tDCS and Tinnitus: A meta-analytic exploration into efficacy and optimization

Alexander Cates
Northwestern University

Evan Davies
University of Wisconsin

Millions of Americans suffer from tinnitus, or ringing of the ears. Despite its prevalence, treatment for tinnitus is limited, with most approaches focusing on making the symptoms tolerable, instead of treating the underlying neurological causes. Recently however, brain stimulation techniques, such as transcranial direct current stimulation (tDCS), have emerged offering a new method to interact with the brain and offering hope as a new approach to treating the underlying causes of tinnitus, not just making the symptoms tolerable. In the present meta-analysis, we analyzed the results from 17 controlled trials and 5 uncontrolled case studies to determine the efficacy of tDCS for treating tinnitus. Additionally, we performed sub-analyses to test how different tDCS parameters may alter the efficacy of treatment. Overall, we found a small but significant effect (Overall Hedges g of 0.17 (95% CI 0.09-0.25)) of tDCS on tinnitus symptoms. However, mechanistically we found that targeting the DLPFC improved symptoms significantly more than other targets, including targeting the auditory cortex directly. This along with the subjective outcome measures currently available, suggest that while tDCS does offer a benefit to treating the symptoms, it does not appear to treat any underlying causes. It is the opinion of the authors therefore that tDCS should be used in addition to traditional interventions to make the symptoms more tolerable. As covered in the discussion, future research should explore more objective measures of tinnitus in order to better assess the efficacy of tDCS and other brain stimulation methods, with the hope of developing a causal treatment of tinnitus.

Practical significance: tDCS offers a small but significant benefit for treating subjective tinnitus and should therefore be considered in addition to traditional therapies as a method to manage tinnitus symptoms..

Data, analysis code, supplementary material: <https://osf.io/zsca4/>

Keywords: tinnitus, tDCS, brain stimulation, auditory disorders

1. Introduction:

Subjective Tinnitus, characterized by a phantom auditory percept, is one of the most common neurological disorders in the United States. An estimated 15% of the general population perceives tinnitus with 25% of tinnitus patients reporting severe distress due to the phantom tones (To, Ost, Hart, De Ridder, & Vanneste, 2017). The management of tinnitus alone costs the United Kingdom healthcare system over \$900 million per year (Stockdale et al., 2017). Tinnitus patients also

report high comorbidity rates with anxiety, depression, insomnia and severe distress (Vanneste & De Ridder, 2011). Despite all of this, current interventions into treating tinnitus are limited, often focusing on psychological interventions which try to improve the tolerability of tinnitus without changing the underlying neurology. Therefore, new techniques are needed if these patients are to get the help and treatment they need.

There are multiple underlying mechanisms which could cause tinnitus. These mechanisms can be separated into three sources: Cochlear damage, auditory cortex dysfunction, and psychosomatic sensitivity in the frontal cortex (Han et al. 2009). Cochlear damage is the most common cause and often initiates the other downstream causes. Sudden or repeated loud noises damage the inner and/or outer hair cells of the cochlea, causing either a loss of signaling or dysfunction in the signaling of cochlear afferents up the auditory stream and

Alexander Cates, Physical Therapy and Human Movement Sciences, Northwestern University; Evan Davies, Audiology Department, University of Wisconsin.

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Correspondence concerning this paper should be addressed to Alexander Cates, Physical Therapy and Human Movement Sciences, Northwestern University,
Email: alexandercates2023@u.northwestern.edu

creating the phantom precepts. In many cases, the cochlear damage is temporary, but can cause long lasting changes to the auditory cortex, such as altering cortical excitability or reorganizing the tonotopic map along edge frequencies. The cortical changes lead to an oversensitivity to tones that previously would have been ignored, leading to the phantom percepts. Finally, the brain can sometimes compensate for the phantom tones by shifting attention away from the sound, similar to tuning out a fan. Such attentional shifts require cognitive control and a deficit in this ability often leads to the third cause of tinnitus, psychosomatic sensitivity. All three mechanisms offer potential intervention points to help with the management and treatment of tinnitus symptoms.

