Effectiveness of Theta-burst Repetitive Transcranial Magnetic Stimulation (rTMS) for Treating Chronic Tinnitus

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INTRODUCTION

Chronic tinnitus is the awareness of sound or noise in the absence of any external acoustic stimulation. It is one represents one of most vexatious symptoms in clinical practice, for which there is no effective and satisfying pharmacological treatment. Currently, chronic tinnitus is thought to be associated with a reorganization of the auditory projection, which is a consequence of neuroplasticity [Muhlnickel et al., 2005]. Advanced functional neuroimaging studies revealed that in patients with tinnitus, the primary auditory cortex (PAC, comprising the gyrus of Heschl and located at Brodmann areas 41 and 42) has a higher activity level than other cortical areas [Shulman et al., 2004; Arnold et al., 1996; Langguth et al., 2006; Wang et al., 2001]. Therefore, tools that allow manipulation of cortical excitability might be useful in suppressing hyperactive auditory cortex in order to influence tinnitus perception.

Repetitive transcranial magnetic stimulation (rTMS), an updated noninvasive method for altering cortical excitability, has been used for treating many diseases, including Parkinsonisms, multiple sclerosis, phantogeusia, and epilepsy [Curra et al., 2002; Cantello, 2002; Henkin et al., 2011]. During rTMS treatment, a strong magnetic field is induced by an electric current circulating in a coil placed on the patient's scalp. When the magnetic waves penetrate the skull, they cause an intracranial inverse current. By altering stimulation parameters, it is possible to manipulate neuronal activity.

Although rTMS has been proposed as a tinnitus treatment for more than 10 years, the exact clinical methods for delivering the treatment have not yet been resolved. For instance, more information is needed on appropriate patterns (tonic or burst), intensity (a fixed value or motor-threshold-based), duration of stimulation, and even ways of "targeting" the abnormal asymmetry. Previous research has shown that rTMS treatments may improve tinnitus symptoms by 40–79%, depending on the exact algorithms used [De Ridder et al., 2005; Kleinjung et al., 2007]. Several rTMS protocols that reduce the abnormal hyperactive auditory cortex have been proposed, the most common of which is a daily application of 1Hz rTMS to produce long-lasting inhibitory effects on the auditory cortex. However, late studies have suggested that it may be effective to direct rTMS towards tempoparietal area in general, rather than just the auditory cortex specifically [Langguth et al., 2010; Frank et al., 2010; Mennemeier et al., 2011]. Only recently has clinical research begun to focus on theta-burst stimulation (TBS), a novel form of rTMS that also creates inhibitory effects [Huang et al., 2005]. Theta-burst stimulation is more convenient than conventional rTMS protocols, which require a higher intensity and longer length of stimulation. In this study, we report the efficacy of theta-burst rTMS in patients with chronic tinnitus, using a noninvasive, EEG-based, and radiation-free technique of navigating the auditory cortex.

MATERIALS AND METHODS

Subjects

Institutional review board approval (DMR98-IRB-041) by the ethical committee of China Medical University Hospital and informed consent were obtained before all procedures.

This is a randomized-controlled study. We enrolled 22 right-handed tinnitus sufferers whose symptoms had not resolved with medication or other adjuvant treatments such as acupuncture and retraining therapy. The mean age of study participants was 52.96 (range: 20–76 years). The study group included patients with tinnitus in 1 ear (17 individuals) and in both ears (5 individuals); all patients had experienced symptoms for at least 6 months (range: 6 months to 20 years). The participants were randomly assigned to an active-stimulation group and a sham-stimulation group. We used high-resolution magnetic resonance imaging (MRI) to screen patients for intracranial space-occupying lesions or anatomical abnormalities. Patients with a known history of metal implantation, head injury, stroke, or epilepsy were also excluded from this study.

We conducted otologic examinations, including pure-tone audiometry (PTA), auditory brainstem response (ABR), and tinnitus frequency- and loudness-matching tests. To be included in this study, patients had to clarify the exact pitch and intensity of their tinnitus so that we could determine whether there had been audiological shifts in tinnitus frequency and loudness after rTMS. Thus, subjects with narrow band, white, or pink tinnitus were not included in this clinical trial. For participants with bilateral pure-tone tinnitus, we calculated an averaged pitch and intensity value across the 2 sides. Changes in tinnitus severity were evaluated by the Tinnitus Questionnaire (TQ) and the Tinnitus Handicap Inventory (THI) [Hallam et al., 1988; Newman et al., 1996]. A free, downloadable program called Tinnitus Questionnaire Software (Programmed by J.J. Barajas and F. Zenker, download available at http://www.auditio.com/tinnitus/aaa2000/) was used to compute subscales. Several factors appeared to describe emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance, and somatic complaints. By comparing patients' responses to questions in each of these categories before and after rTMS treatment, we could evaluate the effectiveness of the treatment. There were no significant differences in age, baseline audiometry, TQ, THI, or tinnitus duration between the 2 groups.

