Magnetic stimulation of the auditory cortex for disabling tinnitus
Preliminary Results

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Summary
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Objective > Tinnitus – the perception of sound in one or both ears or in the head when no external sound is present – can be disabling and is especially difficult to treat. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique for activating or inactivating specific areas of the cortex. The aim of this study was to assess the feasibility of magnetic neurostimulation of the primary and secondary auditory cortex in the treatment of disabling chronic tinnitus.
Tinnitus affects approximately 10% of the population. Nearly 20% of these patients report that this symptom affects their daily quality of life or causes sleep disorders or even depression [1, 2]. The failure of most conventional medical treatment, especially drugs, has led some experts to develop treatment based on different concepts, such as cognitive or behavioral therapy [3]. Although the origin of tinnitus is generally thought to be peripheral, linked for example to the effects of acoustic trauma on the inner ear, the resulting discomfort very probably depends on central processes [4]. Accordingly, some authors suggest tinnitus is an auditory phantom phenomenon, similar to that observed in some cases of chronic pain [5-7]. This central neuropathic pain and tinnitus may be secondary to central nervous system reorganization linked to neuronal plasticity.

Electric stimulation of the auditory cortex in bats modifies the cortical frequency map [8], as does peripheral sensory deprivation in guinea pigs [9]. A shift of the cortical frequency map is also reported in patients with chronic tinnitus, and the shift of cortical reorganization is proportional to the perceived severity of the symptom [10]. These findings from basic and clinical research have led some authors to successful attempts to stimulate the auditory cortex of patients with chronic refractory tinnitus [11]. The aim of our work was to assess the effects of repetitive transcranial magnetic stimulation (rTMS) of dysfunctional areas of the auditory cortex localized by functional magnetic resonance imaging in a series of patients with severe tinnitus resistant to conventional treatments.

### Patients and methods

**Patients**

This study included 13 patients, all with tinnitus that was either unilateral or clearly dominant on one side, had been present for at least one year and was not due to a specific cause that required a particular treatment (for example, otospongiosis, vestibular schwannoma). Patients with a psychiatric dissociative disorder or susceptible to major depression and requiring specialized management were excluded, as were those with cerebrovascular or degenerative disease or a contraindication to rTMS. All patients had already undergone unsuccessful treatment in our tinnitus clinic with all or most of the conventional armamentarium – pharmacologic (antiepileptics etc.), prosthetic (prosthesis, TRT), and psychological (cognitive and behavioral therapy) methods. The only audiometric criterion was the absence of total deafness in either ear.

In all cases, we used validated questionnaires concerning tinnitus handicaps, psychological distress, anxiety and depression to assess functional auditory discomfort, as in an earlier article.
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We considered only the items assessing psychological status and the global discomfort associated with tinnitus. The general psychological distress (GD) associated with tinnitus was assessed with a questionnaire developed by Wilson et al. and adapted by Meric et al. The extent of handicap associated with tinnitus was assessed with the French adaptation of the questionnaire developed by Kuk et al. Three items were used for the analysis: physical (PH), emotional (EE), and social (SoCh) handicaps. The analysis included neither scores for auditory handicap (AH), less relevant to our analysis being more specific to ORL disorders in the strict sense of the term and strongly correlated with auditory loss, nor the subjective handicap (subjH) score, insufficiently robust according to the French translators of the questionnaire. The sum of the scores from the previous three items (PH, EH, and SoCh) was considered to be the Tinnitus Handicap (THQ) score.

Technique of functional magnetic resonance imaging (fMRI)

The aim of the fMRI (with a Siemens Symphony 1.5 T, Quantum gradients) was to determine as precisely as possible the cortical site responsible for the tinnitus perceived by the patient. FMRI exploration relies on the increased intensity of the signal observed in the activated cerebral parenchyma, together with local-regional changes in the deoxyhemoglobin concentration (BOLD effect: blood oxygen level dependent). Determination of the site of the activated parenchyma therefore required comparison of the intensity of the cerebral parenchymal signal in both activated and resting states. The study protocol used rapid sequence 12-weighted echo-planar imaging. This imaging sequence alternated three resting (R) and three activation (A) periods, each 60 seconds in duration and corresponding to 12 successive acquisitions of the same imaging volume. There were a total of 36 adjoining slices, each three mm thick. We used the following parameters: FOV 297 mm, matrix 128x128, that is, a resolution of 2.3 x 2.3 x 3 mm, TR 5010 ms, TE 64 ms, and 72 measures. The equipment we used allowed us to reconstruct the cerebral activation images in real time by setting a predetermined value to define the threshold of significance of the t-test used to define the activation areas, the intensity of whose signal differs statistically from that of the non-activated area. This cut-off point was set at 6.5. To maximize the signal difference between the activity and resting periods only the last ten of twelve acquisitions taken during an activation and/or resting phase were considered for the statistical analysis.

