European Journal of Neurology 2010, **17:** 1141–1147 doi:10.1111/j.1468-1331.2010.02987.x

Burst transcranial magnetic stimulation: which tinnitus characteristics influence the amount of transient tinnitus suppression?

S. Vanneste[a], M. Plazier[a], E. van der Loo[a], J. Ost[a], P. Van de Heyning[b] and D. De Ridder[a]

[a]*Brai²n, & TRI, University Hospital Antwerp; and* [b]*Brai²n, TRI & ENT, University Hospital Antwerp, Wilrijk, Belgium*

Keywords:
burst, distress, duration and tinnitus, laterality, TMS, type

Received 3 September 2009
Accepted 13 January 2010

Background: Transcranial Magnetic Stimulation (TMS) is a method capable of temporarily suppressing tinnitus by delivering tonic or burst stimuli. Burst TMS has a high interindividual variability and low effect size. Tinnitus type and laterality, tinnitus-related distress, and tinnitus duration might contribute to this large individual variation.

Methods: The effect of burst TMS on the auditory cortex in 100 male individuals is evaluated with coil placed over the auditory cortex. For unilateral tinnitus, this coil was placed contralaterally to the tinnitus, whilst for bilateral tinnitus the coil was placed over the right auditory cortex. The site of maximal tinnitus suppression is determined using 1-Hz stimulation with five pulses per burst (intensity of the stimulation set at 90% of the motor threshold). When tinnitus suppression is noted, the patients are asked to estimate the decrease in tinnitus in percentage using the numeric rating scale. The procedure is repeated with stimulations at 5, 10 and 20 Hz, each stimulation session consisting of 200 pulses.

Results: Results demonstrate that burst stimulation can decrease the perceived tinnitus intensity transiently in 57.83% of the patients. Patients with bilateral tinnitus respond better to burst TMS than patients with unilateral tinnitus and highly distressed patients presenting with unilateral pure tone tinnitus fail to bust TMS.

Conclusions: Burst TMS modulates both unilateral and bilateral tinnitus, both high and low distress and both pure tones and narrow band tinnitus. However, the suppression effect is moderated by tinnitus type and laterality, tinnitus-related distress, and tinnitus duration.

Introduction

Tinnitus is characterized by the perception of sound or noise in the absence of any objective external physical source. Functional neuroimaging and electrophysiological studies in humans indicate a reorganization [1] and abnormal spontaneous activity [2] of the auditory central nervous system as a possible neurobiological basis of tinnitus. An increasing number of studies have demonstrated that transcranial magnetic stimulation (TMS) can alter this abnormal activity in the auditory cortex and can suppress tinnitus transiently [3–6]. TMS is a non-invasive tool provoking a strong impulse of magnetic field that induces an electrical current, which can alter the neural activity at the applied area. This makes it possible to selectively and safely stimulate specific regions of the human brain. PET-scan studies have demonstrated that TMS not only modulates the directly stimulated cortical area, but that it has an effect on remote areas functionally connected to the stimulated area [7,8]. TMS has received increased attention as a predominantly investigational but potentially therapeutic tool for the treatment of tinnitus [3–6,9].

Recently, burst TMS has been developed as a new stimulation design, which has a controllable, consistent, long-lasting, and powerful effect on the motor cortex [10]. This theta burst stimulation design that was developed for the motor cortex stimulation was extended to alpha and beta burst stimulation and applied to the auditory cortex for tinnitus suppression [11,12]. Whilst tonic stimulation in these studies could

Correspondence: Sven Vanneste, Brai²n, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium (tel./fax: +32 821 33 36; email: sven.vanneste@ua.ac.be; website: http://www.brai2n.com).

only suppress pure tone tinnitus transiently, burst stimulation could temporarily suppress both pure tone and narrow band tinnitus.

Although burst stimulation seems like a promising investigational tool and potential treatment for both pure tone and narrow band noise tinnitus, results on burst stimulation are still characterized by a high interindividual variability and a moderate effect size. It was recently shown that stimulation intensity only plays a minor role in the efficacy of burst TMS for tinnitus [13]. Three other factors, namely tinnitus laterality [13], tinnitus-related distress, and tinnitus duration might contribute to the large individual variation.

