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Repetitive transcranial magnetic stimulation: Hearing safety considerations

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Background
The guidelines for use of repetitive transcranial magnetic stimulation (rTMS) advise frequent updating of rTMS safety guidelines and recommendations. Although rTMS can produce sound of more than 120 dB C, which is sufficient to induce hearing loss, the effect of rTMS noise on the hearing of both patients and rTMS practitioners is understudied.

Objective
This study investigated the effects of rTMS noise on subjects' hearing using otoacoustic emissions evoked by clicks (transiently evoked otoacoustic emissions, TEOAEs), which is an objective and sensitive method of cochlear exploration.

Methods
Hearing thresholds and TEOAEs were recorded in 24 normal-hearing healthy subjects before and after a real or sham rTMS session (a single 20-minute session applied to the superior temporal gyrus with 1200 pulses at 100% of the individual motor threshold).

Results
No significant difference in hearing thresholds was observed between subjects exposed to real or sham rTMS. However, the difference in TEOAE amplitude between pre- and post-rTMS sessions increased significantly with rTMS noise for those subjects the least protected by earplugs, showing a post-rTMS slight decrease of TEOAE amplitude for high rTMS intensities and hence minor hearing function alteration. However, this correlation was no longer found 1 hour after the rTMS session.

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Conclusions
These findings suggest that, even when rTMS is used within normal safety limits and with good hearing protection, rTMS noise can transiently disturb hearing mechanisms in normal-hearing healthy subjects. This transient effect of rTMS on hearing may be an important consideration for Institutional Review Boards when rTMS is used at higher stimulation intensities.

Keywords repetitive transcranial magnetic stimulation; otoacoustic emissions; hearing; safety; side effect

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive and effective method of direct human brain stimulation[1] that is widely used in neurology, cognitive neuroscience,[2,3] tinnitus therapy,[4,5] and for various psychiatric disorders (e.g., depression,[6,7] anxiety disorders,[8] and auditory hallucinations in schizophrenia[9]). The body of evidence regarding the clinical efficacy of rTMS is growing, including long-term maintenance therapy with multiple rTMS sessions over long periods. Hence, there is a need for frequently updating TMS safety guidelines and recommendations for clinical implementation.[10] However, the effect of sound produced by rTMS on hearing in both patients and rTMS practitioners has been neglected. Indeed, in the first version (2001) of a questionnaire aimed at screening patients before rTMS,[11] no hearing-related item was present, whereas the new 2010 questionnaire[12] identifies hearing deficits and tinnitus as risk factors for rTMS. Indeed, rTMS can produce sound greater than 120 dB p.e. SPL,[13] a level above that known to produce hearing loss.[14] The sound produced by rTMS originates from rapid mechanical deformation of the stimulating coil and consists of a loud click, with the greatest energy at high frequencies (from 2 to 7 kHz),[15] where the human ear is most vulnerable. In addition, human ears show a wide variability of susceptibility to noise,[16] from an absence of symptoms or a temporary hearing threshold shift with intermittent tinnitus to hearing damage with permanent tinnitus, all for the same noise energy.

The amplitude of rTMS noise is directly linked to the coil design and the absolute stimulation intensity, which is tailored to each subject's resting motor threshold (MT). Hence, the amount of noise received by subjects depends on their MT, which varies widely across a population, and also depends on the testing method used and on individual characteristics.[17] Although patients' hearing protection is systematically recommended in the rTMS safety guidelines,[1] most studies dealing with rTMS do not specify whether or which type of hearing protection was used. Furthermore, in practice, subjects sometimes decline hearing protection in the form of earplugs, usually citing discomfort[18] and the desire to communicate with the researcher or rTMS practitioner. Moreover, earplugs are not systematically provided in every laboratory[19] and patients are not usually trained to fit an earplug, leading to lower protection.[20] Indeed, earplug efficacy varies greatly from subject to subject,[21] depending on the type used and the quality of the fit.[20]

Hearing alterations have been identified in audiometric studies as a possible effect of rTMS noise,[1] and a few cases have been reported.[22-24] However, only pure-tone audiometry was used in these studies. Although pure-tone audiometry is the universally accepted method for diagnosing sensorineural hearing loss, it is a subjective method and not as sensitive to noise-induced cochlear alterations as transiently evoked otoacoustic emissions (TEOAEs).[25] TEOAEs are minute sounds recorded within the outer ear canal in response to a click stimulus. They reflect cochlear function[26] and enable early identification of small cochlear alterations caused by noise exposure.[27]

Objective

The aim of this study was to evaluate the potential modifications of hearing thresholds and TEOAE amplitudes in response to rTMS noise in normal-hearing subjects fitted with earplugs. Both hearing thresholds and TEOAEs were recorded before and after a single 20-minute rTMS session, targeted on the left (12 subjects) and right (12 subjects) superior temporal gyrus, corresponding to the primary auditory cortex, hence with the coil close to the pinna.

