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Differences between a single session and repeated sessions of 1 Hz TMS by double-cone coil prefrontal stimulation for the improvement of tinnitus

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ABSTRACT

Tinnitus related distress is associated with increased activity in the anterior cingulate cortex (ACC). In a recent study, it was demonstrated that a single session of low frequency prefrontal TMS using a double-cone coil (DCC) modulating the ACC (AC/DC TMS, anterior cingulate cortex targeted modulation by Double-Cone coil) yields a transient improvement in subjects with chronic tinnitus. An increasing number of studies demonstrated that repeated sessions of low frequency TMS to the temporoparietal area can significantly improve tinnitus complaints. Our aim is to determine the extent to which repeated sessions of AC/DC TMS can modulate tinnitus in comparison to a single session. Seventy-three tinnitus patients received a single ($N = 46$) or repetitive ($N = 27$) session(s) of TMS using a DCC placed over the prefrontal cortex. Our results indicate that both single sessions as well as multiple sessions (i.e. 8 sessions) of AC/DC TMS suppress both tinnitus distress (respectively 7.60% vs. 26.19%) and tinnitus intensity (respectively 7.12% vs. 19.60%) transiently. It was further shown that multiple sessions of AC/DC TMS generate a higher suppression effect in comparison to a single session of AC/DC TMS and that more patients responded to repeated sessions of 1 Hz stimulation in comparison to a single session. Our findings give further support to the fact that non-auditory areas are involved in tinnitus intensity and tinnitus distress and that more patients respond to repeated sessions with a higher suppression effect in comparison to patients who received a single session, suggesting that the approach of daily TMS sessions is relevant.

Introduction

At some point in time most people experience a sound in their ears or head although no external sound is present [19]. This has been related to listening to loud music [2], sudden sensorineural hearing loss [49], use of medication [16], trauma [21] or other causes. Typically, this perception is reversible and subsides approximately between a few seconds to a few days. However, 10–15% of the adult general population perceive these phantom sounds [2], also called tinnitus, chronically. About 6–25% of the affected people report interference with their daily living [25], causing a considerable amount of distress, involving sleep deprivation [1,9], depression [18], annoyance, cognitive problems [23], and work impairment [3,9,19,25,30].

Tinnitus is associated with a reorganization and hyperactivity in the auditory central nervous system [19,26,40,47]. However, tinnitus is not only related to auditory but also to non-auditory brain structures. Tinnitus related distress is associated to increased beta activity in the dorsal part of the anterior cingulate cortex (ACC) and the amount of distress correlates with an alpha network consisting of the sgACC using source localization EEG [13,53]. The ACC might be responsible for the integration of cognitive and emotional processing for tinnitus [43]. A recent study reported that the degree of phase locked coupling between ACC and the right frontal lobe correlates negatively with tinnitus intrusiveness (i.e. how bothersome and obtrusive tinnitus is perceived) [48]. Also, it was hypothesized that the anterior cingulate cortex is critically involved in attentional control of auditory processing [22] and in the generation of tinnitus [41]. Furthermore fluctuations in the dorsal ACC (dACC) and anterior cingulate cortex determine whether an external auditory stimulus is perceived or not [46], suggesting that the ACC and auditory cortex have to be co-activated for conscious auditory perception to occur. Thus modulating the dACC could influence both tinnitus distress and tinnitus loudness.

Over the last decade transcranial magnetic stimulation (TMS) has received increasing attention as a potential therapeutic method for the treatment of tinnitus. TMS is a non-invasive tool provoking

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a strong impulse of magnetic field that induces an electrical current to a specific region of the brain through an intact scalp. An increasing number of clinical studies indeed has demonstrated that TMS on the temporoparietal lobe can alter tinnitus [11,12,15,20,29]. An increasing number of studies also demonstrated that repeated sessions (daily trains of 1200–2000 pulses for 5–10 days) of low frequency TMS to the temporoparietal area can significantly improve tinnitus complaints for a longer time [35,45,50].