Within the present study, we explore the hypothesis that burst stimulation applied to the auditory cortex can temporarily suppress tinnitus and take into account different tinnitus characteristics, namely tinnitus type (pure tone vs. narrow band noise), tinnitus laterality (unilateral vs. bilateral tinnitus) and tinnitus-related distress (low vs. high distress), and tinnitus duration (recent onset vs. chronic). Further, the purpose is to elucidate the neural mechanisms of tinnitus and to develop a diagnostic tool that could distinguish between different characteristics of tinnitus that may benefit from different kinds of treatment. As gender might also have a possible effect on tinnitus suppression, we wanted to keep this variable stable and included only male tinnitus patients in our sample.

Methods

We studied the transient effect of a single session of secondary auditory cortex burst TMS in 100 male individuals (Mean age 51.03, SD = 12.73) with tinnitus evaluating the effect of such stimulation on patients' tinnitus perception. See Table 1 for further patient characteristics. Patients with bilateral tinnitus with an asymmetrical tinnitus characteristics (intensity, pitch, or duration) on both sides were not included in the study as they constitute a group we previously labeled twice unilateral tinnitus [4]. The study protocol has been approved by the Antwerp University Hospital IRB ('Comité voor medische ethiek'). Patients gave an informed consent before the procedure.

TMS is performed as a continuing clinical protocol for selection of candidates for implantation of permanent electrodes for electrical stimulation of the auditory cortex for treatment for tinnitus [12,14] at the multidisciplinary TRI (Tinnitus Research Initiative) tinnitus clinic of Antwerp University, Belgium. All prospective participants undergo a complete ENT and neurological investigation to rule out possible treatable causes for their tinnitus. Tinnitus matching is performed by presenting sounds to the ear in which the tinnitus is not perceived in unilateral tinnitus, bilaterally in bilateral tinnitus patients. Technical investigations include MRI of the brain and posterior fossa, audiometry, and tympanometry. Assessment of tinnitus loudness is analyzed by Visual Analogue Scale (VAS), whilst tinnitus distress grade is analyzed by the Tinnitus Questionnaire (TQ) [15]. Based on the total score on the TQ, participants were assigned to a distress category: low distress (grade 1 and 2: scores 0–46 points) or high distress (grade 3 and 4: scores 47–84). Tinnitus duration was divided into tinnitus with recent onset (<4 years of tinnitus duration) or chronic tinnitus (more than 4 years tinnitus, but <10 years). This cut-off for tinnitus duration is based upon several studies demonstrating that the amount of maximal tinnitus suppression by rTMS [4,16] decreases in time, similarly to what has been described for microvascular decompression surgery (MVD) for tinnitus. In MVD, treatment outcome decreases radically after 3–5 years [17–19] (De Ridder 2009, in press). Furthermore, in a recent MEG connectivity study with selected ROIs, it was shown that in patients with recent tinnitus onset (i.e. <4 years) gamma network connections are concentrated on the left temporal cortex, whilst in chronic tinnitus patients (i.e. >4 years) the network is widely distributed over the entire cortex with less involvement of the temporal areas [20].

TMS is performed using a super rapid stimulator (Magstim Inc, Wales, UK) with a figure-eight coil placed over the auditory cortex. For unilateral tinnitus, this coil was placed contralaterally to the tinnitus; whilst for bilateral tinnitus, the coil was placed over the right auditory cortex.

Before the TMS session, patients grade their tinnitus on a numeric rating scale from 0 to 10. The motor threshold to TMS is first determined by placing the coil over the motor cortex. 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

Table 1 Patients' characteristics

Tinnitus side	Tinnitus type	Tinnitus distress	Tinnitus duration
Unilateral 23 (47.92%)	Pure tone 21 (43.75%)	Low distress 24 (50%)	Recent onset 33 (68.75%)
Bilateral 25 (52.08%)	Narrow Band 27 (56.25%)	High distress 24 (50%)	Chronic 14 (31.25%)

mid-sagittal line. The intensity of the magnetic stimulation is slowly increased until a clear contraction is observed in the contralateral thenar muscle. As the stimulation intensity has only a very limited influence on the amount of tinnitus suppression obtained by burst TMS [13] and as it has been suggested that excitatory measurements of one specific cortex cannot be generalized to the excitability of the whole cortex [21], TMS motor thresholds cannot be assumed to be a guide to auditory [13] and visual cortex excitability [22]. Therefore, it can be acceptable not to use EMG to diagnose the motor threshold exactly.