Transcranial direct current stimulation (tDCS) has emerged as a promising, non-invasive neurological intervention which may offer a possible treatment for Tinnitus. By applying a small electric current to the scalp, tDCS is able to modulate the cortical excitability (Jaberzadeh, Bastani, Zoghi, Morgan, & Fitzgerald, 2015) and synaptic plasticity (Kronberg, Rahman, Lafon, Bikson, & Parra, 2019; Monai et al., 2016) of the underlying tissue. The use of tDCS has exploded in popularity in recent years with thousands of papers being published on a wide range of reported effects. Many studies have examined the efficacy of tDCS on disorders comorbid with tinnitus, including anxiety (Sagliano, Atripaldi, De Vita, D'Olimpio, & Trojano, 2019), depression (Brunoni, Ferrucci, Fregni, Boggio, & Priori, 2012), and insomnia (Frase et al., 2019). Given the comorbidities, it is not surprising that researchers have also looked at the possible benefits of tDCS for tinnitus relief as well.

Two possible mechanisms have emerged for how tDCS may best be used to help treat tinnitus, namely targeting the auditory cortex dysfunction and the frontal cortex cognitive control. Targeting the auditory cortex relies on altering the plasticity of the region with tDCS as an attempt to return the sensitivity to incoming stimuli to normal levels. Similar approaches have shown promise for treating other phantom sensory disorders such as phantom limb pain (Bolognini et al. 2015). The benefit of this approach is that it would be effective for both cochlear damage and auditory dysfunction, as the auditory cortex is higher upstream than the cochlea. Additionally, improving auditory cortex function offers a potential causal treatment by removing the phantom tone entirely.

The second approach targets the dorsolateral prefrontal cortex (DLPFC) in order to improve cognitive control (Nelson et al., 2016). By stimulating the DLPFC, users may be better able to control where their attention is placed and, similar to cognitive behavioral therapy, better ignore the phantom tones characteristic of tinnitus. Such an approach may augment current cognitive behavioral therapy approaches, which are the current standard treatment for tinnitus (Hesser et al. 2011). The approach of combining tDCS with cognitive behavioral therapy is currently being tested on disorders comorbid with tinnitus such as depression (Bajbouj et al., 2017; Welch et al., 2018). Should this approach prove effective, it would be an easy improvement to current therapeutic options.

The present paper provides a comprehensive meta-analysis of the current research using tDCS to treat tinnitus. More importantly, the present paper hopes to provide insight into the best protocol for tDCS through an extensive parameter exploration comparing treatment outcomes.

2. Methods

2.1 Literature Search

To locate relevant articles a literature search was performed in Pubmed, web of science, and the open grey database from their inception to April 2019. Search terms combined stimulation type ("transcranial direct current stimulation", "tDCS", "brain stimulation", or "transcranial stimulation") with "tinnitus". In addition to the database searches, eligible studies were selected from the reference lists of selected studies (backward looking) as well as studies which cited selected studies (forward looking).

2.2 Selection Criteria

Studies selected used transcranial direct current stimulation (tDCS) to treat tinnitus. To be comprehensive, both controlled trials and uncontrolled case studies have been included and analyzed separately. Studies needed to include the mean, standard deviation, and sample size for all groups (either written in the text or in an image from which the data could be extracted as explained in section 2.4 Data Extraction) in order to be included in the analysis.

2.3 Outcome measures

Three primary outcome measures were commonly used amongst all papers and thus will be reported here.

The Tinnitus Handicap Inventory (THI) (Newman, Jacobson, & Spitzer, 1996) is a 25 item, self report measure of the distress caused by or associated with a patient's tinnitus. Each item is scored from 0-4 with the total score ranging from 0 (no handicap) to 100 (catastrophic handicap).

