

# **”Research Prize Tinnitus & Hearing“ 2024 - Application**

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**Habilitation title: “Auditory, neural, and psychological signatures of temporary tinnitus suppression”**

**Habilitation date: 28<sup>th</sup> September 2022**

Tinnitus, the ringing or noise many people occasionally or persistently perceive in their ears, is a multifaceted phenomenon explored across auditory, neural, and psychological dimensions. My habilitation project aimed to craft a comprehensive understanding of this enigmatic condition, with implications both for advancing basic scientific knowledge and for improving therapeutic approaches.

Building upon the foundations of my previous research, the current habilitation delves deeper into the complexities of tinnitus. It does so not just from an auditory perspective but also from a neural and psychological one.

One of the critical takeaways from my research is the efficacy of amplitude-modulated tone stimuli, especially around 10 Hz, in suppressing tinnitus. This discovery sheds light on potential treatments, specifically when matched with the nature of the tinnitus: either tonal or noise-like. Such personalized interventions could offer relief to a significant portion of tinnitus sufferers, emphasizing the importance of this research.

Furthermore, the correlation between tinnitus suppression and changes in cortical neurophysiology was another groundbreaking revelation. The normalization of cortical neurophysiology (as evidenced by resting-state EEG) in tinnitus patients, during (acoustic) tinnitus suppression, provides compelling evidence of the neural basis of this condition.

The habilitation encompassed several studies:

**Tinnitus Matching:** A rapid and reliable methodology for tinnitus matching was developed by head-to-head comparison of the most prominent existing approaches, laying the groundwork for my further studies but also for acoustic interventions in tinnitus.

**Tonal Stimulation:** By deploying 10/40 Hz amplitude-modulated tones at the tinnitus frequency, I discovered their superiority in suppressing tinnitus compared to stationary sounds while being well-tolerated by the participants.

**Noise Stimulation:** The efficacy of amplitude-modulated noise around the tinnitus frequency further refined the distinction between tonal and noise-like tinnitus, additionally resulting in an individualized noise-matching method for those with a noise-like tinnitus.

**Neurophysiological Correlates:** A critical finding was the transient normalization towards a healthy brain state reflected in resting-state EEG during tinnitus suppression, indicating a direct connection between tinnitus and neural activity in the auditory cortex. Further observations, such as the long-term suppression post-stimulation in about 5% of the study sample, gender differences in response to the sounds (women seem to profit more), and the absence of psychological predictors like personality, enrich the scope and applicability of the findings.

## Summary

- Amplitude-modulated pure tone stimuli, especially around 10 Hz, result in greater suppression than unmodulated stimuli.
- Pure tones are more effective for tonal tinnitus, while noise is more effective for noise-like tinnitus.
- Suppression is correlated with evaluation; the stimuli are well-tolerated.
- Induced tinnitus suppression leads to a normalization of cortical neurophysiology (resting-state EEG) in tinnitus patients.

# Patrick Neff, PD Dr.

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## Education

26.9.2022	Habilitation, Experimental Psychiatry, Faculty of Medicine, University of Regensburg, Supervisor: Prof. Dr. Rainer Rupprecht
25.8.2017	PhD in Neuropsychology, University of Zürich, Thesis Title: ‘Neuroplasticity and -modulation in Tinnitus: Understanding Brain Imprints and Suppression of a Phantom Sound’, Supervisor: Prof. Dr. Martin Meyer
9.2012-9.2014	MSc in Neuropsychology, University of Zürich, Minors: General Linguistics, Neuroinformatics
9.2008-9.2012	BSc in Psychology, University of Zürich, Minors: General Linguistics, Neuroinformatics, Film Studies

