

Static magnetic stimulation of human auditory cortex: a feasibility study

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There is a growing interest about the effects of static transcranial magnetic stimulation (tSMS) over different cortical areas, being the motor cortex the most widely studied region. Previous experiments have shown that noninvasive magnetic static stimulation of the human brain may change its excitability in a reversible way for a period that outlasts the time of application of the magnetic field. However, evidence about the effects over the auditory cortex are poor and this is the purpose of the present study. Twelve voluntary subjects were studied in two different sessions, immediately before and 20 min after the placement of a magnet or a sham over the left primary auditory cortex, for 30 min. No significant effects of the magnet were observed on auditory responses, including onset and offset potentials and oscillatory responses to stimulus frequency modulation. A reduction in the amplitude of the cortical onset and offset potentials was observed after the two sessions, both with the

magnet and with the false magnet (sham). No effects of unilateral static magnetic stimulation on cortical auditory responses have been observed. However, we probe the feasibility and tolerability of the protocol performed and suggest the use of different stimulation protocols. *NeuroReport* 33: 487–493 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

There is a growing interest on the effects produced by noninvasive neuromodulation of the cerebral cortex, given its possible applications in clinical practice and its potential role in motor, sensory, and cognitive functions research [1]. Its use is well established for treating a variety of neurological and neuropsychiatric disorders such as chronic pain, drug-resistant depression, dystonia, migraine, and neurorehabilitation, while there are additional indications under study [2,3,4].

These techniques are becoming increasingly popular because of their capacity to modulate the brain in a painless and reversible way [5], with plasticity changes that go beyond the stimulation sessions [6]. The two best-known noninvasive neuromodulation techniques are repetitive transcranial magnetic stimulation (rTMS), which shows the most consistent findings [7] and transcranial direct current electrical stimulation (tDCS). Both methods act at synaptic levels on central pathways, TMS preferentially activates axons and tDCS induces conformational changes in transmembrane proteins, causing potentiation or depression of certain areas (depending on polarity in the case of tDCS, or on stimulation pattern in rTMS).

However, they can cause some discomfort in patients and may require complex protocols, making difficult their specific use.

Transcranial static magnetic stimulation (tSMS) of the cortex can be achieved through the placement of a neodymium magnet over the scalp, decreasing cortical excitability. The placement of the magnet over the motor cortex area in sessions between 10 and 30 min reduces the amplitude of the motor evoked potentials (MEP) induced by TMS, which represents the excitability of the motor system. These effects are painless and reversible, do not generate electrical currents and have been shown to act on a variety of systems by modifying membrane ion channels which could alter activation kinetics [8].

Some of the reported effects of tSMS over subject behavior and performance are interference with visual detection, improvement of somatosensory detection, interference with physiological habituation, decrease in motor strength, and influence on motor learning [9,10]. Nevertheless, there are no studies on the effects of tSMS on the auditory cortex, which could be of interest in the treatment of tinnitus.

According to electrophysiological and imaging studies, tinnitus (defined as an unpleasant sound noticeable by a subject without an external sound source), is associated with increased activity in the central auditory system. In these patients, this activation is greater in the left primary

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auditory cortex, regardless of their laterality [11]. Given the cortical activity changes in patients with tinnitus and the limited efficacy of existing medical and surgical treatments for this condition, rTMS has been proposed as a therapeutic alternative due to its capacity to reduce excitability in cortical and thalamocortical circuits in which tinnitus is involved [12,13]. However, all these results should be taken with caution because of the heterogeneity in the protocols applied, and the low sample of patients studied.

Although evidence of behavioral changes of tDCS are sparse, some studies have demonstrated that it can modulate auditory cortex reactivity as a function of site of stimulation and its polarity, anodal or cathodal [14].

