PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Logistic Regression Analysis of Factors Influencing the Effectiveness of Intensive Sound Masking Therapy in Patients with Tinnitus
AUTHORS	Cai, Yuexin; Zhou, Qian; Yang, Haidi; Jiang, Jiajia; Zhao, Fei; Huang, Xiayin; Mo, Hanjie; Chen, Xiaoting; Xiong, Hao; Chen, Suijun; Zhang, Xueyuan; Zheng, Yiqing

VERSION 1 – REVIEW

REVIEWER	Yu-Chen Chen Nanjing first hospital, Nanjing, China
REVIEW RETURNED	22-Jun-2017

GENERAL COMMENTS	Comments to the Author The authors conducted a retrospective cross-sectional study to prove that flat audiogram, younger age, and high cores for THI are predictive of beneficial treatment outcomes through multivariate logistic regression models. This paper is well conducted and the conclusions are important. I only have a few suggestions for improvement: (1) Introduction, Paragraph 1: the authors stated that there are large discrepancies in terms of effectiveness because of the complex mechanisms on tinnitus. Please elaborate several relevant mechanisms underlying tinnitus here. (2) Introduction, Paragraph 3: the authors mentioned the rTMS intervention but just listed three examples here. A comparison between rTMS and tinnitus sound masking should be stated. (3) Introduction, Paragraph 5: the authors stated that there are few studies available on the factors that affect the effectiveness of sound masking therapy. Any relevant studies in this field should be reported in the introduction. (4) Methods: why did the authors choose seven days' sound masking intervention in this study? (5) Discussions: the discussion seems a little bit short. The authors suggested that patients with flat audiogram, younger in age, as well as higher scores of THI were more likely to have positive outcomes. However, the possible explanations are lacking. These factors need to be explained respectively.

	(6) Discussions, Paragraph 3: the MEG study was reported to confirm the current results. The authors could raise some other examples here utilizing another technique, such as fMRI or PET (Kim, journal of audiology, 2012; Lanting, Hearing research, 2009. etc.). (7) There are several typos in the whole manuscript. The grammar and language needs to be improved.

REVIEWER	Minkevan den Berge University Medical Center Groningen, The Netherlands
REVIEW RETURNED	31-Jul-2017

GENERAL COMMENTS	The authors presented a manuscript with the goal to investigate any factors that are of influence on the treatment effect of sound masking therapy. They do this, by retrospectively investigation a group of patients who underwent intensive sound masking therapy during 7 days. The patient groups were divided based on a pre- and post THI difference of 7 points. The authors performed a multivariate logistic regression analysis and concluded that there are several factors positively influencing the successful outcome of sound masking intervention, i.e. flat audiogram, younger age and THI-score. This is a well-written manuscript, about an interesting subject. However, I have some serious concerns, mainly about the strength with which the authors have put the conclusions they have drawn and with the theoretical explanation of these conclusions. Moreover, the methods are not described completely. 1. Introduction. ' Although a' until ' with tinnitus' the authors state that no particular treatment for tinnitus has been found effective in all patients with tinnitus. This is a quite blunt statement. I assume that the authors refer to tinnitus in general, however they reference this remark with references about research on TRT. 2. Introduction. In general, the authors get to the point quite far in their conclusion. For too long, it is to explorative. Sound masking therapy, which is the main intervention in this study, is only named at the end of the introduction. I advise the authors to get to the point and the scope of this article more early in the introduction. And: please hypothesise which factors might be of influence (the authors do so partially), but also hypothesise why this might be. 3. Materials & Methods. In- and exclusion criteria are missing. What kind of patients were included? Uni- or lateral sided tinnitus? Pulsatile tinnitus? etc. Any exclusion criteria on otological findings? 4. Material & Methods. The authors refer to an article by Hannula for classifying audiograms. I miss a reference of the article here. 5. Material & Methods. Tinnitus pitch and loudness matching was performed in the ipsilateral ear. But what if this ear had severe hearing loss? Is measuring on the contralateral side then more appropriate? And what if patients has bilateral or central tinnitus? Please clarify the procedure.

	6. Materials & Methods. The authors describe that the THI was collected 'before and after treatment'. Especially for the post-treatment measurements, it is important to clarify when exactly this was measured. For future (prospective) research, a VAS scale that was taken at additional moments throughout the session is advisable. 6. Results. The authors describe the the THI scores were significantly reduced in the effective group (and not significantly reduced in the non-effective group), this is quite an open door. This is not worth a figure, like figure 1. I would like to see a baseline table (like table 1, but more information like mean THI pre and post) and start the result session with the description of the included patient group. 7. Results. Can you explain why you choose to decided to look at the difference in hearing threshold in tinnitus and non-tinnitus ears? Moreover, I think there is more to say about Table 1 than just what is written here. 8. Results, Table 1. Tinnitus loudness: scale in dB or VAS-scale? Duration of tinnitus between 1-3 months is subacte, but the authors define chronic tinnitus as >1 months? This does not make sense. Hearing threshold (scale?) is a mean over which frequencies?Please clarify. 9. Results. Please clarify why certain variables (age, audiogram configuration, proper treatment THI and hearing treshold) were selected for the multivariate logistic regression model If this was based on significancy as shown in Table 1, then why was ' hearing threshold' added (p=0.65)? 10. Results. The authors describe that following the multivariate logistic regression analysis, age , flat audiogram and THI score are significantly associated with treatment outcome. However, ' flat audiograms' is not significantly related with a p value >0.056 (alpha was set at 0.05 according to the authors). So I agree that this is borderline significant, but not significant based on the stated alpha and with a very broad confidence interval, probably caused by a low patient group, which makes me question the significancy even more. I think that it is not correct to conclude that ' flat audiogram' is positively associated with successful treatment. 11. Discussion. The authors state rather strongly that a flat audiogram was more likely to respond positively to sound masking therapy, as I mentioned above: I don't think it is correct to state this so firmly. Moreover, I miss a discussion about WHY this would be the case. Is there a possible etiological underlying factor to explain such a finding? And are the ' flat audiograms' possibly norming hearing levels, or lowered hearing levels? Furthermore, authors report that younger patients had more benefit of sound masking. They stat that ' it indicates that your tinnitus subjects are more likely to have a greater need for alleviating stress by using sound masking'. Are you suggestion a placebo effect here? 12. Conclusion: I think there is no sufficient statistical base to conclude that a flat audiogram is related with success of sound masking treatment.