## Current and past positions

10.2022 - current	Scientific Project and Group Lead, Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, University of Zurich
10.2021-10.2023	Postdoctoral Research Fellow, Medical Image Processing lab (MIPlab), Ecole Polytechnique Federale de Genève (EPFL), Switzerland (SNF Postdoc Return), Supervisor: Prof. Dr. Dimitri Van De Ville
8.2019-current	Postdoctoral Research Fellow, Center for Cognitive Neurosciences, University of Salzburg, Austria (SNF Postdoc Mobility), Supervisor: Prof. Dr. Nathan Weisz
10.2018-9.2022	Postdoctoral Research Fellow and Vice Group Leader, E-Health Workgroup, University of Regensburg, Germany (SNF Early Postdoc and Postdoc Mobility), Supervisor: Prof. Dr. Winfried Schlee
10.2017-current	Postdoctoral Research Fellow, Department of Psychiatry and Psychotherapy, Center for Neuromodulation and Multidisciplinary Tinnitus Clinic, University of Regensburg, Germany (SNF Early Postdoc and Postdoc Mobility), Supervisor: Prof. Dr. Berthold Langguth
10.2017-1.2021	Postdoctoral Research Fellow and Lecturer, URPP Dynamics of Healthy Aging, University of Zurich, Switzerland
10.2014-9.2017	Doctoral Student, Neuroplasticity and Learning in the Healthy Aging Brain, URPP Dynamics of Healthy Aging, Department of Psychology, University of Zürich, Supervisor: Prof. Dr. Martin Meyer
5.2014-11.2015	Research Fellow (20%), Institute for Computer Music and Sound Technology, University of the Arts, Zürich, Supervisor: Prof. Dr. Germán Toro-Pérez

## Further Education and Certificates

University didactic diploma (habilitation), Good Clinical Practice (GCP) Level 2, eCRF Formbuilder and Data Management, MRI safety and operation L2

## Awards and Grants

2018

Research Award, PhD Thesis, Swiss Tinnitus League (STL)

2013

Research Grant, "Fonds zur Förderung des Akademischen Nachwuchses (FAN)", Züricher Universitätsverein (ZUNIV)

August 30, 2024

# Publikationsliste PD Dr. Patrick Neff

## 1. Originalarbeiten

1. Shabestari, P.S., Kleinjung, T., Schmidt, F., and **Neff, P.** (2024). Parameterized Cortical Power Spectra as a Novel Neural Feature for Real Time BCI. IEEE 12th Int. Winter Conf. Brain-Comput. Interface (BCI) 00, 1–5. <https://doi.org/10.1109/bci60775.2024.10480515>.
2. Sommerhalder, N., **Neff, P.**, Bureš, Z., Profant, O., Kleinjung, T., and Meyer, M. (2023). Deficient central mechanisms in tinnitus: Exploring the impact on speech comprehension and executive functions. Hearing Res. 440, 108914. <https://doi.org/10.1016/j.heares.2023.108914>.
3. Simoes, J., Bulla, J., **Neff, P.**, Pryss, R., Marcrum, S.C., Langguth, B., and Schlee, W. (2022). Daily Contributors of Tinnitus Loudness and Distress: An Ecological Momentary Assessment Study. Frontiers in Neuroscience. 16, 883665. <https://doi.org/10.3389/fnins.2022.883665>.
4. Basso, L., Boecking, B., **Neff, P.**, Brueggemann, P., Peters, E.M.J., and Mazurek, B. (2022). Hair-cortisol and hair-BDNF as biomarkers of tinnitus loudness and distress in chronic tinnitus. Scientific Reports, 12, 1934. <https://doi.org/10.1038/s41598-022-04811-0>.
5. Isler, B., Burg, N. von, Kleinjung, T., Meyer, M., Stämpfli, P., Zölch, N., and **Neff, P.** (2022). Lower glutamate and GABA levels in auditory cortex of tinnitus patients: a 2D-JPRESS MR spectroscopy study. Scientific Reports, 12, 4068. <https://doi.org/10.1038/s41598-022-07835-8>.
6. Basso, L., Boecking, B., **Neff, P.**, Brueggemann, P., El-Ahmad, L., Brasanac, J., Rose, M., Gold, S.M., and Mazurek, B. (2022). Negative Associations of Stress and Anxiety Levels With Cytotoxic and Regulatory Natural Killer Cell Frequency in Chronic Tinnitus. Frontiers in Psychology 13, 871822. <https://doi.org/10.3389/fpsyg.2022.871822>.
7. Basso, L., Boecking, B., **Neff, P.**, Brueggemann, P., Mazurek, B., and Peters, E.M.J. (2022). Psychological Treatment Effects Unrelated to Hair-Cortisol and Hair-BDNF Levels in Chronic Tinnitus. Frontiers Psychiatry 13, 764368. <https://doi.org/10.3389/fpsyg.2022.764368>.
8. Schlee, W., **Neff, P.**, Simoes, J., Langguth, B., Schoisswohl, S., Steinberger, H., Norman, M., Spiliopoulou, M., Schobel, J., Hannemann, R., et al. (2022). Smartphone-Guided Educational Counseling and Self-Help for Chronic Tinnitus. Journal of clinical medicine 11, 1825. <https://doi.org/10.3390/jcm11071825>.
9. Allgaier, J., **Neff, P.**, Schlee, W., Schoisswohl, S., and Pryss, R. (2021). Deep Learning End-to-End Approach for the Prediction of Tinnitus based on EEG Data. 2021 43rd Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC) 00, 816–819. <https://doi.org/10.1109/embc46164.2021.9629964>.
10. Partyka, M., **Neff, P.**, Bacri, T., Michels, J., Weisz, N., and Schlee, W. (2021). Gender differentiates effects of acoustic stimulation in patients with tinnitus. Prog Brain Res 263, 25–57. <https://doi.org/10.1016/bs.pbr.2021.04.010>.
11. Schoisswohl, S., Schecklmann, M., Langguth, B., Schlee, W., and **Neff, P.** (2021). Neurophysiological correlates of residual inhibition in tinnitus: Hints for trait-like EEG power spectra. Clinical Neurophysiology 132/7, 1694–1707. <https://doi.org/10.1016/j.clinph.2021.03.038>.
12. Brueggemann, P., **Neff, P.K.A.**, Meyer, M., Riemer, N., Rose, M., and Mazurek, B. (2021). On the relationship between tinnitus distress, cognitive performance and aging. Prog Brain Res 262, 263–285. <https://doi.org/10.1016/bs.pbr.2021.01.028>.

