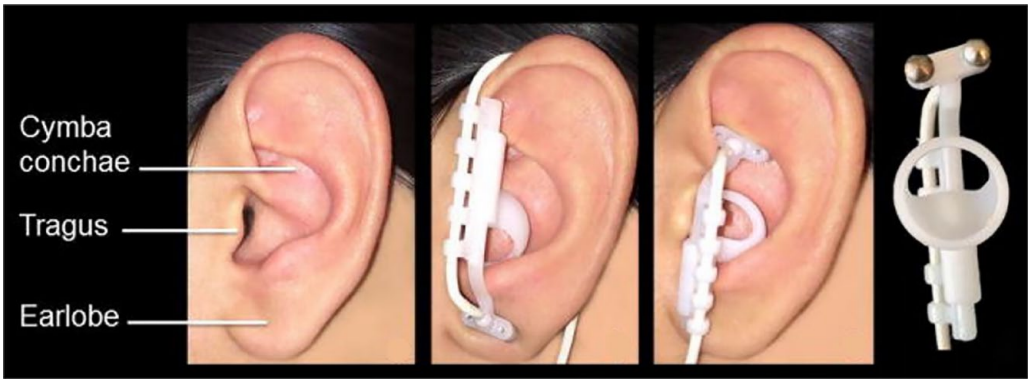

Figure 2. Electrode position of transcutaneous auricular vagal nerve stimulation (taVNS). (Reprinted from Frangos E, Ellrich J, Komisaruk BR. Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans. Brain Stimul. 2015;8(3):624–636. Copyright © 2015 Elsevier, Inc. used with permission.)

terms of clinical effect, the physiological performance of stimulation also depends on whether the affected network of related neural disorders is inhibitory or excitatory. Demographic, clinical, and parameters details extracted from the studies are reported in Table 1.

Left temporoparietal area

The first application of tDCS in the treatment of tinnitus was documented in 2006 by Fregni *et al.*[41] They compared the inhibitory effect of anodal tDCS, cathodal tDCS, 10 Hz rTMS and sham control on tinnitus. Interestingly, 42% of

Table 1. General data from studies of tDCS included in the review.

References	Study type	Intervention	Sample size	Stimulation area	Intensity (mA)	Stimulation (min)	Anode location	Cathode location	Scheme	Outcome
Fregni *et al.*[41]	RCT	tDCS	7	LTA	1	3	LTA/RSO	LTA/RSO	1 session	Positive: anodal stimulation
	(with sham control)									
Garin *et al.*[42]	RCT	tDCS	21	LTA	1	20	LTA/between T4 and F8	LTA/between T4 and F8	3 sessions in 2 weeks	Positive: anodal stimulation
	(with sham control)									
Shekhawat *et al.*[43]	RCT	tDCS	25	LTA	1.5, 2.0	10, 15, 20	LTA	Between T4 and F8	6 sessions	Positive
Shekhawat *et al.*[44]	RCT	tDCS + HA	40	LTA	2	20	LTA	Between T4 and F8	1 session/day, 5 sessions	Negative
	(with sham control)									
Shekhawat *et al.*[45]	RCT	tDCS + RI	10	LTA	2	20	LTA	Between T4 and F8	1 session/day, 4 sessions	Negative
	(with sham control)									
Forogh *et al.*[46]	RCT	tDCS	22	LTA	2	20	LTA	RSO	1 session/day, 5 sessions	Negative
	(with sham control)									

(Continued)

Table 1. (Continued)

References	Study type	Intervention	Sample size	Stimulation area	Intensity (mA)	Stimulation (min)	Anode location	Cathode location	Scheme	Outcome
Souza *et al.*[47]	RCT	tDCS	24	LTA	2	20	LTA	Right DLPFC	1 session/day, 5 sessions	Positive
	(with sham control)									
Hyvärinen *et al.*[48]	RCT	tDCS	43	LTA	2	20	LTA	Right frontal area	1 session/day, 10 sessions	Negative
	(with sham control)			DLPFC			Left frontal area	Right frontal area		
Teismann *et al.*[49]	RCT	tDCS + TMNMT	34	AC	2	30	Left AC/RSO	Left AC/RSO	1 session/day, 5 sessions	Negative
	(with sham control)									
Joos *et al.*[50]	Cohort	tDCS	175	AC	1.5, 2.0	20	Left/Right AC	Left/Right AC	1 session	Positive: 2.0 mA
Pal *et al.*[51]	RCT	tDCS	42	AC	2	20	PFC	Bilateral AC	1 session/day, 5 sessions	Negative
	(with sham control)									
Minami *et al.*[52]	Cohort	tDCS	9	AC	1	10	Right AC	Left AC	1 session	Negative
Henin *et al.*[53]	RCT	HD-tDCS	14	AC	2	20	Bilateral AC	Bilateral PFC	2 sessions	Negative
	(with sham control)	HD-tDCS + CAS								
Abtahi *et al.*[54]	RCT	tDCS	51	AC	2	20	Left/Right AC	Left/Right AC	1 session	Positive: anode
	(with sham control)									
Vanneste *et al.*[55]	RCT	tACS	111	AC	1.5	20	Left/Right AC	Left/Right AC	1 session	Negative
		tDCS								
		tRNS								
Vanneste *et al.*[56]	Cohort	tDCS	543	DLPFC	1.5	20	Left/Right DLPFC	Left/Right DLPFC	1 session	Positive: right anode
										Negative: left anode
Frank *et al.*[57]	Cohort	tDCS	32	DLPFC	1,5	30	Right DLPFC	Left DLPFC	2 sessions/week, 6 sessions	Positive: VAS
Faber *et al.*[58]	RCT	tDCS	15	DLPFC	1.5	20	Left/Right DLPFC	Left/Right DLPFC	6 sessions in 2 weeks	Positive
	(with sham control)									
De Ridder and Vanneste[59]	Cohort	tDCS	675	DLPFC	NA	NA	Right DLPFC	Left DLPFC	NA	Positive: DLPFC
				EEG-driven location			Highest theta band FC	Highest gamma band FC		Negative: EEG-driven location
Vanneste *et al.*[60]	RCT	tDCS, tACS	50	DLPFC	2	20	Right DLPFC	Left DLPFC	1 session	Positive
	(with sham control)									

(Continued)

Table 1. (Continued)