Most studies in tinnitus apply TMS with a figure-eight coil. TMS modulates the superficial cortical areas directly but has an indirect effect on remote areas functionally connected to the stimulated area such as the auditory thalamus [37]. Previous research also showed that combined stimulation of the temporoparietal and dorsolateral prefrontal cortex (DLPFC) using a standard figure-eight coil can suppress tinnitus potentially even better [28]. A recent study using positron emission tomography (PET) revealed that frontal TMS using a double-cone coil (DCC) can modulate both dorsal and sgACC as well (AC/DC TMS, anterior cingulate cortex targeted modulation by Double-Cone coil) as a number of more distal cortical areas [24]. This was further confirmed in a case report from an alcohol dependent patient using fMRI and source localized EEG that AC/DC TMS indeed modulates the dorsal and sgACC [14]. In a recent study, Vanneste and colleagues demonstrated that a single session of low frequency AC/DC TMS yields a moderate transient improvement in subjects with chronic tinnitus [55].

Based on the fact that the AC/DC TMS might modulate the dACC and sgACC [14] and repeated sessions of TMS might generate a stronger effect [35,45,50] the aim of the study is to determine the extent to which repeated sessions of AC/DC TMS can modulate tinnitus.

Methods

Patients

Seventy-three tinnitus patients (48 males, 25 females) participated in this experiment at the multidisciplinary TRI tinnitus clinic of the Antwerp University Hospital, Belgium. The mean age was 58.74 year (Sd = 14.43; range: 20–78 years). Forty patients had narrow band noise and 33 patients presented with pure tone tinnitus, while 49 patients had bilateral tinnitus and 24 unilateral tinnitus. The mean tinnitus duration was 7.23 years (Sd = 7.39; range = 1–30 year). All participants underwent a complete audiological, Ears Nose Throat (ENT) and neurological investigation to rule out possible treatable causes for their tinnitus. Tinnitus matching was performed by presenting sounds to the ear in which the tinnitus is not perceived in unilateral tinnitus, bilaterally in bilateral tinnitus patients. Technical investigations included MRI of the brain and posterior fossa, pure tone and speech audiometry and tympanometry. No patients took on the moment of stimulation any additional drugs.

The study has been approved by the Antwerp University Hospital Institutional review board ('Comité voor medische ethiek'). Patients approved an oral informed consent.

TMS

TMS was performed using a super rapid stimulator (Magstim Inc, Wales, UK) with a double-cone coil (DCC) (P/N 9902-00; Magstim Co. Ltd) placed over medial prefrontal cortex (1.5 cm anterior to 1/3 of the distance from the nasion inion) [24].

The resting motor threshold to TMS was first determined by placing a figure-eight coil over the motor cortex using EMG. The coil was positioned tangentially to the scalp and oriented so that the induced electrical currents would flow approximately perpendicular to the central sulcus, at 45° angle from the mid-sagittal line. The intensity of the stimulation was set at 80% of the motor threshold. Patients received repeated stimulation at 1 Hz, each stimulation session consisting of 1500 pulses. These settings are similar to our study for single sessions of AC/DC TMS [55]. All patients were wearing earplugs during the TMS session.

Originally 110 tinnitus patients were randomly selected and screened with the procedure as described above. Patients were screened one week before the treatment. Only patients who had a placebo negative response on AC/DC TMS on this previous session were selected in this study. The presence of a control procedure (i.e. placebo effect) was tested by placing the coil perpendicular to the prefrontal area at the frequencies that yielded maximal tinnitus suppression rates. A total of 73 tinnitus patients had a placebo negative response and were included in the study. Patients were randomly assigned to the single sessions or the multiple sessions group. Twenty-seven patients had 8 sessions (daily for 8 days except for the weekend) of TMS, while forty-six patients received a single session of TMS. Patients were assessed just before the start of the TMS sessions and immediately at the end of the TMS session(s). Group sizes were different because some of the selected patients could not come for 8 sessions in a row, as such the drop-out rate was relatively high in this group.

Assessment

Before the TMS session, patients graded their tinnitus perception ('How loud is your tinnitus?: 0 = no tinnitus and 10 = as loud as imaginable') and tinnitus distress ('How stressful is your tinnitus? 0 = no distress and 10 = suicidal distress') on a numeric rating scale from 0 to 10. We opted to use these visual analogue scales instead of using tinnitus questionnaires, as these are not sensitive for short-lasting transient changes. This is important as a single session only creates transient differences, for which tinnitus questionnaires are less sensitive.