13. **Neff, P.K.A.**, Schoisswohl, S., Simoes, J., Staudinger, S., Langguth, B., Schecklmann, M., and Schlee, W. (2021). Prolonged tinnitus suppression after short-term acoustic stimulation. *Prog Brain Res* 262, 159–174. <https://doi.org/10.1016/bs.pbr.2021.02.004>.
14. **Neff, P.**, Simões, J., Psatha, S., Nyamaa, A., Boecking, B., Rausch, L., Dettling-Papargyris, J., Funk, C., Brueggemann, P., and Mazurek, B. (2021). The impact of tinnitus distress on cognition. *Scientific Reports* 11, 2243. <https://doi.org/10.1038/s41598-021-81728-0>.
15. Simões, J.P., **Neff, P.K.A.**, Langguth, B., Schlee, W., and Schecklmann, M. (2021). The progression of chronic tinnitus over the years. *Scientific Reports* 11, 4162. <https://doi.org/10.1038/s41598-021-83068-5>.
16. Güntensperger, D., Kleinjung, T., **Neff, P.**, Thüring, C., and Meyer, M. (2020). Combining neurofeedback with source estimation: Evaluation of an sLORETA neurofeedback protocol for chronic tinnitus treatment. *Restorative neurology and neuroscience* 38, 283–299. <https://doi.org/10.3233/rnn-200992>.
17. Beierle, F., Probst, T., Allemand, M., Zimmermann, J., Pryss, R., **Neff, P.**, Schlee, W., Stieger, S., and Budimir, S. (2020). Frequency and Duration of Daily Smartphone Usage in Relation to Personality Traits. *Digital Psychology* 1, 20–28. <https://doi.org/10.24989/dp.v1i1.1821>.
18. Hafner, A., Schoisswohl, S., Simoes, J., Schlee, W., Schecklmann, M., Langguth, B., and **Neff, P.** (2020). Impact of personality on acoustic tinnitus suppression and emotional reaction to stimuli sounds. *Prog Brain Res* 260, 187–203. <https://doi.org/10.1016/bs.pbr.2020.08.004>.
19. Mehdi, M., Stach, M., Riha, C., **Neff, P.**, Dode, A., Pryss, R., Schlee, W., Reichert, M., and Hauck, F.J. (2020). Smartphone and Mobile Health Apps for Tinnitus: Systematic Identification, Analysis, and Assessment. *JMIR mHealth and uHealth* 8, e21767. <https://doi.org/10.2196/21767>.
20. Schlee, W., Hølleland, S., Bulla, J., Simoes, J., **Neff, P.**, Schoisswohl, S., Woelflick, S., Schecklmann, M., Schiller, A., Staudinger, S., et al. (2020). The Effect of Environmental Stressors on Tinnitus: A Prospective Longitudinal Study on the Impact of the COVID-19 Pandemic. *Journal of clinical medicine* 9, 2756. <https://doi.org/10.3390/jcm9092756>.
21. Schleicher, M., Unnikrishnan, V., **Neff, P.**, Simoes, J., Probst, T., Pryss, R., Schlee, W., and Spiliopoulou, M. (2020). Understanding adherence to the recording of ecological momentary assessments in the example of tinnitus monitoring. *Scientific Reports* 10, 1–13. <https://doi.org/10.1038/s41598-020-79527-0>.
22. Schoisswohl, S., Arnds, J., Schecklmann, M., Langguth, B., Schlee, W., and **Neff, P.** (2019). Amplitude Modulated Noise for Tinnitus Suppression in Tonal and Noise-Like Tinnitus. *Audiology & neuro-otology* 24, 309–321. <https://doi.org/10.1159/000504593>.
23. Simoes, J., Schlee, W., Schecklmann, M., Langguth, B., Farahmand, D., and **Neff, P.** (2019). Big Five Personality Traits are Associated with Tinnitus Improvement Over Time. *Scientific Reports* 9, 1–9. <https://doi.org/10.1038/s41598-019-53845-4>.
24. **Neff, P.**, Langguth, B., Schecklmann, M., Hannemann, R., and Schlee, W. (2019). Comparing Three Established Methods for Tinnitus Pitch Matching With Respect to Reliability, Matching Duration, and Subjective Satisfaction. *Trends in hearing* 23, 2331216519887247. <https://doi.org/10.1177/2331216519887247>.
25. **Neff, P.**, Zielonka, L., Meyer, M., Langguth, B., Schecklmann, M., and Schlee, W. (2019). Comparison of Amplitude Modulated Sounds and Pure Tones at the Tinnitus Frequency: Residual Tinnitus Suppression and Stimulus Evaluation. *Trends in hearing* 23, 2331216519833841. <https://doi.org/10.1177/2331216519833841>.

