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RESEARCH ARTICLE

The differential effect of low- versus high-frequency random noise stimulation in the treatment of tinnitus

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Abstract Tinnitus is the sensation of a ringing, buzzing, roaring or hissing sound in the absence of an external sound. As tinnitus has been related to hyperactivity and synaptic plasticity changes in the central auditory system, invasive and noninvasive neuromodulation methods have been used to interfere with this underlying mechanism to reduce tinnitus loudness and distress. Recently, transcranial random noise stimulation applied over the auditory cortex induced a more pronounced effect on tinnitus loudness than transcranial direct current and alternating current stimulation. We performed tRNS over the temporoparietal cortex in 154 patients with non-pulsatile tinnitus. A total of 119 patients received low-frequency tRNS (lf-tRNS), 19 high-frequency tRNS (hf-tRNS) and 16 whole frequency spectrum tRNS (wf-tRNS). The effect was evaluated by using the numeric rating scale loudness and distress pre- and post-stimulation. This study revealed a significant reduction in tinnitus loudness when lf-tRNS and hf-tRNS were applied as well as a reduction in tinnitus-related distress with lf-tRNS. Moreover, we observed a significantly more pronounced reduction in loudness and distress in pure tone (PT) tinnitus compared to narrow band noise (NBN) tinnitus when hf-tRNS was applied, a difference that could not be obtained with lf-tRNS. Based on these results, tRNS might be a promising treatment option for non-pulsatile tinnitus; however, we cannot yet provide a clear mechanistic explanation for the different results obtained with different types of stimulation, i.e., lf-tRNS, hf-tRNS and wf-tRNS, or with different types of tinnitus, i.e., PT and NBN tinnitus.

Keywords Tinnitus · Noninvasive neuromodulation · Transcranial random noise stimulation (tRNS) · Loudness · Distress · Auditory cortex

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Introduction

Tinnitus is the experience of hearing a sound in the absence of an external sound source. Most causes of tinnitus are related to transient or permanent deprivation of auditory input, associated with listening to loud music (Axelsson and Prasher 2000), sudden sensorineural hearing loss (Schreiber et al. 2010), noise trauma (Folmer and Griest 2003) or other causes. The development of tinnitus has been explained as a compensation mechanism to reduce deafferentation-related sensory uncertainty (i.e., lack of information) (De Ridder et al. 2012), possibly explaining its high prevalence in hearing loss (Axelsson and Ringdahl 1989). Tinnitus can lead to distress in about 20 % of tinnitus patients (Axelsson and Ringdahl 1989), which might result into psychological complications such as annoyance, concentration problems, depression, anxiety, irritability,

sleep disturbances and intense worrying (Scott and Lindberg 2000; Erlandsson and Holgers 2001).

Although no consensus has currently been reached about the neurophysiological model of tinnitus, it has been proposed that tinnitus is related to either auditory deafferentation (Jastreboff 1990; Norena and Eggermont 2006; Weisz et al. 2007; Roberts et al. 2010; De Ridder et al. 2011a; Eggermont and Roberts 2012), a deficit in noise canceling (Rauschecker et al. 2010; Leaver et al. 2011) or a combination of both (De Ridder et al. 2013). Neuroimaging and electrophysiological measurements demonstrated increased spontaneous activity in the central auditory nervous system as well as changes in the tonotopic map of the auditory cortex (Lockwood et al. 1998; Muhlnickel et al. 1998; Salvi et al. 2000; Smits et al. 2007) albeit that the topographic map changes are disputed (De Ridder et al. 2012; Langers et al. 2012) and might relate more to the deafferentation than to tinnitus per se (De Ridder et al. 2012). These observations are in accordance to the thalamocortical dysrhythmia model, a deafferentation-based concept, in which there is a constant, pathologic and spontaneous coupled theta-gamma activity due to hyperpolarization of specific thalamic nuclei (Llinas et al. 1999). In the presence of an intact auditory pathway, auditory stimuli induce a transient increase in alpha toward gamma activity (Joliot et al. 1994) in a restricted area (von Stein and Sarnthein 2000), which binds by nesting on theta activity (Lakatos et al. 2005; Canolty et al. 2006), that is, a transient coupling between high- and low-frequencies of ongoing electrical activity (Canolty et al. 2006). In a deafferented state, however, a protracted hyperpolarization of thalamic neurons will result in low-frequency oscillations at the theta frequency band (Llinas and Steriade 2006; Steriade 2006). These theta oscillations will as well be present at the cortical level by true resonance as there is a strong functional coupling between thalamus and cortex (Llinas and Steriade 2006). However, this will lead to a decreased lateral inhibition at the cortical level mediated by γ-amino butyric acid (Llinas et al. 2005), resulting in a persistent and thus pathological gamma activity of the neighboring neurons, also known as the "edge effect" (Llinas et al. 1999, 2005). This coupled presence of theta and gamma activity in tinnitus has been demonstrated by recordings from an implanted electrode overlying the auditory cortex in a tinnitus patient (De Ridder et al. 2011b) and has been shown to change in patients treated with auditory cortex stimulation (Ramirez et al. 2009b). Based on these observations, both invasive (De Ridder et al. 2007a, 2011b; Ramirez et al. 2009a) and noninvasive (De Ridder et al. 2004; Langguth et al. 2012) neuromodulation techniques have been applied successfully with the intention of interfering with the hyperactivity and synaptic plasticity in tinnitus patients.