The electrophysiological effects generated in the auditory cortex can be evaluated by analyzing cortical responses to auditory stimuli, recorded by surface EEG (event-related potentials). Steady-state responses (SSRs) are the result of averaging oscillatory responses generated by the synchronous activity of a large population of neurons to rhythmic stimuli (usually visual or, as in our case, auditory stimuli) that can be detected by EEG and objectively assessed by statistical studies [15]. Steady-state potentials have been extensively used to investigate central responses to rhythmic sensory stimulation in both children and healthy adults. In 1981, Galambos *et al.* described that when the auditory system is stimulated rhythmically (by means of short-duration square wave trains), oscillatory responses could be recorded in the brain at the same frequency as the stimulation. The amplitude of this response depends on the applied frequency [16]. Although the stimulation frequency at which the greatest response amplitude is obtained is around 40 Hz, the range in which responses are obtained is wider, from 10 Hz to more than 120 Hz. Responses in the 40 Hz range originated in cortical regions close to the primary auditory area [16,17].

Artieda *et al.* described a technique that allows the analysis of the oscillatory response to different stimulation frequencies using an amplitude-modulated tone at increasing modulation frequencies (Chirp). With this technique, the frequency at which the maximum response is obtained, as well as the range of frequencies in which an oscillatory response is produced, is easily determined [18,19]. At least four components are observed in the Chirp responses. First, an 'onset' complex consisting of a transient 40 Hz response and two long-latency auditory evoked potentials evoked by the first two clicks of the stimulus is observed. The longer latency of the first long-latency auditory evoked potential and the transient 40 Hz response, compared with other studies, can be explained by pitch modulation. The 'offset' response is also present in the averaged potential, with no clear correlation with frequency changes in the range studied. An oscillatory response to the amplitude-modulation of

the sound is observed between both onset and offset responses.

The purpose of the present study was to test the feasibility and potential effects of static magnetic field stimulation over the auditory cortex on evoked responses and gamma oscillatory activity (using chirp-evoked potentials) in healthy volunteers, as a prior step to studies in patients with tinnitus.

Subjects and methods

Twelve healthy volunteers participated in this study (six males and six females) with an age range between 28 and 49 years (mean: 31, 85 SD: 5, 8 years). All of them had university studies. Only one of the volunteers had low-level musical training. Exclusion criteria were significant medical or psychiatric illness, pregnancy, and concurrent use of neuroactive drugs. We also excluded individuals with pacemakers, brain stimulators, medication pumps, or any type of metal object which might pose a physical hazard during tSMS. The study was approved by the local ethical committee. Informed consent was obtained from all subjects prior to the study.

Two recording sessions were performed on each subject, separated by at least 7 days, using a magnet (tSMS) or a false magnet (sham). The order of the sessions (magnet first or sham first) in each subject was randomized. Total recording time was approximately 1 h and 30 min per session, with a previous additional half an hour for electrode placement and checks.

Both the subject and the EEG trace were continuously monitored by an observer to detect any sign of drowsiness or distraction.

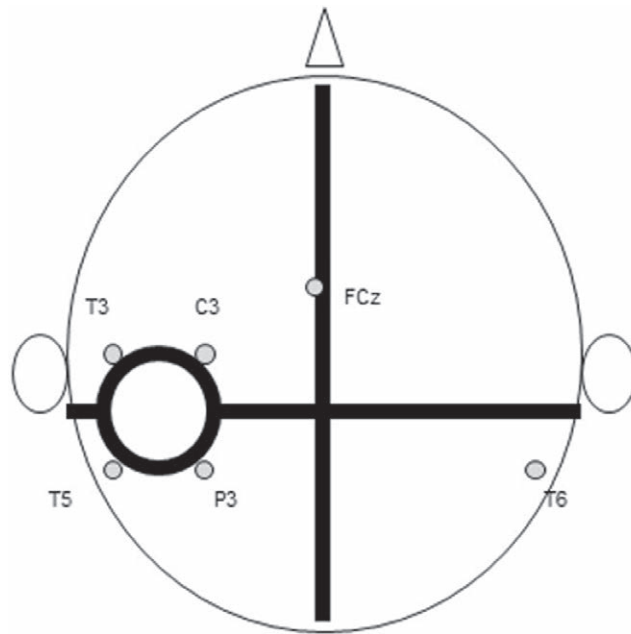
The recordings were made in a room with soft natural lighting, low ambient noise level, and electrical insulation by means of faradizing paint.