Methods

Patient selection

The study was given ethical approval by the local ethics committee (ref 08-021), and written informed consent was obtained from all study participants before examination. Twenty-four healthy adults (12 females, 12 males; mean age: 23.8 years) took part in this study and were split into two groups matched for sex and age, receiving either active or sham rTMS (active group: mean age = 24.3 years (20-33 years), 16 subjects; sham group: mean age = 22.8 years (19-29 years), 8 subjects). None of the volunteers suffered from any diseases. In particular, the neurologic and otologic examinations (including hearing thresholds $<$ 15 dB hearing level [HL], tympanometry and otoscopy) were normal. All subjects were right-handed, according to the Edinburgh handedness inventory.[28]

Auditory responses

Hearing thresholds were measured in a sound-isolated booth using an Interacoustics AC40 clinical audiometer at half-octave frequencies ranging from 0.125 kHz to 8 kHz. As subjects wore disposable foam earplugs (MaxLite, single number rating = 34 dB) during the rTMS session, hearing thresholds were also measured with fitted earplugs just before the rTMS session to assess the level of hearing protection provided by the earplugs. The correct position of the earplugs was checked during the rTMS session to prevent any change in hearing protection.

TEOAEs were recorded and processed using Otodynamics ILO96 hardware and 5.60Y software. Subjects were comfortably seated in an armchair in a different room from the rTMS room. A small probe consisting of a miniaturized microphone and a loudspeaker was fitted within the outer ear canal using the same ear tip for each ear across sessions. Because of magnetic interference with the rTMS, the probe was taken out during the rTMS session and refitted before each recording session. At the beginning of the first session for each subject, the calibration of the probe was checked using the 1 cc calibration cavity supplied with the ILO system. For each recording session and each ear, the probe checkfit procedure was performed,[29] and the probe fit was adjusted until the same click stimulus amplitude and spectrum were obtained in the ear canal for each recording session and for the same ear and click stimulus intensity.

TEOAEs evoked by 80-μs linear clicks were recorded at five click intensities, ranging from 60 to 72 dB peak equivalent (p.e.) SPL in 3 dB steps. TEOAE analysis was performed using standard clinical methods.[29,30] For each click intensity, 2×240 responses were interleaved and averaged separately in two memory buffers over a recording window of 20 milliseconds, yielding two waveforms. The averaged traces were windowed from 3.6 to 20 milliseconds to eliminate the stimulation artifact. The total TEOAE amplitude was then calculated as the overall level of the correlated portions of the two waveforms and expressed in dB p.e. SPL.

Repetitive transcranial magnetic stimulation

rTMS was administered under either active or sham conditions by means of a MagPro X100 MagOption system (Medtronic, Skovlunde, Denmark) coupled with an infrared frameless neuronavigation system (eXimia Navigated Brain Stimulation, Nexstim, Helsinki, Finland). Based on individual T1-weighted brain magnetic resonance imaging, the anterior part of the medial third of the Heschl gyrus (Brodmann area 41), corresponding to primary auditory cortex, was marked as the target for rTMS.[31] The resting MT, defined as the minimum machine power output required to elicit a motor-evoked potential of 50 μV in at least 5 trials of 10 in the abductor digiti minimi muscle of hand,[32] was measured for each subject using the MagPro MEP monitor (Medtronic) with the coil placed at the optimal position over the motor cortex.

A single 20-minute session of 1200 stimulations was performed, either with continuous 1-Hz low-frequency rTMS or with intermittent trains of 10-Hz high-frequency rTMS (one 3-second train every half minute), at an intensity of 100% of MT. A figure-eight coil with fluid cooling (Medtronic MCF-B 65) was used for active stimulations (A group), whereas a specific figure-eight placebo-coil (Medtronic MCF-Placebo-B 65) was used for sham stimulations (S group). Noise levels generated by rTMS were measured using an ANSI/IET type 1 sound level meter (system 824, Larson Davis, Depew, NY) in dB A and dB C (peak level)[33] as a function of maximum percentage power output.

Protocol

The study was placebo-controlled and double-blinded. After the rTMS session, subjects were asked to fill out a short questionnaire about the symptoms they experienced and whether they thought they had undergone a sham or active session. After randomization, subjects were split into four groups matched for sex and side of cortical stimulation: two groups of eight subjects for low- or high-frequency active stimulations and two groups of four subjects for sham low- or high-frequency stimulations. Hearing thresholds and TEOAE amplitudes were recorded before, immediately after, and 1 hour after an active/sham rTMS session in both ears. Within 5 minutes of the rTMS session, TEOAE recording was performed first on the contralateral ear and then on the ipsilateral ear. Each recording lasted approximately 10 minutes, including the probe fit procedure. Hearing thresholds tests were then performed, and the subject had a short break before another recording session began, 1 hour after the end of the rTMS session (Figure 1).