Focusing on noninvasive neuromodulation, most research in tinnitus has made use of transcranial magnetic stimulation (TMS) (De Ridder et al. 2005; Kleinjung et al. 2005; Plewnia et al. 2007; Rossi et al. 2007; Smith et al. 2007; Langguth et al. 2008; Marcondes et al. 2010) and transcranial direct current stimulation (tDCS) (Fregni et al. 2006b; Garin et al. 2011; Joos et al. 2014) with promising results when stimulation was applied over the temporoparietal cortex. In addition to tDCS, two other types of electrical stimulation have recently demonstrated neuromodulatory effects, i.e., transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). TRNS is a type of tACS whereby a random electrical oscillation spectrum is applied over the auditory cortex with a frequency spectrum between 0.1 and 640 Hz with no overall DC offset. Most often a subdivision between low- (lf-tRNS; 0.1–100 Hz) and high-frequency (hf-tRNS; 100–640 Hz) tRNS is made. A recent study evaluated the effect of a single session of tDCS, tACS and lf-tRNS over the auditory cortex in 111 tinnitus patients, whereas only a significant decrease in tinnitus loudness and distress could be observed with lf-tRNS (Vanneste et al. 2013b). Moreover, it has been suggested that application of lf-tRNS and hf-tRNS can lead to dissimilar results (Terney et al. 2008; Fertonani et al. 2011; Saiote et al. 2013). In addition, we wanted to asses whether different effects can be obtained in patients with pure tone (PT) and narrow band noise (NBN) tinnitus. A hypothesis based on the observation that differences in pathophysiology (De Ridder et al. 2007b) and neural activity (Vanneste et al. 2010c) are present as well as on the statement that stimulation characteristics of TMS, i.e., tonic or burst, induce different effects when comparing patients with PT and NBN tinnitus (De Ridder et al. 2007b, 2010).

The main focus of this retrospective study was to evaluate the effect of different subtypes of tRNS, i.e., lf-tRNS, hf-tRNS and whole frequency spectrum tRNS (wf-tRNS), on tinnitus loudness and tinnitus-related distress in patients with chronic non-pulsatile tinnitus. Moreover, we wanted to objectify whether patients with PT and NBN tinnitus respond differently to different types of random noise stimulation.

Methods

Subjects

A total of 154 patients (124 males; 30 females) with chronic, non-pulsatile tinnitus receiving auditory cortex tRNS (see Table 1 for an overview) were included in this retrospective study. The mean age of the patients was 53.28 years (Sd = 12.11), and the mean tinnitus duration was 6.92 years (Sd = 6.64). All patients underwent a single

Table 1 Patient characteristics and tinnitus features

	Stimulation type		
	lf-tRNS	hf-tRNS	wf-tRNS
Age (years)	53.68 ± 12.04	51.89 ± 11.83	51.94 ± 13.46
Gender (female/male)	24/95	3/16	3/13
Tinnitus duration (years)	6.81 ± 6.49	6.85 ± 7.96	5.25 ± 6.5
Tinnitus laterality (left/right/bilateral)	20/30/69	1/2/16	5/4/7
Tinnitus type (PT/NBN)	50/69	8/11	8/7[a]
NRS tinnitus loudness	6.71 ± 1.68	6.63 ± 1.83	6.19 ± 1.83
NRS tinnitus annoyance	6.14 ± 2.05	6.84 ± 1.42	6.00 ± 2.03

[a] One patient could not describe the tinnitus sound as PT or NBN tinnitus

session of tRNS in the treatment of tinnitus at the Tinnitus Research Initiative (TRI), Antwerp. Of these 154 patients, 119 patients received lf-tRNS, 19 patients hf-tRNS and 16 patients received wf-tRNS. Of these 154 patients, 66 patients described the perception of a PT tinnitus, 87 a NBN tinnitus and one could not describe the sound appropriately to make a subdivision between PT and NBN tinnitus. Individuals with pulsatile tinnitus, Ménière disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders were not included in the study in order to obtain a homogeneous sample. Therefore, all patients included for this study firstly underwent a complete audiological, ENT and neurological investigation. In addition, several technical investigations were performed including MRI of the brain. Collection of the data was under approval of IRB UZA OGA85. All patients gave an informed consent.

Transcranial random noise stimulation

TRNS was performed using a pair of electrodes with a surface of 35 cm^2 placed in saline (0.9 % NaCl) solution-soaked sponges connected to a battery, which can deliver an alternating constant current with a maximum output of 10 mA (Neuroconn; http://www.neuroconn.de/). The application of tRNS consisted of an alternating current of 2.0 mA intensity with a 0 mA offset applied at random frequencies during 20 min. In the low-frequency group, frequencies varied between 0.1 and 100 Hz, in the high-frequency group between 100 and 640 Hz, while in the third group the whole frequency spectrum from 0.1 to 640 Hz was applied. The alternating current was initially increased in a ramp-like fashion over several seconds (10 s) until reaching the target intensity. For all patients, the electrodes were positioned equally, i.e., one electrode was placed on T3 and one was placed over T4 as determined by the International 10–20 Electroencephalogram System. The application of tRNS has been considered a safe neuromodulation technique by measurement of neuron-specific enolase and electroencephalography (Terney et al. 2008).