26. Güntensperger, D., Thüring, C., Kleinjung, T., **Neff, P.**, and Meyer, M. (2019). Investigating the Efficacy of an Individualized Alpha/Delta Neurofeedback Protocol in the Treatment of Chronic Tinnitus. *Neural plasticity* 2019, 3540898–15. <https://doi.org/10.1155/2019/3540898>.
27. Simoes, J., **Neff, P.**, Schoisswohl, S., Bulla, J., Schecklmann, M., Harrison, S., Vesala, M., Langguth, B., and Schlee, W. (2019). Toward Personalized Tinnitus Treatment: An Exploratory Study Based on Internet Crowdsensing. *Frontiers in Public Health* 7, 157. <https://doi.org/10.3389/fpubh.2019.00157>.
28. Beierle, F., Tran, V.T., Allemand, M., **Neff, P.**, Schlee, W., Probst, T., Zimmermann, J., and Pryss, R. (2019). What data are smartphone users willing to share with researchers? *Journal of Ambient Intelligence and Humanized Computing* 134, 1–13. <https://doi.org/10.1007/s12652-019-01355-6>.
29. **Neff, P.**, Hemsley, C., Kraxner, F., Weidt, S., Kleinjung, T., and Meyer, M. (2018). Active listening to tinnitus and its relation to resting state EEG activity. *Neuroscience Letters* 694, 176–183. <https://doi.org/10.1016/j.neulet.2018.11.008>. **(shared first authorship)**
30. Beierle, F., Tran, V.T., Allemand, M., **Neff, P.**, Schlee, W., Probst, T., Pryss, R., and Zimmermann, J. (2018). Context Data Categories and Privacy Model for Mobile Data Collection Apps. *Procedia Computer Science* 134, 18–25. <https://doi.org/10.1016/j.procs.2018.07.139>.
31. Pryss, R., Probst, T., Schlee, W., Schobel, J., Langguth, B., **Neff, P.**, Spiliopoulou, M., and Reichert, M. (2018). Prospective crowdsensing versus retrospective ratings of tinnitus variability and tinnitus–stress associations based on the TrackYourTinnitus mobile platform. *International Journal of Data Science and Analytics* 43, 1–12. <https://doi.org/10.1007/s41060-018-0111-4>.
32. Jagoda, L., Giroud, N., **Neff, P.**, Kegel, A., Kleinjung, T., and Meyer, M. (2018). Speech perception in tinnitus is related to individual distress level - A neurophysiological study. *Hearing Res* 367, 48–58. <https://doi.org/10.1016/j.heares.2018.07.001>.
33. **Neff, P.**, Michels, J., Meyer, M., Schecklmann, M., Langguth, B., and Schlee, W. (2017). 10 Hz Amplitude Modulated Sounds Induce Short-Term Tinnitus Suppression. *Frontiers in Aging Neuroscience* 9, 215–11. <https://doi.org/10.3389/fnagi.2017.00130>.
34. Meyer, M., **Neff, P.**, Grest, A., Hemsley, C., Weidt, S., and Kleinjung, T. (2017). EEG oscillatory power dissociates between distress- and depression-related psychopathology in subjective tinnitus. *Brain Research* 1663, 194–204. <https://doi.org/10.1016/j.brainres.2017.03.007>.
35. Meyer, M., **Neff, P.**, Liem, F., Kleinjung, T., Weidt, S., Langguth, B., and Schecklmann, M. (2016). Differential tinnitus-related neuroplastic alterations of cortical thickness and surface area. *Hearing Res* 342, 1–12. <https://doi.org/10.1016/j.heares.2016.08.016>. **(shared first authorship)**
36. Meyer, M., Luethi, M.S., **Neff, P.**, Langer, N., and Büchi, S. (2014). Disentangling Tinnitus Distress and Tinnitus Presence by Means of EEG Power Analysis. *Neural Plasticity* 2014, 1–13. <https://doi.org/10.1155/2014/468546>.