The subjects were comfortably seated in a padded armchair with a backrest and armrests.

Recording and auditory stimulation

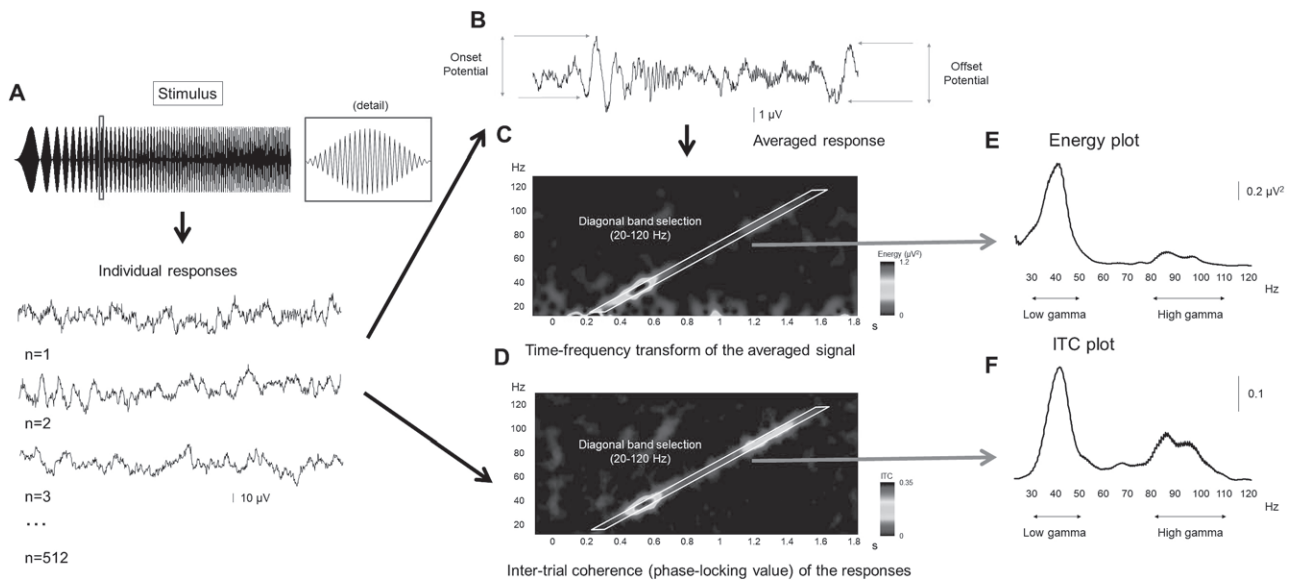
Brain electrical activity was recorded using disposable Ag/AgCl electrodes attached with collodion to the scalp. Electro-Gel conductive paste (Electro-Cap International) was used. Recording electrodes were placed at positions T3, C3, T5, and P3 of the International System 10-10, around the area covered by the magnet or sham in the left hemisphere, with two additional recording electrodes at FCz and T6 (Fig. 1). Impedances were systematically maintained below 5 K Ω at all electrodes. BrainAmps amplifiers and Brain Vision Recorder software (Brain vision, Gilching, Germany) were used for the recording. The signal was amplified, filtered 0.3–200 Hz, and digitized with a frequency of 500 Hz and a resolution of 0.1 μ V. After these steps, the signal was converted to CED Spike2 format (.smr) (CED, Cambridge, UK).

Fig. 1



Positioning method of the magnet or sham and recording electrodes C3, T3, T5, P3, T6, and FCz, according to the International System 10-10. The position of the magnet or sham was performed as previously described.