Data analysis

For each subject, the mean hearing thresholds obtained at each one of the 10 tested pure-tone frequencies was calculated and termed average hearing threshold. The average hearing thresholds were calculated with fitted earplugs and were used to divide subjects into two 12-subject groups according to degree of protection (i.e., a well-protected group [P+], with average hearing thresholds greater than 34 dB HL, and a less-protected group [P−], with average hearing thresholds less than or equal to 34 dB HL).

The differences in dB between TEOAE amplitudes recorded before (pre-rTMS) and after rTMS (post-rTMS) were calculated and termed deltadB.

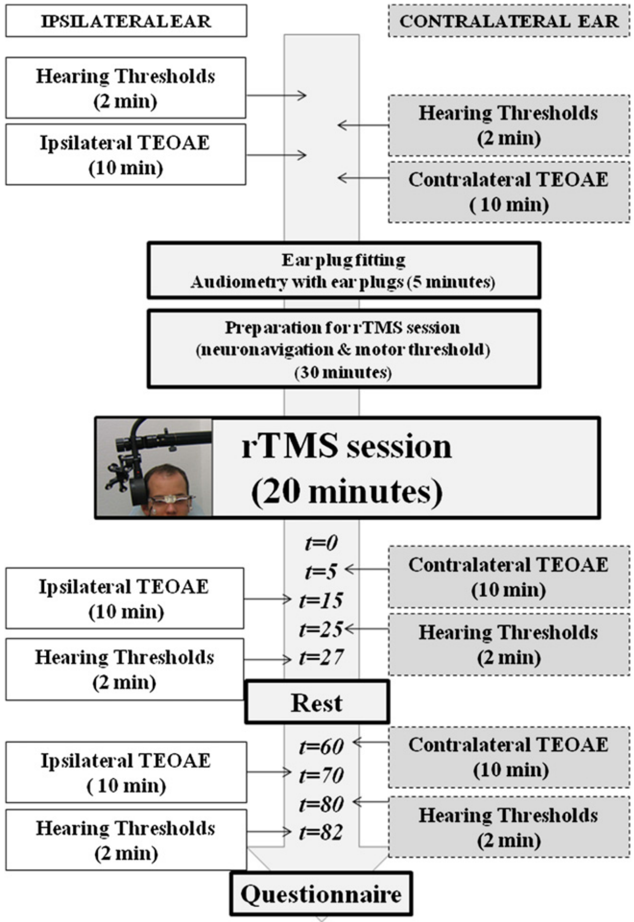

Figure 1 Protocol outline: The different tests successively performed before and after a 20-minute rTMS session are listed from top to bottom, with the time in minutes in the central arrow. The tests for the ipsilateral ear (closest to the rTMS coil) are in white, whereas the tests for the contralateral ear (furthest from the rTMS coil) are in grey. (Color version of figure is available online.)

Statistical analyses

Hearing thresholds in dB HL and TEOAE amplitude in dB p.e. SPL were compared before and after rTMS and for the different subject groups by mixed analysis of variance (M-ANOVA). The three different recording sessions and five different TEOAE stimulus intensities were considered intrasubject factors. As there were differences in stimulation conditions according to the side (with more than 15-dB rTMS noise difference between the ears ipsilateral and contralateral to the stimulation site) and because the rTMS session was performed only on one side per subject, the side was considered an intersubject factor. The other intersubject factors were the level of earplug protection (P+/P−), the sham/active groups (S/A) and the four different stimulation groups (1 Hz and 10 Hz active; 1 Hz and 10 Hz sham = four groups). When criteria for parametric tests were not met, Friedman tests were used.

Regression analysis was used to analyze TEOAE amplitude differences (deltadB) as a function of rTMS-related noise levels for each of the five TEOAE click stimulus intensities. The magnitude of the correlation coefficients was compared using *t* tests on Fisher *z* transformed correlation coefficients. In addition, linear mixed effects models from the R nlme library package[34,35] were used to account for repeated measures data corresponding to the five different levels of click intensities used to record TEOAEs for each subject. The level of statistical significance (*P*) was set at 0.05, with "ns" indicating nonsignificant.

Results

rTMS noise

The sound levels obtained with rTMS pulses at 1 Hz and 10 Hz were within 1 dB of each other. As all subjects received a total of 1200 stimuli in 20 minutes, regardless of the 1 Hz or 10 Hz stimulation rate, the amount of noise generated by both stimulation rates was identical.