VERSION 1 – AUTHOR RESPONSE

Reply to Reviewer: 1

Reviewer Name: Yu-Chen Chen
Institution and Country: Nanjing first hospital, Nanjing, China
Please state any competing interests or state 'None declared': None declared

General comments
The authors conducted a retrospective cross-sectional study to prove that flat audiogram, younger age, and high cores for THI are predictive of beneficial treatment outcomes through multivariate logistic regression models. This paper is well conducted and the conclusions are important. I only have a few suggestions for improvement:

Response：
We are delighted to hear this positive comment. We would like to thank you for the most helpful comments and suggestions. We believe that all comments and suggestions have contributed significantly towards improving the quality of this manuscript.

Specific comments
(1) Introduction, Paragraph 1: the authors stated that there are large discrepancies in terms of effectiveness because of the complex mechanisms on tinnitus. Please elaborate several relevant mechanisms underlying tinnitus here.

Response：
Thank you for this useful comment. We have revised it accordingly in the manuscript (i.e., on page 4, highlighted in yellow).
"Tinnitus is the perception of noise in the absence of any external sound. It is considered as one of the most common and disturbing health problems1. It is widely accepted that tinnitus is a symptom caused by diverse pathologies as a result of not only peripheral hearing loss, but also the aberrant neural activity in central auditory nervous system2-4. Subsequently various theories have been proposed to elaborate underlying possible mechanisms, such as Discordant theory (i.e., the discordant dysfunction of damaged outer hair cells and intact inner hair cells)5, and Auditory plasticity theory (damaged cochlea activates auditory plasticity by enhancing neural activity in the central auditory pathway, which results in abnormal input to the central auditory system)4."

(2) Introduction, Paragraph 3: the authors mentioned the rTMS intervention but just listed three examples here. A comparison between rTMS and tinnitus sound masking should be stated.

Response：
Thank you for this useful comment. Unfortunately no relevant studies are found on the comparison of the effectiveness between the rTMS and sound masking therapy on tinnitus. However, previous studies suggest that there are many influencing factors such as age, tinnitus characteristics and hearing status, along with other demographic factors, which affect effeciveness of tinnitus management1, 6. For example, Kleinjung et al.7 suggests that mild hearing loss and shorter duration of tinnitus are more likely to being beneficial using rTMS. These results are generally in keeping with influencing factors obtained from using sound masking therapy1. Further studies are needed to evaluate the associated factors to the effectiveness of sound masking on tinnitus.
We have revised this sentence in the manuscript accordingly. (i.e., on page 4-5, highlighted in yellow)
"Furthermore, evidence has shown that no single treatment for tinnitus is found effective in all patients with tinnitus8, 9. These discrepancies in terms of effectiveness are largely due to the complex mechanisms behind the symptoms as indicated above, and the severity of impact on sufferers.

Previous studies suggest that there are many influencing factors such as age, tinnitus characteristics and hearing status, along with other demographic factors, which affect effeciveness of tinnitus management1, 6. However, the results appear inconsistent. For example, Koizumi et al.10 found better outcomes with TRT for patients with higher levels of tinnitus loudness, while Ariizumi et al.11 reported lower tinnitus loudness to be predictive of better outcomes with TRT.
In addition, Kleinjung et al.7 suggests that mild hearing loss and shorter duration of tinnitus are more likely to being beneficial using rTMS. These results are generally in keeping with influencing factors obtained from using sound masking therapy1. It is also noteworthy that young in age and more severe depression contributed to a positive response with CBT12. Conrad et al.13 further clarifies that dysfunctional cognition is associated with CBT outcome, i.e., more severe dysfunctional cognition results in a more negative emotional outcome after CBT intervention."

(3) Introduction, Paragraph 5: the authors stated that there are few studies available on the factors that affect the effectiveness of sound masking therapy. Any relevant studies in this field should be reported in the introduction.

Response：
Thank you for this comment. We feel this comment is important and essential. As suggested, we have added a small paragraph in the manuscript accordingly, i.e., on page 5, i.e.,
"To our best knowledge, there are few studies available on the factors that affect the effectiveness of sound masking therapy. A recent study by Theodoroff et al.1 appears the only report directly investigating the factors associated with effective tinnitus treatment using sound masking therapy1. Although they found several positive predictors, such as younger age, better self-reported hearing difficulty, shorter durations of tinnitus and better hearing threshold at low frequency region, these results were obtained by combining tinnitus treatment data of either using sound masking therapy or TRT. The separate analysis showed that participants with younger age perceived significantly better response to intervention only in TRT group ($p<0.017$), but age was not a significant factor in the group using sound masking therapy ($p=0.143$). Such bias indicated that further investigation is needed to clarify possible factors associated with effective sound masking therapy."

