opposite polarity generated by the second TMS coil loop. This cancellation is nearly complete in certain symmetric positions of the TMS coil relative to the MRI bore, such as configurations Fringe-V, B0-V, and B0-H in Fig. 2 as well as i and iv in Fig. 3 by Yau et al. On the other hand, configurations Fringe-H in Fig. 2 and ii, iii, and v in Fig. 3 have different coupling between each of the two windings of the TMS coil and the MRI scanner magnet. Therefore, we would expect stronger TMS field reduction effect in the latter compared to the former, as is indeed observed. Since the effect depends on differential coupling of the two TMS coil loops, it is understandable why the effect strength correlates with the magnetic field gradient (Fig. 4 of Yau et al.): High spatial gradient of the static magnetic field reveals, via reciprocity, high spatial gradient in the electromagnetic coupling to the superconducting coil. Thus, the two TMS coil loops are more likely to have different coupling to the scanner where the static field gradient is high. Indeed, the strongest effect in configuration iii among the conditions in Fig. 3 is expected, since the plane of the TMS coil is parallel to the MRI superconducting coils, enabling strong coupling, and one of the TMS coil loops is more offset from the scanner z-axis, resulting in differential coupling for the two loops.

While the analysis above is only qualitative, it does lend support to the hypothesis that the TMS field reduction results from electromagnetic coupling between the TMS coil and the MRI superconducting magnet. This coupling is not related to the direct current in the MRI magnet that generates the static field in the scanner—the TMS field reduction effect should persist even if the static field of the scanner were turned down to zero. An important implication of the explanatory framework proposed here is that there may be TMS coil placements inside the scanner bore that have stronger coupling to the superconducting magnet than the symmetric configurations tested in the B0 field in Fig. 2, and hence may result in more substantial TMS field suppression effects. This possibility amplifies the concern of Yau et al. about an impact on TMS dosing, and warrants further characterization of the TMS field reduction effect, especially inside the scanner bore. A practical approach to mitigate this issue could be to incorporate a small search coil with the TMS coil that would allow monitoring of the induced electric field as well as adjustments of the stimulator output to compensate for the pulse reduction effect. More broadly, the observations of Yau et al. remind us once again that the manufacturers of TMS equipment as well as the researchers and clinicians using it should be aware of the various possible electromagnetic interactions between TMS devices and other electronic equipment including imaging systems.

Acknowledgment

The author thanks Dr. Jeffrey M. Yau for sharing additional information and data from the experiments in Ref. [1].

Auditory Cortex Stimulation Might be Efficacious in a Subgroup of Tinnitus Patients

With interest we read the paper by Engelhardt and coworkers on auditory cortex stimulation via an implanted electrode overlying the posterior superior temporal lobe (i.e. secondary auditory cortex) contralateral to lateralized tinnitus [1]. The study attempts to scientifically evaluate whether auditory cortex stimulation has the potential to become a possible treatment option for tinnitus. The authors conclude the technique is not efficacious in general but find some intriguing differences between the blinded stimulation and the long-term open label outcome data. This asks for some clarification, some of which the authors have provided: (1) placebo effect of surgery, (2) defined target, (3) a too short randomized phase.