References	Study type	Intervention	Sample size	Stimulation area	Intensity (mA)	Stimulation (min)	Anode location	Cathode location	Scheme	Outcome
Shekhawat *et al.*[61]	RCT	HD-tDCS	27	DLPFC	1, 2	10, 20	Right DLPFC	F2, FC4, F6, AF4	2 sessions	Positive
				LTA			LTA	C5, TP7, CP3, P5		
Lee *et al.*[62]	Cohort	tDCS + TMNMT	14	DLPFC	1.5	20	Right DLPFC	Left DLPFC	4 sessions in 2 weeks	Positive
Rabau *et al.*[63]	RCT	tDCS	65	DLPFC	2	20	Right DLPFC	Left DLPFC/ Shoulder	2 sessions/week, 8 sessions	Negative
To *et al.*[64]	RCT	tDCS	40	DLPFC (tDCS)	tDCS: 1.5	tDCS: 20	Right DLPFC	Left DLPFC	2 sessions/week, 8 sessions	Positive: TQ, VAS
		tDCS + tRNS		AC (tRNS)	tRNS: 2	tRNS: 20				Negative: THI
Shekhawat and Vanneste[65]	RCT	tDCS	111	DLPFC	1.5, 2.0	20, 30	Right DLPFC	Left DLPFC	2, 4, 6, 8, 10 sessions, respectively	Positive
Shekhawat and Vanneste[66]	RCT	HD-tDCS	13	DLPFC	2	20	Right DLPFC	F2, FC4, F6, AF4	1 session	Positive
	(with sham control)									
Jacquemin *et al.*[67]	Cohort	tDCS	117	DLPFC/LTA	2	20	Right DLPFC/ RSO	Left DLPFC/LTA	2 sessions/week, 8 sessions	Positive: TFI
	HD-tDCS						Right DLPFC	F2, FC4, F6, AF4		
Lee[68]	Cohort	tDCS + Conventional	70	DLPFC	1.5	20	Right DLPFC	Left DLPFC	1–6 sessions	Positive
Jacquemin *et al.*[69]	Cohort	HD-tDCS	22	DLPFC	2	20	Right DLPFC	F2, FC4, F6, AF4	2 sessions/week, 8 sessions	Positive
Bae *et al.*[70]	RCT	tDCS	80	DLPFC	1.5	20	Left DLPFC	Right DLPFC	1 session	Positive
	tDCS + TMS									
Jacquemin *et al.*[71]	Cohort	HD-tDCS	117	DLPFC	2	20	Right DLPFC	F2, FC4, F6, AF4	2 sessions/week, 6 sessions	Positive: TFI, TQ
										Negative: HQ, HADS, VAS
Bae *et al.*[72]	Cohort	tDCS	70	DLPFC	1	10	Right DLPFC	Left DLPFC	1 session/day, 5 sessions	Positive: VAS
										Negative: THI

AC, auditory cortex; CAS, compensatory auditory stimulation; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalogram; HA, hearing aid; HADS, hospital anxiety and depression scale; HD-tDCS, high-definition transcranial direct current stimulation; HQ, hyperacusis questionnaire; LTA, left temporoparietal area; PFC, prefrontal cortex; RCT, randomized controlled trial; RI, residual inhibition; RSO, right supraorbital area; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TFI, tinnitus functional index; THI, tinnitus handicap inventory; TMNMT, tailor-made notched music training; TMS, transcranial magnetic stimulation; TQ, tinnitus questionnaire; tRNS, transcranial random noise stimulation; VAS, visual analog scale.
Electrode location according to the 10–20 system of EEG.

patients experienced a significant reduction in tinnitus distress after anodal tDCS of left temporoparietal area (LTA), but the effect lasted only for a few minutes. Garin *et al.*[42] investigated the differences between anodal and cathodal stimulation on tinnitus suppression in setting up a sham control. Consistent with the above results, anodal tDCS yielded a significant suppressive effect on

tinnitus intensity immediately after stimulation. Shekhawat *et al.*[43] conducted a dose-response trial for the parameters of the stimulus. Currents of 1 and 2 mA for 10, 15, and 20 min were used, and all subjects received the six resultant settings of a two-by-two sum of the above current intensity and stimulation time parameters, with a 10 min washout time between each stimulus. The final results showed that a current of 2 mA for 20 min was the most effective stimulus parameter for anodal tDCS of LTA. It is important to note that interpretation of these results requires caution because it is uncertain that the wash-time is enough to eliminate the accumulation effects of multiple stimulations. Contradicting results were reported by Forogh *et al.*,[46] Hyvärinen *et al.*,[48] and Souza *et al.*,[47] who used effective stimulus parameter settings, anodal LTA stimulation, 2 mA current intensity, and 20 min stimulation time. Shekhawat *et al.*[45] combined tDCS and acoustic therapy to explore the joint effects of tinnitus suppression and found that tDCS with residual inhibition yielded no significant effect on tinnitus minimum masking level. The tDCS combined with hearing aids showed a significant reduction in the overall tinnitus functional index score with time, but no significant difference was observed between sham tDCS and tDCS groups.[44] Therefore, this trial could only prove the inhibitory effect of hearing aids on tinnitus, and the effects were independent of tDCS.

Auditory cortex

A total of seven studies discussed the effect of AC stimulation on tinnitus suppression using anode stimulation ($n=1$),[53] cathode stimulation ($n=2$),[51,52] and both ($n=4$).[49,50,54,55] Joos *et al.*[50] and Abtahi *et al.*[54] reported positive results, while other experiments did not observe the positive effect of AC stimulation on tinnitus regulation, irrespective of anode or cathode regulation. Although positive results were documented by Joos *et al.*,[50] there was no sham-control group in the study. The positive results were limited to a current of 2.0 mA, while a current of 1.5 mA was not effective for tinnitus treatment. Although a sham-control group was set up in the study of Abtahi *et al.*,[54] from the description in the original text, it remains unclear whether the study followed the general paradigm of sham-tDCS setting. Interestingly, in these two positive studies, the researchers placed the reference electrode on the opposite upper limb of the subject, unlike in other studies where it was placed on the head. Rabau *et al.*[63] found that placing the reference electrode on the shoulder did not affect the stimulation effect of dorsolateral prefrontal cortex (DLPFC). We hypothesize that the location of the reference electrode outside the skull may not affect the stimulation electrode on the AC. However, the relationship between the tinnitus suppressive effect and the location of the reference electrode remains largely understudied, and its impact warrants further exploration by rigorous experiments.

Teismann *et al.*[49] and Pal *et al.*[51] conducted an RCT study with a sham control and adopted the design scheme of 2 mA current intensity and five sessions. The former only reported the positive effect of TMNMT and did not observe any inhibition effect by AC stimulation on tinnitus. Pul *et al.*[51] used cathodic stimulation but did not observe any positive effect.

Dorsolateral prefrontal cortex

A total of 18 studies involving DLPFC were found.[48,56–72] Vanneste *et al.*[60] showed that single bilateral DLPFC stimulation significantly inhibited tinnitus loudness and annoyance. Faber *et al.*[58] reported that multiple sessions of tDCS of DLPFC only yielded benefits in improving tinnitus distress, while Shekhawat and Vanneste[66] found that DLPFC was effective for improving tinnitus loudness. Although the degree of distress of subjects after stimulation improved, the difference was not statistically significant.

Vanneste *et al.*[56] conducted a tDCS trial focusing on the bilateral DLPFC with a large sample of 543 participants. A significant reduction in tinnitus intensity and distress was observed in 29.9% of patients with anodal right/cathodal left tDCS, while reversed location stimulation showed no effect. In a large retrospective study including 675 participants, De Ridder and Vanneste[59] compared the effects of bilateral DLPFC stimulation with electroencephalogram (EEG)-driven tDCS. The rationale is that, based on the pathophysiology of tinnitus and the polarity-dependent effects of tDCS, the cathode in the area of tinnitus-related gamma energy band activity or the area of gamma energy band functional connectivity may be more effective for tinnitus suppression since functional connectivity determines the tinnitus network. It was found that both bifrontal tDCS

and EEG-driven tDCS could significantly suppress tinnitus loudness, and distress, but no advantage was observed with the latter.