Evaluation

A numeric rating scale (NRS) for tinnitus loudness ('How loud do you perceive your tinnitus?': 0 = no tinnitus and 10 = as loud as imaginable) and distress ('How annoying is your tinnitus?': 0 = not annoying and 10 = extremely annoying) was asked before (pre) and directly after tRNS stimulation (post).

Statistical analysis

Calculations were performed using SPSS 22.0 software package. A paired *t* test was conducted to evaluate the difference between pre- and post-treatment NRS scores for both tinnitus loudness and distress for the three subgroups, i.e., patients receiving lf-tRNS, hf-tRNS and wf-tRNS. The Holm's method was performed to correct for multiple comparisons. In addition, we conducted an independent sample *t* test to compare the difference in tinnitus loudness and distress reduction between patients with PT and NBN tinnitus for lf-tRNS and hf-tRNS.

Results

The effect of low-frequency, high-frequency and whole frequency spectrum tRNS on tinnitus loudness and distress

A paired *t* test was performed for both tinnitus loudness and distress in the patient group receiving lf-tRNS, which revealed a significant effect for loudness ($t(118) = 3.47$, $p = 0.001$) and distress ($t(118) = 2.90$, $p = 0.004$). These results indicate that tinnitus loudness significantly decreased when we compared post-stimulation ($M = 6.24$, Sd = 2.02) to pre-stimulation ($M = 6.71$, Sd = 1.68) NRS scores (see Fig. 1). A similar decrease in tinnitus-related distress was present when we compared post-treatment ($M = 5.75$, Sd = 2.30) scores with pre-treatment ($M = 6.14$, Sd = 2.05) (see Fig. 2).

In the patient group receiving hf-tRNS, the paired *t* test demonstrated significant results for both tinnitus loudness ($t(18) = 2.38$, $p = 0.03$) and tinnitus-related distress ($t(18) = 2.28$, $p = 0.04$). These results confirm the significant decrease in tinnitus loudness post-treatment

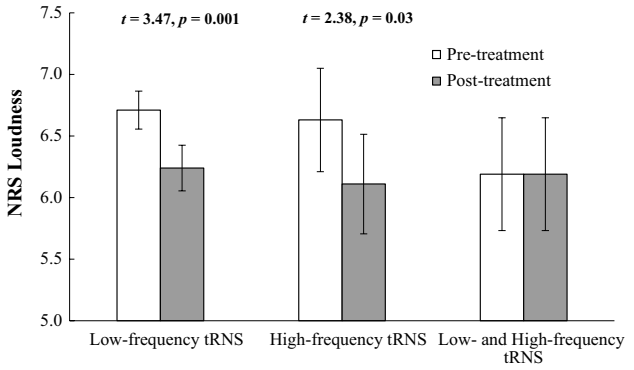

Fig. 1 Effect of low-frequency, high-frequency and whole spectrum frequency tRNS on tinnitus loudness

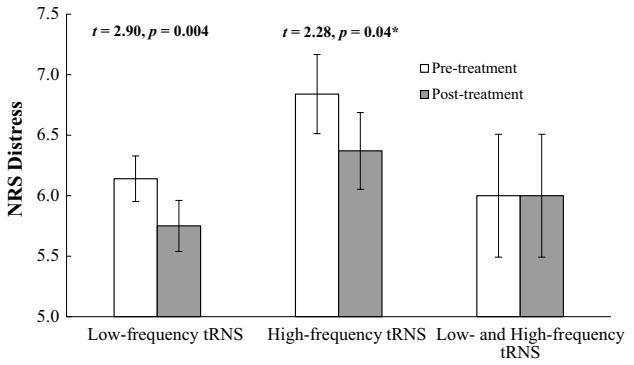

Fig. 2 Effect of low-frequency, high-frequency and whole frequency spectrum tRNS on tinnitus-related distress. *Asterisk* significant result that did not withstand the Holm's correction for multiple comparisons

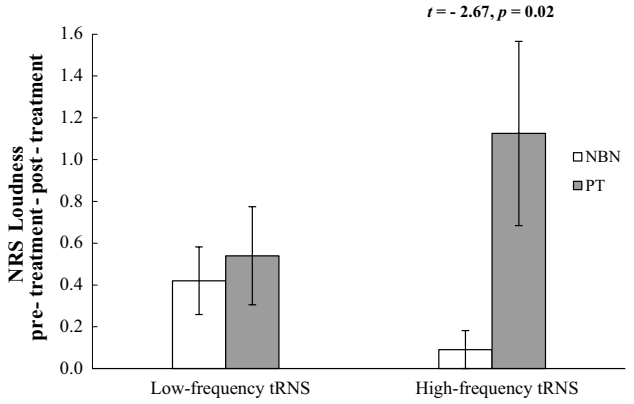

Fig. 3 Effect of low- and high-frequency tRNS on loudness reduction in PT and NBN tinnitus