The auditory stimulation involved listening to either text being read or a musical theme. Auditory areas are usually larger following a textual rather than a musical stimulus. We defined the targets for rTMS from the fusion of the activated images and the anatomical T1 images, followed by 3D reconstruction of this fusion.

Transcranial magnetic stimulation

The stimulation protocol consisted of two series of magnetic transcranial cortical stimulation, at different frequencies and durations, focused on the auditory cortex contralateral to the tinnitus. The stimulation used a focal “figure-of-eight” coil combined with a Magstim Super Rapid stimulator. In all cases, stimulation intensity was set at 120% of the motor threshold, defined as the intensity of stimulation necessary and sufficient to induce a motor response in the hand in half of a series of ten stimulations. The subject perceived a slight contraction of the temporal muscle during stimulation.

First, a short (3-sec) high frequency (10 Hz) stimulation was aimed at cortical areas corresponding to the target determined by fMRI and then, by shifting the stimulation probe several centimeters, aimed at adjacent regions (anterior, posterior, median, and lateral). Immediately after stimulation, patients were asked to assess the perceived variation in tinnitus intensity and the possible duration of its persistence. Then, after a resting period, lower-frequency (1 Hz) stimulation was applied for twenty minutes (1200 stimulations) on targets corresponding to either the site of maximum cortical activity, as determined by fMRI (8 patients), or to a more posterior, temporo-cortical region, corresponding to the secondary auditory areas (5 patients). The optimal effect of the 20-min rTMS sessions was not necessarily immediate, but appeared within 48 hours, as in the treatment of chronic pain [12]. We therefore asked all patients to note changes in the intensity of their tinnitus in the days following the rTMS and contacted them by telephone ten days afterwards to determine the effects of rTMS on perceived intensity of tinnitus.

Results

Patients’ characteristics

Our sample included 10 men and 3 women, with a mean age of 44 years (22 years - 64 years, standard error: 3). They had had tinnitus for periods ranging from 12 to 540 months (mean: 104 months, SE 38 months). Ten patients had tinnitus in the left ear, and 3 in the right. It was perceived as either ringing (n=12) or complex tones (n=1). Sources were acoustic trauma (n=5, 35.7% patients), sudden deafness (n=4, 28.6%), barometric pressure accident (n=1), postoperative deafness (n=1), progressive deafness of undetermined origin (n=1), and tympanic perforation (n=1). There were ipsilateral sensorineural hearing losses in all cases: aural “blind” spots for the frequencies 4-6 kHz (n=7, 53.8% of patients), unilateral perceptual deafness (n=4), and bilateral conductive deafness (n=2). Five patients (38.5%) had clear hyperacusis. All patients had already tried several treatments (on average, 5.81 treatments SE 0.58). These treatments included vasodilators (n=13, 100%), anxiolytics (n=13, 100%), antidepressants (n=8, 61.5%), neuroleptics (n=3), auditory pro-
Effects of tinnitus

Tinnitus severity was assessed by questionnaires that examined tinnitus, anxiety, and depression (Table I). The tinnitus handicap score (THQ) was particularly high before treatment: its different subscores (SoCH, PH, and EH) were at 42% of their maximum value and the psychological distress score at 55%. The assessments of anxiety and depression before rTMS showed that these symptoms were clearly more pronounced in tinnitus patients than in a normal population, where the HADa or HADd score is less than 7.

Efficacy of repetitive transcranial magnetic stimulation

Table II presents the results of rTMS according to frequency and site. Short pulses of high-frequency stimulation (10 Hz) on the fMRI-determined target or adjacent regions never modified the tinnitus, except for a transient improvement lasting a maximum of several seconds in one patient. Prolonged stimulation at a low frequency (1 Hz) reduced tinnitus in 5 of 8 patients receiving stimulation to the fMRI-determined target. Clear improvement was seen in four cases and moderate in one. In three cases, tinnitus severity did not change until 48 hours after stimulation, and in one case, a week afterwards. Immediate modification never occurred. Duration of improvement varied from two to ten days (mean: 4.6 days). The other three patients observed no change in their tinnitus.