(4) Methods: why did the authors choose seven days' sound masking intervention in this study?

Response：
Thank you for this comment. Actually the reason of choosing seven days for sound masking intervention was briefly addressed in the methodology section. One of the main reasons for choosing seven days' sound marking intervention is due to patient adherence in the context of Chinese culture and Healthcare system, and high drop-out rate when they were provided a longer duration of sound masking intervention. Therefore, considering the nature of (i.e., a retrospective study) and main purpose of the present study, current data was obtained only from intensive sound masking intervention within such a short duration.
To further clarify this issue, we have revised the relevant part in the manuscript accordingly. (i.e., on page 8, highlighted in yellow)
"Due to patient adherence in the context of Chinese culture and Healthcare system, high drop-out rate was occurred when they were provided a longer duration of sound masking intervention. Considering the nature of (i.e., a retrospective study) and main purpose of the present study, current data was obtained only from intensive sound marking intervention, and the short-term effectiveness was subsequently assessed. The narrow-band noise at 10 dB above the tinnitus frequency was delivered to mask the tinnitus through headphones (Beyerdynamic DT880 pro) 4-6 times daily for 20-30 minutes, for a week14, 15. "

(5) Discussions: the discussion seems a little bit short. The authors suggested that patients with flat audiogram, younger in age, as well as higher scores of THI were
more likely to have positive outcomes. However, the possible explanations are lacking. These factors need to be explained respectively.

Response：
Thank you for this useful comment. We completely agree with your suggestion. As a result, we have revised the discussion section accordingly. (i.e., on pages 12 to 14, highlighted in yellow)
“In the present study, participants with flat audiogram were more likely to respond positively to intensive sound masking intervention compared with those with a HFSS audiogram but unrelated to average hearing threshold. To our best knowledge, no previous study investigated the influence of audiometric configuration on the outcome of tinnitus intervention, even though the study by Chang et al. 16 showed that patients with a flat pattern audiogram benefited more from hearing aids compared to those with rising or decreasing audiogram in terms of improvement of psychological handicap and quality of life. The present result is likely due to tinnitus characteristics together with their associated hearing status. By recording Transient Otoacoustic Emiisions (TEOAEs), Kim et al.17 found that normal TEOAE rates were significantly higher in tinnitus patients with flat audiogram than those in the HFGS and HFSS groups. Moreover, tinnitus patients with HFSS had significantly lower response rates of TEOAEs at 3, 4 and 6 kHz than tinnitus patients with flat audiogram. Therefore, better hearing status in tinnitus patients with flat audiogram may be underlying factor, which is consistent with the previous finding reported by Theodoroff et al.1. However, this result should be interpreted with cautious due to the retrospective nature of this study. The further prospective research is needed using systematic approaches, such as randomized controlled trail18.
Furthermore, higher THI scores before treatment were correlated with a better response to sound masking. These results are consistent with the findings of Koizumi et al.10 and Theodoroff et al.1, who found tinnitus retraining therapy (TRT) more effective in patients with higher THI scores. Koizumi et al.10 further suggested that TRT should be introduced to tinnitus patients with THI score higher than 50 points. Because overall THI score may reflect the distress in tinnitus patients, these results suggested that sound masking may be regarded as a useful therapy to alleviate the distress cause by tinnitus, particularly in patients in severe distress19.
There are several possible mechanisms behind sound masking therapy, but the exact mechanism is still unclear. Overall, it is generally accepted that there is a reduction of a response to a signal due to the presence of another. The neuro-physiological mechanism can be explained that the original neural activity caused by the first sound signal (tinnitus) is reduced by the neural activity of the other sound (e.g., masking noise). For example, recent magnetoencephalography (MEG) data reported by Adjamianet al.,20 support the efficacy of sound masking on psychological handicap (depression and anxiety), reflecting a reduction in delta band activity, which is considered a possible neuronal marker for the effect of masking21. Various advanced neuroimaging techniques such as fMRI and PET appeared a valuable tool to explore the mechanism of tinnitus. For example, Lanting et al.22 suggested that tinnitus may correspond to enhance neural activity across several areas of the central auditory system using fMRI and PET. In the meantime, they also found that neural activities in non-auditory areas (i.e., frontal areas, limbic system and cerebellum) seems also associated with the perception of tinnitus. Therefore, further studies on the comparison of the subjective perception of tinnitus and central neural activity changes between pre- and post-sound masking therapy are needed in order to clarify the neural marker as well as the mechanisms of the effective sound masking therapy.

In the present study, younger age had a positive effect on the benefits of sound masking therapy. Von Wedel et al.23 suggested that younger tinnitus patients are more likely to report distress and tinnitus annoyance than older patients. Moreover, Seydel et al.24 demonstrated that younger tinnitus subjects suffered distress more severely than older tinnitus subjects, which is due to higher levels of occupational and personal stress among younger subjects24. As a result, younger subjects are likely to be more beneficial of alleviating their high level distress provided by sound masking intervention21. In addition, the other explanation could be due to better coping capability in younger tinnitus suffers than older subjects 24."

(6) Discussions, Paragraph 3: the MEG study was reported to confirm the current results. The authors could raise some other examples here utilizing another technique, such as fMRI or PET (Kim, journal of audiology, 2012; Lanting, Hearing research, 2009. etc.).