The coil is then moved to a location over the auditory cortex contralateral to the side where the patients refer their unilateral tinnitus, and for bilateral tinnitus the coil was moved to right auditory cortex (5–6 cm above the auditory meatus on straight line to the vertex). With the intensity of the stimulation set at 90% of the motor threshold, the site of maximal tinnitus suppression is determined using 1-Hz stimulation with five pulses per burst. When tinnitus suppression is noted, the patients are asked to estimate the decrease in tinnitus in percentage using the numeric rating scale. The procedure is repeated with stimulations at 5, 10 and 20 Hz, each stimulation session consisting of 200 pulses. The order of the stimulation frequencies (1, 5, 10, and 20 Hz) is randomized over subjects. When tinnitus suppression is induced by TMS, the patient is asked to notify when tinnitus has returned back to baseline, i.e. when the tinnitus intensity is back to its initial VAS before the next TMS frequency is applied. For each patient, the frequency that yields maximal tinnitus suppression was included in the analyses.

The presence of placebo effect is tested by placing the coil perpendicular to the auditory cortex. This sham TMS was randomly performed in between the real stimulations.

Data were analyzed with SPSS 15.0. Tinnitus suppression (% reduction in tinnitus perception) data were analyzed using a univariate ANOVA with amount of suppression by burst TMS as dependent variable, and type (narrow band noise vs. pure tone), laterality (unilateral vs. bilateral tinnitus), and tinnitus distress (low vs. high) as independent variables. In further analyses, tinnitus duration is also included into the model.

Results

Forty-eight patients (57.83%; Mean age 54.25, SD = 11.05) who were placebo-free TMS responders are analyzed. A comparison between the different burst frequencies for the placebo-free TMS responders reveals no differences in suppression effect (see Fig. 1). However, important to note is the large variability in

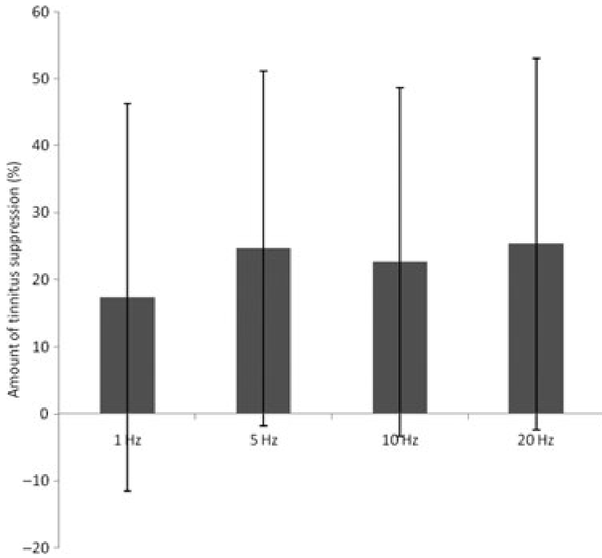

Figure 1 A comparison between the different burst frequencies for the placebo free TMS responders.

suppression effect between the different responders for the different burst frequencies.