Shekhawat and Vanneste[65] conducted a dose-response trial to explore the optimal stimulation parameters for DLPFC. This study discussed the current intensities of 1.5 and 2.0 mA, the stimulation time of 20 and 30 min, and the effects of different stimulation sessions on tinnitus perception. Tinnitus loudness decreased significantly after tDCS with DLPFC. There was no significant difference between stimulus intensity and duration. The tinnitus loudness reached a nadir after six treatment sessions. Finally, the author recommended six sessions with a current of 1.5 mA for 20 min over 3 weeks with a washout period of 3–4 days to apply tDCS stimulation by DLPFC.

In the study by Rabau *et al.*,[63] a cathode was placed on the left DLPFC and the left shoulder, respectively, and the anode on the right DLPFC. The former stimulated the DLPFC and hippocampus, while the latter stimulated the cingulate cortex, right hippocampus, and temporal lobe. However, there was no significant difference in VAS and TFI scores between the two groups. Other studies on tDCS stimulation of DLPFC validated its inhibitory effect on tinnitus perception

High-definition tDCS

The spatial resolution of tDCS is limited because of the low current conductivity of the skull. It has been found that the rectangular pad configuration peak–induced electric field magnitude was not directly under the pads but at an intermediate lobe, which brings difficulties to the anatomical interpretation of the tinnitus inhibitory effect.[73] HD-tDCS, including the 4×1 ring configuration, results in enhanced spatial focus, with peak induced electric field magnitude directly underneath the active electrode.[74,75] At present, six studies have explored the effect of HD-tDCS in chronic tinnitus relief,[53,61,66,67,69,71] Three studies of DLPFC stimulation by Jacquemin *et al.*[67,69,71] found that tinnitus improved in 47%, 36%, and 31% of patients. The RCT study by Shekhawat *et al.*[61] found that 77.8% of subjects responded to HD-tDCS, with no difference between DLPFC and LTA stimulation effects. The most effective inhibition was achieved after 15 min stimulation with a current of 2 mA. Henin *et al.*[53] did not clarify the effect of tDCS due to the small sample size.

Taken together, the above findings suggest that HD-tDCS stimulation at the right DLPFC with a 2 mA current intensity for 20 min yielded promising results.

Transcranial alternating current stimulation

The tACS uses alternating currents with specified frequency to affect cortical oscillation to regulate the neuronal activity of the target brain area. Therefore, tACS is suitable for regulating the functions closely related to brain oscillation at a specific frequency.[76,77] Recent studies have substantiated that tACS at alpha frequency leads to an elevation of alpha power, and the coupling in alpha- and gamma-phase synchronization between frontal, parietal, and cingulate brain areas is reportedly related to tinnitus distress.[78–81] Only three clinical studies have assessed tACS in tinnitus treatment using alpha-modulated tACS (6–13 Hz), but no significant results were found irrespective of whether AC or DLPFC was stimulated.[55,60,82] Demographic, clinical, and parameters details extracted from the studies are reported in Table 2.

Transcranial random noise stimulation

The tRNS is a non-invasive brain stimulation method using alternating currents with random frequencies to interfere with oscillatory neural activity.[83] This technology can be applied in the low frequency (0.1–100 Hz) or the high-frequency range (101–640 Hz). One proposed mechanism is that tRNS may induce repeated opening of Na(+) channels, which shortens the hyperpolarization phase and causes an inward sodium current, resulting in a depolarization of the neural membrane.[84] Direct evidence of tRNS interfering with the auditory-evoked activity of the AC was provided by an EEG study.[85] Claes *et al.*[82] and Vanneste *et al.*[55] found that tRNS induced the most significant suppressive effect on tinnitus loudness compared with tDCS and tACS. However, another prospective study on tRNS yielded the opposite results. Joos *et al.*[86] reported that low-frequency tRNS and high-frequency tRNS could significantly reduce tinnitus loudness and distress, whereas whole-frequency tRNS

Table 2. General data from studies of tACS included in the review.

References	Study type	Intervention	Sample size	Stimulation area	Intensity (mA)	Stimulation (min)	Frequency (Hz)	Scheme	Outcome
Claes *et al.*[82]	Cohort	tACS, tRNS	228	AC	2	20	tACS (6–13)	8 sessions	Negative
							tRNS (0.1–100)		
Vanneste *et al.*[55]	RCT	tACS	111	AC	1.5	20	tACS (6–13) tRNS (0.1–100)	1 session	Negative
		tDCS							
		tRNS							
Vanneste *et al.*[60]	RCT	tDCS, tACS	50	DLPFC	2	20	tACS (6–13)	1 session	Negative
	(with sham control)								

AC, auditory cortex; DLPFC, dorsolateral prefrontal cortex; RCT, randomized controlled trial; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tRNS, transcranial random noise stimulation.

yielded no effect on tinnitus in a single-session scheme. Mohsen *et al.*[87] investigated the effect of multiple-sessions treatment regimens on tinnitus suppression and showed significant suppression of tinnitus loudness and annoyance compared with the single-session scheme. However, the study by Kreuzer *et al.*[88] reported negative results for tRNS in the treatment of tinnitus. Demographic, clinical, and parameters details extracted from the studies are reported in Table 3.

Transcutaneous auricular vagal nerve stimulation

The vagus nerve is the tenth pair of cranial nerves consisting of approximately 80% sensory afferent fibers and 20% motor afferent fibers.[89] Stimulation of the vagus nerve modulates the release of norepinephrine and acetylcholine.[90,91] These neuromodulators enhance neuroplasticity by modulating the cortex, hippocampus, and amygdala. It has also been demonstrated that norepinephrine and acetylcholine can affect the selective plasticity of auditory cortical neurons.[92–94] Engineer *et al.*[95] used VNS paired with tones that exclude the tinnitus frequency to successfully eliminate the behavioral and physiologic manifestations of tinnitus in a rat model. The follow-up pilot clinical trials achieved significant results in about half of tinnitus patients.[96] Despite the high acceptability of patients with implanted VNS,[97] invasive intervention is inevitably accompanied by potential risks. Acute side effects include infection, vocal cord paralysis, lower facial weakness, and so on. Long-term risks include voice changes, hoarseness, and sore throat.[98] Anatomy and imaging studies have confirmed that stimulation of ABVN can also activate the central nerve pathway, similar to implanted VNS.[99–101] Therefore, taVNS has huge prospects and exploration value in treating tinnitus.

Four clinical studies reported meaningful results for applying taVNS combined with sound therapy (ST) in tinnitus relief.[102–105] The taVNS + TRT alleviated tinnitus stress in 76% of patients at 1-year follow-up.[105] Half of the patients in the study by Shim *et al.*[102] reported symptom relief after taVNS plus notched music therapy. Lehtimäki *et al.*[103] demonstrated the neuromodulatory effect of taVNS and tailored ST on evoked auditory cortical response. There was significant heterogeneity in parameter settings, follow-up time, and the types of ST used in these studies. Three studies used taVNS only as an intervention to clarify the effect of taVNS on tinnitus inhibition.[106–108] In the cohort study by Kreuzer *et al.*,[106] phase I was terminated prematurely due to cardiac side effects, with a slight significant decrease in TQ score reported. Although there were no adverse events in the second phase, the difference observed before and after treatment was not significant. Suk *et al.*[107] reported a positive outcome after 2 weeks of taVNS treatment. Importantly, the results of this study were collected 1 month after the end of stimulation, suggesting the possible long-term after-effects of taVNS. A recent RCT study found that taVNS had a significant inhibitory effect on unilateral and bilateral tinnitus.[108] Although the control group also showed a

Table 3. General data from studies of tRNS included in the review.