The Tinnitus Handicap Questionnaire (Kuk, Tyler, Russell, & Jordan, 1990) is a 27 item, self report measure which also measures the distress caused by or associated with a patient's tinnitus. Each item is scored from 0-100 with all scores averaged at the end to produce a percent handicap score.

Finally, a visual analog scale (VAS) (Adamchic, Langguth, Hauptmann, & Tass, 2012) is a common, validated measure for both loudness and distress (annoyance) associated with tinnitus.

2.4 Data Extraction

Mean, standard deviation, and sample size were taken to calculate effect size for inclusion in the meta-analysis. When not directly reported in the text, these values were extracted from figures using a digital plot analyzer (Rohtagi 2019) which pulls data points from graphs based on pixel locations. In addition to the effect size, the following stimulation parameters were extracted when reported: stimulation amplitude, duration, montage, current density, and number of stimulation sessions. In cases where a study reported the results of multiple groups, each group was separated and treated as a separate study. Finally, to provide insight towards the best possible benefit of tDCS, the goal of the intervention (reducing loudness or distress) was extracted for analysis.

2.5 Data Analysis

For controlled trials, following data extraction a hedges g effect size, along with associated standard error was calculated for each study. All effect sizes, standard errors, sample sizes, and 95% confidence intervals were then used for all meta analysis calculations and parameter comparisons. All meta analysis calculations and comparisons were done using a custom python script based on the Meta Essentials toolbox (Suurmond, van Rhee, & Hak, 2017).

Study	Number of biases	Risk Details
Lee 2019	3/6	Selection bias, performance bias, detection bias
Teismann 2014	3/6	Performance bias, detection bias, attrition bias
Abtahi 2018	1/6	Detection bias
Garin 2011	2/6	Detection bias, attrition bias
Yadollahpour 2018	3/6	Detection bias, attrition bias, reporting bias
Faber 2012	1/6	Detection bias
To 2017	2/6	Performance bias, Detection bias
Shekhawat 2018	1/6	Detection bias
De Ridder 2012	4/6	Selection bias, performance bias, detection bias
Vanneste 2013	2/6	Performance bias, detection bias
Vanneste 2010	4/6	Selection bias, performance bias, detection bias, attrition bias
Vanneste 2011	3/6	Selection Bias, performance bias, detection bias
Henin 2016	3/6	Performance bias, detection bias, attrition bias
Hyvarinen 2016	3/6	Performance bias, detection bias, other bias
Pal 2015	2/6	Detection bias, attrition bias
Shekhawat 2015	3/6	Performance bias, detection bias, attrition bias
Forough 2016	2/6	Detection bias, attrition bias
Shekhawat 2014	1/6	Detection bias

Table 1. Bias Assessment: Table 1 lists each study with the number of biases that had a medium or high risk (out of a possible 6 biases).

For uncontrolled case studies, the mean and standard error of the percent change from baseline was calculated for each study. A weighted average (based on sample size) was used to calculate the combined mean percent change, while the combined standard error was calculated by first calculating each study's summed squared error (based on the standard deviation), then recalculating the total standard deviation based on the total summed

squared error and the total sample size. A 95% confidence interval was calculated for plotting all results.

3. Results

3.1 Risk of bias assessment

A risk of bias assessment was conducted on all controlled trials and is reported below (Table 1). Overall, while most studies had an overall low risk of bias, due to the self report nature of the metrics, all studies had a medium risk of detection bias. Additionally, a few of the studies were open label and as such did not blind participants or personnel. To offer the most complete picture possible and because all risks were deemed to have a low overall impact on the outcome, the authors chose to include all studies in the further analysis.