Because the TMS equipment generates a clicking sound on each magnitude pulse delivery, using only results from placebo negative patients prevents the possible influence of sound from the TMS masking the tinnitus. For each patient, the frequency that yields maximal tinnitus suppression was included in the analyses. The analysis yields a significant main effect of laterality, where bilateral tinnitus (M = 65.0%, SD = 26.66) was significantly better suppressed in comparison with unilateral tinnitus (M = 48.9%, SD = 27.43, $F(1,40) = 4.04$, $P < 0.05$). This effect is moderated by a three-way interaction effect between type × laterality × tinnitus grade ($F(1,40) = 5.68$, $P < 0.05$; see Fig. 2). A simple contrast shows that there is a trend for significant difference for pure tone unilateral tinnitus between low and high distress ($F(1,40) = 3.10$, $P < 0.10$) and a significant effect for pure tone high distress between unilateral and bilateral tinnitus ($F(1,40) = 6.61$, $P < 0.01$). As for the first significant effect, unilateral pure tone patients with low distress have more suppression than with high distress. As for the latter significant effect, pure tone with high distress patients with unilateral tinnitus show less suppression than with bilateral tinnitus. The simple contrast yielded no other significant effects.

A possible reason for these findings might be that the tinnitus duration is mediating these results. Taking tinnitus duration into account in this model yielded no significant effects for narrow band noise tinnitus patients. In contrast, analyses for pure tone tinnitus

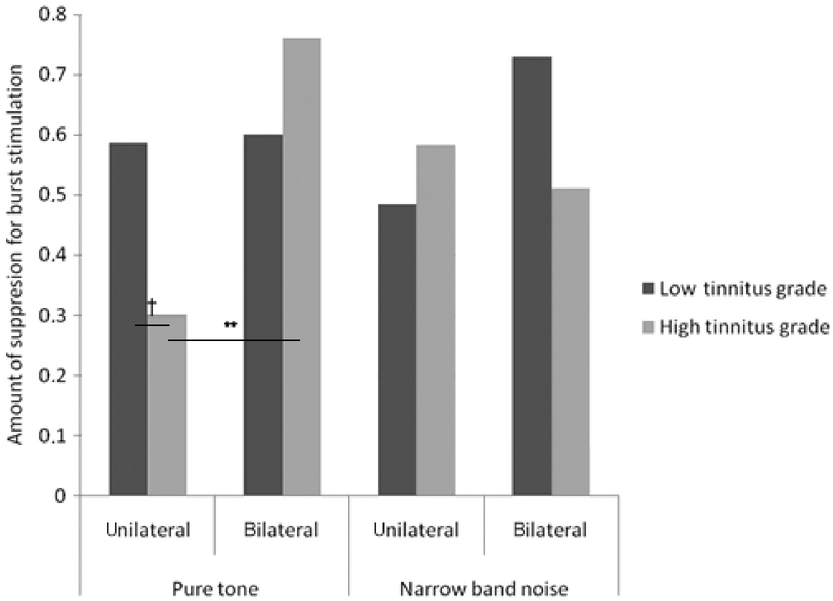

Figure 2 Mean tinnitus suppression with burst rTMS (%) for tinnitus side (unilateral vs. bilateral), tinnitus type (pure tone or noise-like tinnitus), and tinnitus-related distress (low vs. high tinnitus distress).

patients revealed a significant effect for laterality ($F(1,17) = 9.71$, $P < 0.01$), demonstrating that bilateral tinnitus ($M = 68.89\%$, SD = 24.21) was suppressed more than unilateral tinnitus ($M = 49.17\%$, SD = 29.99). Also a significant two-way interaction effect between laterality and duration for pure tone tinnitus patients was found ($F(1,17) = 10.42$, $P < 0.01$; see Fig. 3). A simple contrast revealed a significant effect between unilateral tinnitus and bilateral tinnitus for chronic pure tone tinnitus ($F(1,17) = 15.62$, $P < 0.001$), indicating that burst TMS suppresses bilateral tinnitus better than unilateral tinnitus. No significant effect was found between unilateral and bilateral tinnitus for pure tone tinnitus with a recent onset. Furthermore, a simple contrast demonstrated that there is a significant difference between recent and chronic onset for unilateral pure tone tinnitus ($F(1,17) = 10.35$, $P < 0.01$) and a significant difference between recent onset bilateral and chronic onset unilateral tinnitus for pure tone patients ($F(1,17) = 5.35$, $P < 0.05$). As for these latter effects, recent onset tinnitus patients had more suppression than chronic tinnitus patients, and recent onset bilateral patients had more suppression than chronic onset unilateral tinnitus patients, respectively. No effect was obtained for tinnitus-related distress.