Fig. 2



Stimulus and response analysis process. The stimulus (a) consists of a tone at 1200 Hz frequency and 1.6 s duration amplitude modulated by means of a sinusoid of increasing frequency between 1 and 130 Hz. A minimum of 512 responses to each sound were recorded in each session. On the one hand, the average of all responses is obtained (b), a signal in which the onset and offset potentials are measured. From this averaged signal, a time-frequency representation is obtained by means of a Gabor transform (c). In this representation, the energy of the signal-averaged over time is plotted on a color scale; as the cortex responds to the modulation frequency of the signal and the signal increases linearly over the duration of the stimulus, the response is observed as a diagonal (increasing energy at an increasing frequency over time). From the individual responses, the inter-trial coherence or phase-locking value can also be calculated. This calculation provides a time-frequency plot similar to the previous one in which the ITC value is plotted for each frequency over time (again, the response appears as a diagonal) (d). In both the energy and ITC plots, a diagonal 'cut' can be made to plot the energy of the response at each frequency linearly (e and f). Time-frequency plot, ITC.

Auditory stimulation was performed using the NeuroScan STIM module (NeuroSoft, El Paso, USA), synchronized with the recording system, and transmitted through bilaterally calibrated stereo intracanalicular headphones, with airborne sound transmission through a tube and pad placed in the external auditory canal. The stimuli consisted of 1200 Hz tones (carrier frequency) modulated in amplitude at increasing frequency (chirp-type signal). This signal (chirp) is a sinusoid with linearly increasing oscillations from 1 to 120 Hz (Fig. 2a). With this stimulus, the cortical response to sound modulation in the range 1–120 Hz can be explored using a single test. Stimuli were generated using Matlab and subsequently stored in WAV format for presentation using the Neuroscan STIM stimulation module. A minimum of 512 stimuli, 1.6 s in duration, with an inter-stimulus interval of 2.2 s, were delivered in each recording. All signals were continuously stored for later analysis.

The recording electrodes were placed at the beginning of the session. Once the impedances had been checked, a basal recording was performed. After a basal recording, the magnet or sham (in a randomized order) was placed for 30 min (without auditory stimulation). At the end of the stimulation/sham stimulation session, the magnet or sham was removed, and two new 20-min recordings were made. As our focus was on long-term effects of tSMS, only the second recording was used for analysis (from 20 to 40 min after the end of the stimulation or sham stimulation). In both stimulation phases, the subject had to be relaxed and silent.

Stimulation with magnet or sham

To deliver tSMS we used a cylindrical Nickel-plated (Ni-Cu-Ni) NdFeB magnet of 45 mm diameter and 30 mm thickness with a weight of 360 g (Model S-45-30-N; Supermagnete, Gottmadingen, Germany). The maximum amount of magnetic energy stored in the magnet was 45 MGOe, with a force equivalent to 765 N (78 kg). A nonmagnetic metal cylinder of identical appearance and weight to the real magnet was used as sham. Both, the magnet and the sham, were held over the left auditory cortical representation using a custom-made strip cap. There are several methods described for the placement of the magnet over the auditory region. Our placement was based on the study by Plewnia *et al.*, where rTMS was proposed as a treatment for chronic tinnitus [20]. The placement of the magnet/sham was performed by drawing an imaginary line between T3 and Cz, 2.5 cm away from T3 and from that point, 1.5 cm posteriorly, being located slightly posterior to the ear. This area is considered representative of the primary auditory cortex (A1) as shown by studies that use neuronavigational techniques prior to the placement of the rTMS coil [3,20]. The magnet or sham was inserted in a circular holder attached to horizontal and vertical fastening strips. That position could be varied manually according to the differences in the

head measurements of the subjects, remaining centered in the desired area. The holding strips were placed at the beginning of the test, at the same time as the recording electrodes, so that only the magnet or sham had to be placed after the basal recording and removed after the stimulation period (Fig. 1).

The study was performed safely under the recommendations of the WHO, which establishes standards for safe exposure to static magnetic fields, and the Helsinki declaration of 1975.

At the end of each session, subjects were asked if they could identify whether the study had been performed with the real magnet or with the sham. The percentage of correct guesses was within the range expected by chance.

Signal analysis

First, the continuous signal from each recording session was segmented into 2-second-long sweeps, from 200 ms. before stimulus onset to 200 ms. after stimulus offset, using a custom script on CED Signal software (CED, Cambridge, UK). An offline review of all recorded segments was performed manually excluding all sweeps with visible artifacts.

