Author's response to reviews

Title: Munster tinnitus randomized controlled clinical trial-2013 based on Tailor-Made Notched Music Treatment (TMNMT)

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Author's response to reviews: see over
Answers to Reviewers

Title: Münster tinnitus randomized controlled clinical trial-2013 based on Tailor-Made Notched Music Training (TMNMT)

Dear Reviewers, thank you very much for your critical, but constructive remarks, which have helped us improving our protocol.

Best regards

Univ.-Prof. Dr. Christo Pantev and co authors

Reviewer 1: Deborah Hall

Reviewer's report:
The authors describe an RCT protocol to assess the efficacy of tailor made notched music training (TMNMT), compared to an active placebo comparator.

Major Compulsory Revisions
The following describes my recommendations for major compulsory revisions.

1. Will the study test the hypothesis adequately?
The study is carefully designed in terms of most of the facets outlined in the CONSORT checklist. However, there are a number of aspects, which I envisage could make the data interpretation problematic. I would therefore recommend the authors to address these in advance at the design phase of the trial protocol.

   i) Group allocation. The team propose to stratify for age and hearing loss – further details of how this is to be carried out would be informative – e.g. information about stratification categories of age and HL. Here, it is also worthwhile learning from previous RCTs for tinnitus. The RESET1 trial for example did not stratify according to baseline tinnitus severity and as a result the control group (GPS) had a lower initial severity score, thus leading to bias. I recommend accounting for severity of tinnitus distress.

Stratification is an appropriate allocation method for improving power in small trials (< 400 patients) and preventing type 1 errors (Kernan et al., 1999). It was proposed to use a minimum number of strata to improve statistical efficiency, since this allows the assignment of an equal number of subjects to each treatment and assures an equal distribution of the stratification factor between groups (Kernan et al., 1999; Kahan and Morris, 2011).

Age is known to influence auditory evoked responses (Alain and Snyder, 2008) and neural plasticity in general (Jones et al., 2006). Therefore, it is likely that age might have an influence on the inhibition-induced plasticity evoked by TMNMT resulting in reduced training effects in older subjects. Hearing loss might also have a great influence on the training effect, since the neurons coding the frequencies around the notch need to be excited in order to inhibit the neurons coding the tinnitus frequency. This can only be achieved, if the frequencies around the notch are still audible.

We chose these two variables as stratification categories to keep the number of strata minimal (n = 4) but include the two variables, which probably will influence the
treatment outcome. The specific stratification categories were age (young: < 51 years, old: >= 51 years) and maximum hearing loss ½ octaves below or above the tinnitus frequency (minor HL: < 40 dB, major HL: >= 40 dB). This information is also included in the manuscript now.

ii) Primary outcome. CONSORT recommends use of a validated outcome tool when available and so the THQ is a good choice of primary outcome. One primary outcome is sufficient – VAS (loudness, annoyance, awareness, and handicap) would be considered secondary outcomes in my view.

We think that both, the THQ and the VAS, are valid outcome variables. It was demonstrated in two previous studies that ratings on VAS were significantly reduced after TMNMT (Okamoto et al., 2010; Tetsmann et al., 2011). Therefore, we think that the VAS is a very important outcome variable allowing us to replicate the results of previous studies and to validate the results in our clinical trial.

iii) Sample size. CONSORT recommends that the outcome of greatest importance is used to compute sample size, preferably using a priori (published where possible) knowledge about typical sample mean, SD and the known minimal clinically important difference. A study by Henry et al 2006 Acta otolaryngol 126 pp64 can be useful in this respect. At present, the authors’ description of the process by which they computed the power calculation is not sufficient for a reader to fully understand what was done. I would expect a ‘medium’ effect size to be closer to 0.5 than 0.25.

We agree and in order to enable the reader to fully understand the process of power computation, we added more details concerning the estimation of the expected effect size. This has been added into the protocol.

iv) Blinding. For transparency, the authors should explain how they will ensure double blinding throughout the RCT.

Thank you for this valuable recommendation, we realized a more detailed description of the blinding process in the protocol.

v) Missing data. In order to preserve fully the benefit of randomization, all participants should be included in the analysis (intention-to-treat). The authors should at least report how they will deal with missing outcomes, preferably using imputation rather than last observation carried forward.

We agree on the necessity to include all participants that were randomized in an intention-to-treat analysis. Following Mallinckrodt (2001) we think that a likelihood-based mixed-effects model for repeated measures analysis is an adequate way to deal with missing data. Therefore, we have changed the section describing our primary statistical analyses in the protocol.

vi) Interim analysis. The authors state that they will carry out 2 interim analyses. Here, the purpose of these interim analyses is unclear.
CONSORT describes circumstances where it is appropriate – i.e. to enable a decision making and/or stopping rule. Any statistical guidelines and stopping rules should be in place a priori: Typically these analyses are overseen by an Independent Data Monitoring Committee with group sequential statistical methods to adjust for multiple comparisons and procedures to maintain double blinding. Further clarification is needed.