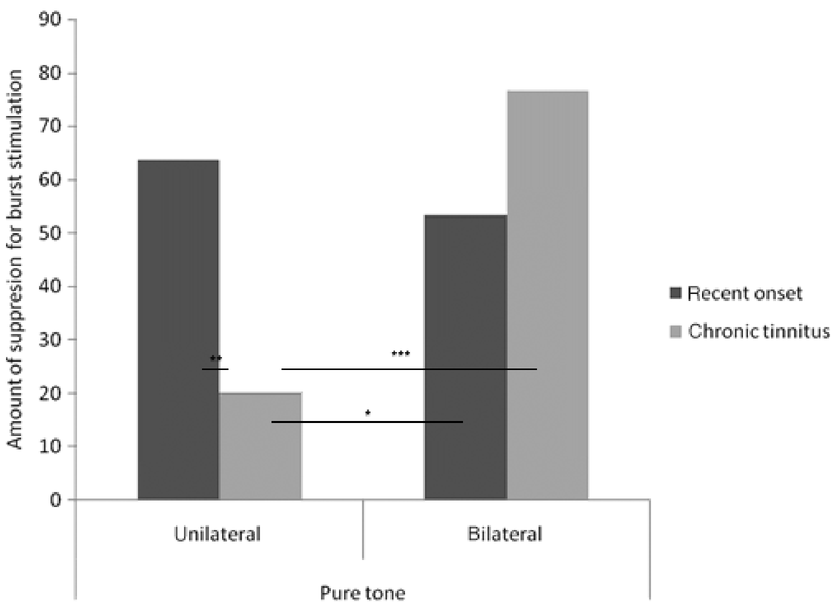

Figure 3 Mean tinnitus suppression with burst rTMS (%) for tinnitus side (unilateral or bilateral), and tinnitus duration (recent onset vs. chronic tinnitus).

When concentrating exclusively on the difference of suppression for burst TMS within pure tone unilateral tinnitus, analyses further confirmed that these differences could mainly be explained also by tinnitus duration. Only a main effect for tinnitus duration ($F(1,8) = 4.94$, $P < 0.05$). Tinnitus with a recent onset ($M = 68.75\%$, SD = 25.03) was significantly better suppressed in comparison with chronic tinnitus ($M = 20.00\%$, SD = 11.54) in pure tone unilateral tinnitus patients. No effect could be found for tinnitus distress nor for the two-way interaction tinnitus duration x tinnitus grade.

Discussion

The present findings reveal that burst TMS of the superior temporal gyrus for male individuals is an effective method for transiently suppressing tinnitus. This is in accordance with previous burst TMS studies [11,13]. The amount of responders to burst TMS is similar to what has been reported for tonic stimulation and averages at about half of the people who undergo TMS [4,6,16,23]. To find out which patient benefits from burst TMS analyses with TMS suppression as dependent variable, and type (narrow band noise vs. pure tone), laterality (unilateral vs. bilateral tinnitus), and tinnitus grade (low vs. high) as independent variables was undertaken. The results suggest that burst TMS might be modulating both unilateral and bilateral tinnitus, both high and low distress and both pure tones and narrow band tinnitus, which is in accordance with previous studies [11–13]. Patients with bilateral tinnitus respond better than patients with unilateral tinnitus to burst stimulation. Highly distressed patients presenting with unilateral pure tone tinnitus are significantly worse. However, further analyses revealed that these differences in pure tone patients in the amount of suppression could mainly be explained by tinnitus duration and tinnitus laterality, and not by tinnitus-related distress.

There is no good explanation for the differential effect of burst TMS on pure tones and noise-like tinnitus. It has been speculated that this could be because of a differential effect of tonic and burst TMS on the lemniscal and extralemniscal system, but no firm proof exists for this idea [11,12].