Discussion

RTMS has been proposed as a technique for treating cerebral cortical dysfunction in diverse pathological situations, including chronic pain, depression, and certain auditory hallucinations associated with dissociative disorders [13]. The stimulation zone is limited in area and depth, and efficacy thus depends on the distance of the target from the scalp, although distant effects, in areas involving the anatomical projections of the stimulated structures, are quite possible. The auditory cortex is located in the posterior superior temporal gyrus. It includes an external part (AE), visible at the brain surface and an internal portion buried at the bottom of the lateral fissure (of Sylvius), at the transverse temporal gyrus, that is, Heschl’s gyrus. Magnetic stimulation was superficial (rectangles).

Table I

Assessment of tinnitus severity

<table>
<thead>
<tr>
<th>Type of stimulation</th>
<th>n</th>
<th>Mean</th>
<th>DS</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>SoCH</td>
<td>13</td>
<td>247.1</td>
<td>146.2</td>
<td>0</td>
<td>600</td>
</tr>
<tr>
<td>PH</td>
<td>13</td>
<td>212.2</td>
<td>132.1</td>
<td>10</td>
<td>500</td>
</tr>
<tr>
<td>EH</td>
<td>13</td>
<td>255.7</td>
<td>104.7</td>
<td>20</td>
<td>600</td>
</tr>
<tr>
<td>THQ</td>
<td>13</td>
<td>724.4</td>
<td>341.9</td>
<td>70</td>
<td>1550</td>
</tr>
<tr>
<td>DG</td>
<td>13</td>
<td>15.8</td>
<td>9.9</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>HADa</td>
<td>13</td>
<td>10.3</td>
<td>3.6</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>HADd</td>
<td>13</td>
<td>6.8</td>
<td>4.8</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

Table II

Results after transcranial magnetic cortical stimulation (n=13)

<table>
<thead>
<tr>
<th>Type of stimulation</th>
<th>High frequency (10 Hz)</th>
<th>Low frequency (1 Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of stimulation</td>
<td>Target fMRI and adjacent regions</td>
<td>Target fMRI</td>
</tr>
<tr>
<td>Positive effect</td>
<td>1 (immediate)</td>
<td>5 (delayed)</td>
</tr>
<tr>
<td>Negative effect</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not effective</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

* not specific for a specific site of stimulation.

Figure 1

Anatomy of the auditory cortex

The cortex includes an external part visible at the surface of the brain and an internal portion buried at the bottom of the lateral fissure (of Sylvius), at the transverse temporal gyrus, that is, Heschl’s gyrus. Magnetic stimulation was superficial (rectangles).
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Méric (THQ), calculated over 100, was 46.7 compared with 42.5 in PH, EH, and SocH scores on the handicap questionnaire. In our study, the mean of the sum of the PH, EH, and SocH scores on the handicap questionnaire accurately reflects the clinical situation of patients after failure of numerous conventional treatments. Nonetheless, in the sample studied, all treated at a university hospital center, informed consent to rTMS. Accordingly, there is an inherent bias of the sample in cases of central neuropathic pain. Accordingly, phantom limb pain is associated with a major reorganization of the sensitive cortex, and the extent of reorganization correlates with intensity of pain [14]. This reorganization is reversible, in particular in patients successfully treated by medullary stimulation, as magnetoencephalographic studies have shown [15].

Tinnitus usually begins with an alteration of the peripheral auditory system (acoustic trauma, presbyacusis, otologic or neurotologic intervention, etc.). It is associated with modifications of the tonotopic map of the peripheral auditory cortex contralateral to the tinnitus [10]. Its subjective intensity appears to be linked to the degree of the shift of the tinnitus frequency in the cortex [10]. Neuroanatomical studies show substantial interindividual variability in the anatomical location of the primary and secondary auditory cortex in humans [16]. For this reason we systematically performed fmri studies in these patients, to localize as accurately as possible the projection area of the primary auditory cortex, and therefore the ideal site for stimulation. The usefulness of fmri in specific identification of the auditory cortex responsible for the perception of tinnitus remains controversial, because it shows variations in activity and not an absolute state of activity. Thus, as De Ridder [17] showed, the auditory cortex contralateral to the tinnitus may paradoxically appear hypoactive in fmri during vocal or musical stimulation. Because of the contralateral basal cortical hyperactivity associated with tinnitus, sound stimulation does not substantially increase local blood flow. The already hyperactive area cannot be activated any further and may thus appear hypointense in fmri.