References	Study type	Intervention	Sample size	Stimulation area	Intensity (mA)	Stimulation (min)	Frequency (Hz)	Scheme	Outcome
Joos *et al.*[86]	Cohort	tRNS	154	AC	2	20	0.1–100	1 session	Positive: 0.1–100, 100–640 Hz
							100–640		Negative: 0.1–640 Hz
							0.1–640		
Kreuzer *et al.*[88]	Cohort	tRNS	30	AC	2	20	100–640	10 sessions	Negative
Mohsen *et al.*[87]	RCT	tRNS	29	AC + DLPFC	2	20	0.1–100	1 session/8 sessions	Positive
							100–640		
To *et al.*[64]	RCT	tDCS	40	DLPFC (tDCS)	tDCS: 1.5	tDCS: 20	0.1–100	8 sessions	Positive
		tDCS + tRNS		AC (tRNS)	tRNS: 2	tRNS: 20			
Claes *et al.*[82]	Cohort	tACS, tRNS	228	AC	2	20	tACS (6–13)	8 sessions	Positive
							tRNS (0.1–100)		
Vanneste *et al.*[55]	RCT	tACS	111	AC	1.5	20	tACS (6–13) tRNS (0.1–100)	1 session	Positive
		tDCS							
		tRNS							

AC, auditory cortex; DLPFC, dorsolateral prefrontal cortex; RCT, randomized controlled trial; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tRNS, transcranial random noise stimulation.

significant decrease in tinnitus handicap inventory (THI) score, further analysis showed that the decreased THI score of taVNS was significantly higher than the control group.

The pre-clinical research obtained promising results using implanted VNS combined with acoustic stimulation. The effect of taVNS on AC was observed in functional magnetic resonance imaging (fMRI) studies. However, significant heterogeneity is found in current clinical reports, and the quality of trials is not high. The results of three studies using taVNS alone are inconsistent, making it difficult to evaluate the clinical effect of taVNS. Demographic, clinical, and parameters details extracted from the studies are reported in Table 4.

Discussion

Tinnitus is a disease with significant heterogeneity in terms of etiology, perception, and degree of severity, ranging from mild annoyance to disastrous impact on daily life.[109] Our review of the literature identified four non-invasive electrical therapy themes. Most studies that focused on tDCS provided significant results. tACS and tRNS have also been applied as novel modulation technology, but the clinical research in tinnitus is still in its early stage. taVNS has demonstrated promising effects in tinnitus management, but there is a lack of high-quality research to exclude the placebo effect.

Although there is a rich literature on tDCS available, significant heterogeneity in scheme design and results prevail. In clinical studies that applied tDCS for tinnitus treatment, the stimulation sites included AC, LTA, and DLPFC. The selection of these areas depends on neuroimaging and electrophysiological evidence of tinnitus.[110–113] AC is a part of the classical auditory pathway, and the functional changes of DLPFC are considered to be a deficiency of the top–down inhibitory system in tinnitus patients.[114] Plewnia *et al.*[115] documented that LTA is the most effective scalp position for repeated TMS to inhibit tinnitus, validated in a subsequent tDCS study by

Table 4. General data from studies of taVNS included in the review.

References	Study type	Intervention	Sample size	Stimulation area	Intensity (mA)	Stimulation (min)	Frequency (Hz)	Scheme	Outcome
Lehtimäki *et al.*[103]	Cohort	taVNS + tailored ST	10	Left tragus	Suprathreshold	45–60	25	7 sessions in 10 days	Positive
Mei *et al.*[104]	RCT	taVNS + sound masking	63	Concha	1	20	20	2 sessions/day, 8 weeks	Positive
Ylikoski *et al.*[105]	Cohort	taVNS + TRT	78	Left tragus	Suprathreshold	60–90	25	1 session/day, 5 days/week, 1 year	Positive
Shim *et al.*[102]	Cohort	taVNS + notched music	30	Left concha	Suprathreshold	30	25	10 sessions	Positive
Kreuzer *et al.*[106]	Cohort	taVNS	50	Cymba conchae	Suprathreshold	phase 1: 6 h/day	25	24 weeks	Negative
						phase 2: 4 h/day			
Suk *et al.*[107]	Cohort	taVNS	24	Cavum, cymba, outer surface of the tragus	Suprathreshold	4 at each site	30	4 sessions	Positive
Tutar *et al.*[108]	RCT	taVNS	60	Cymba conchae	Suprathreshold	30	200	10 sessions	Positive

RCT, randomized controlled trial; ST, sound therapy; taVNS, transcutaneous vagal nerve stimulation; TRT, tinnitus-retraining therapy.

Fregni *et al.*[41] Many studies selected DLPFC as the stimulation area and reported significant improvement in tinnitus irrespective of the number of sessions. Moreover, there is no lack of high-quality RCT studies with sham control and some studies even observed the after-effects 1 month after treatment. However, in the study with AC or LTA as the stimulation target area, the number of positive results is close to negative results. It is well-established that AC and LTA are very close stimulation areas, corresponding to the halfway point between C3 and T5 and T3 (EEG 10/20 system), respectively. Applying 35 cm^2 electrodes in these studies may activate additional cortical regions around the target area, which inevitably lead to partial overlap. This finding accounts for the comparable stimulation effects of AC and LTA on tinnitus. These findings suggest that DLPFC stimulation with tDCS seems to be more promising for tinnitus suppression.

The difference between tACS and tRNS lies in the difference in current frequency. tACS often adopts 6–13 Hz, while the tRNS frequency range is 0.1–640 Hz. In this review, no tACS studies reported significant effects on tinnitus perception. tRNS was found to significantly inhibit the loudness and distress of tinnitus irrespective of the number of sessions, with superior effects compared with tDCS. Interestingly, the study by To *et al.*[64] found an added value of tRNS to the DLPFC tDCS protocol for tinnitus relief. This finding brings hope for the joint application of two or even more neuromodulation modes in the later stage.

In addition to the stimulation area, the stimulation parameters are also worthy of further exploration. Stimulation with a current of 2 mA for 20 min was adopted by most studies on tDCS. Simulation of electric field distribution has proven its safety in the human body.[116,117] LTA stimulation with a current intensity of 2 mA and 20 min duration was most effective for transient tinnitus suppression. However, the study did not attempt to optimize the number of sessions. The main adverse events of tDCS were itching, tingling, headache, discomfort, and burning sensation and were generally mild and disappeared soon after

stimulation.[118,119] No serious adverse events have been reported in existing studies about tDCS in tinnitus. The current tDCS parameters have been demonstrated to be relatively safe in tinnitus research, and further high-quality RCTs with sham control are needed to explore different parameter settings on tinnitus suppression. At present, tACS and tRNS are rarely used in tinnitus, and almost all of the studies adopted 2.0 mA intensity and 20 min duration. tACS has no inhibitory effect on tinnitus, but tRNS showed significant inhibition on tinnitus loudness and annoyance. The current tRNS studies suggest the effect of high and low frequencies on tinnitus inhibition, and the effect of multiple sessions seems to yield a more significant effect, but the number of studies on tRNS is significantly less than that on tDCS, with no RCT study to control placebo effect. Accordingly, double-blinded sham-controlled trials with different parameter settings are needed in future studies.