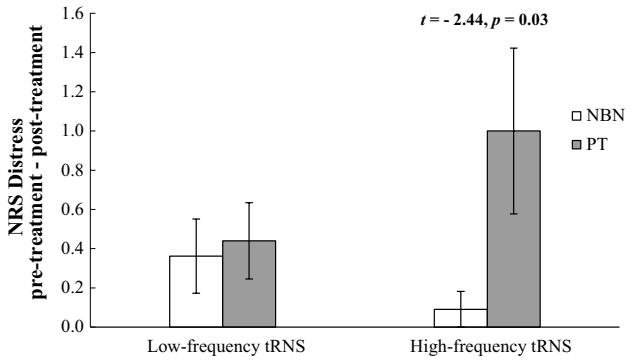

Fig. 4 Effect of low- and high-frequency tRNS on distress reduction in PT and NBN tinnitus

(M = 6.11, Sd = 1.76) versus pre-treatment (M = 6.63, Sd = 1.83) (see Fig. 1). However, the significant reduction in tinnitus-related distress induced by hf-tRNS did not withstand the Holm's correction for multiple comparisons (see Fig. 2).

Moreover, we performed a paired t test in the patient group receiving wf-tRNS. In contrast to low- and high-frequency tRNS separately, this stimulation type could not reveal any significant effect, neither for tinnitus loudness (see Fig. 1), nor for tinnitus-related distress (see Fig. 2).

The effect of stimulation type on NRS loudness and distress score reduction in PT and NBN tinnitus

An independent sample t test was performed to evaluate the effect of lf-tRNS on tinnitus loudness (see Fig. 3) and distress reduction (see Fig. 4) in patients with PT (N = 50) and NBN (N = 69) tinnitus. This analysis could not reveal a significant effect.

The same analysis was performed for the patients with PT (N = 8) and NBN (N = 11) tinnitus receiving hf-tRNS, which demonstrated a significant effect for both tinnitus loudness ($t(17)$ = 2.67, p = 0.02) and distress ($t(17)$ = 2.44, p = 0.03). These results indicate a significant difference in loudness reduction between patients with NBN (M = 0.09, Sd = 0.30) and PT (M = 1.13, Sd = 1.25) tinnitus (see Fig. 3), as well as in distress reduction between patients with NBN (M = 0.09, Sd = 0.30) and PT (M = 1.00, Sd = 1.20) tinnitus (see Fig. 4).

Discussion

The present study was performed to evaluate whether different subtypes of tRNS, including lf-tRNS, hf-tRNS and wf-tRNS, have different effects on tinnitus loudness and tinnitus-related distress. Interestingly, when we looked at lf-tRNS and hf-tRNS separately, both could demonstrate a significant reduction in tinnitus loudness, while only lf-tRNS induced a significant reduction in tinnitus-related distress. However, when we evaluated the effect in patients receiving wf-tRNS any significant effect could be revealed.

In addition, we wanted to evaluate whether tinnitus type influences the outcome of different types of tRNS. Consequently, we demonstrated that reduction in loudness and distress significantly differed for PT and NBN tinnitus when hf-tRNS was applied; however, no preference for PT or NBN could be demonstrated when performing lf-tRNS or wf-tRNS.

One of the putative mechanisms of tRNS is that tRNS repeatedly opens and closes voltage-gated sodium (Na^+) channels, leading to a repetitive influx of Na^+ ions, which finally results in a temporal summation of smaller depolarizing currents, which brings the resting membrane potential closer to the action potential threshold (Laureys et al. 2000; Boly et al. 2005). Secondly, hf-tRNS has demonstrated to ameliorate both implicit and perceptual learning (Terney et al. 2008; Fertonani et al. 2011), an improvement that has been hypothesized to be related to facilitation of brain plasticity by strengthening synaptic transmission between neurons via a stochastic resonance-like phenomenon (Fertonani et al. 2011). It has been shown that mainly oscillations within a frequency range of 80–200 Hz are associated with plasticity processes (Grenier et al. 2001) and learning (Ponomarenko et al. 2008). However, these mechanisms are contradictory to the results obtained with tRNS in tinnitus patients, i.e., a reduction in tinnitus loudness and distress, in patients where hyperactivity and synaptic plasticity of the auditory cortex have been stated to underlie the pathophysiological mechanism of tinnitus (Muhlnickel et al. 1998; Kaltenbach and Afman 2000; Salvi et al. 2000; Eggermont and Roberts 2004; Weisz et al. 2007; van der Loo et al. 2009; Vanneste et al. 2010c). A possible explanation is that there is a brain state-dependent effect of tRNS (Vanneste et al. 2013b), similar to what has been seen in tDCS (Plazier et al. 2012), meaning that adding a noise to an already present hypersynchronization of the auditory cortex in tinnitus patients might induce a disruption of the ongoing hyperactivity, ultimately resulting in a transient suppression of tinnitus. In contrast, resting state activity in the auditory cortex of a healthy subject represents a noise-like signal (Rodieck et al. 1962; Siebert 1965; Luczak et al. 2009) and adding a noise might therefore result in an increased synchronization or even the absence of any effect. This concept of a brain state-dependent effect is supported by research making use of functional magnetic resonance imaging (fMRI), whereas the application of hf-tRNS during a passive condition led to an increased BOLD activity and excitability decreased during the performance of a visuomotor learning task (Saiote et al. 2013). A similar attenuation of BOLD level was observed in the sensorimotor, premotor and supplementary motor cortex after hf-tRNS when a finger tapping task was performed (Chaieb et al. 2009).