Neuronavigation of the auditory cortex by stereotaxy

In adults, the depressed waveforms can be recorded in event-related potentials

(ERPs) in response to playback of a monotonic stimulus interlaced with occasional deviant sounds [Näätänen et al., 1978; Näätänen and Winkler, 1999]. This phenomenon, called mismatch negativity (MMN), resulted from the auditory cortex (most probably secondary and associated cortices) [Näätänen et al., 1997; Schröger E, 1997; Näätänen et al., 2001]. Functional neuroimaging revealed a correlation between the predominant laterality of the auditory cortex and the enhancement of MMN [Opitz et al., 1999; Celsis et al., 1999; Tervaniemi et al., 2000].

We used MMN to determine auditory cortex laterality in a pilot trial on 4 individuals in our active-stimulation group. A 32-lead electroencephalography (EEG) provided information about which side of the brain experiences shifts in wave activity in response to shifts in acoustic frequency stimuli. In our pioneer patients, the dominant auditory cortices were all located on the left side of the brain, indicating that this was the side on which patients should receive stimulation. Using information collected during MRIs, we used the Curry 6® (Compumedics USA, Charlotte, NC, USA) software to create surface reconstructions of each patients' head and brain.

In order to focus more closely on the auditory cortex, which is located in the temporoparietal area, we created a 3 × 3 grid adjacent to this region using 9 leads (F1, Fc, F3, C3, C, C4, P5, Pc, and P6) from the 32-lead EEG system [Plewnia et al., 2003]. The software allowed for orientation of the orthogonal projection of the auditory cortex on the scalp, according to spatial localization between leads and several anatomical landmarks (Figure 1, left).

Intensity

The rTMS was applied using a figure-eight-shaped coil (Magstim SuperRapid; The Magstim Company Ltd., Whitland, UK). The resting motor threshold (RMT) was the basic intensity of proper rTMS dosing. In order to determine this value, we placed the coil approximately 5 cm above the left auricle and rotated it around the horizontal axis, after which the handle of the coil was pointing backwards, approximately 45° from the mid-sagittal line [Mishory et al., 2004]. The minimal intensity for right abductor digiti minimi movement was determined by averaging values from 5 identical measuring procedures.

Stimulations

In the active-stimulation group, the coil was placed over the targeted region with the intensity setting at 80% of the RMT. Continuous theta-burst rTMS (cTBS) was delivered at a burst frequency of 5 Hz (the theta rhythm in the EEG); each burst consisted of 3 pulses repeated at 50 Hz. We administered 900 pulses (300 bursts) of stimulation once daily for 10 consecutive business days. The sham-stimulation group

patients received the identical protocol as the active-stimulation group, but with the sham coil (The Magstim Company Ltd., Whitland, UK). After completing the rTMS treatment, each patient was subjected to a second round of evaluation testing and asked to respond to the TQ and THI at 1 week and at 1 month after treatment.

Statistical analysis

We used paired *t*-tests and one-way ANOVAs to analyze differences between baseline, post-treatment, and 1-month follow-up data. Significance was defined as $p < 0.05$. All analyses were performed using the SAS statistical package (version 9.1.3; SAS Institute Inc., Cary, NC, USA).

RESULTS

Responses to questionnaires

Nine of twelve patients (75%) in the active-stimulation group reported tinnitus suppression following treatment with rTMS and achieved a "therapeutic success" (TQ reduction > 5) [Kleinjung et al., 2007]. After active stimulation, the TQ global scores of 5 participants (42%) were > 33% less than the baseline value. TQ global scores averaged 8.58 points lower 1 week after treatment, a significant decrease compared to the sham-stimulation group ($p < 0.01$). Similarly, THI scores were, on average, 8.33 points lower after treatment, which were also significantly lower than those of patients in the sham-stimulation group ($p < 0.01$) (Table 1).