Both active and sham coils showed a nonlinear increase in sound level with rTMS stimulus intensity (Figure 2). A second-order polynomial was fitted to each function,

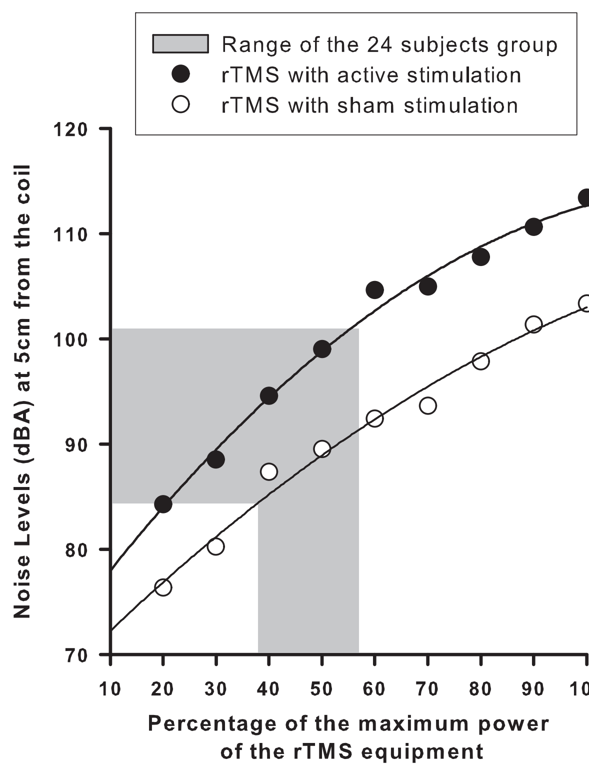

Figure 2 rTMS noise levels in dB A as a function of the percent of the maximum output power delivered by the Magstim equipment for the active probe (black dots) and the sham probe (white dots). The grey area corresponds to the range of the subjects' motor thresholds and the related rTMS noise level.

allowing calculation of the sound levels generated by rTMS corresponding to each subjects' MT, with the highest sound level at 101 dB A and 131 dB C (peak noise). The spectra of active and sham coil noises were overall similar, with the highest amplitude for high frequencies (between 3 and 10 kHz) (Figure 3). However, the sham coil presented an octave-wide band centered around 1 kHz, with an amplitude 15 dB greater than the active coil.

There was no significant relationship between the sham/active session and the subjects' answers to the question about the nature of their rTMS session (χ^2 = 0.1, P = ns).

Resting motor thresholds

The mean MT was 46.08% (SEM = 1.19), with no significant difference between active (45.5%, SEM = 1.49) and sham groups (45.89%, SEM = 2.02).

There was no significant difference in MTs ($F[1,22] = 0.25$, P = ns) or rTMS noise between protection groups ($F[1,22] = 0.04$, P = ns).

Hearing thresholds

Before rTMS, no difference in mean hearing thresholds was detected between ipsilateral and contralateral ears ($F[1,44] = 0.77$, P = ns), with a mean average hearing threshold of 10.36 dB HL (SD = 5.2).

The average hearing threshold with earplugs was 34.7 dB HL (SD = 6.7 dB) and hearing thresholds increased significantly with pure-tone frequencies (Friedman test, $\chi^2 = 175$, df = 9, $P < 0.0001$) from 32.1 dB HL (SD = 3) at 250 Hz to 41.1 dB HL (SD = 9.3) at 8 kHz (Figure 4). Hearing thresholds obtained with earplugs showed a highly significant correlation between the two ears of the same subjects ($r = 0.79$, $P < 0.0001$). As expected, an M-ANOVA (intrasubjects factors: frequency, ipsilateral/contralateral ear;

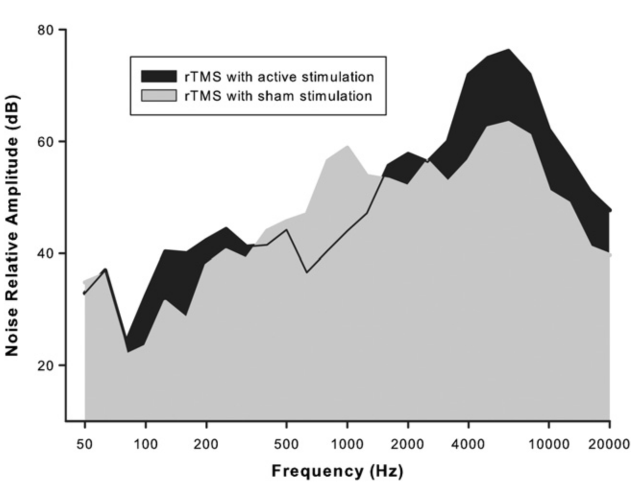

Figure 3 Frequency composition (obtained by fast Fourier Transform by one third octave) of the rTMS noise measured 1 m from the active coils (black area) and the sham coils (grey area).