Over the years, taVNS has been widely used in the psychological fields of depression, epilepsy, migraine, pain, and tinnitus.[120] Most taVNS studies reported a positive effect on tinnitus suppression, with taVNS intervention alone or in combination with ST. However, the lack of sham-control design leads to an inevitable placebo effect. The body surface distribution map of ABVN depends on anatomical evidence, which has been limited due to the difficulty of nerve anatomy.[99] According to anatomical evidence, ABVN is distributed in the external auditory meatus (EAM), especially in the posterior wall of the EAM. However, fMRI studies found that stimulation of the cymba concha, inner tragus, and anterior wall of the EAM could activate the vagal afferent pathway.[121] The stimulation sites used in the clinical study of taVNS include the inner tragus, cymba concha, and cavum concha. The significant clinical effects can be mutually verified with the results of fMRI. Moreover, the research by Yakunina *et al.*[122] further pointed out that the cymba concha may be a more suitable site because stimulating the cymba concha can result in the most robust activation of the vagal afferent pathway in the brainstem. Almost all taVNS studies adopted suprathreshold current intensity settings in this review. Current flow patterns and intensity, and resulting regions of interest influence, were highly specific to taVNS electric montage.[123] Considering the substantial influence of electrode and tissue impedance, the amount or amplitude of energy delivered to the tissue remains largely unknown, suggesting that using suprathreshold is an alternative choice.[124] In this review, only the study by Kreuzer *et al.*[106] reported two cardiac events that were not related to the taVNS. Evidence substantiates that taVNS is a safe and well-tolerated technology.[125] The most common side effects are local skin irritation caused by electrode placement, headache, and nasopharyngitis. No special therapies were required. However, the results of existing studies of pure taVNS application were inconsistent. Whether pairing of the vagus stimulation with non-tinnitus or tinnitus-matched sounds is essential is still to be determined.[126] In conclusion, taVNS is a feasible and safe technique, but much heterogeneity surrounds the parameter settings making it challenging to summarize and reproduce. Further research should follow the recommendations for reporting standards in research on taVNS to achieve transparency, completeness, and reproducibility.[127]

Conclusion

NIES broadens the therapeutic landscape for the treatment of subjective tinnitus. This approach is safe and with only a few relatively minor side effects. The variety of options (tDCS, tACS, tRNS, taVNS) and stimulation parameters opens up unlimited neuromodulation possibilities in tinnitus management. More high-quality studies are warranted to substantiate the robustness of our results.

Declarations

Ethics approval and consent to participate

Ethical approval is not required as the current study was based on published data.

Consent for publication

Not applicable.

Author contributions

Shanwen Chen: Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Maoshan Du: Data curation; Formal analysis; Methodology; Writing – review & editing.

Yang Wang: Conceptualization; Data curation; Formal analysis; Writing – review & editing.

Yifan Li: Conceptualization; Writing – review & editing.

Busheng Tong: Conceptualization; Writing – review & editing.

Jianxin Qiu: Conceptualization; Writing – review & editing.

Feihu Wu: Conceptualization; Project administration; Writing – review & editing.

Yehai Liu: Conceptualization; Project administration; Supervision; Writing – review & editing.

Acknowledgements
We would like to give our sincere appreciation to the reviewers for their helpful comments on this article.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Project of Science and Technology of National Health Commission (No. 20003), Anhui Province collaborative research project of Chinese and Western medicine for major and difficult diseases (Grant No. 2021-70), and Project of Health Commission of Anhui Province (Grant No. AHWJ2021b160).

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
All data are included in the article.

ORCID iDs
Shanwen Chen https://orcid.org/0000-0002-4204-2968

Yehai Liu https://orcid.org/0000-0003-3977-2481

Supplemental material
Supplemental material for this article is available online.

References
1. Baguley D, McFerran D and Hall D. Tinnitus. *Lancet* 2013; 382: 1600–1607.
2. Weidt S, Delsignore A, Meyer M, *et al.* Which tinnitus-related characteristics affect current health-related quality of life and depression? A cross-sectional cohort study. *Psychiatry Res* 2016; 237: 114–121.
3. Zeman F, Koller M, Langguth B, *et al.* Which tinnitus-related aspects are relevant for quality of life and depression: results from a large international multicentre sample. *Health Qual Life Outcomes* 2014; 12: 7.
4. Bartels H, Middel BL, van der Laan BF, *et al.* The additive effect of co-occurring anxiety and depression on health status, quality of life and coping strategies in help-seeking tinnitus sufferers. *Ear Hear* 2008; 29: 947–956.
5. Bhatt JM, Bhattacharyya N and Lin HW. Relationships between tinnitus and the prevalence of anxiety and depression. *Laryngoscope* 2017; 127: 466–469.
6. Zenner HP, Delb W, Kröner-Herwig B, *et al.* A multidisciplinary systematic review of the treatment for chronic idiopathic tinnitus. *Eur Arch Otorhinolaryngol* 2017; 274: 2079–2091.
7. Choi SJ, Lee JB, Lim HJ, *et al.* Intratympanic dexamethasone injection for refractory tinnitus: prospective placebo-controlled study. *Laryngoscope* 2013; 123: 2817–2822.
8. Figueiredo RR, Langguth B, Mello de Oliveira P, *et al.* Tinnitus treatment with memantine. *Otolaryngol Head Neck Surg* 2008; 138: 492–496.
9. Wang H, Tang D, Wu Y, *et al.* The state of the art of sound therapy for subjective tinnitus in adults. *Ther Adv Chronic Dis* 2020; 11: 2040622320956426.
10. Sereda M, Xia J, El Refaie A, *et al.* Sound therapy (using amplification devices and/or sound generators) for tinnitus. *Cochrane Database Syst Rev* 2018; 12: CD013094.
11. Hobson J, Chisholm E and El Refaie A. Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database Syst Rev* 2012; 11: CD006371.
12. Fuller T, Cima R, Langguth B, *et al.* Cognitive behavioural therapy for tinnitus. *Cochrane Database Syst Rev* 2020; 1: CD012614.
13. Beukes EW, Baguley DM, Allen PM, *et al.* Audiologist-guided internet-based cognitive

behavior therapy for adults with tinnitus in the United Kingdom: a randomized controlled trial. *Ear Hear* 2018; 39: 423–433.