Statistical analyses

Calculations were performed using SPSS software package. Repeated measures ANOVA was conducted with as dependent variable pre and post-TMS for both tinnitus distress and tinnitus perception and as independent variables session (single vs. repeated). A Bonferroni correction for multiple comparisons was applied. A χ^2 was applied to verify whether patients responded more to the repeated sessions in comparison to single sessions. A responder was defined as patient who had a suppression effect of more than 10% ((pre-TMS − post-TMS)/pre-TMS) on both tinnitus distress and tinnitus perception). This latter criterion is based on previous research conducted in our lab [52,54].

Results

A repeated measures ANOVA revealed a significant main effect for pre vs. post-TMS (F = 13.24, $P < .001$) and a significant interaction effect for pre vs. post-TMS and sessions (single vs. repeated) (F = 4.01, $P < .05$). No significant main effect was obtained for session (F = 1.86, $P < .16$), indicating that there was no effect between the single and repeated sessions independent of pre vs. post-TMS. For the main effect pre vs. post-TMS, after applying a Bonferroni correction for multiple comparisons, post-TMS tinnitus patients had a suppression on both tinnitus distress (F = 3.59, $P < .05$) and tinnitus perception (F = 3.48, $P < .05$) in comparison to pre-TMS (see Fig. 1). Simple contrasts were used to further explore the obtained interaction. For distress, a significant

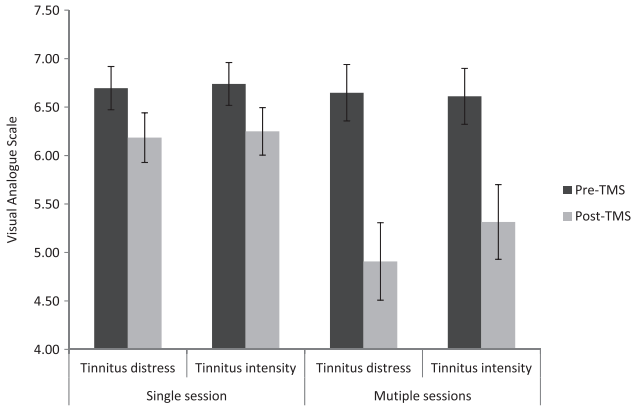

Figure 1. Comparisons between pre-TMS and post-TMS on the visual analogue scale for both tinnitus distress and tinnitus intensity for respectively a single session and repeated sessions.

effect was obtained when comparing pre vs. post-TMS for both a single session ($F = 3.69$, $P < .05$) as well as repeated sessions ($F = 25.15$, $P < .001$), indicating that for both a single session as well as repeated sessions a suppression of tinnitus distress was obtained after TMS (see Fig. 1). For perception similar results were obtained, revealing that for both a single session ($F = 4.29$, $P < .05$) as well as repeated sessions ($F = 17.66$, $P < .05$) a suppression of tinnitus perception was obtained after TMS (see Fig. 1). A further simple contrast analysis yielded also significance between a single session and repeated sessions for both tinnitus distress ($F = 6.89$, $P < .05$) and tinnitus perception ($F = 3.71$, $P < .05$) (see Fig. 1) post-TMS demonstrating that repeated sessions obtain a higher suppression effect in comparison to a single session. When conducting a similar analysis for pre-TMS no significant differences were demonstrated using a single session and repeated sessions for both tinnitus distress ($F = .06$, $P = .81$) and tinnitus perception ($F = .12$, $P = .73$) (see Fig. 1).

Of the 46 tinnitus patients who had received a single session of AC/DC TMS 11 patients (23.91%) responded to the simulation with a mean transient suppression effect of 29.23% on both tinnitus distress and tinnitus perception (See Table 1). For the tinnitus patients who received repeated sessions of AC/DC TMS respectively 13 (48.15%) and 12 (44.44%) responded on tinnitus distress and tinnitus perception with a respectively transient suppression of 55.67% and 48.76%. Significantly more tinnitus patients responded to the repeated sessions than to a single session for tinnitus distress ($\chi^2 = 4.53$, $P < .05$). For tinnitus perception a similar effect was obtained, however this was only marginally significant ($\chi^2 = 4.53$, $P < .05$) (See Table 1).

It is important to note that no patient reported an adverse event for the single sessions. However for the multiple sessions 2 patients reported a worsening of their tinnitus distress and 3 patients reported a worsening of their tinnitus perception.