Response：
Thank you for this comment. We have revised this paragraph in the manuscript accordingly. (i.e., on pages 13, highlighted in yellow)
"There are several possible mechanisms behind sound masking therapy, but the exact mechanism is still unclear. Overall, it is generally accepted that there is a reduction of a response to a signal due to the presence of another. The neuro-physiological mechanism can be explained that the original neural activity caused by the first sound signal (tinnitus) is reduced by the neural activity of the other sound (e.g., masking noise). For example, recent magnetoencephalography (MEG) data reported by Adjamianet al.,20 support the efficacy of sound masking on psychological handicap (depression and anxiety), reflecting a reduction in delta band activity, which is considered a possible neuronal marker for the effect of masking21.
Various advanced neuroimaging techniques such as fMRI and PET appeared a valuable tool to explore the mechanism of tinnitus. For example, Lanting et al.22 suggested that tinnitus may correspond to enhance neural activity across several areas of the central auditory system using fMRI and PET. In the meantime, they also found that neural activities in non-auditory areas (i.e., frontal areas, limbic system and cerebellum) seem also associated with the perception of tinnitus. Therefore, further studies on the comparison of the subjective perception of tinnitus and central neural activity changes between pre- and post-sound masking therapy are needed in order to clarify the neural marker as well as the mechanisms of the effective sound masking therapy."

(7) There are several typos in the whole manuscript. The grammar and language needs to be improved.

Response：
We apologize for the careless mistake. This error has been amended accordingly.

Reply to Reviewer 2

Reviewer Name: Minkevan den Berge
Institution and Country: University Medical Center Groningen, The Netherlands
Please state any competing interests or state ‘None declared’: None declared

General comment 1
The authors presented a manuscript with the goal to investigate any factors that are of influence on the treatment effect of sound masking therapy. They do this, by retrospectively investigation a group of patients who underwent intensive sound masking therapy during 7 days. The patient groups were divided based on a pre- and post THI difference of 7 points. The authors performed a multivariate logistic regression analysis and concluded that there are several factors positively influencing the successful outcome of sound masking intervention, i.e. flat audiogram, younger age and THI-score. This is a well-written manuscript, about an interesting subject.

Response：
We are delighted to hear this positive comment. We would like to thank you for the most helpful comments and suggestions. We believe that all comments and suggestions have contributed significantly towards improving the quality of this manuscript.

General comment 2
However, I have some serious concerns, mainly about the strength with which the authors have put the conclusions they have drawn and with the theoretical explanation of these conclusions. Moreover, the methods are not described completely.

Response：
We would like to thank you for these important comments. We completely agree the comments on both sections of methodology and conclusion.
Regarding the issue on in-completed methods, we have revised the methodology section by adding the following paragraphs accordingly in the manuscript (i.e., on pages 6-8, highlighted in yellow)
“Participants
The present research was a retrospective study. A total of 102 patients with tinnitus who underwent audiological investigations and specific tinnitus examinations, follow by seven days sound masking intervention at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University, China were initially considered. The detailed selection criteria are as follows:
(1) They had sought clinical help for their tinnitus problem, which had lasted more than 2 weeks;
(2) They had no history of head trauma or central nervous system disorders;
(3) They had mild to severe sensorineural hearing loss. All tinnitus patients with either current conductive hearing loss or previous middle ear surgery (e.g., mastoidectomy) were excluded1.
(4) The tinnitus patients with pulsatile tinnitus due to aberrant vascular malformation were also excluded.

Tinnitus Specific Assessments
Patients were asked to describe the tinnitus characteristics, including duration and laterality (i.e., being in the right, left or both ears, central in the head). Tinnitus pitch and loudness matching measurements were performed ipsilaterally to the ear with predominant or louder tinnitus if there was a difference between the two sides. However, if the tinnitus ear had severe hearing loss, the contralateral ear was tested instead2. When the tinnitus was equally loud on both sides or was localized in the head, the matching tones were given to the ear with the better hearing. Otherwise, the ear was chosen randomly if there was no difference between the acuity of the two ears.
During the tinnitus pitch matching tests, the 9 audiometric frequencies between 125 Hz and 8.0 kHz (i.e., 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 3.0 kHz, 4.0 kHz, 6.0 kHz, and 8.0kHz) were firstly used to roughly match the tinnitus pitch.

Participants were initially asked to make a clear distinction between the tinnitus pitch perception and presented matching tones, and then they reported verbally whether the matching tone needed to go higher or lower until the exact matching tone or a close approximation to their tinnitus was obtained. The test tone was adjusted in a half-octave step. If there was no matching with a pure tone perceived by participants, narrow-band noise was used instead.
When the matching frequency was found, the level was initially set to 5 dB above the measured audiometric threshold to find an approximate tinnitus loudness level, then the level was adjusted in 1 dB step until the subject indicated that the tone matched the loudness of their tinnitus2.

The Sound Masking Intervention
Due to patient adherence in the context of Chinese culture and Healthcare system, high drop-out rate was occurred when they were provided a longer duration of sound masking intervention. Considering the nature of (i.e., a retrospective study) and main purpose of the present study, current data was obtained only from intensive sound marking intervention, and the short-term effectiveness was subsequently assessed. The narrow-band noise at 10 dB above the tinnitus frequency was delivered to mask the tinnitus through headphones (Beyerdynamic DT880 pro) 4-6 times daily for 20-30 minutes, for a week3, 4"
Regarding the query on the accuracy of conclusion section, after serious considerations, reanalyzed the data and searched for relevant references, we totally agree with reviewer's comments. As a result, we have revised the relevant paragraphs, including statistical analysis method, results, discussion and conclusion sections. For example, final conclusion section was revised as followed, (i.e., on page 14, highlighted in yellow)
"Conclusions
This retrospective study suggests that factors of audiometric configuration, age, and THI scores pre-treatment are predictive of beneficial sound masking outcomes. Further analysis indicates that tinnitus patients with flat audiogram configuration are more likely to achieve successfully intervention when compared to those with high-frequency steeply sloping audiograms. Gender, tinnitus laterality, duration and hearing threshold are not related to the effectiveness of intensive sound masking treatment. However, these results should be interpreted with caution due to the retrospective nature of this study. A future randomized control study is needed to provide further evidence for prognostic factors (e.g. audiometric configuration, age, THI score) and their contributing to the effectiveness of tinnitus interventions."