The analysis of the oscillatory responses was performed by means of Gabor transforms of the averaged signal, and by computing the inter-trial coherence (Morgan-Short *et al.*, 2014) (Fig. 2c and d). On the time–frequency (or ITC) plots, a diagonal cut was made following the temporal evolution of the stimulus frequency, in order to obtain a linear representation of the energy or ITC of the response at each frequency (Fig. 2e and f). Subsequently, the total energy or coherence in the range 30–50 Hz and in the range 80–110 Hz was calculated in each linear plot (ITC or power). All the necessary calculations were performed using software specifically developed on the Matlab platform (Mathworks, Natick, USA).

Also, the amplitude and latency values of the onset and offset potentials present in each averaged response were measured using the segmented sweeps in CED Signal software (CED, Cambridge, UK) (Fig. 2b).

To compare the hypothetical effects of magnet or sham on each of these variables, two-factor repeated-measures analysis of variance test (baseline vs. intervention (before/after magnet or sham), and magnet vs sham) were used. Statistics were performed using STATA version 12 (StataCorp, Texas, USA).

Results

A typical response was observed in all analyzed subjects, in the form of an onset potential (onset) followed by an oscillation at the frequency of the modulation (chirp), with greater amplitude at frequencies around 40 Hz and in the range 80–120 Hz. After the end of the stimulus, a final positive wave (offset potential) was observed also

in all cases. Figure 2b shows an example response corresponding to one of the study volunteers. The oscillatory response showed a greater amplitude in the midline electrode (FCz) in all subjects, so the analysis was focused on this electrode.

Figure 3 (left) shows the average of the oscillatory activity power in the four conditions (before and after magnet or sham). Figure 3 (right) shows the average ITC in the four conditions. No effect of the time factor (baseline vs. intervention) was observed in the statistical analysis of the power and ITC of oscillatory activity in the high gamma (80–110 Hz) and low gamma (30–50 Hz) bands, nor of the type of intervention factor (magnet vs. sham) or interaction between both ($P > 0.05$ in all cases).

Figure 4 shows the comparison of the amplitude values of the onset and offset potentials also in the four conditions. A decrease in the amplitude of both potentials (onset and offset) was observed after both magnet and sham (significant effect for baseline vs intervention in the onset ($F = 4.73, P = 0.036$) and offset potentials ($F = 10.17, P = 0.003$)). In the onset potential only, a lower amplitude was observed in the magnet sessions (both before and after the intervention) than in the sham sessions ($F = 9.49, P = 0.004$). The type of intervention had no effect on the amplitude decrease between the baseline and the post-intervention recording (interaction between type of intervention and before/after the intervention measurements was NS in both onset and offset potentials). All subjects tolerated the procedure with minimal side effects (transient headache as the only effect in some cases, both magnet and sham).

Discussion

As mentioned in the introduction, the two most widely used noninvasive neuromodulation techniques are