Remarkably, our study demonstrated a decrease in tinnitus loudness with both lf-tRNS and hf-tRNS, although no significant results could be obtained when wf-tRNS was applied. A mechanistic explanation for this finding cannot yet be provided, although it is very intriguing and merits further research.

Secondly, we observed that there was a significantly more pronounced effect of high-frequency stimulation in patients perceiving PT tinnitus compared to those with NBN, while no preference for PT or NBN could be demonstrated with lf-tRNS. Previously, it has been revealed that noise-like tinnitus can best be suppressed by burst TMS (De Ridder et al. 2007b) and burst electrical stimulation (De Ridder et al. 2010), while PT tinnitus can equipotentially be suppressed by tonic and burst stimulation (De Ridder et al. 2007b, 2010). An effect that can be explained by the differences in the underlying neurophysiological mechanism of PT and NBN tinnitus as it has been suggested that NBN might be the result of increased burst firing in the extralemniscal/non-tonotopic pathway, which projects to the secondary auditory cortex and association cortices, while PT tinnitus might be caused by increased tonic firing of the lemniscal/tonotopic system, which projects to the primary auditory cortex (De Ridder et al. 2007b). The results of this study are reminiscent of previous observations, with the effect of hf-tRNS being similar to tonic stimulation and lf-tRNS to burst stimulation. This might be related to the selective influence of the T-type Ca^{2+} channels and Na^+ channels present on the neural membrane. One could hypothesize that lf-tRNS activates the slow Ca^{2+} channels, which subsequently leads to the activation of Na^+ channels and the generation of a burst-like pattern of action potentials, while hf-tRNS results in the activation of Na^+ channels and the inactivation of the T-type Ca^{2+} channels due to depolarization of the cell membrane, which finally leads to a tonic firing pattern (Freeman et al. 2010).

Additionally, lf-tRNS demonstrated a suppressive effect on tinnitus-related distress when stimulation was applied over the auditory cortex, analogous to what has been revealed with tDCS (Joos et al. 2014). This is in agreement with a voxel-based morphometry study that implicated the auditory cortex in tinnitus-related distress (Schecklmann et al. 2013), and other studies demonstrating that stimulation of the posterior part of the superior temporal lobe is capable of changing mood (De Ridder et al. 2004). We further assume that tRNS might induce a reduction in tinnitus-related distress due to the non-focal effect of transcranial electrical stimulation and therefore the modulation of adjacent brain areas involved in the distress network or by modulating remote areas due to their functional connectivity, for example, between the auditory cortex and the

parahippocampal region (Burwell 2000) or dorsolateral prefrontal cortex (Barbas et al. 2011).

The unified tinnitus percept involves multiple parallel dynamically adaptive networks involved in the different characteristics of tinnitus, including tinnitus-related distress and tinnitus loudness (De Ridder et al. 2013; Vanneste et al. 2013a). Distress is related to alpha and beta activity in the dorsal anterior cingulate cortex, while the amount of the perceived distress is related to increased alpha activity in a network comprising the amygdala–subgenual anterior cingulate cortex–insula–parahippocampal area and decreased alpha activity in the posterior cingulate cortex, precuneus and dorsolateral prefrontal cortex (Vanneste et al. 2010a). A recent independent component analysis revealed that distress correlates with increased alpha activity in the subgenual anterior cingulate cortex/ventromedial prefrontal cortex and increased beta activity in the dorsal anterior cingulate cortex, in addition to decreased alpha and beta activity in the posterior cingulate cortex (Vanneste et al. 2013a). Moreover, they stated that there is a highly specific pathological connection between the tinnitus loudness and distress network, i.e., the connection between the parahippocampal region and the subgenual anterior cingulate cortex/ventromedial prefrontal cortex (Vanneste et al. 2013a). Thus summarizing these data, it can be posited that auditory cortex stimulation modulates parahippocampal activity (De Ridder and Vanneste, in Press), which will then influence parahippocampal–subgenual anterior cingulate cortex functional connectivity, thereby reducing tinnitus-related distress. In addition, bilateral tDCS applied over the dorsolateral prefrontal cortex induces a suppressive effect on tinnitus-related distress as well (Vanneste et al. 2010b; Vanneste and De Ridder 2011). The dorsolateral prefrontal cortex has been shown to be involved in depression (Fregni et al. 2006a), the affective component of pain (Lorenz et al. 2003) as well as in the processing of aversive sounds (Mirz et al. 2000). Moreover, the dorsolateral prefrontal cortex has direct connections to the auditory cortex as well as indirect connections via the posterior orbitofrontal cortex and is implicated in selecting salient auditory signals and suppressing distractors via its projections the reticular nucleus of the thalamus (Barbas et al. 2011).