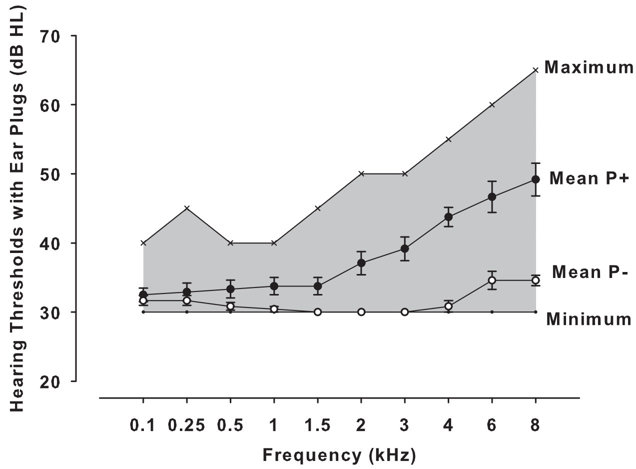

Figure 4 Hearing thresholds with earplugs (in dB HL) as a function of frequency (in kHz) in the 24 subjects (48 ears). The lower (dots) and upper (crosses) lines represent the minimum and maximum hearing thresholds obtained for each frequency, respectively, within the whole group. Mean hearing thresholds, with standard error of the mean, were calculated for the most protected subjects (P+ group, black symbols) and for the least protected subjects (P− group, white symbols).

intrasubject factor: protection group) showed highly significant effects of frequency ($F[9,198] = 30$, $P < 0.0001$) and protection group ($F[1,22] = 44$, $P < 0.0001$), with a significant interaction between the two ($F[9,198] = 14$, $P < 0.0001$). In addition, highly significant differences were obtained between P+ and P− hearing thresholds at all frequencies above 500 Hz.

Individual data failed to show any significant hearing threshold shift after rTMS. The greatest variation in mean hearing threshold occurred primarily for the two lowest frequencies (125 Hz and 250 Hz) and were less than or equal to 5 dB. M-ANOVA (intrasubjects factors: frequency*pre/post rTMS; intersubject factor: ipsilateral/contralateral ear) revealed no significant difference between pre- and post-rTMS pure-tone thresholds ($F[9, 207] = 1.69$, P = ns). Similar absence of differences were obtained for average hearing thresholds ($F[1,22] = 0.22$, P = ns) and according to the P+/P− groups.

TEOAEs

For pre-rTMS recordings, an M-ANOVA (intersubject factors: group*side; intrasubject factor: click intensity) did not show any significant group effect (A/S or four groups) but identified the known highly significant click intensity effect on TEOAE amplitude, with TEOAE amplitudes increasing with click intensity ($F[1,19] = 377$, $P < 0.0001$).

Group data for TEOAE amplitude (M-ANOVA: intersubject factors: group*side; intrasubject factors: click intensity*session) did not show any significant group effect (protection, A/S or four groups). However, TEOAE amplitudes showed a trend of increasing during sessions on the ipsilateral side (by 0.25 dB), but this trend was not statistically significant. The TEOAE deltadB averaged across the five click intensities for each subject ranged from −2.4 to 1.3 dB on the ipsilateral side. Individual data are shown for a click stimulus intensity of 72 dB SPL p.e. in Figure 5. When the deltadB was considered, no significant effect of the session or of the group was obtained.

Because no significant differences were found between the four stimulation groups, data obtained from 1-Hz and 10-Hz rTMS stimulation frequencies were pooled together, resulting in a sham group of eight subjects and an active group of 16 subjects.

As the rTMS intensity increases, the associated coil noise also increases. We then hypothesized that the effect of noise on TEOAE amplitude would be greater for the highest rTMS intensities. Based on the difference in rTMS noise levels depending on A/S coils, we performed correlations between the deltadB and the calculated noise exposure in dB A from each subject's MT and type of coil. No significant relationship was observed in the group of 24 subjects. However, when this group was split according to the level of earplug protection, a general linear mixed effects model revealed a significant correlation between deltadB and rTMS noise level ($t = 3.0$, $P = 0.01$, AIC = 106, n = 12) only for the ipsilateral ear of the P− group (Figure 6A). This finding indicates that TEOAE amplitude decreased in the ipsilateral ear (Figure 6B) between pre- and post-rTMS sessions for high rTMS noise levels in P− subjects but not in P+ subjects (Figure 6B), nor in contralateral ear (Figure 6C).

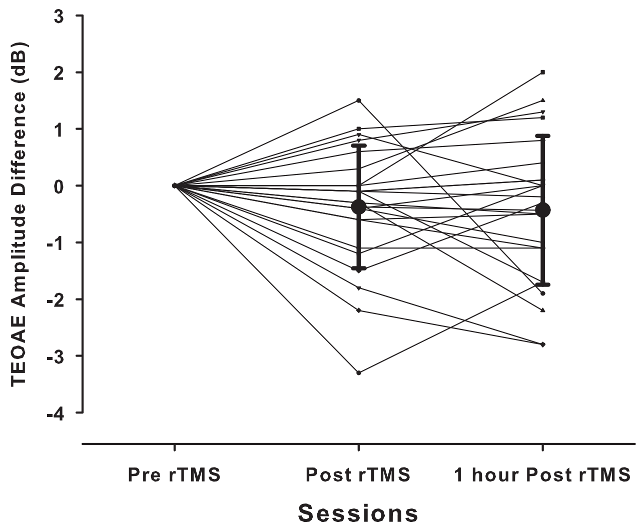

Figure 5 TEOAE amplitude difference in dB (TEOAE amplitude before rTMS minus TEOAE amplitude after rTMS, or deltadB) plotted for each post-rTMS session (immediately after rTMS and 1 hour after rTMS) and for each of the 24 subjects. The mean and standard deviation are specified as black dots and error bars, respectively.