## 2. Fallbeschreibungen (case reports)

## 3. Übersichtsarbeiten (Reviews)

1. Isler, B., **Neff, P.**, and Kleinjung, T. (2023). Möglichkeiten der funktionellen Bildgebung bei Tinnitus. *HNO* 71, 640–647. <https://doi.org/10.1007/s00106-023-01319-5>.

2. Mehdi, M., Riha, C., **Neff, P.**, Dode, A., Pryss, R., Schlee, W., Reichert, M., and Hauck, F.J. (2020). Smartphone Apps in the Context of Tinnitus: Systematic Review. *Sensors* 20, 1725. <https://doi.org/10.3390/s20061725>.
3. Schoisswohl, S., Agrawal, K., Simoes, J., **Neff, P.**, Schlee, W., Langguth, B., and Schecklmann, M. (2019). RTMS parameters in tinnitus trials: a systematic review. *Scientific Reports* 9, 12190–11. <https://doi.org/10.1038/s41598-019-48750-9>.
4. Kleinjung, T., Thüring, C., Güntensperger, D., **Neff, P.**, and Meyer, M. (2018). [Neurofeedback for the treatment of chronic tinnitus : Review and future perspectives]. *HNO* 66, 198–204. <https://doi.org/10.1007/s00106-017-0432-y>.
5. Güntensperger, D., Thüring, C., Meyer, M., **Neff, P.**, and Kleinjung, T. (2017). Neurofeedback for Tinnitus Treatment - Review and Current Concepts. *Frontiers in Aging Neuroscience* 9, 386. <https://doi.org/10.3389/fnagi.2017.00386>.