Discussion

In this study we want to describe the transient effect of low frequency prefrontal AC/DC TMS on tinnitus and compare a single session with multiple sessions. The rationale for using 1 Hz stimulation was that a previous study revealed that 1 Hz AC/CC TMS yielded the best suppressing effect on tinnitus [55].

The obtained results indicate that both single sessions as well as multiple sessions of AC/C TMS suppress both tinnitus distress and tinnitus perception transiently. These results confirm a previous AC/DC TMS study demonstrating a transient improvement of both tinnitus-related distress as well as tinnitus perception [55]. In addition, it was shown that multiple sessions of AC/DC TMS generate a higher suppression effect in comparison to a single session of AC/DC TMS and that more patients responded to repeated sessions of 1 Hz stimulation in comparison to a single session. The reason use 1 Hz stimulation was based on a previous pilot study demonstrating that 1 Hz AC/DC TMS yielded the best suppressive effect on tinnitus.

Similarly to a previous study both tinnitus perception and tinnitus distress are transiently improved [55]. The ACC might be involved in integrating motivationally important information with appropriate bodily responses [8] related to the survival needs of the body [7]. It has been hypothesized that the function of the ACC in tinnitus could be related to the fact that the internally generated phantom sound is considered as motivationally important information i.e. salient and that the ACC responds with an appropriate bodily response, i.e. it keeps the tinnitus in the focus of attention which ultimately can lead to tinnitus related distress [10,53]. The sgACC is characterized by an anticorrelated activity with the dACC [36], and voxel based morphometry has shown that the sgACC is involved in tinnitus [32,39], possibly controlling a noise cancelling mechanism [44] via the reticular nucleus of the thalamus, thereby modulating pathological thalamocortical activity implicated in tinnitus [33]. This suggests that the ACC is involved in tinnitus perception modulation. It was also shown that the amount of tinnitus distress suppression obtained by temporal TMS is related to metabolism in the ACC [42], further demonstrating the importance of the area in tinnitus distress.

Based on work in healthy volunteers it has been demonstrated that whether or not a near threshold auditory stimulus is perceived depends on activity fluctuations in the dACC and anterior insula [46]. If this holds for tinnitus, which is an internally generated sound but externally attributed by patients, tinnitus is likely only perceived when the auditory cortex and dACC/insula are co-activated. Thus targeting the dACC by AC/DC stimulation could potentially reduce tinnitus perception by this mechanism as well.

Table 1
An overview of the patients responding to DCC TMS targeting the ACC.

	Tinnitus distress			Tinnitus intensity		
	N	Amount of suppression (%)	Range (%)	*N*	Amount of suppression (%)	Range (%)
Single session						
Worse	0	–	–	0	–	–
No improvement	34	–	–	35	–	–
Very small improvement (≤10%)	1	10.00	–	0	–	–
Improvement (>10%)	11	29.23	14.29–42.86	11	29.23	14.29–42.86
Repeated sessions						
Worse	2	27.15	14.29–40	3	22.26	12.50–40
No improvement	12	0	–	10	0	–
Very small improvement (≤10%)	0	–	–	2	6.91	6.67–7.14
Improvement (>10%)	13	55.67	11.11–100	12	48.76	28.57–100

A third potential hypothetical working mechanism explaining the effect of AC/DC TMS is by top-down modulation of the auditory cortex. As mentioned, based on electrophysiological data it has been suggested that tinnitus might occur as the result of a dysfunction in the top-down inhibitory processes [41,57], and a preliminary study has demonstrated that modulating the frontal cortex in addition to auditory cortex TMS yields better long-term results [28]. In a PET study increased neural activity for tinnitus sufferers was shown in the right hemisphere, on the middle frontal and middle temporal regions as well as in lateral mesial posterior sites [38]. In MEG studies more reduction in alpha (8–12 Hz) and an increase in delta (1.5–4 Hz) was found in temporal regions, left frontal and right parietal areas [56] as well as functional connectivity in the right frontal lobe and ACC [48]. Indirect support for this mechanism is related to mechanisms known to be involved in tDCS suppression of tinnitus by DLPFC stimulation. Anodal stimulation of the right DLPFC with cathodal stimulation of the left DLPFC can improve tinnitus perception. This is mediated via the ACC and results in decreased gamma band activity in the auditory cortex associated with a decrease in tinnitus perception [51]. As the AC/DC TMS effectively stimulates the superior frontal area bilaterally, but exerts its main effect in the ACC [24], which could be similar to the bilateral DLPFC tDCS mechanism.

