Author's response to reviews

Title: The Tinnitus Research Initiative (TRI) database: A new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome

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Author's response to reviews: see over
Dear Mrs. Pafitis,

according to your mail from June 22nd we discuss each point of the reviewer’s comments including an exact location of our revisions in the article. All changes have been highlighted in the manuscript by the track changes option. Furthermore, we have clarified the role of the Manathea GmbH in the competing interests section of the manuscript (page 13, lines 6-9).

Responses to comments of the reviewers:

Reviewer Robert Folmer:
As requested by the reviewer, we give information on how researchers can participate in the database project either by collecting data or accessing the data in the TRI database (page 8, lines 8-16).

Reviewer Nathan Weisz:
As suggested by the reviewer, we list the different treatments included in the database so far (page 7, lines 19-23). This list may be extended by further treatments in the future. The database has been constructed in the most flexible way, so that any kind of treatment can be documented within this database. The preconditions for implementation in the database are described in the manuscript (page 7, lines 23 ff).

The reviewer also remarks, that variability of treatment results may not only be explained by different pathophysiological subgroups but also by other factors completely unrelated to tinnitus. We agree and added this argument to the manuscript (page 3, lines 12 ff).

The reviewer asked how the not validated translations of questionnaires have been validated. These not-validated translations represents the minority of questionnaires implemented in the database and have been translated by tinnitus experts assuring high quality and accuracy of the translation. So far, these questionnaires have not yet been validated, but the database
offers the opportunity to cross-validate the questionnaires. This has been planned for the near future. These further details have been added to the manuscript (page 7, lines 8 ff).

The present set of measures in the database represents a first core set, which is available in all collaborating centers. However, the database has been constructed in a most flexible way, so that at any time additional items may be added or may be removed. This information has been added to the manuscript (page 12, lines 7 ff).

As suggested, we added further information on how to join the database and how to get access to the data (page 8, lines 8 ff).

**Reviewer William Noble:**

As suggested by the reviewer, we improved the quality of the language by a native English speaker.

The reviewer raises the question that there is no good evidence that repetitive transcranial magnetic stimulation (rTMS) induces more than transient changes in tinnitus patients. Indeed, up to now, there is no clear evidence (e.g., based on a large randomized controlled trial) that rTMS is an effective treatment for tinnitus patients. However, there is accumulating evidence from smaller studies that rTMS may at least have a moderate beneficial effect in tinnitus patients (see e.g. [1-4]). A large multicenter trial of rTMS in chronic tinnitus patients [5] is underway and results will probably be available next year. rTMS but also other interventions (e.g., pharmacological, psychotherapeutic or acoustic stimulation) have in common that not all tinnitus patients benefit from it (this argument has been added to the manuscript: page3, lines 4 ff). Therefore, the search for predictors for any kind of intervention in tinnitus patients is necessary. Nevertheless, the emphasis of rTMS in the manuscript may have been misleading. The TRI database has been constructed in a way that all kinds of therapeutic
interventions can be documented. The TRI database is not exclusively dedicated to evaluate efficacy of rTMS. This has been stated more clearly in the manuscript (page 7, lines 18 ff).

The reviewer asks whether the THI has been validated against other tinnitus questionnaires and for what it has been validated. Indeed, the THI has been cross-validated with the tinnitus questionnaire (TQ) and shows high convergent validity with the TQ [6]. The THI is widely used to assess tinnitus-related self-reported handicap and has a high test-retest reliability [7]. These arguments have been added to the manuscript (page 5, lines 3-15). However, the THI (as well as all other at present available tinnitus questionnaires) has not been specially developed to detect changes in tinnitus severity. Nevertheless, it has been suggested to use the THI total score for clinical research [8]. Therefore, as stated in the manuscript, the THI has been chosen since it is available in many different languages and the database enables evaluation of the sensitivity of the THI to detect changes (page 12, lines 14 ff).

The reviewer notes that the section “ethical considerations, database construction and technical details” is hard to read. We agree but decided that the given technical information may be of interest for researchers planning similar projects. Furthermore, it is of importance to describe the attempts to guarantee data safety.

**Reviewer Gerhard Andersson:**

The reviewer correctly argues that the tinnitus handicap inventory has been used in several treatment studies and has been shown to decrease after therapeutic intervention. Nevertheless, our statement in the manuscript is still correct, since the THI has neither been developed nor validated with respect to its sensitivity to detect change. The THI has been developed and is widely used to assess tinnitus-related, self-reported handicap [7,8]. However, as discussed in the manuscript, the THI has been chosen as a core instrument, since it is available in many different languages and has been shown to have a high test-retest reliability [7]. Furthermore,
the TRI database offers the possibility to assess the sensitivity of the THI to detect changes (page 12, lines 14 ff).

The reviewer suggests acknowledging the role of other treatment opportunities like psychological treatments. We agree and have extended the manuscript accordingly (page 3, lines 4 ff).

Furthermore, as described in the manuscript, one of the major goals of the TRI database is to document any kind of treatment not only results from rTMS studies. For this purpose, the database has been constructed in a most flexible way. This is described in more detail in the manuscript (page 7, lines 18 ff).
Reference List


4. Khedr EM, Rothwell JC, El-Atar A: One-year follow up of patients with chronic tinnitus treated with left temporoparietal rTMS. *Eur J Neurol* 2009, **16**:404-408.


8. Baguley DM, Andersson G: **Factor analysis of the Tinnitus Handicap Inventory.** *Am J Audiol* 2003, **12:**31-34.