#### 4. Buchbeiträge

1. **Neff, P.K.A.**, and Meyer, M. (2024). Neurofeedback. In *Textbook of Tinnitus*. (Springer Nature), pp. 653–666. [https://doi.org/10.1007/978-3-031-35647-6\\_51](https://doi.org/10.1007/978-3-031-35647-6_51).
2. **Neff, P.K.A.**, Shabbir, M., Goedhart, H., Vesala, M., Burns-O’Connell, G., and Hall, D.A. (2024). Public and Patient Involvement in Tinnitus Research. In *Textbook of Tinnitus*. (Springer Nature), pp. 717–729. [https://doi.org/10.1007/978-3-031-35647-6\\_56](https://doi.org/10.1007/978-3-031-35647-6_56).
3. Schlee, W., Kraft, R., Schobel, J., Langguth, B., Probst, T., **Neff, P.**, Reichert, M., and Pryss, R. (2019). Momentary Assessment of Tinnitus—How Smart Mobile Applications Advance Our Understanding of Tinnitus. In *Studies in Neuroscience, Psychology and Behavioral Economics. New Developments in Psychoinformatics.*, H. B. C. Montag and C. Montag, eds. (Springer), pp. 209–220. [https://doi.org/10.1007/978-3-030-31620-4\\_13](https://doi.org/10.1007/978-3-030-31620-4_13).

#### 5. Monographien

#### 6. Angeleitete Dissertationen

#### 7. Sonstige wissenschaftliche Publikationen, die als wichtig erachtet werden

1. Cederroth, C.R., Kleinjung, T., Langguth, B., Noreña, A., **Neff, P.**, Mazurek, B., Dijk, P.V., and Schlee, W. (2024). Editorial: Towards an understanding of tinnitus heterogeneity, volume II. *Frontiers in Aging Neuroscience*. 16, 1376600. <https://doi.org/10.3389/fnagi.2024.1376600>. (Editorial)
2. Kleinjung, T., Meyer, M., and **Neff, P.** (2023). Neurofeedback for tinnitus treatment: an innovative method with promising potential. *Brain Commun.* 5, fcad209. <https://doi.org/10.1093/braincomms/fcad209>. (Perspective)
3. Simoes, J.P., Schoisswohl, S., Schlee, W., Basso, L., Bernal-Robledano, A., Boecking, B., Cima, R., Denys, S., Engelke, M., Escalera-Balsera, A.,....**Neff, P.**... et al. (2023). The statistical analysis plan for the unification of treatments and interventions for tinnitus patients randomized clinical trial (UNITI-RCT). *Trials* 24, 472. <https://doi.org/10.1186/s13063-023-07303-2>. (Protocol)
4. Martins, M.L., Kleinjung, T., Meyer, M., Raveenthiran, V., Wellauer, Z., Peter, N., and **Neff, P.** (2022). Transcranial electric and acoustic stimulation for tinnitus: study protocol for a randomized double-blind controlled trial assessing the influence of combined transcranial random noise and



acoustic stimulation on tinnitus loudness and distress. *Trials* 23, 418. <https://doi.org/10.1186/s13063-022-06253-5>. (Protocol)

5. Ridder, D.D., Schlee, W., Vanneste, S., Londero, A., Weisz, N., Kleinjung, T., Shekhawat, G.S., Elgoyhen, A.B., Song, J.-J., Andersson, G., ... **Neff, P.**,... et al. (2021). Tinnitus and tinnitus disorder: Theoretical and operational definitions (an international multidisciplinary proposal). *Prog Brain Res* 260, 1–25. <https://doi.org/10.1016/bs.pbr.2020.12.002>. (Perspective)

6. Schlee, W., Schoiswohl, S., Staudinger, S., Schiller, A., Lehner, A., Langguth, B., Schecklmann, M., Simoes, J., **Neff, P.**, Marcum, S.C. and Spiliopoulou, M., 2021. Towards a unification of treatments and interventions for tinnitus patients: The EU research and innovation action UNITI. *Prog Brain Res*, 260, pp.441–451. <https://doi.org/10.1016/bs.pbr.2020.12.005>. (Project description)