Our study also shows that multiple sessions of AC/DC TMS generate a higher suppression effect and response rate after 8 (repeated) sessions in comparison to a single session. It has been demonstrated that high frequency TMS induced a significantly greater increase in motor evoked potentials (MEP) when performed 24 h following a prior TMS session using the same stimulation parameters [5,34]. In a recent study it was further confirmed that repeated sessions of TMS had a better effect when a night with sleep follows TMS, indicating that the sleep–wake/circadian cycle may be a critical factor in the cumulative effect of treatment [5]. Further research is needed to confirm this hypothesis.

One limitation of this study relates to the coil positioning. These were not performed under neuronavigated control and were only defined by anatomical landmarks. Yet, recent studies for TMS demonstrated that consistent results can be obtained with a probabilistic approach (i.e. non-neuronavigated) [31]. Nevertheless even if fMRI-guided stimulation might be accurate within the range of millimetres for targeting purposes, the area of modulation might still be as large as 3 cm [6], questioning the value of fMRI-guided TMS of the auditory cortex [15], and thus certainly also for the ACC.

What remains to be done is to compare pre-AC/DC TMS EEG or fMRI with post-AC/DC TMS EEG or fMRI images to verify whether indeed an activity decrease within the ACC results from these stimulations. Another limitation of the study was that there was no placebo-arm included within the study. Although only patients were included who had a placebo negative response on a previous session, future research could also include a placebo-arm. Potential clinical effects of promising new treatments should be tested first in an open-trial-design, which can give important information about the effect size of the treatment, similarly to what has been proposed for medication for tinnitus [17]. This information is necessary to design prospective placebo-controlled clinical trials, which are more costly and time consuming [17]. In addition, we had a high drop-out rate in the repetitive sessions, as not all patients could come for all consecutive sessions. It is furthermore important for future research to do long-term follow-up evaluations to verify how long the effect of multiple sessions of AC/DC TMS remains. Previous research evaluating the effect of TMS to the temporoparietal cortex observed long lasting effects up to one year, and even up to 4 years [4,27].

In conclusion, AC/DC TMS might become clinically relevant in the treatment of tinnitus. Our findings give support to the fact that non-auditory areas are involved in tinnitus perception and tinnitus distress and that more patients respond to repeated sessions with a higher suppression effect in comparison to patients who receive a single session, suggesting that the approach of daily TMS sessions is relevant. Combining this stimulation method with functional imaging will refine our understanding of the neural circuits involved in auditory phantom perceptions such as chronic tinnitus.