Cortical electric stimulation may cause tinnitus to vanish [11]. The mechanism is poorly understood. It may be similar to that associated with disappearance of pain after cortical stimulation of the motor areas [18]. Cochlear implants have improved tinnitus in some patients [19], perhaps through a similar mechanism. Such electric stimulation of the cortex appears to act on cortical neurons as well as on descending efferent pathways. The major advantage of rTMS over electric stimulation of the cortex is its safety [11]. Such stimulation is currently an ideal tool for modifying cortical reorganization [20]. Teams in Belgium and Germany recently used it to treat tinnitus refractory to conventional treatment [11, 21].

Our study considered only patients with severe tinnitus that had failed to respond to numerous treatments and who had provided informed consent to rTMS. Accordingly, there is an inherent bias in the sample studied, all treated at a university hospital center after failure of numerous conventional treatments. Nonetheless, the sample accurately reflects the clinical situation of patients with chronic disabling tinnitus. In our study, the mean of the sum of the PH, EH, and SocH scores on the handicap questionnaire (THQ), calculated over 100, was 46.7 compared with 42.5 in Méric et al. [22]. Initial values for anxiety and depression were also elevated (HADa = 10.3, HADd = 6.8) and showed a marked state of anxiety or depression in our patients. This result is consistent with the data from the literature: anxiety and depression are recognized as important comorbidity factors in tinnitus. All the patients had received several unsuccessful treatments before rTMS (on average, 5.81 treatments SE 0.58). As described above, these treatments covered a variety of methods and etiological theories.

The preliminary results of this work suggest that rTMS may effectively modify the intensity of tinnitus. They therefore point in the same direction as two recent original publications [11, 21] and provide additional information as well. We performed two types of stimulation: brief pulsed high-frequency stimulation (10 Hz) and prolonged low-frequency stimulation (1 Hz). The high-frequency stimulation consisted of a brief pulse of stimulation, applied to different anatomical sites (target areas determined by fmri, as well as the adjacent cortical areas). The principle of this stimulation is essentially to induce a masking effect, by very briefly affecting the cortical circuits. Immediately after stimulation patients were asked to assess the variation in perceived intensity of their tinnitus and duration of its persistence. In the absence of immediate improvement, stimulation of an adjacent site may have been performed. Of the 13 subjects receiving stimulation, only one reported an immediate positive effect: the intensity of the tinnitus diminished for several seconds, without any specific localizing effect from the stimulation. Therefore we do not feel that high-frequency rTMS is the most appropriate technique in this setting. De Ridder suggested that the ineffectiveness of high frequency rTMS might be associated with the duration of tinnitus [17]. In contrast, low-frequency stimulation (1 Hz) for 20 minutes was intended to induce cortical plasticity, which usually does not occur immediately, but only after a delay, and is sustained for some time after stimulation stops. This type of stimulation has been shown to be particularly efficacious when applied to a target defined by fmri. Moreover, patients were not told that there is usually a delay in the onset of clinical effects after a prolonged session of rTMS. Accordingly, the delay of approximately 48 hours observed between the stimulation session and the onset of improvement, seen in all our patients, supports an effect distinct from placebo. This notable difference in the effect of high and low frequency stimulation may be explained by physiological data. That is, rTMS appears to have opposite effects depending on whether stimulation uses high or low frequencies. When stimulation involves a frequency of 10 Hertz or more, metabolic activity increases in the underlying cortex [23], while lower frequency stimulation diminishes this metabolism [23, 24]. This increased metabolism may be associated with an increase in excitability, and its reduction with a decrease in cortical excitability. The delayed effect observed after low-frequency rTMS may be associated with the delay necessary for the cortical reorganization induced by this stimulation.
The duration of stimulation (less than 5 days) limits its application in regular clinical practice. Nonetheless, placement of an implanted stimulator may be possible, as already performed for treatment of some chronic neuropathic pain resistant to drug treatment. When rTMS was performed on a site posterior to that defined by fMRI (that is, on temporo-occipital topography), stimulation was not effective. Stimulation was totally ineffective in three patients; the immediate harmful effect observed in one patient may be considered a nocebo effect and the immediate positive effect a placebo effect. Thus, the role of stimulation of the site identified by fMRI justifies this examination before rTMS. Placement of any permanent stimulator should probably be based on the site identified by fMRI.

Conclusion

These first French results with rTMS open a new pathway in the treatment of patients with disabling tinnitus. They stress the importance of the cortical structures in perpetuating tinnitus perception. New studies must examine the specific role of rTMS and consider the possibility of implanting permanent stimulators operating similarly to those currently successfully used in the treatment of chronic pain that does not respond to conventional treatments.

Conflicts of interest: none

References