3.2 Overall Results

Overall, tDCS provided a significant benefit in reducing tinnitus symptoms (unadjusted mean of .26, 95% confidence interval 0.18-0.34, $p < 0.001$) found across all studies (figure 1). Additionally, while an Egger's regression did reveal a publication bias ($p < .001$), after correcting with the trim and fill method (supplementary figure 1), there was still a significant combined effect (adjusted mean .17, 95% confidence interval 0.09 – 0.25). This effect was mirrored in the case studies (supplementary figure 2) which found a 13.5% improvement (95% confidence interval: 8.6-18.4%). All data is available at: <https://osf.io/zsca4/>

3.3 Stimulation Amplitude

Stimulating at 1mA, 1.5mA, or 2mA all had positive effects for treating tinnitus (supplementary figure 3a). Additionally, while only 1mA and 1.5mA reached a significant effect size, none of the three stimulation intensities significantly differed from each other. That said, the overall trend of 1.5 mA being the best is supported by the case studies (supplementary figure 3b) where only studies which

Figure 1. Overall Results of RCTs: Forest plot showing results of all studies and groups with a control group. Overall effect size found is 0.17 (95% CI 0.09-0.25)

Figure 2: Effect of stimulation target on distress and loudness: Both graphs show the effect of tDCS montage on distress and loudness as compared amongst controlled (left) and case (right) studies. In both cases, targeting the DLPFC out performed targeting the LTA for both distress and loudness.

used 1.5 mA provided a significant improvement in tinnitus symptoms.

3.4 Stimulation Montage

For the purpose of comparison, the different montages have been divided into 2 groups based on the area being targeted (LTA or DLPFC) in the stimulation. The results suggest a difference between the different areas being targeted. While targeting DLPFC or LTA provided a significant positive effect size, targeting DLPFC provided a larger effect (supplementary figure 4a). The difference between the two targets is exaggerated within the case studies (supplementary figure 4b), with DLPFC providing significantly more benefit than targeting LTA (which did not produce a significant change from baseline).

3.5 Number of stimulation sessions

Overall, there was an increase in effect size with number of stimulation sessions completed (supplementary figure 5). However, with a $p = 0.15$ and R^2 of 0.065, it is not possible to reject the null and suggest that the number of sessions completed significantly affected treatment outcomes. There was not enough variety in number of sessions amongst the case studies (all but 2 studies included only one session) to be considered relevant and was therefore not included.

3.6 Treatment outcome/measure

Due to the two different metrics of treatment effectiveness, we decided to compare the two to see

if tDCS helped one over the other (supplementary figure 6). No significant difference was found for improving loudness vs distress of the tinnitus, however both were significantly improved when compared to sham. The same result was found within the case studies.

3.7 Montage $\times$ treatment outcome

Finally, in order to test whether the different target areas had specific benefits for the different treatment outcomes, we separated them into 4 groups (although none of the case studies contained both an LTA target and a measure of distress, therefore only 3 groups are reported here). While not a clean separation, there is a significant difference between DLPFC vs LTA when focused on distress (with RCT's) and in loudness (with case studies). More importantly, there is an overall grouping of DLPFC being more effective than LTA regardless of target benefit, mirroring the results shown in section 3.5 (figure 2).

4. Discussion

Overall, the present meta analysis supports the use of tDCS to treat the symptoms of tinnitus. In particular, the subgroup analysis comes out in support of targeting the DLPFC, which provided a significant benefit compared to targeting the LTA, regardless of the treatment goal. Additionally, no significant difference was found based on the number of stimulation sessions or the intensity of stimulation, disputing ideas that more is better. Finally, and encouragingly, the effects were the

same for loudness and distress, pointing to the interrelatedness of the two outcome measures and the potential to benefit either. The rest of the discussion will focus on the results of the subgroup analyses and what they may mean for optimizing tinnitus treatment outcomes with tDCS.