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References

[1] Alster J, Shemesh Z, Ornan M, Attias J. Sleep disturbance associated with chronic tinnitus. Biol Psychiatry 1993;34:84–90.
[2] Axelsson A, Prasher D. Tinnitus induced by occupational and leisure noise. Noise Health 2000;2:47–54.
[3] Baguley DM. Mechanisms of tinnitus. Br Med Bull 2002;63:195–212.
[4] Burger J, Frank E, Kreuzer P, Kleinjung T, Vielsmeier V, Landgrebe M, et al. Transcranial magnetic stimulation for the treatment of tinnitus: 4-year follow-up in treatment responders-a retrospective analysis. Brain Stimul 2011;4:222–7.
[5] Cohen DA, Freitas C, Tormos JM, Oberman L, Eldaief M, Pascual-Leone A. Enhancing plasticity through repeated rTMS sessions: the benefits of a night of sleep. Clin Neurophysiol 2010;121:2159–64.
[6] Cohen LG, Roth BJ, Nilsson J, Dang N, Panizza M, Bandinelli S, et al. Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. Electroencephalogr Clin Neurophysiol 1990;75:350–7.
[7] Craig AD. Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 2003;13:500–5.
[8] Critchley HD, Mathias CJ, Dolan RJ. Neural activity in the human brain relating to uncertainty and arousal during anticipation. Neuron 2001;29:537–45.
[9] Cronlein T, Langguth B, Geisler P, Hajak G. Tinnitus and insomnia. Prog Brain Res 2007;166:227–33.
[10] De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci U S A 2011a;108:8075–80.
[11] De Ridder D, van der Loo E, Van der Kelen K, Menovsky T, van de Heyning P, Moller A. Do tonic and burst TMS modulate the lemniscal and extralemniscal system differentially? Int J Med Sci 2007a;4:242–6.
[12] De Ridder D, van der Loo E, Van der Kelen K, Menovsky T, van de Heyning P, Moller A. Theta, alpha and beta burst transcranial magnetic stimulation: brain modulation in tinnitus. Int J Med Sci 2007b;4:237–41.
[13] De Ridder D, Vanneste S, Congedo M. The distressed brain: a group blind source separation analysis on tinnitus. PLoS One 2011;6(10):e24273.
[14] De Ridder D, Vanneste S, Kovacs S, Sunaert S, Dom G. Transient alcohol craving suppression by rTMS of dorsal anterior cingulate: an fMRI and LORETA EEG study. Neurosci Lett 2011b;496:5–10.
[15] De Ridder D, Verstraeten E, Van der Kelen K, De Mulder G, Sunaert S, Verlooy J, et al. Transcranial magnetic stimulation for tinnitus: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otol Neurotol 2005;26:616–9.
[16] Dille MF, Konrad-Martin D, Gallun F, Helt WJ, Gordon JS, Reavis KM, et al. Tinnitus onset rates from chemotherapeutic agents and ototoxic antibiotics: results of a large prospective study. J Am Acad Audiol 2010;21:409–17.
[17] Dobie R. Clinical trials and drug therapy for tinnitus. In: Snow JB, editor. Tinnitus: theory and management. Hamilton: BC Decker; 2004. p. 266–77.
[18] Dobie RA. Depression and tinnitus. Otolaryngol Clin North Am 2003;36:383–8.
[19] Eggermont JJ, Roberts LE. The neuroscience of tinnitus. Trends Neurosci 2004;27:676–82.
[20] Eichhammer P, Kleinjung T, Landgrebe M, Hajak G, Langguth B. TMS for treatment of chronic tinnitus: neurobiological effects. Prog Brain Res 2007;166:369–75.
[21] Folmer RL, Griest SE. Chronic tinnitus resulting from head or neck injuries. Laryngoscope 2003;113:821–7.
[22] Grunwald T, Boutros NN, Pezer N, von Oertzen J, Fernandez G, Schaller C, et al. Neuronal substrates of sensory gating within the human brain. Biol Psychiatry 2003;53:511–9.
[23] Hallam RS, McKenna L, Shurlock L. Tinnitus impairs cognitive efficiency. Int J Audiol 2004;43:218–26.
[24] Hayward G, Mehta MA, Harmer C, Spinks TJ, Grasby PM, Goodwin GM. Exploring the physiological effects of double-cone coil TMS over the medial frontal cortex on the anterior cingulate cortex: an H_2(15)O PET study. Eur J Neurosci 2007;25:2224–33.
[25] Heller AJ. Classification and epidemiology of tinnitus. Otolaryngol Clin North Am 2003;36:239–48.