Although we could reveal some interesting results, certain limitations of this study should be noted. Firstly, although 154 patients were included, only 19 patients received hf-tRNS and 16 patients received wf-tRNS, while lf-tRNS was applied in 119 patients. This unequal distribution is due to the retrospective aspect of this study. Secondly, this was not a placebo-controlled study, as we mainly wanted to observe the effect of the different types of tRNS, meaning lf-tRNS, hf-tRNS and wf-tRNS, rather than the therapeutic effect per se. In addition, if the effect of lf-tRNS or hf-tRNS was influenced by a placebo effect, we would expect a similar result in the patient group receiving wf-tRNS, which was not present.

In conclusion, our findings show an effect of both low- and high-frequency stimulation on tinnitus loudness and of lf-tRNS on tinnitus-related distress. However, no significant effect could be obtained when wf-tRNS was performed bilaterally over the temporoparietal cortex, neither on tinnitus loudness nor on tinnitus-related distress. In addition, we suggest that hf-tRNS preferentially influences PT tinnitus, while lf-tRNS equally influences PT and NBN tinnitus, analogous to tonic and burst TMS, respectively. These effects could be the result of a selective influence of voltage-gated calcium and sodium channels with lf-tRNS and hf-tRNS, but this is only a hypothesis, and further research should be performed.

Conflict of interest The authors declare that they have no conflict of interest.

References

Axelsson A, Prasher D (2000) Tinnitus induced by occupational and leisure noise. Noise Health 2:47–54

Axelsson A, Ringdahl A (1989) Tinnitus–a study of its prevalence and characteristics. Br J Audiol 23:53–62

Barbas H, Zikopoulos B, Timbie C (2011) Sensory pathways and emotional context for action in primate prefrontal cortex. Biol Psychiatry 69:1133–1139. doi:10.1016/j.biopsych.2010.08.008

Boly M, Faymonville ME, Peigneux P et al (2005) Cerebral processing of auditory and noxious stimuli in severely brain injured patients: differences between VS and MCS. Neuropsychol Rehabil 15:283–289. doi:10.1080/09602010443000371

Burwell RD (2000) The parahippocampal region: corticocortical connectivity. Ann N Y Acad Sci 911:25–42

Canolty RT, Edwards E, Dalal SS et al (2006) High gamma power is phase-locked to theta oscillations in human neocortex. Science 313:1626–1628. doi:10.1126/science.1128115

Chaieb L, Kovacs G, Cziraki C, Greenlee M, Paulus W, Antal A (2009) Short-duration transcranial random noise stimulation induces blood oxygenation level dependent response attenuation in the human motor cortex. Exp Brain Res 198:439–444. doi:10.1007/s00221-009-1938-7

De Ridder D, Vanneste S (In Press) Targeting the parahippocampal area by auditory cortex stimulation in tinnitus. Brain Stimul

De Ridder D, De Mulder G, Walsh V, Muggleton N, Sunaert S, Moller A (2004) Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus: case report. J Neurosurg 100:560–564. doi:10.3171/jns.2004.100.3.0560

De Ridder D, Verstraeten E, Van der Kelen K et al (2005) Transcranial magnetic stimulation for tinnitus: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otol Neurotol 26:616–619

De Ridder D, De Mulder G, Verstraeten E et al (2007a) Auditory cortex stimulation for tinnitus. Acta Neurochir Suppl 97:451–462

De Ridder D, van der Loo E, Van der Kelen K, Menovsky T, van de Heyning P, Moller A (2007b) Do tonic and burst TMS modulate the lemniscal and extralemniscal system differentially? Int J Med Sci 4:242–246

De Ridder D, Vanneste S, van der Loo E, Plazier M, Menovsky T, van de Heyning P (2010) Burst stimulation of the auditory cortex: a

new form of neurostimulation for noise-like tinnitus suppression. J Neurosurg 112:1289–1294. doi:10.3171/2009.10.JNS09298

De Ridder D, Elgoyhen AB, Romo R, Langguth B (2011a) Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci USA 108:8075–8080. doi:10.1073/pnas.1018466108

De Ridder D, van der Loo E, Vanneste S et al (2011b) Theta-gamma dysrhythmia and auditory phantom perception. J Neurosurg 114:912–921. doi:10.3171/2010.11.JNS10335

De Ridder D, Vanneste S, Freeman W (2012) The Bayesian brain: phantom percepts resolve sensory uncertainty. Neurosci Biobehav Rev. doi:10.1016/j.neubiorev.2012.04.001

De Ridder D, Vanneste S, Weisz N, Londero A, Schlee W, Elgoyhen AB, Langguth B (2013) An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks. Neurosci Biobehav Rev. doi:10.1016/j.neubiorev.2013.03.021

Eggermont JJ, Roberts LE (2004) The neuroscience of tinnitus. Trends Neurosci 27:676–682

Eggermont JJ, Roberts LE (2012) The neuroscience of tinnitus: understanding abnormal and normal auditory perception. Front Syst Neurosci 6:53. doi:10.3389/fnsys.2012.00053

Erlandsson SI, Holgers KM (2001) The impact of perceived tinnitus severity on health-related quality of life with aspects of gender. Noise Health 3:39–51

Fertonani A, Pirulli C, Miniussi C (2011) Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci 31:15416–15423. doi:10.1523/JNEUROSCI.2002-11.2011

Folmer RL, Griest SE (2003) Chronic tinnitus resulting from head or neck injuries. Laryngoscope 113:821–827