Specific Issues
1. Introduction. ' Although a' until ' with tinnitus' the authors state that no particular treatment for tinnitus has been found effective in all patients with tinnitus. This is a quite blunt statement. I assume that the authors refer to tinnitus in general, however they reference this remark with references about research on TRT.

Response：
Thank you for this useful comment. We apologize for these unclear statements. As requested, we have revised the relevant parts accordingly in the manuscript (i.e., on page 4, highlighted in yellow).
"Furthermore, evidence has shown that no single treatment for tinnitus is found effective in all patients with tinnitus5, 6. These discrepancies in terms of effectiveness are largely due to the complex mechanisms behind the symptoms as indicated above, and the severity of impact on sufferers. Previous studies suggest that there are many influencing factors such as age, tinnitus characteristics and hearing status, along with other demographic factors, which affect effeciveness of tinnitus management7, 8. However, the results appear inconsistent. For example, Koizumi et al.9 found better outcomes with TRT for patients with higher levels of tinnitus loudness, while Ariizumi et al.10 reported lower tinnitus loudness to be predictive of better outcomes with TRT."

2. Introduction. In general, the authors get to the point quite far in their conclusion. For too long, it is to explorative. Sound masking therapy, which is the main intervention in this study, is only named at the end of the introduction. I advise the authors to get to the point and the scope of this article more early in the introduction. And: please hypothesise which factors might be of influence (the authors do so partially), but also hypothesise why this might be.

Response：
Thank you for this comment. We feel this comment is important and essential. As suggested, we have added a small paragraph in the manuscript accordingly, i.e., on pages 4-5, i.e., (highlighted in yellow)
“Furthermore, evidence has shown that no single treatment for tinnitus is found effective in all patients with tinnitus5, 6. These discrepancies in terms of effectiveness are largely due to the complex mechanisms behind the symptoms as indicated above, and the severity of impact on sufferers. Previous studies suggest that there are many influencing factors such as age, tinnitus characteristics and hearing status, along with other demographic factors, which affect effeciveness of tinnitus management7, 8. However, the results appear inconsistent. For example, Koizumi et al.9 found better outcomes with TRT for patients with higher levels of tinnitus loudness, while Ariizumi et al.10 reported lower tinnitus loudness to be predictive of better outcomes with TRT.
In addition, Kleinjung et al.11 suggests that mild hearing loss and shorter duration of tinnitus are more likely to being beneficial using rTMS. These results are generally in keeping with influencing factors obtained from using sound masking therapy1. It is also noteworthy that young in age and more severe depression contributed to a positive response with CBT12. Conrad et al.13 further clarifies that dysfunctional cognition is associated with CBT outcome, i.e., more severe dysfunctional cognition results in a more negative emotional outcome after CBT intervention.
To our best knowledge, there are few studies available on the factors that affect the effectiveness of sound masking therapy. A recent study by Theodoroff et al.7 appears the only report directly investigating the factors associated with effective tinnitus treatment using sound masking therapy7. Although they found several positive predictors, such as younger age, better self-reported hearing difficulty, shorter durations of tinnitus and better hearing threshold at low frequency region, these results were obtained by combining tinnitus treatment data of either using sound masking therapy or TRT. The separate analysis showed that participants with younger age perceived significantly better response to intervention only in TRT group ($p<0.017$), but age was not a significant factor in the group using sound masking therapy ($p=0.143$). Such bias indicated that further investigation is needed to clarify possible factors associated with effective sound masking therapy.”

3. Materials & Methods. In- and exclusion criteria are missing. What kind of patients were included? Uni- or lateral sided tinnitus? Pulsatile tinnitus? etc. Any exclusion criteria on otological findings?

Response：
Thank you for this comment. We feel this comment is important and essential. As suggested, we have added a small paragraph in the methodology section accordingly, i.e., on pages 6, i.e., (highlighted in yellow)
“The detailed selection criteria are as follows:
(5) They had sought clinical help for their tinnitus problem, which had lasted more than 2 weeks;
(6) They had no history of head trauma or central nervous system disorders;
(7) They had mild to severe sensorineural hearing loss. All tinnitus patients with either current conductive hearing loss or previous middle ear surgery (e.g., mastoidectomy) were excluded.
(8) The tinnitus patients with pulsatile tinnitus due to aberrant vascular malformation were also excluded1. ”

4. Material & Methods. The authors refer to an article by Hannula for classifying audiograms. I miss a reference of the article here.

Response：
We apologize for the careless mistake. Actually this reference should be coded as reference number 15. This error has been amended accordingly in the revised manuscript, i.e.,
15. Hannula, S. Bloigu, R.Majamaa,K. et al. Audiogram configurations among older adults: prevalence and relation to self-reported hearing problems. Int J Audiol, 2011, 50(11), 793-801

5. Material & Methods. Tinnitus pitch and loudness matching was performed in the ipsilateral ear. But what if this ear had severe hearing loss? Is measuring on the contralateral side then more appropriate? And what if patients has bilateral or central tinnitus? Please clarify the procedure.