Such correlations were statistically significant at each TEOAE stimulus intensity but are shown only for a TEOAE stimulus intensity of 72 dB SPL p.e. (Figure 6A-F).

Overall, the magnitude of the correlation coefficients was significantly larger for the P− subjects than for the P+ subjects ($t = 22$, $P < 0.0001$) in the ipsilateral ear but not in the contralateral ear ($t = 0.39$, P = ns).

When a similar relationship was analyzed for the sham/active groups, regardless of the protection level, the sham group showed a similar correlation, i.e., significantly greater deltadB for high rTMS noise levels ($t = 3.3$, $P < 0.02$, AIC = 87, n = 8, Figure 6E) for the ipsilateral ear but not for the contralateral ear. The magnitude of the correlation coefficients for the sham group was significantly greater than that for the active group ($t = 11$, $P < 0.001$): no significant relationship was obtained for the active group (n = 16). However, splitting the active group into the two levels of protection revealed a weakly significant relationship between deltadB and rTMS noise for the ipsilateral ear of the least protected group (AIC = 28, $t = 2.3$, $P = 0.05$, n = 8, Figure 6F) but not for the most protected group or for the contralateral ear (with correlation coefficients significantly greater for the ipsilateral ear of the P− group than the P+ group [$t = 3.6$, $P < 0.01$]). The magnitude of the correlation coefficients obtained in the sham group was not significantly greater than the one in the active, least protected group ($t = 1.8$, P = ns).

Finally, the deltadB calculated between pre-rTMS and more than 1 hour post-rTMS revealed no significant correlation with rTMS noise levels, regardless of whether the groups were split into A/S or protection groups (example, Figure 6D).

Discussion

International standards for hearing damage risk criteria indicate that sounds above 110 dB SPL, a level that can be exceeded by rTMS noise, may cause hearing loss.[14] In the current study, levels of 101 dB A and 131 dB C (peak noise) were obtained close to the coil at the highest MT tested. Indeed, acute and permanent deafness was obtained in chinchillas and rabbits after rTMS with maximum output power.[36] Temporary hearing threshold shifts greater than 5 dB after a 15-minute session of rTMS, with a peak at 119.8 dB, have been reported, but only on three unprotected subjects.[15] The few other studies dealing with this topic have reported cases of threshold shifts of more than 10 dB in protected subjects, with an absence of long-term changes in hearing thresholds[23] or, in one case, permanent hearing loss.[37]

As expected, we did not find any difference in hearing thresholds before and after rTMS in well-protected subjects, as pure-tone audiometry was the last test performed after the rTMS session (approximately 25-30 minutes later) and is less sensitive to impulse noise damage than TEOAE