Our results indicate that burst TMS can suppress tinnitus patients with low as well as high tinnitus-related distress. It might be that burst TMS modulates the extralemniscal auditory system directly and that this system provides information to the limbic system via dorsal and medial thalamus [24]. Using electrical burst stimulation in animals, it has indeed been shown that auditory cortex burst stimulation exerts its effect predominantly on the extralemniscal medial geniculate body [25], which fires predominantly in burst mode [26]. Voxel-based morphometry studies in 1-Hz tonic rTMS of the auditory cortex demonstrate that the auditory thalamus is modulated by rTMS [27]. Thus, burst TMS, if it exerts a similar effect as electrical burst stimulation, might influence the extralemniscal thalamus preferentially, which is the connection to the limbic system [28]. This does not exclude that tonic stimulation does not influence the limbic system, but its effect might be less direct; and therefore it is different from burst TMS.

Tinnitus-related distress has been linked to a right-sided fronto-cingulate-parietal network [29], and left-sided tinnitus has been epidemiologically shown to be more distressing than right-sided tinnitus [30], a reason why it seems to be more prevalent [31]. This could be related to the assumption that left sided tinnitus is related to a right superior temporal gyrus (STG) generator [32] or intensity modulator [33]. It is of interest that in post-traumatic stress disorder, subjects have significantly greater STG gray matter volumes than controls [34], suggesting that the right superior temporal gyrus is involved in the generation of distress. This is functionally confirmed by auditory-evoked potential studies: a marked shift of auditory-evoked potentials to the right is noted in PTSD subjects during the unpleasant memory in comparison with controls [35].

Even though most PET studies suggest that all kinds of tinnitus are generated in the left auditory cortex [36], some suggest it might be contralaterally generated [37]. The idea that unilateral tinnitus is generated in the contralateral auditory cortex is further supported by fMRI [38] and MEG [32]. If there is a hemispheric dominance in tinnitus generation, then left-sided TMS should be better in general than right-sided TMS, if not, then contralateral TMS stimulation should be better. However, it is possible that the extralemniscal system projects to the secondary auditory cortex bypassing the primary auditory cortex in a bilateral fashion, similar to what is seen in allodynic pain in the somatosensory system [39,40]. Indeed, in the rat, cat, and squirrel monkey, there are descending projections from the posterior intralaminar thalamus to the inferior colliculus in a bilateral fashion, some of which are reciprocal [41]. These pathways are considered a phylogenetically ancient feedback system onto the acoustic tectum, one that predates the corticocollicular system and modulates non-auditory centers and brainstem autonomic nuclei [41]. As burst stimulation might modulate both lemniscal and extralemniscal system [11] and TMS has effect on remote areas functionally connected with the stimulated area [7,8], tinnitus laterality might be of less importance for burst TMS outcome. Animal studies should be performed to validate or disprove this hypothesis. Modulating pure tone tinnitus by burst TMS seems complicated as suppression depends on the tinnitus laterality and duration. In pure tone tinnitus patients with a recent onset, burst TMS can suppress tinnitus with 50% or more independently of the laterality. In contrast, laterality has an obvious influence for chronic patients. That is, compared to bilateral tinnitus, unilateral tinnitus is less suppressed by burst TMS for pure tone patients. As to why this is so, no clear answers can be provided yet. It has been repeatedly shown that tinnitus suppression by tonic TMS worsens in time [9,42], and this does not seem to hold for burst TMS, except for unilateral pure tone tinnitus. Unfortunately, not enough is known on the differences in the pathophysiology of unilateral versus bilateral tinnitus and pure tone versus narrow band noise tinnitus to try and explain this differential effect.

One limitation of this study is sham control condition. As the sham coil only mimics the sound of active TMS but lacks the somatosensory sensation, it is not an optimal control condition. However, it has already been shown that TMS effect on tinnitus is not mediated by the somatosensory stimulation [6,43]. Moreover, as patients in this study were naïve for TMS, they might not be able to identify whether they were stimulated with active or sham TMS.

Another limitation might be the coil position as these were only defined by anatomical landmarks and were not performed under neuronavigated control. Recent studies for TMS indicate that consistent results can be obtained with a probabilistic approach (i.e. non-neuronavigated) [44,45]. Nevertheless, fMRI-guided stimulation might be accurate within the range of millimeters for targeting purposes, but the area of modulation might be as large as 3 cm [46], questioning the value of fMRI-guided TMS of the auditory cortex. Still, it could influence the results and be one of the multiple factors explaining interindividual variability.