Within the active-stimulation group, the TQ software descriptive analysis revealed that significant improvements occurred in patients' reports of emotional distress and somatic symptoms ($p < 0.05$). However, there were no significant differences in cognitive distress, sleep disturbances, auditory perceptual difficulties, and intrusiveness ($p > 0.05$)(Table 2). After 1 month, TQ and THI scores had risen in some patients and were no longer significantly different from baseline values ($p > 0.05$), indicating that the positive effects of theta-burst rTMS might not be permanent.

Auditory tests and tinnitus matching

Pre-treatment PTAs indicated that study subjects differed widely in their auditory abilities. Eight patients had normal hearing thresholds, 5 patients had downward-sloping sensorineural hearing loss, 4 patients had high-tone sensorineural hearing loss, 3 patients had low-tone hearing loss, and 2 patients had trough-shaped sensorineural hearing loss. Values for pre-treatment mean hearing threshold, and tinnitus frequency- and loudness-matching were 42 dB (± 26 dB), 4,910 Hz (± 2,410 Hz), and 62.32 dB (± 14.1 dB), respectively.

There were no obvious improvements in post-treatment pure-tone hearing thresholds in either the active- or sham-stimulation groups. In the active-stimulation group, tinnitus frequency- and loudness-matching tests revealed an increase in tone (5,167 Hz ± 2,167 Hz, $p > 0.05$) and a significant decrease in loudness (54.67 dB, ± 16.7 dB, $p < 0.05$) after the treatment.

All of the patients tolerated the procedures well. Five patients complained of transient jaw soreness; 3 individuals developed temporary orbital twitching; and 1 patient experienced facial myalgia during the stimulation. Previous study had mentioned that prefrontal rTMS is not thought to change brain structure (as assessed by MRIs) in depressed patients who received 10 days of treatment [Nahas et al., 2000]. May et al. [2007] used voxel-based morphometry and confirmed the existence of post-TMS dynamic transformation in gray matter within one week. Eight responders in this study received post-treatment MRIs one month later and there were no evident changes (i.e., intracranial hemorrhage or ventricular dilation) in the brain parenchyma. No patients experienced sustained side effects after the rTMS treatment. Multivariate analyses revealed no correlations between post-treatment scores and patient traits such as age, gender, duration of tinnitus, pre-treatment scores, and tinnitus laterality.

DISCUSSION

rTMS is thought to treat chronic tinnitus by modulating neuronal circuits, thus disturbing the reorganization or plasticity of the auditory projection; this process may interfere with both the high and low routes of the auditory pathway [Paus et al., 2001]. Although the depth of rTMS penetration is only approximately 2-3 cm, connectivity of the neurons may lead to effects in deeper brain structures, the opposite cerebral hemisphere, and superficial brain cortex [Kimbrell et al., 1999; Fox et al., 1997].

In order to modulate tinnitus, the initial step is determining which side of the brain requires stimulation. This can be accomplished using a combination of positron emission tomography and computed tomography (PET-CT), which indicates the areas that experience the highest levels of cortical activation [Mennemeier et al., 2011]. However, this is an invasive procedure and requires that researchers first convince patients to submit to injection of radioactive isotopes. Drawbacks of the procedure include drug allergies, renal insufficiencies, or exposure to harmful rays. Use of such an invasive procedure is particularly unappealing when it is in preparation for a treatment that, by itself, does not require invasive techniques.

Several previous studies have indicated that tinnitus patients experience increased metabolic activity predominantly on the left side of their brains, in some cases regardless of tinnitus severity, laterality, and duration [Arnold et al., 1996; Langguth et al., 2006; Wang et al., 2001]. These findings were supported by the

results of our MMN pilot trial. Because this work suggests that increased metabolism in the left PAC is related to the perception of tinnitus in most patients, we decided to continue delivering rTMS on the left side of the brain in our remaining patients. Another option would be to deliver the treatment on the side opposite the ear with tinnitus, or, if tinnitus is bilateral, on the side with the loudest tinnitus [De Ridder et al., 2005; De Ridder et al., 2007; Smith et al., 2007].