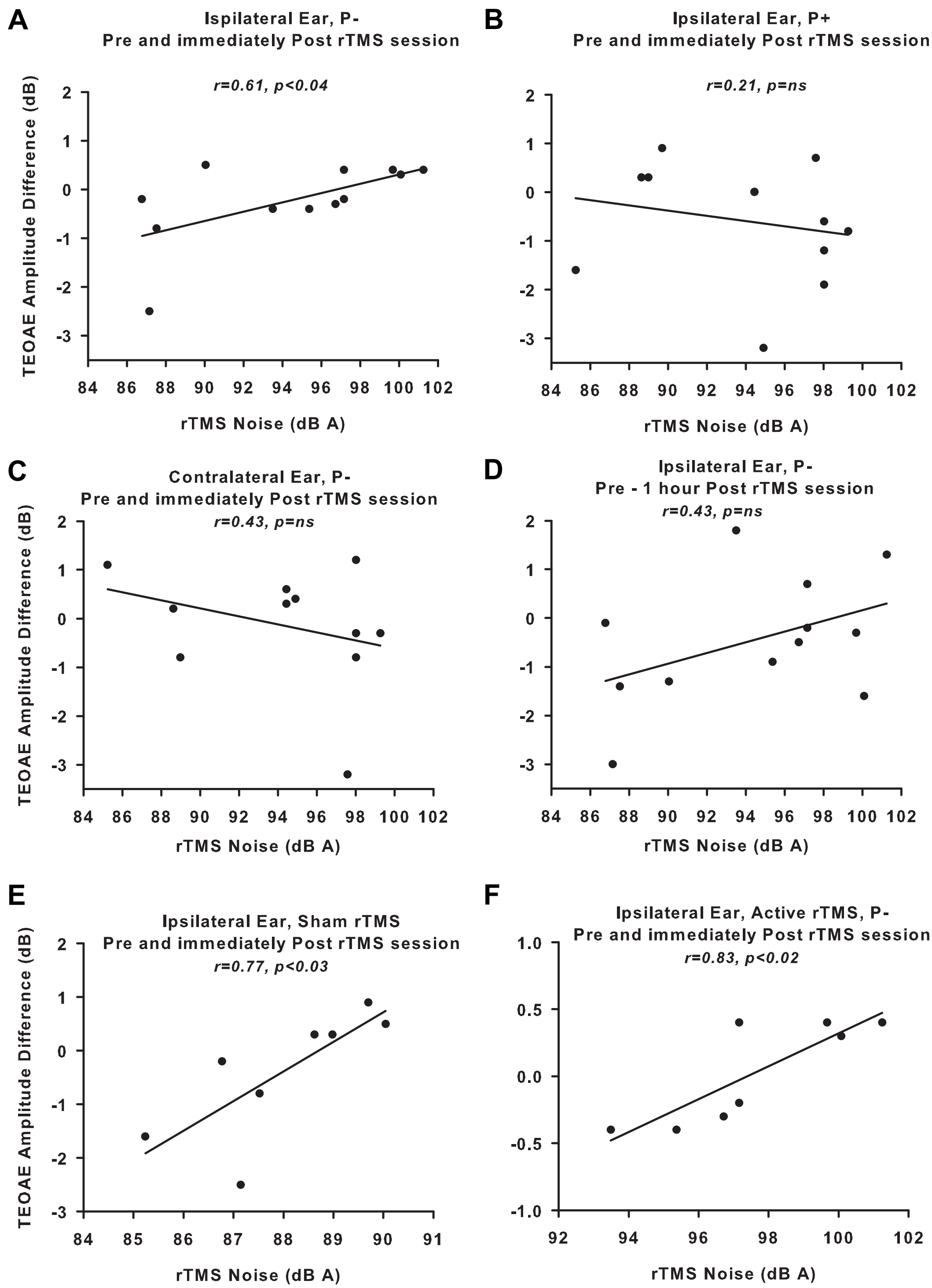

Figure 6 TEOAE amplitude difference in dB (TEOAE amplitude before rTMS minus TEOAE amplitude after rTMS) plotted against rTMS noise intensity in dB A (calculated from individual subjects' motor threshold and coil used). The TEOAEs were recorded at 72 dB p.e. SPL. A positive value on the *y*-axis corresponds to a post-rTMS decrease in TEOAE amplitude (and hence a small cochlear alteration). Correlation coefficients are specified as "r," with the corresponding levels of statistical significance (*P*) and ns for statistically nonsignificant. The lines represent the best fit linear regressions. **A** and **B** show results for the ipsilateral ear immediately after rTMS for the least protected subjects (P−, **A**) and for the most protected subjects (P+, **B**), respectively. **C** and **D** show results for the least protected subjects (P−) immediately after the rTMS session for the contralateral ear (C) and 1 hour after rTMS session for ipsilateral ear (**D**). **E** and **F** show results immediately after the rTMS session for the ipsilateral ear of the sham group (**E**) and for the active and least protected group (**F**).

recordings. Indeed, noise exposure can cause inner-ear damage that is not reflected in an audiogram. Both animal studies[38] and human studies[39] have shown that the cochlear outer hair cells are vulnerable to impulse noise. The damage can be extensive, with no concomitant change in hearing thresholds.[40,41] Indeed, TEOAEs provide a way of detecting subtle inner ear changes in normal hearing ears before hearing loss occurs and detecting who is susceptible to noise-induced hearing loss[25] or to persistent tinnitus.[42]

TEOAE amplitude comparisons between pre and post-rTMS session did not show any significant changes, but TEOAE amplitude tended to increase slightly (by 0.25 dB), which is similar to the spontaneous increase (0.28 dB) reported in TEOAE reproducibility studies.[43] The lack of significant effect on TEOAE amplitude in the whole group of subjects is rather reassuring, but it must be kept in mind that a potential effect might have been lessened by the time delay between the rTMS session and TEOAE recordings. Indeed, decreases in TEOAE responses are known to be maximal during the first 5 minutes after noise exposure, with a recovery during the following 15-20 minutes.[25,44] It is therefore possible that a small TEOAE decrease during the first 10 minutes would have been missed because ipsilateral TEOAEs were recorded roughly 15 minutes after the end of rTMS session. In addition, each subject had been exposed to a different noise level caused by different MTs, sham/active stimulation, and ear protection. If we consider that, for a single subject, an individual TEOAE amplitude modification is significant above 1.33 dB (criteria established by a TEOAE reproducibility study,[43] with measurements repeated after 60 minutes), then only three subjects met this criteria: TEOAE increased for two sham and decreased for one active stimulation. To see if the individual TEOAE amplitude modifications were related to the actual noise exposure, we analyzed the correlations between deltadB and the measured rTMS noise for the whole group of subjects and for the least and most protected by their earplugs: in the least protected subjects and in the ipsilateral ear (closest to the coil), we observed a significant positive correlation between the TEOAE deltadB and individual subjects' rTMS noise exposure, i.e., a decrease in TEOAE amplitude for high rTMS intensities (and hence noisier settings). Such changes cannot be attributed to a potential magnetic-induced modulation of the cochlear responses by the auditory cortex via the auditory efferent system[45] because they are present in the sham group and absent in the contralateral ear. In the active group, this correlation was observed only in the group of subjects with the least earplug protection. The relatively (but not significantly) stronger correlation obtained in the sham group, given that the sham coil makes about 10 dB less noise than the active coil, may appear surprising. In fact, the frequency composition of the rTMS noise might explain this finding: the octave wide frequency band centered on 1 kHz is more than 15 dB louder in the sham coil than in the active coil. As TEOAEs explore mostly low- to mid-frequencies, it is probable that they would be more susceptible to 1-kHz centered noise (such as the sham coil noise) than to high-frequency noise.