Future research is needed to further explore whether other variables could also influence results obtained by burst TMS, such as the motor threshold, audiometry auditory threshold as well as gender.

Conclusion

Burst TMS seems to modulate both unilateral and bilateral tinnitus, both high and low distress and both pure tones and narrow band tinnitus. Patients with bilateral tinnitus respond better than patients with unilateral tinnitus to burst stimulation, and highly distressed patients presenting with unilateral pure tone tinnitus fare significantly worse. This last effect seems to be because of the tinnitus duration and tinnitus laterality.

References

1. Muhlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. *Proc Natl Acad Sci USA* 1998; **95:** 10340–10343.
2. 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.
3. De Ridder D, De Mulder G, Walsh V, Muggleton N, Sunaert S, Moller A. Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus. Case report. *J Neurosurg* 2004; **100:** 560–564.
4. De Ridder D, Verstraeten E, Van der Kelen K, *et al.* Transcranial magnetic stimulation for tinnitus: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. *Otol Neurotol* 2005; **26:** 616–619.
5. Langguth B, Eichhammer P, Wiegand R, *et al.* Neuronavigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment. *Neuroreport* 2003; **14:** 977–980.
6. Londero A, Langguth B, De Ridder D, Bonfils P, Lefaucheur JP. Repetitive transcranial magnetic stimulation (rTMS): a new therapeutic approach in subjective tinnitus? *Neurophysiol Clin* 2006; **36:** 145–155.
7. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 2000; **406:** 147–150.
8. Kimbrell TA, Dunn RT, George MS, *et al.* Left prefrontal-repetitive transcranial magnetic stimulation (rTMS) and regional cerebral glucose metabolism in normal volunteers. *Psychiatry Res* 2002; **115:** 101–113.
9. Plewnia C, Reimold M, Najib A, *et al.* Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation. *Hum Brain Mapp* 2007; **28:** 238–246.
10. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 2005; **45:** 201–206.
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* 2007; **4:** 242–246.
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* 2007; **4:** 237–241.
13. Meeus O, Blaivie C, Ost J, De Ridder D, Van de Heyning P. Influence of Tonic and Burst Transcranial Magnetic Stimulation Characteristics on Acute Inhibition of Subjective Tinnitus. *Otol Neurotol* 2009; **30:** 697–703.
14. De Ridder D, De Mulder G, Verstraeten E, *et al.* Primary and secondary auditory cortex stimulation for intractable tinnitus. *ORL J Otorhinolaryngol Relat Spec* 2006; **68:** 48–54; discussion 54–45.
15. Hiller W, Goebel G, Rief W. Reliability of self-rated tinnitus distress and association with psychological symptom patterns. *Br J Clin Psychol* 1994; **2** (Pt 2)**:** 231–239.
16. Kleinjung T, Steffens T, Londero A, Langguth B. Transcranial magnetic stimulation (TMS) for treatment of chronic tinnitus: clinical effects. *Prog Brain Res* 2007; **166:** 359–551.
17. Brookes GB. Vascular-decompression surgery for severe tinnitus. *Am J Otol* 1996; **17:** 569–576.