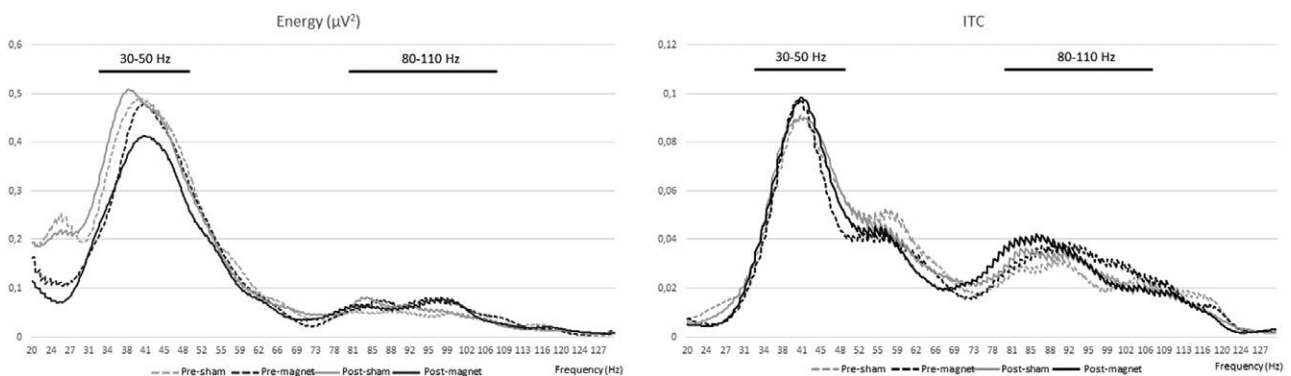
transcranial direct current electrical stimulation (tDCS) and transcranial magnetic stimulation (TMS). A new form of noninvasive neuromodulation based on the application of transcranial static magnetic stimulation focally on the scalp (tSMS), by means of a powerful neodymium magnet, was described and characterized by the group of Oliviero and Foffani. They observed that the placement of the magnet over the motor cortex could produce long-lasting focal effects, decreasing cortical excitability after its use, demonstrated in a reduction of the amplitude of motor evoked potentials. Subsequently, several studies have demonstrated modulating effects of static magnetic fields applied over the supplementary motor area, increasing the time to initiate movement while decreasing errors in choice-reaction time tasks. These results may encourage a possible therapeutic use in patients with Parkinson’s disease, among other pathologies [9]. Effects on the visual cortex have also been described, causing a decrease in photophobia [10].

Besides that, the use of noninvasive brain stimulation has also been postulated for the treatment of tinnitus. However, the mechanisms of TMS in this field are less clear, and the results are controversial.

Studies with PET have shown that the greatest auditory cortical activation is in the left temporal region [21], regardless of the side on which the sound is perceived. For that reason, our study was focused on this location, as in previous neuromodulation studies [10].

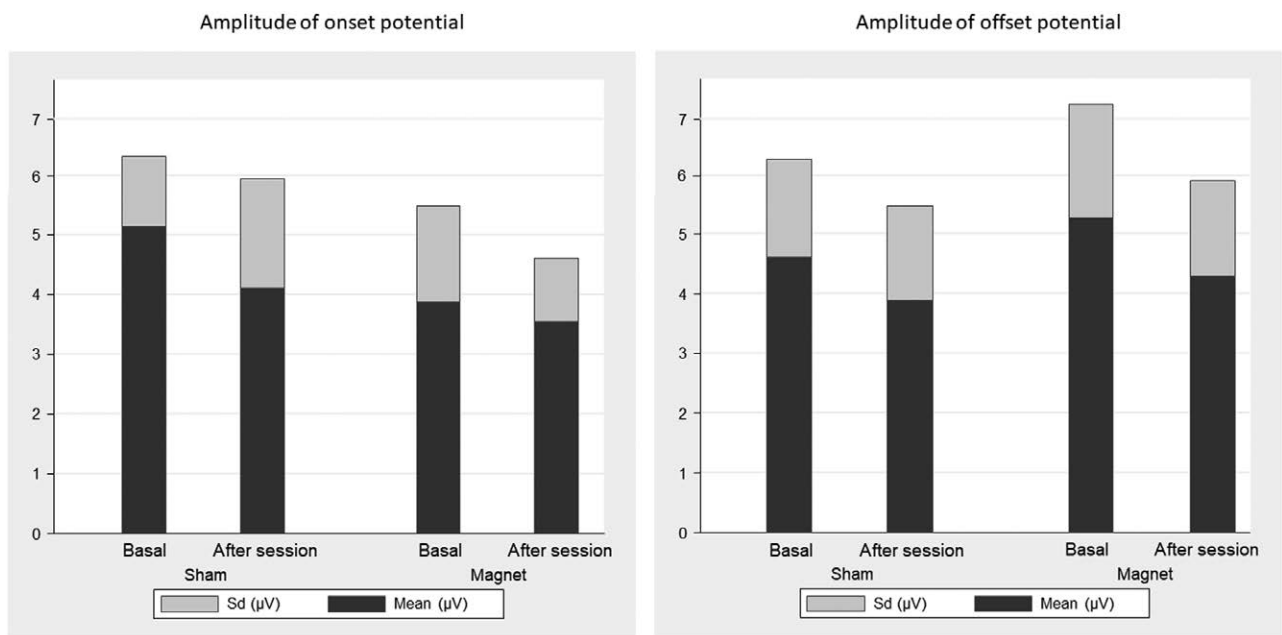
In patients with tinnitus, rTMS over the left auditory cortex can modulate cortical activity. This has been objectively demonstrated by a decrease in the metabolism of the auditory cortex [22,23], and by a decrease in gamma band activity, mostly involved in this pathology, in MEG and EEG studies [10,13,21]. These changes accompany