The fact that the changes are present only in subjects with the least earplug protection and that they are missing in the contralateral ear (the first tested ear but the furthest from the coil (hence, receiving 15 to 20 dB less noise because of the head shadow effect) argues in favor of a genuine noise effect. Lastly, the changes observed in this study were no longer observed for TEOAEs recorded more than 1 hour after the rTMS session, arguing for a temporary effect on the cochlea. Although small, such an effect reflects changes in cochlear sensitivity, in particular to the fine frequency selectivity related to cochlear outer hair cells, that could alter perception of auditory fine spectral cues. This effect should be taken into account when, for instance, performing psychoacoustical tasks immediately after rTMS,[46] especially for tasks involving low sound intensities close to the subject's auditory threshold. This control is especially important as the sham coil does not provide a perfect control due to differences in noise intensities between sham and active coils.

Although the noise effect of rTMS appears smaller than the noise effect of, for instance, an hour of MP3 music listening, which decreases TEOAEs by 0.7 dB and increases hearing thresholds by 1.8 dB,[47] it must be stressed that it was obtained in well-protected, healthy young subjects at an intensity corresponding to 100% of the MT. This effect could be increased by individual susceptibility to noise. Indeed, several factors tend to increase noise susceptibility[16] and hearing loss[48]: solvent exposure, smoking, and cardiovascular risk factors, concomitant ototoxic treatments (the most well-cited being aminoglycoside antibiotics and antineoplastic agents, but the most widely used by patients being aspirin), ethnicity, and gender. In addition, recent research in mice[49] has suggested the possibility of a delayed degeneration of cochlear neurons after a fully recovered temporary threshold shift and normalization of otoacoustic emissions, suggesting the possibility of subclinical losses affecting complex auditory processing.

rTMS noise increases with the power used, hence, with the subjects' MT. As several conditions are associated with an elevated MT (e.g., multiple sclerosis,[50] anxiety disorder treated by long-term benzodiazepines,[51] or chronic cocaine-dependency[52]), care should be taken with regard to the absolute rTMS intensity. Furthermore, most studies report great variability in MTs,[53] and hence, wide variability in the noise exposure given to patients.

Two others factors can also affect rTMS noise levels reaching the ears: the proximity of the coil to the ear (with differences of up to 13 dB according to coil positions on the ipsilateral side,[54] and more than 15 dB on the contralateral side in the current study), and the highly variable protection provided by disposable earplugs.[55,56] Indeed, our results confirm this wide variability of protection, up to 30 dB at high frequencies, which correspond to the highest energy of the rTMS noise spectrum and are the most likely to cause cochlear damage. This known variability is explained by differences in external auditory canal anatomy[21] and by the variability of earplug fit by subjects.[20,57] Earmuffs offer better attenuation, 10-15 dB higher than earplugs for frequencies between 0.5 to 5 kHz,[58] and could be a simple yet efficient solution (however, more for the practitioner than for the patient as they could interfere with the accurate position of the coil, in particular for parietotemporal stimulation). In patients with several factors of susceptibility to noise and undergoing several sessions of rTMS, custom noise reduction earplugs specifically adapted to the patients' ear canal could be a solution.

The small effect of rTMS noise observed here has been obtained in well-hearing protected healthy young subjects, well within rTMS safety limits. However, to ascertain the rTMS noise influences on patients' hearing in the most frequently used therapeutic conditions (including rTMS at greater than 100% MT and in patients with higher MTs), further studies monitoring otoacoustic emissions before and after rTMS are warranted.

Conclusion

The current study showed a small, temporary effect of rTMS noise on cochlear functioning of hearing-protected, healthy young subjects, an effect that was rTMS intensity dependent. The precautionary principle should be applied, and extra care should be taken regarding the rTMS noise levels reaching the subjects and healthcare professionals' ears, as well as the use of well fitted earplugs, especially in cases of protocols with high rTMS intensity. This precaution will be all the more important as the therapeutic use of rTMS is increasing. This possible effect of rTMS on hearing is an important consideration for Institutional Review Boards.

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