To date, most researchers focused their efforts on the left auditory cortex, though some have based their treatment locations only on surface anatomy markers [Langguth et al., 2008]. For instance, both Meeus et al. [2009] and De Ridder et al. [2007] placed the coil 5 cm above the EAC inlet along a straight line to the vertex, without any other navigational guides. These non-stereotactical positioning strategies seem particularly inaccurate in targeting the auditory cortex, but even methods such as frameless stereotactic localization have limitations, due to cytoarchitectonic mismatches between external anatomical landmarks and defined boundaries of the auditory cortex [Morosan et al., 2001; Morosan et al., 2005]. As the penetrability of rTMS is confined to 2-3 cm under the scalp, it is unclear whether this technique can actually have an effect on the auditory cortical area (i.e., Brodmann area 41,42 and 22). We used Curry 6® software to create a virtual transparent scalp and cortex of 1 subject, allowing us to calculate that the distance between the superficial cortex and skin was 2.38 cm (Figure 1, right). Thus, in some cases, the coverage of rTMS may include the auditory cortex. Even where there are no direct interactions, propagation of brain activity from the stimulant foci can result in widespread changes [Mennemeier et al., 2011]. It seemed that targeting on the auditory cortex was no more mainstreamed into the tinnitus treatment. Nevertheless, we still advocate the use of functional or structural topography for detailed navigation. Langguth et al., [2010] summarized the different methods of coil positioning, it is noteworthy that the brain mapping techniques remained necessary when the authors tried to stimulate the areas beyond the temporoparietal cortex (i.e., dorsolateral prefrontal cortex).

One popular paradigm for tinnitus is low-frequency tonic stimulation (mostly at 1 Hz, with an intensity of 110%–120% RMT), although time-saving burst stimulation has become increasingly popular in recent years [De Ridder et al., 2007; Meeus et al., 2009; Arfeller et al., 2009; Richter et al., 2006]. The 1-Hz protocol takes 25 minutes, whereas the theta-burst stimulation (consisting of 900 pulses per session), takes less than 5 minutes. In our study, stimulation was initially applied at a rate of 1 Hz and an intensity of 110% (the most common pattern). However, our first 2 patients complained of forceful facial muscular twitching during stimulation, which prompted us to use lower-intensity (80% RMT) theta-burst stimulations for the remainder of the study. Previous work has shown that increases in burst stimulation intensity do not

lead to increases in tinnitus reduction; thus, we are confident that the intensity used in our study was adequate. After examining the effectiveness of tonic and burst TMS on 46 patients with narrow band or white noise tinnitus, De Ridder et al. [2007] found the following: 1) response rate was 30.4%; 2) burst TMS resulted in better tinnitus suppression than tonic TMS; 3) alpha and beta burst, as well as theta burst, can be used to control narrow band noise or white noise tinnitus. Later, the same group suggested that burst TMS can be used to control noise-like tinnitus, while tonic TMS resulted in greater tinnitus reduction on pure tone tinnitus [Meeus et al., 2009]. Our outcomes also indicate that theta-burst rTMS can have a significant effect on pure-tone tinnitus (42% of patients experienced > 33% reduction in tinnitus). Poreisz et al. [2009] treated chronic tinnitus patients with 1 of 3 patterns of 600-pulses theta-burst stimulations: cTBS, intermittent TBS (iTBS), and intermediate TBS (imTBS). Significant (but short-lived) improvements were only observed in response to the cTBS treatment. Thus, a single session of cTBS might not be capable of obtaining a therapeutic modulation. However, by delivering a similar cTBS protocol repeatedly over 10 subsequent business days, we have shown that the effects of this treatment are cumulative.

We did not find consistent patterns in the duration of benefits derived from rTMS treatment; furthermore, we failed to demonstrate a significant long-term outcome. Previous reports have indicated that the effects of rTMS could last for as long as 6 months to 4 years [Khedr et al., 2009; Kleinjung et al., 2005]. Perhaps our relatively weaker results were caused by use of a shorter-acting cTBS (compared with tonic 1Hz stimulation), or weaker delivery intensity (80% of RMT, compared with 110% of RMT). Further work should investigate methods of lengthening the active duration of cTBS, such as varying intensity increments and burst delivery patterns.

There are 3 mainstream methods of evaluating the outcome of tinnitus therapy: (1) questionnaires, such as TQ and THI; (2) self-rating of tinnitus, for example, 10-grading or 100-grading visual analogue scores (VAS); and (3) audiometric examinations, for instance, tinnitus frequency- and loudness-matching or residual inhibition measures [Henkin et al., 2011; Kleinjung et al., 2008; Kleinjung et al., 2005; Lee et al., 2008; Mennemeier et al., 2008]. Because measurements based on these methods are variable, and because each method contains its own inherent biases, we felt it was particularly important and useful to employ a multidirectional assessment. Specifically, our tinnitus evaluation consisted of TQ, THI, and tinnitus-matching (pitch and loudness); we opted not to use VAS because it directly correlates with tinnitus loudness [Smith et al., 2007; Herraiz et al., 2007]. Our otologic results are similar to those found in previous research: Although the audiometric threshold was not altered by the rTMS treatment, there were significant reductions in tinnitus

loudness [Folmer et al., 2006]. In such cases, accurate evaluation might be difficult because tinnitus "characteristics" are not perceived as being proportional to "severity," due to the emotional comorbidity of anxiety and depression in tinnitus sufferers [Lee et al., 2005; Poulet et al., 2005].