A primary takeaway from the present meta analytic study is the effect of montage, namely that targeting the DLPFC yielded better results than the LTA, regardless of the treatment outcome. This effect goes against the author's expectations that the benefits of targeting DLPFC would be focused on distress while the benefits of targeting the LTA would be focused on loudness. One explanation for this may be that the two treatment outcomes are too interrelated to be separately measured by the self report metrics currently used. Alternatively, while the effects of targeting the DLPFC have been shown to have a more immediate effect (as may be captured here), the effects of targeting the LTA may require a longer treatment procedure, possibly paired with acoustic retraining to take advantage of the effects of tDCS on synaptic plasticity. While the authors do not want to discourage research into targeting LTA, the results presented here suggest that clinical treatment should focus on targeting DLPFC for now.

Another takeaway was the lack of effect of increasing current or the number of treatment sessions on the outcome measures, suggesting that more is not better. The similarity of effects from the different current amplitudes is counter to the reports in the literature (Joos, De Ridder, Van de Heyning, & Vanneste, 2014; Shekhawat, Stinear, & Searchfield, 2013), not only finding no significant difference between the different amplitudes, but numerically the lower amplitudes performed better. One possibility is that the system is being saturated and thus the additional current does not supply any additional benefit. The lack of effect of the number of sessions, similarly, may point to a saturation of the benefit and thus that there is not an additive effect from additional sessions. However, there was also not a drop off and, as the studies included did not measure treatment outcomes beyond the intervention period, this may suggest that the effects are both fleeting and repeatable. It may be that tDCS does not provide causal treatment for tinnitus but is able to provide temporary relief from its symptoms. Future research is needed to explore whether tDCS provides a temporary or lasting relief to tinnitus symptoms.

The present study was unable to compare the effects of stimulation duration or current density on treatment outcomes due to lack of available data. In a case study, Shekhawat and colleagues demonstrated a near linear benefit towards increasing the stimulation duration from 10 to 15 to 20 minutes (Shekhawat et al., 2013), but as the included RCTs all used 20 minutes, this comparison did not factor in to the present results. Additionally, many tDCS researchers have speculated on the relevance of current density on stimulation effectiveness; however, because all included studies used the same electrode size, the differences in current density reflect the differences in intensity reported above. Future research should further explore the role of current density and how it may modulate the effectiveness of tDCS for tinnitus treatment.

There are a few limitations with this study. First, as with any meta analysis, our conclusions are limited by the studies which have already been done. This manifests itself both in the questions we can ask (such as being unable to explore the effect of stimulation time or current density) but also in the reliability of the result. Because we did find evidence of a publication bias, there is a risk that there are more studies that were done and were not published which would change the results. We tried to control for this with the trim and fill method, but it should be noted none the less. Additionally, we prioritized quantity over quality when we were selecting our studies, with the goal of providing a complete picture of the literature available. That said, methodological problems, such as the reliance on self report metrics, reduces the reliability of the result and controlling for this in the future may shift the overall effect in either direction. There is a need for objective measures of this subjective disorder, and the development of such methods would significantly improve the quality of the research. However, despite these limitations, the authors believe that this meta analysis accurately portrays the current state of the research on tDCS and tinnitus, while also proposing interesting avenues for future research.

5. Conclusion

In conclusion, tDCS offers a small but significant benefit for providing temporary relief from tinnitus symptoms. In particular, targeting the DLPFC offers the most benefit, regardless of the stimulation intensity or the treatment goal. While the present

meta analysis does not support the hope that tDCS may treat the cause of tinnitus, it is nevertheless the opinion of the authors that due to the clean safety profile of tDCS that clinicians should consider it as a viable intervention for temporary relief from the symptoms of tinnitus, particularly in combination with traditional therapy. However additional research into long term benefits of tDCS for tinnitus is needed before it should be considered a solution.

6. Data Availability

The meta-analytic database, analysis code, and supplemental material for this paper are available online as (Cates & Davies, 2020, <https://osf.io/zsca4/>). These materials include (1) the study-level data that constitute the raw data for all the meta-analyses reported in this paper (sample sizes, uncorrected means and standard deviations), (2) python code to reproduce all results reported in the paper and produce forest plots for each meta-analysis.

7. References

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