Response：
Thank you for this comment. We feel this comment is important and essential. As suggested, we have added a small paragraph in the manuscript accordingly, i.e., on pages 7-8, i.e., (highlighted in yellow)
“Tinnitus Specific Assessments
Patients were asked to describe the tinnitus characteristics, including duration and laterality (i.e., being in the right, left or both ears, central in the head). Tinnitus pitch and loudness matching measurements were performed ipsilaterally to the ear with predominant or louder tinnitus if there was a difference between the two sides. However, if the tinnitus ear had severe hearing loss, the contralateral ear was tested instead2. When the tinnitus was equally loud on both sides or was localized in the head, the matching tones were given to the ear with the better hearing. Otherwise, the ear was chosen randomly if there was no difference between the acuity of the two ears.
During the tinnitus pitch matching tests, the 9 audiometric frequencies between 125 Hz and 8.0 kHz (i.e., 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 3.0 kHz, 4.0 kHz, 6.0 kHz, and 8.0kHz) were firstly used to roughly match the tinnitus pitch. Participants were initially asked to make a clear distinction between the tinnitus pitch perception and presented matching tones, and then they reported verbally whether the matching tone needed to go higher or lower until the exact matching tone or a close approximation to their tinnitus was obtained. The test tone was adjusted in a half-octave step. If there was no matching with a pure tone perceived by participants, narrow-band noise was used instead. When the matching frequency was found, the level was initially set to 5 dB above the measured audiometric threshold to find an approximate tinnitus loudness level, then the level was adjusted in 1 dB step until the subject indicated that the tone matched the loudness of their tinnitus2. ”

6a. Materials & Methods. The authors describe that the THI was collected 'before and after treatment'. Especially for the post-treatment measurements, it is important to clarify when exactly this was measured. For future (prospective) research, a VAS scale that was taken at additional moments throughout the session is advisable.

Response：
Thank you for this comment. As suggested, we have added a small paragraph in the manuscript accordingly, i.e., on page 8. (highlighted in yellow). In addition, we totally agree that your suggestion and VAS measurement will take it into account in the future study.
“According to the tinnitus sound masking therapy protocol, the effectiveness of the sound masking intervention was evaluated using the Tinnitus Handicap Inventory (THI) pre and post intervention, i.e., THI questionnaire was provided to investigate their tinnitus issues before the treatment initially, and this procedure was conducted again seven days after sound masking therapy at tinnitus review clinics.”

6b. Results. The authors describe the THI scores were significantly reduced in the effective group (and not significantly reduced in the non-effective group), this is quite an open door. This is not worth a figure, like figure 1. I would like to see a baseline table (like table 1, but more information like mean THI pre and post) and start the result session with the description of the included patient group.

Response：
Thank you for this comment. We feel this comment is helpful in terms of having an efficient way to present our results. As suggested, we have deleted Figure 1, and subsequently added the relevant data in the Table 1. In addition, a small paragraph has been written in the manuscript accordingly to explain the data, i.e., on pages 9 and 10 (highlighted in yellow)
“On the basis of the THI score changes pre-and post-sound masking intervention (i.e., equal or greater than7 points), fifty-one participants were entered in the effective group, whereas the remaining 51 participants were in the non-effective group. Table 1 shows comparisons of related factors between effective and ineffective groups, respectively. In the present study, age and gender factors were compared between the effective group and the non-effective group using Student t-test and Chi-square test, respectively. Student t-test showed that participants in the effective group were significantly younger than those in the non-effective group ($t=-2.55$, $p=0.012$). However, there was no significant difference in gender between these two groups ($x2=2.53$, $df=1$, $p=0.163$).”
“Furthermore, as shown in Table 1, the THI score of pre-sound masking intervention was used as baseline measurement. The averaged THI scores of pre-sound masking intervention were 54.04 (SD=18.45) and 37.57 (SD=21.86) for the effective and non-effective groups, respectively. Significantly lower THI score of pre-sound masking intervention was found in the non-effective group than that in the effective group ($t=4.11$, $p<0.001$). However, there was no significant difference in the THI score of post-sound masking intervention between two groups. As a result, significant difference of the THI score changes between pre and post treatments was found when comparing two groups (19.10 vs. 0.98, $t=12.54$, $p<0.001$). Further analysis showed that THI scores were significantly reduced in the effective group ($t=-14.07$, $p<0.001$), whereas no significant reduction in the THI scores was found in the non-effective group in comparison of THI score between pre- and post- sound masking ($t=-1.98$, $p=0.054$).”

7. Results. Can you explain why you choose to decided to look at the difference in hearing threshold in tinnitus and non-tinnitus ears? Moreover, I think there is more to say about Table 1 than just what is written here.

Response：
Thank you for this comment. We feel this comment is important and essential. In order to clarify whether the hearing threshold of non-tinnitus ears may contribute to the effectiveness of sound masking intervention and the peripheral auditory status of non-tinnitus ears during tinnitus suffer, difference in hearing threshold in tinnitus and non-tinnitus ears was analyzed. As suggested, we have amended the paragraphs in the manuscript accordingly, i.e., on pages 9 and 10 (highlighted in yellow)
“On the basis of the THI score changes pre-and post-sound masking intervention (i.e., equal or greater than7 points), fifty-one participants were entered in the effective group, whereas the remaining 51 participants were in the non-effective group. Table 1 shows comparisons of related factors between effective and ineffective groups, respectively. In the present study, age and gender factors were compared between the effective group and the non-effective group using Student t-test and Chi-square test, respectively. Student t-test showed that participants in the effective group were significantly younger than those in the non-effective group ($t=-2.55$, $p=0.012$). However, there was no significant difference in gender between these two groups ($x2=2.53$, $df=1$, $p=0.163$).
For the purpose of understanding the basic hearing status, the averaged pure tone hearing thresholds across frequencies from 125 Hz to 8000 Hz on tinnitus ears and non-tinnitus ears were analyzed in both effective and ineffective groups.