18. Moller MB, Moller AR, Jannetta PJ, Jho HD. Vascular decompression surgery for severe tinnitus: selection criteria and results. *Laryngoscope* 1993; **103:** 421–427.
19. Ryu H, Yamamoto S, Sugiyama K, Nozue M. Neurovascular compression syndrome of the eighth cranial nerve. What are the most reliable diagnostic signs? *Acta Neurochir (Wien)* 1998; **140:** 1279–1286.
20. Schlee W, Hartmann T, Langguth B, Weisz N. Abnormal resting-state cortical coupling in chronic tinnitus. *BMC Neurosci* 2009; **10:** 11.
21. Stewart LM, Walsh V, Rothwell JC. Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. *Neuropsychologia* 2001; **39:** 415–419.
22. Antal A, Nitsche MA, Kincses TZ, Lampe C, Paulus W. No correlation between moving phosphene and motor thresholds: a transcranial magnetic stimulation study. *Neuroreport* 2004; **15:** 297–302.
23. 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* 2007; **78:** 152–156.
24. Moller AR. Neural plasticity in tinnitus. *Prog Brain Res* 2006; **157:** 365–372.
25. Xiong Y, Yu YQ, Chan YS, He J. Effects of cortical stimulation on auditory-responsive thalamic neurones in anaesthetized guinea pigs. *J Physiol* 2004; **560:** 207–217.
26. He J, Hu B. Differential distribution of burst and single-spike responses in auditory thalamus. *J Neurophysiol* 2002; **88:** 2152–2156.
27. May A, Hajak G, Ganssbauer S, *et al*. Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. *Cereb Cortex* 2007; **17:** 205–210.
28. Moller A. *Sensory systems: Anatomy and Physiology*. Amsterdam: Academic Press, 2003.
29. 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.
30. Hallberg LR, Erlandsson SI. Tinnitus characteristics in tinnitus complainers and noncomplainers. *Br J Audiol* 1993; **27:** 19–27.
31. Axelsson A, Ringdahl A. Tinnitus – a study of its prevalence and characteristics. *Br J Audiol* 1989; **23:** 53–62.
32. Weisz N, Muller S, Schlee W, Dohrmann K, Hartmann T, Elbert T. The neural code of auditory phantom perception. *J Neurosci* 2007; **27:** 1479–1484.
33. van der Loo E, Gais S, Congedo M, *et al*. Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. *PLoS ONE* 2009; **4:** e7396.
34. De Bellis MD, Keshavan MS, Frustaci K, *et al*. Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. *Biol Psychiatry* 2002; **51:** 544–552.
35. Schiffer F, Teicher MH, Papanicolaou AC. Evoked potential evidence for right brain activity during the recall of traumatic memories. *J Neuropsychiatry Clin Neurosci* 1995; **7:** 169–175.
36. Langguth B, Eichhammer P, Kreutzer A, *et al*. The impact of auditory cortex activity on characterizing and treating patients with chronic tinnitus–first results from a PET study. *Acta Otolaryngol Suppl* 2006; **556:** 84–88.
37. Lockwood AH, Salvi RJ, Coad ML, Towsley ML, Wack DS, Murphy BW. The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity. *Neurology* 1998; **50:** 114–120.
38. Smits M, Kovacs S, de Ridder D, Peeters RR, van Hecke P, Sunaert S. Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. *Neuroradiology* 2007; **49:** 669–679.
39. Maihofner C, Forster C, Birklein F, Neundorfer B, Handwerker HO. Brain processing during mechanical hyperalgesia in complex regional pain syndrome: a functional MRI study. *Pain* 2005; **114:** 93–103.
40. Moller AR. Similarities between severe tinnitus and chronic pain. *J Am Acad Audiol* 2000; **11:** 115–124.
41. Winer JA, Chernock ML, Larue DT, Cheung SW. Descending projections to the inferior colliculus from the posterior thalamus and the auditory cortex in rat, cat, and monkey. *Hear Res* 2002; **168:** 181–195.
42. Khedr EM, Rothwell JC, Ahmed MA, El-Atar A. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: comparison of different stimulus frequencies. *J Neurol Neurosurg Psychiatry* 2008; **79:** 212–215.
43. Langguth B, Hajak G, Kleinjung T, Pridmore S, Sand P, Eichhammer P. Repetitive transcranial magnetic stimulation and chronic tinnitus. *Acta Otolaryngol Suppl* 2006; **556:** 102–105.
44. Langguth B, Zowe M, Landgrebe M, *et al*. Transcranial magnetic stimulation for the treatment of tinnitus: a new coil positioning method and first results. *Brain Topogr* 2006; **18:** 241–247.
45. Sparing R, Mottaghy FM. Noninvasive brain stimulation with transcranial magnetic or direct current stimulation (TMS/tDCS)-From insights into human memory to therapy of its dysfunction. *Methods* 2008; **44:** 329–337.
46. Cohen LG, Roth BJ, Nilsson J, *et al*. Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. *Electroencephalogr Clin Neurophysiol* 1990; **75:** 350–357.