After subclassifying the TQ scores, we observed that the highest values were related to emotional distress and somatic symptoms, rather than auditory perceptual difficulties. This indicates that nonauditory brain areas, such as the limbic system, also experience rTMS-induced neuroplasticity via alterations in thalamocortical processing [Poulet et al., 2005; Langguth et al., 2005]. Unlike previous studies that relied solely on TQ global scores to evaluate treatment effectiveness, we performed a subscript analysis. We found that the beneficial results of rTMS may be derived from psychological amelioration of symptoms, rather than acoustic improvements. However, the reasons behind this result remain unclear. There are 2 potential explanations. First, burst rTMS may neuromodulate the lemniscal and extralemniscal auditory systems differently through connecting neural pathways between superficial and deeper brain structures; second, there is a "neglect-like" effect subsequent to theta-burst stimulation [Fox et al., 1997; De Ridder et al., 2007; Nyffeler et al., 2009]. Mennemeier et al. [2011] used 1-Hz rTMS to target temporal lobe PET asymmetry and reported that there were significantly changes in PET following active treatment, including in the inferior lateral parietal temporal cortex, primary visual cortex, sensory motor cortex, and superior lateral temporal cortex. A subsequent nervous propagation to other brain structures might lead to changes in tinnitus perception. Kleinjung et al. [2008] also performed rTMS on both auditory (temporal) and non-auditory (dorsolateral prefrontal) cortex and demonstrated a pathophysiologic association between tinnitus and the prefrontal cortex. To resolve which of these relationships drives the success of rTMS treatment, further work are needed to investigate post-TMS neurobiological changes in emotion-related structures, such as the prefrontal area or the limbic system.

We are particularly interested in understanding why the greatest effect of rTMS was found in the patient who had long-lasting tinnitus (20 years). This greatly contrasts with the results of other studies, in which the strongest responses were mainly observed in patients who had experienced tinnitus for no more than 3-4 years [Kleinjung et al., 2007]; further, others have found that the difficulty in suppressing tinnitus depended on the length of disease history [De Ridder et al., 2005; Frank et al., 2010]. However, the aforementioned studies used tonic stimulation, leaving open the possibility that whether burst or tonic stimulation might have better results for patients suffering from chronic tinnitus for more than 4 years. In a case report on a female patient who suffered from incapacitating tinnitus, accompanied by severe depression,

for 5 years, Soekadar et al. [2009] described how cTBS reduced TQ from 84 to 59 points. Thus, compared with tonic TMS, burst TMS may provide more extensive and powerful neuromodulation in the extralemniscal auditory system, as well as influencing the limbic system via the doral and medical thalamic projections [Moller, 2006; De Ridder et al., 2007]. Cumulatively, both our current results and previous research suggested that cTBS had the potential to manage long-term tinnitus in the future.

CONCLUSION

Repetitive TMS has been demonstrated as an effective treatment for chronic tinnitus. In this parallel, randomized control study, we found that the treatment achieved a significant suppression rate with additional improvements in emotional distress and somatic complaint levels. Patients obtained psychological improvement as well as tinnitus loudness inhibition. Theta-burst rTMS achieves a similar outcome as 1-Hz tonic rTMS but saves time and requires less intensity. The Navigational system based on EEG worked as well as other methods, such as PET guide and surface anatomical landmarks. Adverse effects, if any, subside with time, and there are no sustained neurological sequelae. Given these results, we feel that theta-burst rTMS is an important new tool for tinnitus suppression.

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Figure 1. (Left) Topography of 9 leads from the 32-lead EEG system. The auditory cortex was identified as the blue spot below LN and next to C3. Temporoparietal leads (F1, Fc, F3, C3, C, C4, P5, Pc, and P6) and anatomical landmarks (bilateral entrances of the external auditory canals and the glabella, shown as red spots) were labeled on the reconstructed scalp. We placed the coil over the targeted region (shown as LN) and generated stimulation. (Right) The distance between electrodes on the scalp (blue dots) and cortex is calculated as 23.8 mm.