Freeman DK, Eddington DK, Rizzo JF 3rd, Fried SI (2010) Selective activation of neuronal targets with sinusoidal electric stimulation. J Neurophysiol 104:2778–2791. doi:10.1152/jn.00551.2010

Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A (2006a) Treatment of major depression with transcranial direct current stimulation. Bipolar Disord 8:203–204. doi:10.1111/j.1399-5618.2006.00291.x

Fregni F, Marcondes R, Boggio PS et al (2006b) Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Eur J Neurol 13:996–1001. doi:10.1111/j.1468-1331.2006.01414.x

Garin P, Gilain C, Van Damme JP, de Fays K, Jamart J, Ossemann M, Vandermeeren Y (2011) Short- and long-lasting tinnitus relief induced by transcranial direct current stimulation. J Neurol 258:1940–1948. doi:10.1007/s00415-011-6037-6

Grenier F, Timofeev I, Steriade M (2001) Focal synchronization of ripples (80–200 Hz) in neocortex and their neuronal correlates. J Neurophysiol 86:1884–1898

Jastreboff PJ (1990) Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res 8:221–254

Joliot M, Ribary U, Llinas R (1994) Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. Proc Natl Acad Sci USA 91:11748–11751

Joos K, De Ridder D, Van de Heyning P, Vanneste S (2014) Polarity specific suppression effects of transcranial direct current stimulation for tinnitus. Neural Plast 2014:930860. doi:10.1155/2014/930860

Kaltenbach JA, Afman CE (2000) Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus. Hear Res 140:165–172

Kleinjung T, Eichhammer P, Langguth B et al (2005) Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. Otolaryngol Head Neck Surg 132:566–569. doi:10.1016/j.otohns.2004.09.134

Lakatos P, Shah AS, Knuth KH, Ulbert I, Karmos G, Schroeder CE (2005) An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. J Neurophysiol 94:1904–1911. doi:10.1152/jn.00263.2005

Langers DR, de Kleine E, van Dijk P (2012) Tinnitus does not require macroscopic tonotopic map reorganization. Front Syst Neurosci 6:2. doi:10.3389/fnsys.2012.00002

Langguth B, de Ridder D, Dornhoffer JL et al (2008) Controversy: does repetitive transcranial magnetic stimulation/transcranial direct current stimulation show efficacy in treating tinnitus patients? Brain Stimul 1:192–205. doi:10.1016/j.brs.2008.06.003

Langguth B, Schecklmann M, Lehner A et al (2012) Neuroimaging and neuromodulation: complementary approaches for identifying the neuronal correlates of tinnitus. Front Syst Neurosci 6:15. doi:10.3389/fnsys.2012.00015

Laureys S, Faymonville ME, Degueldre C et al (2000) Auditory processing in the vegetative state. Brain 123(Pt 8):1589–1601

Leaver AM, Renier L, Chevillet MA, Morgan S, Kim HJ, Rauschecker JP (2011) Dysregulation of limbic and auditory networks in tinnitus. Neuron 69:33–43. doi:10.1016/j.neuron.2010.12.002

Llinas RR, Steriade M (2006) Bursting of thalamic neurons and states of vigilance. J Neurophysiol 95:3297–3308. doi:10.1152/jn.00166.2006

Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP (1999) Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci USA 96:15222–15227

Llinas R, Urbano FJ, Leznik E, Ramirez RR, van Marle HJ (2005) Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci 28:325–333

Lockwood AH, Salvi RJ, Coad ML, Towsley ML, Wack DS, Murphy BW (1998) The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity. Neurology 50:114–120

Lorenz J, Minoshima S, Casey KL (2003) Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 126:1079–1091

Luczak A, Bartho P, Harris KD (2009) Spontaneous events outline the realm of possible sensory responses in neocortical populations. Neuron 62:413–425. doi:10.1016/j.neuron.2009.03.014

Marcondes RA, Sanchez TG, Kii MA, Ono CR, Buchpiguel CA, Langguth B, Marcolin MA (2010) Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: a double-blind controlled, clinical and neuroimaging outcome study. Eur J Neurol 17:38–44. doi:10.1111/j.1468-1331.2009.02730.x

Mirz F, Gjedde A, Sodkilde-Jrgensen H, Pedersen CB (2000) Functional brain imaging of tinnitus-like perception induced by aversive auditory stimuli. Neuroreport 11:633–637

Muhlnickel W, Elbert T, Taub E, Flor H (1998) Reorganization of auditory cortex in tinnitus. Proc Natl Acad Sci USA 95:10340–10343

Norena AJ, Eggermont JJ (2006) Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus. Neuroreport 17:559–563

Plazier M, Joos K, Vanneste S, Ost J, De Ridder D (2012) Bifrontal and bioccipital transcranial direct current stimulation (tDCS) does not induce mood changes in healthy volunteers: a placebo controlled study. Brain Stimul 5:454–461. doi:10.1016/j.brs.2011.07.005

Plewnia C, Reimold M, Najib A, Brehm B, Reischl G, Plontke SK, Gerloff C (2007) Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation. Hum Brain Mapp 28:238–246. doi:10.1002/hbm.20270