[26] Kaltenbach JA, Afman CE. Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus. Hear Res 2000;140:165–72.
[27] Khedr EM, Rothwell JC, El-Atar A. One-year follow up of patients with chronic tinnitus treated with left temporoparietal rTMS. Eur J Neurol 2009;16:404–8.
[28] Kleinjung T, Eichhammer P, Landgrebe M, Sand P, Hajak G, Steffens T, et al. Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: a pilot study. Otolaryngol Head Neck Surg 2008;138:497–501.
[29] Kleinjung T, Eichhammer P, Langguth B, Jacob P, Marienhagen J, Hajak G, et al. Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. Otolaryngol Head Neck Surg 2005;132:566–9.
[30] Langguth B, Kleinjung T, Fischer B, Hajak G, Eichhammer P, Sand PG. Tinnitus severity, depression, and the big five personality traits. Prog Brain Res 2007; 166:221–5.
[31] Langguth B, Kleinjung T, Landgrebe M, de Ridder D, Hajak G. rTMS for the treatment of tinnitus: the role of neuronavigation for coil positioning. Neurophysiol Clin 2010;40:45–58.
[32] Leaver AM, Renier L, Chevillet MA, Morgan S, Kim HJ, Rauschecker JP. Dysregulation of limbic and auditory networks in tinnitus. Neuron 2011;69: 33–43.
[33] Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 1999;96:15222–7.
[34] Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000;111:800–5.
[35] Marcondes RA, Sanchez TG, Kii MA, Ono CR, Buchpiguel CA, Langguth B, et al. Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: a double-blind controlled, clinical and neuroimaging outcome study. Eur J Neurol 2010;17:38–44.
[36] Margulies DS, Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Mapping the functional connectivity of anterior cingulate cortex. Neuroimage 2007;37:579–88.
[37] May A, Hajak G, Ganssbauer S, Steffens T, Langguth B, Kleinjung T, et al. Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. Cereb Cortex 2007;17:205–10.
[38] Mirz F, Pedersen B, Ishizu K, Johannsen P, Ovesen T, Stodkilde-Jorgensen H, et al. Positron emission tomography of cortical centers of tinnitus. Hear Res 1999;134:133–44.
[39] Muhlau M, Rauschecker JP, Oestreicher E, Gaser C, Rottinger M, Wohlschlager AM, et al. Structural brain changes in tinnitus. Cereb Cortex 2006;16:1283–8.
[40] Muhlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. Proc Natl Acad Sci U S A 1998;95:10340–3.
[41] Norena A, Cransac H, Chery-Croze S. Towards an objectification by classification of tinnitus. Clin Neurophysiol 1999;110:666–75.
[42] Plewnia C, Reimold M, Najib A, Brehm B, Reischl G, Plontke SK, et al. Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation. Hum Brain Mapp 2007a;28:238–46.
[43] Plewnia C, Reimold M, Najib A, Reischl G, Plontke SK, Gerloff C. Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study. J Neurol Neurosurg Psychiatry 2007b;78:152–6.
[44] Rauschecker JP, Leaver AM, Muhlau M. Tuning out the noise: limbic-auditory interactions in tinnitus. Neuron 2010;66:819–26.
[45] Rossi S, De Capua A, Ulivelli M, Bartalini S, Falzarano V, Filippone G, et al. Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: a randomised, crossover, double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 2007;78:857–63.
[46] Sadaghiani S, Hesselmann G, Kleinschmidt A. Distributed and antagonistic contributions of ongoing activity fluctuations to auditory stimulus detection. J Neurosci 2009;29:13410–7.
[47] Salvi RJ, Wang J, Ding D. Auditory plasticity and hyperactivity following cochlear damage. Hear Res 2000;147:261–74.
[48] 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:e3720.
[49] Schreiber BE, Agrup C, Haskard DO, Luxon LM. Sudden sensorineural hearing loss. Lancet 2010;375:1203–11.
[50] Smith JA, Mennemeier M, Bartel T, Chelette KC, Kimbrell T, Triggs W, et al. Repetitive transcranial magnetic stimulation for tinnitus: a pilot study. Laryngoscope 2007;117:529–34.
[51] Vanneste S, De Ridder D. Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. Eur J Neurosci 2011;34:605–14.
[52] Vanneste S, Focquaert F, Van de Heyning P, De Ridder D. Different resting state brain activity and functional connectivity in patients who respond and not respond to bifrontal tDCS for tinnitus suppression. Exp Brain Res; 2011a.
[53] Vanneste S, Plazier M, der Loo E, de Heyning PV, Congedo M, De Ridder D. The neural correlates of tinnitus-related distress. Neuroimage 2010a;52: 470–80.
[54] 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 2010b; 202:779–85.
[55] Vanneste S, Plazier M, Van de Heyning P, De Ridder D. Repetitive transcranial magnetic stimulation frequency dependent tinnitus improvement by double cone coil prefrontal stimulation. J Neurol Neurosurg Psychiatry; 2011b.
[56] Weisz N, Moratti S, Meinzer M, Dohrmann K, Elbert T. Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. PLoS Med 2005;2:e153.
[57] Weisz N, Voss S, Berg P, Elbert T. Abnormal auditory mismatch response in tinnitus sufferers with high-frequency hearing loss is associated with subjective distress level. BMC Neurosci 2004;5:8.