Fig. 3



Mean of the averaged response energy values (left) and ITC values (right) for each modulation frequency, in the two conditions (pre- and post-stimulation) and with the two stimulus types (magnet and sham). Statistical comparison in the two bands of interest (30–50 Hz and 80–110 Hz, black lines) showed no significant effects. Time–frequency plot, ITC.

Fig. 4.



Comparison of the amplitude values of the onset and offset responses in the two conditions (pre- and post-stimulation) and with the two stimulus types (magnet and false magnet-sham). A significant decrease in amplitude of the two types of potentials is observed after both magnet and sham stimulation. Onset potential values were lower in the magnet sessions than in the sham sessions, both before and after stimulation.

a decrease in the perception of tinnitus after rTMS sessions in a lasting manner [3].

The studies carried out to evaluate the effect of rTMS on tinnitus have used different protocols: on the one hand, some describe the use of high-frequency rTMS trains (10–20 Hz) in a single session, achieving an immediate, although short-lasting, reduction in tinnitus perception in patients with acute tinnitus [20]. On the other hand, studies of low-frequency rTMS (1 Hz) in several consecutive sessions (5–10 days) achieve a longer-lasting modulation and greater therapeutic interest in patients with chronic tinnitus [21]. In addition to these two protocols, there is a third one, in a single session study at low frequency, but performing rTMS in both temporal regions and in the prefrontal region. This last one discusses that the effects of rTMS are mediated not by direct changes in the directly stimulated area but by achieving a modulation in the thalamocortical circuits [24].

tDCS has also demonstrated polarity-specific effects over the temporal and temporoparietal cortex [14], so, the induced after-effects of tDCS depend on polarity, neural orientation with respect to electrical field, duration, and intensity of the stimulation. Specifically, a reduction in the amplitude of the N1 potential (approximate equivalent to our onset potential) was only observed after temporoparietal stimulation. Temporal stimulation (as in our protocol) induced changes in the P50 amplitude, but not in the N1, similarly to our

results. However, studies with tSMS have not shown any differences in polarity [5,8].

The study by Lorenz *et al.* (2010) described a decrease in auditory SSRs after left auditory cortex rTMS in tinnitus patients. In our study, we did not find significant effects of static magnetic stimulation of the left auditory cortex on cortical auditory oscillatory responses. There are different possibilities that may explain our negative results.

In first place, none of our volunteers had established tinnitus, unlike most studies in which neuromodulation effects of rTMS were found. The changes in oscillatory activity (ASSR) after rTMS have been described in tinnitus patients, who have a pathological increase in gamma activity compared to normo-hearing subjects [23,24]. It is possible that patients with tinnitus have hyperexcitability of the auditory cortex that is modulated by stimulation, while in healthy patients, in the absence of such hyperexcitability, no effects are clearly observed.

In the second place, there is the question of the location and intensity of the magnetic stimulus and the area affected. We used the same magnet as in previous studies in which motor cortex excitability changes have been described [5,9,25]. Although the cortical area reached by tSMS stimulation with this magnet is considered to be about 2×3 cm [13], the primary auditory cortex is located deeper than the primary motor cortex, primary visual cortex, or supplementary motor area. Moreover, it is also difficult to establish an equal magnetic flux with

the same intensity for each area, because some central nervous system areas have more surface thickness than others. Also, the exact cortical area in which rTMS exerts its clinical effects in tinnitus patients is still questionable. It has been suggested that the primary auditory cortex may be difficult to reach by TMS (and thus also by tSMS) because of its localization in the Sylvian fissure in a latero-medial direction, far from the brain surface, so that rTMS may not act directly but transynaptically via cortico-cortical or thalamocortical connections.