14. Beukes EW, Allen PM, Baguley DM, *et al*. Long-term efficacy of audiologist-guided internet-based cognitive behavior therapy for tinnitus. *Am J Audiol* 2018; 27: 431447.
15. Poncet-Wallet C, Mamelle E, Godey B, *et al*. Prospective multicentric follow-up study of cochlear implantation in adults with single-sided deafness: tinnitus and audiological outcomes. *Otol Neurotol* 2020; 41: 458–466.
16. Távora-Vieira D, Marino R, Krishnaswamy J, *et al*. Cochlear implantation for unilateral deafness with and without tinnitus: a case series. *Laryngoscope* 2013; 123: 1251–1255.
17. Levy DA, Lee JA, Nguyen SA, *et al*. Cochlear implantation for treatment of tinnitus in single-sided deafness: a systematic review and meta-analysis. *Otol Neurotol* 2020; 41: e1004–e1012.
18. Deklerck AN, Marechal C, Pérez Fernández AM, *et al*. Invasive neuromodulation as a treatment for tinnitus: a systematic review. *Neuromodulation* 2020; 23: 451–462.
19. Lefebvre-Demers M, Doyon N and Fecteau S. Non-invasive neuromodulation for tinnitus: a meta-analysis and modeling studies. *Brain Stimul* 2021; 14: 113–128.
20. Shi Y, Burchiel KJ, Anderson VC, *et al*. Deep brain stimulation effects in patients with tinnitus. *Otolaryngol Head Neck Surg* 2009; 141: 285–287.
21. Dijkstra E, Figee M, Schuurman PR, *et al*. Effective deep brain stimulation of intractable tinnitus: a case study. *Brain Stimul* 2018; 11: 1205–1207.
22. Cheung SW, Racine CA, Henderson-Sabes J, *et al*. Phase I trial of caudate deep brain stimulation for treatment-resistant tinnitus. *J Neurosurg*. Epub ahead of print 24 September 2019. DOI: 10.3171/2019.4.JNS19347.
23. Lehner A, Schecklmann M, Greenlee MW, *et al*. Triple-site rTMS for the treatment of chronic tinnitus: a randomized controlled trial. *Sci Rep* 2016; 6: 22302.
24. Noh TS, Kyong JS, Park MK, *et al*. Dual-site rTMS is more effective than single-site rTMS in tinnitus patients: a blinded randomized controlled trial. *Brain Topogr* 2020; 33: 767–775.
25. Theodoroff SM and Folmer RL. Repetitive transcranial magnetic stimulation as a treatment for chronic tinnitus: a critical review. *Otol Neurotol* 2013; 34: 199–208.
26. Meng Z, Liu S, Zheng Y, *et al*. Repetitive transcranial magnetic stimulation for tinnitus. *Cochrane Database Syst Rev* 2011; 2011: CD007946.
27. Merrill DR, Bikson M and Jefferys JGR. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. *J Neurosci Methods* 2005; 141: 171–198.
28. Peter N and Kleinjung T. Neuromodulation for tinnitus treatment: an overview of invasive and non-invasive techniques. *J Zhejiang Univ Sci B* 2019; 20: 116–130.
29. Langguth B. Non-invasive neuromodulation for tinnitus. *J Audiol Otol* 2020; 24: 113–118.
30. Yang T, Zhang J, Wang B, *et al*. Electrical stimulation to treat tinnitus: a meta-analysis and systemic review of randomized controlled trials. *Ther Adv Chronic Dis*. Epub ahead of print 13 September 2021. DOI: 10.1177/20406223211041069.
31. Martins ML, Souza DDS, Cavalcante MEOB, *et al*. Effect of transcranial direct current stimulation for tinnitus treatment: a systematic review and meta-analysis. *Neurophysiol Clin* 2022; 52: 1–16.
32. Labree B, Hoare DJ, Gascoyne LE, *et al*. Determining the effects of transcranial direct current stimulation on tinnitus, depression, and anxiety: a systematic review. *Brain Sci* 2022; 12: 484.
33. Stegeman I, Velde HM, Robe P, *et al*. Tinnitus treatment by vagus nerve stimulation: a systematic review. *PLoS ONE* 2021; 16: e0247221.
34. Palm U, Hasan A, Strube W, *et al*. tDCS for the treatment of depression: a comprehensive review. *Eur Arch Psychiatry Clin Neurosci* 2016; 266: 681–694.
35. Knotkova H, Hamani C, Sivanesan E, *et al*. Neuromodulation for chronic pain. *Lancet* 2021; 397: 2111–2124.
36. Elsner B, Kugler J, Pohl M, *et al*. Transcranial direct current stimulation (tDCS) for idiopathic Parkinson's disease. *Cochrane Database Syst Rev* 2016; 7: CD010916.
37. Nitsche MA and Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000; 527: 633–639.
38. Opitz A, Paulus W, Will S, *et al*. Determinants of the electric field during transcranial direct current stimulation. *Neuroimage* 2015; 109: 140–150.

39. Saturnino GB, Antunes A and Thielscher A. On the importance of electrode parameters for shaping electric field patterns generated by tDCS. *NeuroImage* 2015; 120: 25–35.
40. Bikson M, Inoue M, Akiyama H, *et al*. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J Physiol* 2004; 557: 175–190.
41. Fregni F, Marcondes R, Boggio PS, *et al*. Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation. *Eur J Neurol* 2006; 13: 996–1001.
42. Garin P, Gilain C, Van Damme JP, *et al*. Short- and long-lasting tinnitus relief induced by transcranial direct current stimulation. *J Neurol* 2011; 258: 1940–1948.
43. Shekhawat GS, Stinear CM and Searchfield GD. Transcranial direct current stimulation intensity and duration effects on tinnitus suppression. *Neurorehabil Neural Repair* 2013; 27: 164–172.
44. Shekhawat GS, Searchfield GD and Stinear CM. Randomized trial of transcranial direct current stimulation and hearing aids for tinnitus management. *Neurorehabil Neural Repair* 2014; 28: 410–419.
45. Shekhawat GS, Kobayashi K and Searchfield GD. Methodology for studying the transient effects of transcranial direct current stimulation combined with auditory residual inhibition on tinnitus. *J Neurosci Methods* 2015; 239: 28–33.
46. Forogh B, Mirshaki Z, Raissi GR, *et al*. Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: a pilot randomized controlled trial. *Neurol Sci* 2016; 37: 253–259.
47. Souza DDS, Almeida AA, Andrade SMDS, *et al*. Transcranial direct current stimulation improves tinnitus perception and modulates cortical electrical activity in patients with tinnitus: a randomized clinical trial. *Neurophysiol Clin* 2020; 50: 289–300.
48. Hyvärinen P, Mäkitie A and Aarnisalo AA. Self-administered domiciliary tDCS treatment for tinnitus: a double-blind sham-controlled study. *PLoS ONE* 2016; 11: e0154286.
49. Teismann H, Wollbrink A, Okamoto H, *et al*. Combining transcranial direct current stimulation and tailor-made notched music training to decrease tinnitus-related distress – a pilot study. *PLoS ONE* 2014; 9: e89904.
50. Joos K, De Ridder D, Van de Heyning P, *et al*. Polarity specific suppression effects of transcranial direct current stimulation for tinnitus. *Neural Plast* 2014; 2014: 930860.
51. Pal N, Maire R, Stephan MA, *et al*. Transcranial direct current stimulation for the treatment of chronic tinnitus: a randomized controlled study. *Brain Stimul* 2015; 8: 1101–1107.
52. Minami SB, Oishi N, Watabe T, *et al*. Auditory resting-state functional connectivity in tinnitus and modulation with transcranial direct current stimulation. *Acta Otolaryngol* 2015; 135: 1286–1292.
53. Henin S, Fein D, Smouha E, *et al*. The effects of compensatory auditory stimulation and high-definition transcranial direct current stimulation (HD-tDCS) on tinnitus perception – a randomized pilot study. *PLoS ONE* 2016; 11: e0166208.
54. Abtahi H, Okhovvat A, Heidari S, *et al*. Effect of transcranial direct current stimulation on short-term and long-term treatment of chronic tinnitus. *Am J Otolaryngol* 2018; 39: 94–96.
55. Vanneste S, Fregni F and 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.
56. Vanneste S, Plazier M, Ost J, *et al*. Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. *Exp Brain Res* 2010; 202: 779–785.
57. Frank E, Schecklmann M, Landgrebe M, *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: 327–333.
58. Faber M, Vanneste S, Fregni F, *et al*. Top down prefrontal affective modulation of tinnitus with multiple sessions of tDCS of dorsolateral prefrontal cortex. *Brain Stimul* 2012; 5: 492–498.
59. De Ridder D and Vanneste S. EEG driven tDCS versus bifrontal tDCS for tinnitus. *Front Psychiatry* 2012; 3: 84.
60. Vanneste S, Walsh V, Van De Heyning P, *et al*. Comparing immediate transient tinnitus suppression using tACS and tDCS: a placebo-controlled study. *Exp Brain Res* 2013; 226: 25–31.
61. Shekhawat GS, Sundram F, Bikson M, *et al*. Intensity, duration, and location of high-definition transcranial direct current stimulation for tinnitus relief. *Neurorehabil Neural Repair* 2016; 30: 349–359.