As shown in Figure 1, the hearing threshold of each frequency from 125 Hz to 8000 Hz revealed no significant differences between the two groups in both tinnitus ($p>0.05$) and non tinnitus ears ($p>0.05$). Significantly worse hearing threshold at each frequency in tinnitus ears were found in both effective ($p<0.05$) and ineffective groups ($p<0.05$) when compared to hearing threshold in non-tinnitus ears."
"Furthermore, as shown in Table 1, the THI score of pre-sound masking intervention was used as baseline measurement. The averaged THI scores of pre-sound masking intervention were 54.04 (SD=18.45) and 37.57 (SD=21.86) for the effective and non-effective groups, respectively. Significantly lower THI score of pre-sound masking intervention was found in the non-effective group than that in the effective group ($t=4.11$, $p<0.001$). However, there was no significant difference in the THI score of post-sound masking intervention between two groups. As a result, significant difference of the THI score changes between pre and post treatments was found when comparing two groups (19.10 vs. 0.98, $t=12.54$, $p<0.001$). Further analysis showed that THI scores were significantly reduced in the effective group ($t=-14.07$, $p<0.001$), whereas no significant reduction in the THI scores was found in the non-effective group in comparison of THI score between pre- and post- sound masking ($t=-1.98$, $p=0.054$)."

8. Results, Table 1. Tinnitus loudness: scale in dB or VAS-scale? Duration of tinnitus between 1-3 months is subacte, but the authors define chronic tinnitus as >1 months? This does not make sense. Hearing threshold (scale?) is a mean over which frequencies? Please clarify.

Response：
We apologize for the careless mistake and unclear descriptions regarding the tinnitus duration and calculation of hearing threshold. Tinnitus loudness was scale in dB. Chronic tinnitus was defined as longer than 3 months but not 1 month. We have corrected the figures in Table 1. The mean hearing threshold is the average of hearing sensitivity at the frequencies of 500, 1000, 2000 and 4000 Hz. To clarify this issue, we have revised relevant part, i.e., on pages 7-8 (highlighted in yellow)
"The mean hearing threshold (dB HL) is the average of hearing sensitivity at the frequencies of 500, 1000, 2000 and 4000 Hz."
"During the tinnitus pitch matching tests, the 9 audiometric frequencies between 125 Hz and 8.0 kHz (i.e., 125 Hz, 250 Hz, 500 Hz, 1.0 kHz, 2.0 kHz, 3.0 kHz, 4.0 kHz, 6.0 kHz, and 8.0kHz) were firstly used to roughly match the tinnitus pitch. Participants were initially asked to make a clear distinction between the tinnitus pitch perception and presented matching tones, and then they reported verbally whether the matching tone needed to go higher or lower until the exact matching tone or a close approximation to their tinnitus was obtained. The test tone was adjusted in a half-octave step. If there was no matching with a pure tone perceived by participants, narrow-band noise was used instead. When the matching frequency was found, the level was initially set to 5 dB above the measured audiometric threshold to find an approximate tinnitus loudness level, then the level was adjusted in 1 dB step until the subject indicated that the tone matched the loudness of their tinnitus."

9. Results. Please clarify why certain variables (age, audiogram configuration, proper treatment THI and hearing threshold) were selected for the multivariate logistic regression model If this was based on significance as shown in Table 1, then why was ' hearing threshold' added ($p=0.65$)?

Response：
Thank you for this comment. We feel this comment is important. We apologized for including this non-significant factor (i.e., hearing threshold,$p=0.65$) into multivariate logistic regression analysis. As a result, we have removed the factor of hearing threshold from the multivariate logistic regression and re-analyzed the data. The revised statistical results were summarized in the amended Table 2.

10. Results. The authors describe that following the multivariate logistic regression analysis, age , flat audiogram and THI score are significantly associated with treatment outcome. However, ' flat audiograms' is not significantly related with a p value >0.056 (alpha was set at 0.05 according to the authors). So I agree that this is borderline significant, but not significant based on the stated alpha and with a very broad confidence interval, probably caused by a low patient group, which makes me question the significancy even more. I think that it is not correct to conclude that ' flat audiogram' is positively associated with successful treatment.

Response：

Thank you for this comment. We feel this comment is important and crucial. We apologized for the unclear description of the method and results sections. According to the logistic regression analysis of the associated factors, audiogram configurations was defined as a categorical variable with four categories and estimates of each pair of comparisons were obtained using CLASS and CONTRAST statements of SAS PROC LOGISTIC program. After careful reanalysis of the data, audiogram configurations was found to be an independent factor of treatment (p=0.027). And only significant results were found when compared between flat audiogram and HFSS (OR=5.45, 95% CI: 1.67, 17.86, p=0.005). No significant results were found between flat audiogram and others (OR=7.06, 95% CI: 0.95, 52.20, p=0.056), HFGS and HFSS (OR=2.24, 95% CI: 0.56, 8.93, p=0.252), Others and HFSS (OR=1.05, 95% CI: 0.14, 7.89, p=0.960).