Additionally, our study was limited to the side with the largest auditory representation, despite the fact that the auditory cortex is bilateral. It is possible that performing the stimulation in patients who did not have established hyperactivity, in a single session, and with a unilateral magnetic field, may have limited the opportunity of finding any significant difference.

Finally, although the number of subjects included may have limited the statistical power of the study, the paired design and the results obtained ($P > 0.2$ in all intervention vs time interactions) make it unlikely that large differences could be found despite the inclusion of a larger sample of subjects. Indeed, we found a significant reduction in the amplitude of the onset and offset potentials in both the postsham and postmagnet recordings (probably due to habituation to the stimulus, as the postsham and postmagnet recordings were obtained after 20 min of auditory stimulation), indicating that the statistical power was enough to detect differences of that size. It should be noted that only two of the volunteers described a head-ness during the session with the magnet that did not exceed the stimulation time. It is very important because its application is simple, economical, and reversible. Translated into the clinical context, it appears to be a safe and promising tool in the treatment of neurological diseases. But more studies are required to unravel the basic mechanisms underlying the effects of tSMS and to establish the optimal protocol over the auditory cortex.

In summary, despite being negative, we consider that the results of this work may be helpful in the design of future research protocols in this field, demonstrating the feasibility and tolerability of the protocol performed, and suggesting the inclusion of patients with proven hyperexcitability or the use of different stimulation protocol.

Acknowledgements

Conflicts of interest

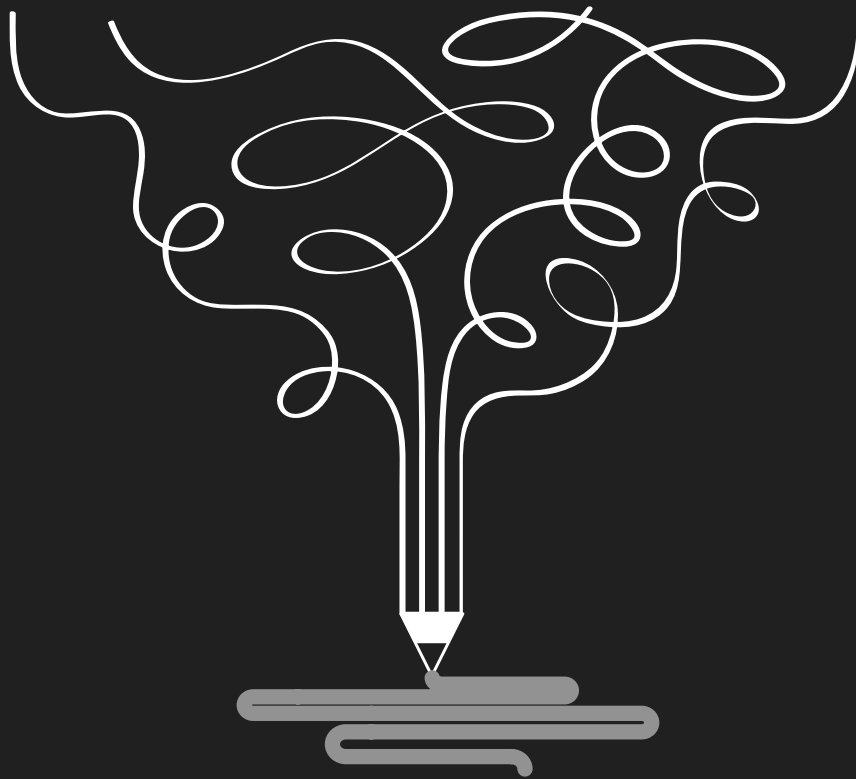
There are no conflicts of interest.

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