62. Lee HY, Choi MS, Chang DS, *et al*. Combined bifrontal transcranial direct current stimulation and tailor-made notched music training in chronic tinnitus. *J Audiol Otol* 2017; 21: 22–27.

63. Rabau S, Shekhawat GS, Aboseria M, *et al*. Comparison of the long-term effect of positioning the cathode in tDCS in tinnitus patients. *Front Aging Neurosci* 2017; 9: 217.

64. To WT, Ost J, Hart J Jr, *et al*. The added value of auditory cortex transcranial random noise stimulation (tRNS) after bifrontal transcranial direct current stimulation (tDCS) for tinnitus. *J Neural Transm (Vienna)* 2017; 124: 79–88.

65. Shekhawat GS and Vanneste S. Optimization of transcranial direct current stimulation of dorsolateral prefrontal cortex for tinnitus: a non-linear dose-response effect. *Sci Rep* 2018; 8: 8311.

66. Shekhawat GS and Vanneste S. High-definition transcranial direct current stimulation of the dorsolateral prefrontal cortex for tinnitus modulation: a preliminary trial. *J Neural Transm (Vienna)* 2018; 125: 163–171.

67. Jacquemin L, Shekhawat GS, Van de Heyning P, *et al*. Effects of electrical stimulation in tinnitus patients: conventional versus high-definition tDCS. *Neurorehabil Neural Repair* 2018; 32: 714–723.

68. Lee HY. Adjunctive role of bifrontal transcranial direct current stimulation in distressed patients with severe tinnitus. *J Korean Med Sci* 2019; 34: e19.

69. Jacquemin L, Mertens G, Van de Heyning P, *et al*. An exploratory study on the use of event-related potentials as an objective measure of auditory processing and therapy effect in patients with tinnitus: a transcranial direct current stimulation study. *Otol Neurotol* 2019; 40: e868–e875.

70. Bae EB, Lee JH and Song JJ. Single-session of combined tDCS-TMS may increase therapeutic effects in subjects with tinnitus. *Front Neurol* 2020; 11: 160.

71. Jacquemin L, Mertens G, Shekhawat GS, *et al*. High definition transcranial direct current stimulation (HD-tDCS) for chronic tinnitus: outcomes from a prospective longitudinal large cohort study. *Prog Brain Res* 2021; 263: 137–152.

72. Bae SH, Moon SJ, Lee JG, *et al*. Comparison of treatment outcome between repetitive transcranial magnetic stimulation (rTMS) and transcutaneous direct current stimulation (tDCS) in intractable tinnitus. *J Clin Med* 2021; 10: 635.

73. Nitsche MA, Doemkes S, Karaköse T, *et al*. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol* 2007; 97: 3109–3117.

74. Datta A, Elwassif M, Battaglia F, *et al*. Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. *J Neural Eng* 2008; 5: 163–174.

75. Datta A, Bansal V, Diaz J, *et al*. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimul* 2009; 2: 201–207, 207.e1.

76. Buzsáki G and Draguhn A. Neuronal oscillations in cortical networks. *Science* 2004; 304: 1926–1929.

77. Herrmann CS, Rach S, Neuling T, *et al*. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front Hum Neurosci* 2013; 7: 279.

78. Zaehle T, Rach S and Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS ONE* 2010; 5: e13766.

79. Vossen A, Gross J and Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. *Brain Stimul* 2015; 8: 499–508.

80. Cabral-Calderin Y, Williams KA, Opitz A, *et al*. Transcranial alternating current stimulation modulates spontaneous low frequency fluctuations as measured with fMRI. *NeuroImage* 2016; 141: 88–107.

81. Vanneste S, Plazier M, der Loo E, *et al*. The neural correlates of tinnitus-related distress. *NeuroImage* 2010; 52: 470–480.

82. Claes L, Stamberger H, Van de Heyning P, *et al*. Auditory cortex tACS and tRNS for tinnitus: single versus multiple sessions. *Neural Plast* 2014; 2014: 436713.

83. Terney D, Chaieb L, Moliadze V, *et al*. Increasing human brain excitability by transcranial high-frequency random noise stimulation. *J Neurosci* 2008; 28: 14147–14155.

84. Schoen I and Fromherz P. Extracellular stimulation of mammalian neurons through repetitive activation of Na+ channels by weak

capacitive currents on a silicon chip. *J Neurophysiol* 2008; 100: 346–357.