However, even though significant effects were found that audiogram configuration was significantly related to the effectiveness of intensive sound masking treatment, this result should be interpreted with cautious due to the retrospective nature of this study. A future randomized control study is needed to provide further evidence for prognostic factors (e.g. audiometric configuration, age, THI score) and their contributing to the effectiveness of tinnitus interventions.

To clarify these issues, we have revised the table 2 and relevant paragraphs across different sections, i.e., on pages 9,11 and 14 (highlighted in yellow)

“Multivariate logistic regression models were performed to assess the independent association of demographic and tinnitus relevant factors with effective therapy. ”

“Because audiometric configuration variable was categorised as four sub-groups, estimates of pair comparisons were subsequently performed.”

“Audiometric configuration factor was also found to be an independent factor associated with the effectiveness of the sound masking treatment (p=0.027). Further analysis showed flat audiometric configuration was 5.45 times more likely to be successfully intervention when compared to those with HFSS configurations (OR=5.45, 95% CI: 1.67, 17.86, p=0.005). However, no significant results were found when conducting the pair comparisons of other audiometric configurations. ”

“Conclusion

This retrospective study suggests that factors of audiometric configuration, age, and THI scores pre-treatment are predictive of beneficial sound masking outcomes. Further analysis indicates that tinnitus patients with flat audiogram configuration are more likely to achieve successfully intervention when compared to those with high-frequency steeply sloping audiograms. Gender, tinnitus laterality, duration and hearing threshold are not related to the effectiveness of intensive sound masking treatment. However, these results should be interpreted with caution due to the retrospective nature of this study. A future randomized control study is needed to provide further evidence for prognostic factors (e.g. audiometric configuration, age, THI score) and their contributing to the effectiveness of tinnitus interventions.”

11. Discussion. The authors state rather strongly that a flat audiogram was more likely to respond positively to sound masking therapy, as I mentioned above: I don't think it is correct to state this so firmly. Moreover, I miss a discussion about WHY this would be the case. Is there a possible etiological underlying factor to explain such a finding? And are the ' flat audiograms' possibly norming hearing levels, or lowered hearing levels? Furthermore, authors report that younger patients had more benefit of sound masking. They stat that ' it indicates that your tinnitus subjects are more likely to have a greater need for alleviating stress by using sound masking'. Are you suggestion a placebo effect here?

Response：
Thank you for this comment. We totally agree with these comments and apologize for the unclear statements to explain and discuss the results clearly. To further clarify these issues raised by the reviewer, with re-analyzed results, we have re-written the relevant parts in the discussion section. In the meantime, we have revised the conclusion section with more accurate interpretation of our results, , i.e., on page 12 ((highlighted in yellow).
“In the present study, participants with flat audiogram were more likely to respond positively to intensive sound masking intervention compared with those with a HFSS audiogram but unrelated to average hearing threshold. To our best knowledge, no previous study investigated the influence of audiometric configuration on the outcome of tinnitus intervention, even though the study by Chang et al.14 showed that patients with a flat pattern audiogram benefited more from hearing aids compared to those with rising or decreasing audiogram in terms of improvement of psychological handicap and quality of life. The present result is likely due to tinnitus characteristics together with their associated hearing status. By recording Transient Otoacoustic Emiisions (TEOAEs), Kim et al.1 found that normal TEOAE rates were significantly higher in tinnitus patients with flat audiogram than those in the HFGS and HFSS groups. Moreover, tinnitus patients with HFSS had significantly lower response rates of TEOAEs at 3, 4 and 6 kHz than tinnitus patients with flat audiogram. Therefore, better hearing status in tinnitus patients with flat audiogram may be underlying factor, which is consistent with the previous finding reported by Theodoroff et al.7. However, this result should be interpreted with cautious due to the retrospective nature of this study. The further prospective research is needed using systematic approaches, such as randomized controlled trail15”
In addition, to answer the question of “And are the ' flat audiograms' possibly norming hearing levels, or lowered hearing levels?”. Our answer is all subjects with flat audiogram had mild to severe sensorineural hearing loss.

12. Conclusion: I think there is no sufficient statistical base to conclude that a flat audiogram is related with success of sound masking treatment.

Response：
Thank you for this comment. We totally agree with this comment and apologize for the unclear statement of the results. As mentioned in issues 10 and 11, we have revised conclusion section with more accurate interpretation of our results, , i.e., on page 14 (highlighted in yellow)
“This retrospective study suggests that factors of audiometric configuration, age, and THI scores pre-treatment are predictive of beneficial sound masking outcomes. Further analysis indicates that tinnitus patients with flat audiogram configuration are more likely to achieve successfully intervention when compared to those with high-frequency steeply sloping audiograms. Gender, tinnitus laterality, duration and hearing threshold are not related to the effectiveness of intensive sound masking treatment. However, these results should be interpreted with caution due to the retrospective nature of this study. A future randomized control study is needed to provide further evidence for prognostic factors (e.g. audiometric configuration, age, THI score) and their contributing to the effectiveness of tinnitus interventions.”

VERSION 2 – REVIEW

REVIEWER	Minke van den Berge University of Groningen, University Medical Center Groningen, ENT-departement, The Netherlands
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	The authors have adressed the comments of the reviewers in an acceptable way, so that the quality of the manuscript has approved significantly.

VERSION 2 – AUTHOR RESPONSE

Reply to Reviewer 2
Reviewer Name: Minke van den Berge
Institution and Country: University of Groningen, University Medical Center Groningen, ENT-departement, The Netherlands

General comment
Please state any competing interests or state 'None declared': None declared

Response:
Thank you for your comment. We have revised this sentence in the manuscript accordingly. (i.e., on page 15, highlighted in yellow)
"Competing interests: None declared"