7. Schoiswohl, S., Langguth, B., Schecklmann, M., Bernal-Robledano, A., Boecking, B., Cederroth, C.R., Chalanouli, D., Cima, R., Denys, S., Dettling-Papargyris, J., ... **Neff, P.**,... et al. (2021). Unification of Treatments and Interventions for Tinnitus Patients (UNITI): a study protocol for a multi-center randomized clinical trial. *Trials* 22, 875. <https://doi.org/10.1186/s13063-021-05835-z>. (Protocol)

8. Pryss, R., Schlee, W., Reichert, M., Kurthen, I., Giroud, N., Jagoda, L., Neuschwander, P., Meyer, M., **Neff, P.**, Schobel, J., et al. (2019). Ecological Momentary Assessment based Differences between Android and iOS Users of the TrackYourHearing mHealth Crowdsensing Platform. In 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)., pp. 3951–3955. <https://doi.org/10.1109/embc.2019.8857854>. (Conference)

9. **Neff, P.**, Bisig, D., and Schacher, J.C. (2019). State Dependency - Audiovisual interaction through brain states. *Sound and Music Computing (SMC) Conference*, pp. 1–8. [https://smc2019.uma.es/articles/P1/P1\\_04\\_SMC2019\\_paper.pdf](https://smc2019.uma.es/articles/P1/P1_04_SMC2019_paper.pdf). (Conference)

10. Beierle, F., Tran, V.T., Allemand, M., **Neff, P.**, Schlee, W., Probst, T., Pryss, R., and Zimmermann, J. (2018). TYDR – Track Your Daily Routine. Android App for Tracking Smartphone Sensor and Usage Data. In the 5th International Conference., pp. 72–75. <https://doi.org/10.1145/3197231.3197235>. (Conference)

11. Pryss, R., Probst, T., Schlee, W., Schobel, J., Langguth, B., **Neff, P.**, Spiliopoulou, M., and Reichert, M. (2017). Mobile Crowdsensing for the Juxtaposition of Realtime Assessments and Retrospective Reporting for Neuropsychiatric Symptoms. 2017 IEEE 30th Int. Symp. Comput.-Based Med. Syst. (CBMS), 642–647. <https://doi.org/10.1109/cbms.2017.100>. (Conference)

12. Schacher, J.C., and **Neff, P.** (2016). Skill development and stabilisation of expertise for electronic music performance. *Music, Mind, and Embodiment. CMMR 2015. Lecture Notes in Computer Science*. 9617, 111–131. [https://doi.org/10.1007/978-3-319-46282-0\\_7](https://doi.org/10.1007/978-3-319-46282-0_7). (Conference)

13. Schacher, J.C., Strinning, H.J.C., Strinning, C., and **Neff, P.** (2015). Movement perception in music performance-a mixed methods investigation. *Proceedings of the International Conference on Sound and Music Computing*. [10.5281/ZENODO.851106](https://doi.org/10.5281/ZENODO.851106). (Conference)

14. Serquera, J., Schlee, W., Pryss, R., **Neff, P.**, and Langguth, B. (2015). Music Technology for Tinnitus Treatment Within Tinnit. *Proceedings of 58th International AES Conference: Music Induced Hearing Disorders*. <https://aes2.org/publications/elibrary-page/?id=17783>. (Conference)



## Habilitationsschrift

# **Auditory, neural, and psychological signatures of temporary tinnitus suppression**

Zur Erlangung der Venia Legendi der Universität Zürich

Verfasst von  
Patrick Neff

Zürich, 30.8.2024

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**Auditory, neural, and psychological signatures of temporary tinnitus  
suppression**