85. Van Doren J, Langguth B and Schecklmann M. Electroencephalographic effects of transcranial random noise stimulation in the auditory cortex. *Brain Stimul* 2014; 7: 807–812.
86. Joos K, De Ridder D and Vanneste S. The differential effect of low- versus high-frequency random noise stimulation in the treatment of tinnitus. *Exp Brain Res* 2015; 233: 1433–1440.
87. Mohsen S, Pourbakht A, Farhadi M, *et al*. The efficacy and safety of multiple sessions of multisite transcranial random noise stimulation in treating chronic tinnitus. *Braz J Otorhinolaryngol* 2019; 85: 628–635.
88. Kreuzer PM, Poeppl TB, Rupprecht R, *et al*. Daily high-frequency transcranial random noise stimulation of bilateral temporal cortex in chronic tinnitus – a pilot study. *Sci Rep* 2019; 9: 12274.
89. Yu ZJ, Weller RA, Sandidge K, *et al*. Vagus nerve stimulation: can it be used in adolescents or children with treatment-resistant depression? *Curr Psychiatry Rep* 2008; 10: 116–122.
90. Bonaz B, Picq C, Sinniger V, *et al*. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. *Neurogastroenterol Motil* 2013; 25: 208–221.
91. Manta S, Dong J, Debonnel G, *et al*. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. *J Psychiatry Neurosci* 2009; 34: 272–280.
92. Seol GH, Ziburkus J, Huang S, *et al*. Neuromodulators control the polarity of spike-timing-dependent synaptic plasticity. *Neuron* 2007; 55: 919–929.
93. Manunta Y and Edeline JM. Noradrenergic induction of selective plasticity in the frequency tuning of auditory cortex neurons. *J Neurophysiol* 2004; 92: 1445–1463.
94. Edeline JM, Manunta Y and Hennevin E. Induction of selective plasticity in the frequency tuning of auditory cortex and auditory thalamus neurons by locus coeruleus stimulation. *Hear Res* 2011; 274: 75–84.
95. Engineer ND, Riley JR, Seale JD, *et al*. Reversing pathological neural activity using targeted plasticity. *Nature* 2011; 470: 101–104.
96. Tyler R, Cacace A, Stocking C, *et al*. Vagus nerve stimulation paired with tones for the treatment of tinnitus: a prospective randomized double-blind controlled pilot study in humans. *Sci Rep* 2017; 7: 11960.
97. Engineer ND, Rosellini WM and Tyler RS. Willingness to accept and pay for implantable tinnitus treatments: a survey. *Neuromodulation* 2013; 16: 154–162.
98. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol* 2002; 1: 477–482.
99. Butt MF, Albusoda A, Farmer AD, *et al*. The anatomical basis for transcutaneous auricular vagus nerve stimulation. *J Anat* 2020; 236: 588–611.
100. Kraus T, Hösl K, Kiess O, *et al*. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. *J Neural Transm (Vienna)* 2007; 114: 1485–1493.
101. Kraus T, Kiess O, Hösl K, *et al*. CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal – a pilot study. *Brain Stimul* 2013; 6: 798–804.
102. Shim HJ, Kwak MY, An YH, *et al*. Feasibility and safety of transcutaneous vagus nerve stimulation paired with notched music therapy for the treatment of chronic tinnitus. *J Audiol Otol* 2015; 19: 159–167.
103. Lehtimäki J, Hyvärinen P, Ylikoski M, *et al*. Transcutaneous vagus nerve stimulation in tinnitus: a pilot study. *Acta Otolaryngol* 2013; 133: 378–382.
104. Mei ZG, Yang SB, Cai SJ, *et al*. Treatment of tinnitus with electrical stimulation on acupoint in the distribution area of ear vagus nerve combining with sound masking: randomized controlled trial. *World J Acup – Moxibust* 2014; 24: 30–35.
105. Ylikoski J, Markkanen M, Pirvola U, *et al*. Stress and tinnitus; transcutaneous auricular vagal nerve stimulation attenuates tinnitus-triggered stress reaction. *Front Psychol* 2020; 11: 570196.
106. Kreuzer PM, Landgrebe M, Resch M, *et al*. Feasibility, safety and efficacy of transcutaneous vagus nerve stimulation in chronic tinnitus: an open pilot study. *Brain Stimul* 2014; 7: 740–747.
107. Suk WC, Kim SJ, Chang DS, *et al*. Characteristics of stimulus intensity in transcutaneous vagus nerve stimulation for chronic tinnitus. *J Int Adv Otol* 2018; 14: 267–272.
108. Tutar B, Atar S, Berkiten G, *et al*. The effect of transcutaneous electrical nerve stimulation

(TENS) on chronic subjective tinnitus. *Am J Otolaryngol* 2020; 41: 102326.

109. Stouffer JL and Tyler RS. Characterization of tinnitus by tinnitus patients. *J Speech Hear Disord* 1990; 55: 439–453.

110. Giraud AL, Chéry-Croze S, Fischer G, *et al*. A selective imaging of tinnitus. *Neuroreport* 1999; 10: 1–5.

111. Mirz F, Pedersen B, Ishizu K, *et al*. Positron emission tomography of cortical centers of tinnitus. *Hear Res* 1999; 134: 133–144.

112. Seydell-Greenwald A, Leaver AM, Turesky TK, *et al*. Functional MRI evidence for a role of ventral prefrontal cortex in tinnitus. *Brain Res* 2012; 1485: 22–39.

113. Alain C, Woods DL and Knight RT. A distributed cortical network for auditory sensory memory in humans. *Brain Res* 1998; 812: 23–37.

114. Rauschecker JP, Leaver AM and Mühlau M. Tuning out the noise: limbic-auditory interactions in tinnitus. *Neuron* 2010; 66: 819–826.

115. Plewnia C, Bartels M and Gerloff C. Transient suppression of tinnitus by transcranial magnetic stimulation. *Ann Neurol* 2003; 53: 263–266.

116. Bikson M, Grossman P, Thomas C, *et al*. Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimul* 2016; 9: 641–661.

117. Im C-H, Park J-H, Shim M, *et al*. Evaluation of local electric fields generated by transcranial direct current stimulation with an extracephalic reference electrode based on realistic 3D body modeling. *Phys Med Biol* 2012; 57: 2137–2150.

118. Matsumoto H and Ugawa Y. Adverse events of tDCS and tACS: a review. *Clin Neurophysiol Pract* 2017; 2: 19–25.

119. Brunoni AR, Amadera J, Berbel B, *et al*. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol* 2011; 14: 1133–1145.

120. Wang Y, Li SY, Wang D, *et al*. Transcutaneous auricular vagus nerve stimulation: from concept to application. *Neurosci Bull* 2021; 37: 853–862.

121. Badran BW, Dowdle LT, Mithoefer OJ, *et al*. Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: a concurrent taVNS/fMRI study and review. *Brain Stimul* 2018; 11: 492–500.

122. Yakunina N, Kim SS and Nam EC. Optimization of transcutaneous vagus nerve stimulation using functional MRI. *Neuromodulation* 2017; 20: 290–300.

123. Kreisberg E, Esmaeilpour Z, Adair D, *et al*. High-resolution computational modeling of the current flow in the outer ear during transcutaneous auricular Vagus Nerve Stimulation (taVNS). *Brain Stimul* 2021; 14: 1419–1430.

124. Yap JYY, Keatch C, Lambert E, *et al*. Critical review of transcutaneous vagus nerve stimulation: challenges for translation to clinical practice. *Front Neurosci* 2020; 14: 284.

125. Redgrave J, Day D, Leung H, *et al*. Safety and tolerability of transcutaneous vagus nerve stimulation in humans; a systematic review. *Brain Stimul* 2018; 11: 1225–1238.

126. De Ridder D, Langguth B and Vanneste S. Vagus nerve stimulation for tinnitus: a review and perspective. *Prog Brain Res* 2021; 262: 451–467.

127. Farmer AD, Strzelczyk A, Finisguerra A, *et al*. International consensus based review and recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (Version 2020). *Front Hum Neurosci* 2020; 14: 568051.

Visit SAGE journals online journals.sagepub.com/home/taj

SAGE journals