1. It is unlikely that the placebo effect can explain the clinical long-term benefit the patients perceive. A recent systematic review and meta-analysis has been shown that principally the clinical effect of placebo is rather small [2–4] and induces on average a 7% improvement [2]. The average improvement in the patient group who had a long-term follow-up (n = 5/8) was average 27.27%.
2. Other targets might be superior. This is based on novel data that were not available when the authors initiated their study. At that time it was conceived that the auditory cortex was the final common pathway in all tinnitus patients, but recent research suggests that the auditory cortex might be involved predominantly in patients without hearing loss, and in patients with hearing loss the parahippocampal gyrus becomes more pronounced [5–8]. Furthermore, the affective component of tinnitus is generated by a network different from the loudness network, involving the anterior cingulate cortex and medial temporal lobe, anteriorly from the amygdala extending posteriorly to the parahippocampal gyrus [9–13]. Further confirmation that the affective component is separable from the loudness perception can be found in frontal lobotomy data that demonstrate that the “head noises were still the same but bothered them less” [14]. Hence targeting the auditory cortex and evaluating using a Strukturiertes Tinnitus-Interview (STI), a measure that mainly evaluates the psychological effect of the tinnitus, is probably not ideal as you do not directly measure the loudness percept, but rather the affective component. A loudness measure using as a visual analog score or numeric rating scale might be preferred, as we know that this measure correlates with auditory cortex activity in tinnitus patients [15].
3. The short randomization phase might be another problem as it is known that after a long time of auditory cortex stimulation residual inhibition is long [16]. This might bias the results as patients were already stimulated for 4 months before they were randomized. It is possible that during this 4 months Hebbian plasticity could already be induced due to the constant stimulation.

Apart from these limitations there are some other factors to consider. We agree with the authors that using a biomarker might be preferable to unselectively implanting patients with severe intractable tinnitus. We know that transcranial magnetic stimulation (TMS) is poor in predicting responders to auditory cortex stimulation via an implanted electrode [16]. The reason is that in the largest study so far [16] only one out of three patients responded to auditory cortex stimulation via an implanted electrode, although all patients responded to TMS targeting the auditory cortex. Crucial for future studies will be to select the responders in a correct way. It is clear by all studies performed so far, only a subgroup of tinnitus patients respond to auditory cortex stimulation via an implanted electrode. Therefore an important goal is to find selection criteria that permit us to define likely responders before implantation. These have not been elucidated yet, but brain activity and connectivity could be potential candidates as suggested in recent research [17].

Another reason why this study might have an inferior outcome could relate to the standardized stimulation protocol that was used. In most invasive neuromodulation studies personalized stimulation settings are required for obtaining optimal results. Furthermore in a larger study on auditory cortex stimulation via an implanted electrode, it was revealed that switching the stimulation design from classic “tonic” stimulation to burst mode [18] could rescue half of non-responders with an improvement of 50% [16] as measured by a visual analogue scale for loudness, which adds to the differences in outcome.

In conclusion, we agree with the authors that it important to study whether auditory cortex stimulation using an implantable electrode is efficacious or not in placebo controlled fashion. The heterogeneity in the tinnitus population, the likely best target, the stimulation parameters and the suboptimal outcome measure chosen should be taken into account in future studies to clearly define the role of auditory cortex stimulation in severe intractable tinnitus. Because ultimately 5 out of 8 patients in this study do prefer to continue auditory cortex stimulation even with suboptimal results, which is analogous to other studies [16,19,20], it is worthwhile to optimize this potentially beneficial treatment for a subgroup of severe intractable tinnitus patients.

References


One Swallow Does Not a Summer Make

In this issue, Zibetti et al. from Turin describe their experience of Deep Brain Stimulation (DBS) in movement disorders from the point of view of the safety of their microelectrode recording (MER)-based surgical technique [1]. The authors present a consecutive series of 221 mainly Parkinsonian patients who underwent implantation of 442 DBS electrodes using the Ben Gun and a total of 590 MER tracks (“a mean of 1.33 tracks for each procedure; more than 3 tracks in 4 procedures; 3 tracks in 13 procedures; 2 tracks in 109 procedures and 1 track in 316 procedures”). Forty-two of their patients (19%) suffered from hypertension. All patients underwent an immediate postoperative CT scan followed by a cranial MRI 7 days later. Not a single hemorrhagic complication (HC) occurred, neither during intraoperative nor during postoperative period.

After a brief discussion of a couple of papers from the literature the authors conclude by suggesting that “the use of MER in DBS procedures is not necessarily associated with a high risk of HC, given a careful patient selection accompanied by the application...