Ponomarenko AA, Li JS, Korotkova TM, Huston JP, Haas HL (2008) Frequency of network synchronization in the

hippocampus marks learning. Eur J Neurosci 27:3035–3042. doi:10.1111/j.1460-9568.2008.06232.x

Ramirez RR, Kopell BH, Butson CR, Gaggl W, Friedland DR, Baillet S (2009a) Neuromagnetic source imaging of abnormal spontaneous activity in tinnitus patient modulated by electrical cortical stimulation. Conf Proc IEEE Eng Med Biol Soc 2009:1940–1944. doi:10.1109/IEMBS.2009.5333457

Ramirez RR, Kopell BH, Butson CR, Gaggl W, Friedland DR, Baillet S (2009b) Neuromagnetic source imaging of abnormal spontaneous activity in tinnitus patient modulated by electrical cortical stimulation. Conf Proc IEEE Eng Med Biol Soc 1:1940–1944. doi:10.1109/IEMBS.2009.5333457

Rauschecker JP, leaver AM, Muhlau M (2010) Tuning out the noise: limbic-auditory interactions in tinnitus. Neuron 66:819–826

Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA (2010) Ringing ears: the neuroscience of tinnitus. J Neurosci 30:14972–14979. doi:10.1523/JNEUROSCI.4028-10.2010

Rodieck RW, Kiang NY, Gerstein GL (1962) Some quantitative methods for the study of spontaneous activity of single neurons. Biophys J 2:351–368

Rossi S, De Capua A, Ulivelli M, Bartalini S, Falzarano V, Filippone G, Passero S (2007) Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: a randomised, crossover, double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 78:857–863. doi:10.1136/jnnp.2006.105007

Saiote C, Polania R, Rosenberger K, Paulus W, Antal A (2013) High-frequency TRNS reduces BOLD activity during visuomotor learning. PLoS One 8:e59669. doi:10.1371/journal.pone.0059669

Salvi RJ, Wang J, Ding D (2000) Auditory plasticity and hyperactivity following cochlear damage. Hear Res 147:261–274

Schecklmann M, Lehner A, Poeppl TB et al (2013) Auditory cortex is implicated in tinnitus distress: a voxel-based morphometry study. Brain Struct Funct 218:1061–1070. doi:10.1007/s00429-013-0520-z

Schreiber BE, Agrup C, Haskard DO, Luxon LM (2010) Sudden sensorineural hearing loss. Lancet 375:1203–1211. doi:10.1016/S0140-6736(09)62071-7

Scott B, Lindberg P (2000) Psychological profile and somatic complaints between help-seeking and non-help-seeking tinnitus subjects. Psychosomatics 41:347–352

Siebert WM (1965) Some implications of the stochastic behavior of primary auditory neurons. Kybernetik 2:206–215

Smith JA, Mennemeier M, Bartel T, Chelette KC, Kimbrell T, Triggs W, Dornhoffer JL (2007) Repetitive transcranial magnetic stimulation for tinnitus: a pilot study. Laryngoscope 117:529–534. doi:10.1097/MLG.0b013e31802f4154

Smits M, Kovacs S, de Ridder D, Peeters RR, van Hecke P, Sunaert S (2007) Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. Neuroradiology 49:669–679. doi:10.1007/s00234-007-0231-3

Steriade M (2006) Grouping of brain rhythms in corticothalamic systems. Neuroscience 137:1087–1106. doi:10.1016/j.neuroscience.2005.10.029

Terney D, Chaieb L, Moliadze V, Antal A, Paulus W (2008) Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci 28:14147–14155. doi:10.1523/JNEUROSCI.4248-08.2008

van der Loo E, Gais S, Congedo M et al (2009) Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS One 4:e7396. doi:10.1371/journal.pone.0007396

Vanneste S, De Ridder D (2011) Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. Eur J Neurosci 34:605–614. doi:10.1111/j.1460-9568.2011.07778.x

Vanneste S, Plazier M, der Loo E, de Heyning PV, Congedo M, De Ridder D (2010a) The neural correlates of tinnitus-related distress. Neuroimage 52:470–480. doi:10.1016/j.neuroimage.2010.04.029

Vanneste S, Plazier M, Ost J, van der Loo E, Van de Heyning P, De Ridder D (2010b) Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. Exp Brain Res 202:779–785. doi:10.1007/s00221-010-2183-9

Vanneste S, Plazier M, van der Loo E, Van de Heyning P, De Ridder D (2010c) The differences in brain activity between narrow band noise and pure tone tinnitus. PLoS One 5:e13618. doi:10.1371/journal.pone.0013618

Vanneste S, Congedo M, De Ridder D (2013a) Pinpointing a highly specific pathological functional connection that turns phantom sound into distress. Cereb Cortex. doi:10.1093/cercor/bht068

Vanneste S, Fregni F, De Ridder D (2013b) Head-to-head comparison of transcranial random noise stimulation, transcranial AC stimulation, and transcranial DC stimulation for tinnitus. Front Psychiatry 4:158. doi:10.3389/fpsyt.2013.00158

von Stein A, Sarnthein J (2000) Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. Int J Psychophysiol 38:301–313

Weisz N, Muller S, Schlee W, Dohrmann K, Hartmann T, Elbert T (2007) The neural code of auditory phantom perception. J Neurosci 27:1479–1484