Indeed, we are lacking a more detailed description of this analysis and its intention. Therefore we added both to the study protocol. Additionally, we reduced the number of interim analysis to one.

2. Are sufficient details provided to allow replication? See points iii), v) and vi).

3. Does the manuscript adhere to the relevant reporting standards?
Some aspects of the trial protocol do not fully report on some of the key steps outlined in the CONSORT guidelines to which the authors intend to use in their final reporting. The protocol would be greatly strengthened if these key aspects were described a priori.

4. Is the writing acceptable? Yes.

Discretionary Revisions
The following describes my recommendations for discretionary revisions:

1. The background is heavily biased towards reporting the authors own work.
We have included additional references.


The correct reference (Friedman et al., 1998) has been inserted.

3. Dominant tinnitus pitch should be calculated using the geometric mean, not arithmetic mean as freq is measured on a log scale.
We calculate the arithmetic mean after we transform the frequency from Hertz to Cent scale, which is linear. After calculating the mean we transform the frequency back into Hertz. This has now been clarified in the trial protocol.

4. Secondary efficacy end points should be stated. Are these also 3 months?
As described in the clinical trial design, the secondary outcome measures are administered in pre, post and follow-up (four weeks after the end of the training) measurement.

5. Para 1 top of P9 is not needed.
We completely agree and therefore this paragraph has been deleted.
6. Discussion makes claims about treatment cost. Does this study design include an economic analysis to support that claim?

We did not perform a formal economic analysis. The claim is a rough estimate of the comparison of the price of an App in the App store (realization of our treatment protocol) with the price of other treatments available on the market.

7. Level of interest: An article whose findings are important to those with closely related research interests

8. Quality of written English: Acceptable

9. Statistical review: No, the manuscript does not need to be seen by a statistician.

10. Declaration of competing interests: I declare that I have no competing interests

References


Reviewer 2: Martin Schecklmann

Reviewer’s report:
Minor Essential Revisions (see attachment)
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.

TNMNT is one of the up-to-date highly promising approaches for treatment of chronic tinnitus. The RCT of the TNMNT in a large sample is highly important and the next logical step to evaluate the efficacy of this treatment. I suggest acceptance of this paper after “minor revisions” without resubmission to the reviewer. The study protocol is concisely written lacking only in the precision in some issues. This is especially of high relevance for a methods paper.

1. Abstract: The methods should be described in more detail (e.g. sample description, treatment description).

Thank you very much for this advice. We have added now more details describing the methods.

2. Page 2: The last sentence is not understandable without more detailed explanation of habituation and lateral inhibition.

The required more detailed explanation was provided as much as possible.

3. Page 3, section 2: References are missing.

References have been complemented: (Eggermont and Roberts, 2004; Cazals et al., 1998; Bauer et al., 2008; Ochi and Eggermont, 1997; Norena and Eggermont, 2003).

4. Page 3, section 3: The naïve reader might ask why the music is filtered with respect to the tinnitus pitch and not with respect to the hearing loss which is the cause for the tinnitus pitch.

The TMNMT treatment is based on lateral inhibitory effects on the cortical area generating the tinnitus percept, which can be more closely defined through matching procedures than the hearing loss.

5. Trial design: The rationale for the duration of the treatment (2 hours per day, 3 months) is missing.

The rationale of the treatment duration is based (i) on our experience with TMNMT in previous studies and (ii) on information about the duration of constrained induced therapy treatments that are usually performed during two weeks to six months.

6. Is the time of day for the VAS ratings constant?
The main outcome variable will be a paper pencil version of the VAS. This will be rated by the participant together with other paper pencil questionnaires. Additionally, we will investigate the time course of changes measured by the VAS more deeply with the iPod version. Therefore, the participant is reminded twice a week (Wednesday and Sunday) at 12 o’clock to perform a measurement with the iPod based VAS.

7. Page 5: The TQ is not mentioned.

Due to efficiency and economy reasons we do not administer the TQ in our entry examination described on page 5. In all steps regarding the clinical trial we do use this questionnaire, which is specified under “4. Outcome Measures”.

8. Page 5: What are drop-out criteria?

We added a description of the drop-out criterion to the protocol.

9. Page 6: What are the subjects allowed to do during the stimulation (e.g. reading)?

A paragraph “Instructions for subjects during TMNMT” has been added to the protocol.

10. Page 6: How is the octave error test done?

We added a description of the octave error test to the protocol.

Page 8: How was the medium effect size reasoned?

The reasoning for the medium effect size is now described in more detail in the protocol.

12. Page 8: What are the consequences of the interim analyses?

Thank you very much for the hint. We added this information to the protocol.

BMC Neurology reviewer criteria

1. Will the study design adequately test the hypothesis?
   Yes.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

   Some minor information is missing, see above.

3. Does the manuscript adhere to the relevant standards for reporting and data deposition: if not, in what ways?
   Yes.
4. Is the writing acceptable?
Yes.

References