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# Index

<b>1 Introduction</b>	<b>3</b>
1.1 Tinnitus . . . . .	3
1.2 Acoustic stimulation, tinnitus suppression, and neural correlates . . . . .	4
<b>2 Methods</b>	<b>6</b>
2.1 Audiometry, tinnitometry, and acoustic stimulation . . . . .	6
2.2 EEG neurophysiology . . . . .	8
<b>3 Synopsis</b>	<b>9</b>
3.1 Study 1: Comparing Three Established Methods for Tinnitus Pitch Matching With Respect to Reliability, Matching Duration, and Subjective Satisfaction . . . . .	9
3.2 Study 2: Comparison of Amplitude Modulated Sounds and Pure Tones at the Tinnitus Frequency: Residual Tinnitus Suppression and Stimulus Evaluation . . . . .	11
3.3 Study 3: Amplitude Modulated Noise for Tinnitus Suppression in Tonal and Noise-Like Tinnitus . . . . .	13
3.4 Study 4: Neurophysiological correlates of residual inhibition in tinnitus: Hints for trait-like EEG power spectra . . . . .	15
<b>4 Conclusion and future directions</b>	<b>17</b>
<b>5 Bibliography</b>	<b>21</b>
<b>6 Acknowledgments</b>	<b>34</b>
<b>7 Copies of the four original articles</b>	<b>35</b>

# 1 Introduction

## 1.1 Tinnitus

Subjective tinnitus is a phantom perception of a sound lacking any external physical source [30] and becomes chronic after a continuous presence of 3 to 12 months [36]. In the remainder of this thesis, the term tinnitus refers to this particular and most prevalent form of tinnitus. Tinnitus is becoming more prevalent and relevant in the steadily aging demographic [50] as it is often linked to naturally occurring presbycusis [79, 32]. Moreover, tinnitus seems to affect all age groups, putatively linked to lifestyle choices (e.g., in-ear headphones and high sound levels in music listening), as seen in recent studies with adolescents [63]. Currently, tinnitus is reported by about 70 million people in the EU alone [3]. In more detail, prevalence rates reported span from 12% to 30% [37] with about 1–2% suffering immensely under the condition [30]. Societal impact and health costs of tinnitus are considerable, as tinnitus may lead to disrupted functional (e.g., perceptual disorders like decreased speech comprehension [43, 24] or impaired auditory stream segmentation and/or sound localization [22]), reduced emotional health and well-being (affective disorders like depression and anxiety, sleep disturbances, social isolation), and in consequence reduced quality of life [30]. Tinnitus may thus also influence productivity at work and even can lead to complete disability in extreme cases [9].

Currently, the purely phenomenological definition of tinnitus (i.e., auditory phantom perception in the absence of an external source) is revised and dichotomized as auditory phantom sound vs. tinnitus-related distress or simply ‘tinnitus disorder’ [60]. This newly proposed definition reflects the insights of the tinnitus research community from recent years and enables more specific basic as well as clinical research. Notably, this is also reflected in respective outcome measures in tinnitus research: Basic, especially auditory, research is focused on tinnitus loudness or presence (i.e., the auditory phantom percept [41, 45]), whereas clinical research rather focuses on changes in tinnitus dis-

tress scores (i.e., emotional and cognitive aspects of the tinnitus disorder [76, 75, 46]) assessed by tinnitus questionnaires (e.g., [49, 15, 40]). In the research presented in the thesis at hand, there is a clear focus on the auditory phantom percept aspect of tinnitus.

Tinnitus, in most cases, is caused by hearing loss, either objective [28, 5] or ‘hidden’ [33, 87, 65], and triggers maladaptive plasticity in the auditory pathway and brain leading to the phantom sound perception [25, 70, 58]. The tinnitus sensation usually is heard as a tone or noise at a frequency between 3-8 kHz [66, 73, 47, 44], mostly bilaterally in the two ears or with a slight preference to one ear [34]. Tinnitus loudness, pitch, and laterality are the main auditory, or acoustic, tinnitus parameters of interest [18]. Moreover, the tinnitus (minimum) masking level and temporary acoustic suppression are further relevant auditory aspects of tinnitus [62, 10, 45, 47, 67, 48]. The phenomenon of RI [61] is especially helpful for the study of basic mechanisms as the perception of tinnitus can be actively manipulated.

## **1.2 Acoustic stimulation, tinnitus suppression, and neural correlates**

The phenomenon of short-term tinnitus suppression following acoustic stimulation was first observed over 100 years ago [77]. It was later defined as ‘residual inhibition’ (RI) and can be observed in 50-90 % of tinnitus sufferers, whereby depth and duration of suppression patterns vary among individuals [82, 61, 62, 45, 47, 67]. Different acoustic stimuli have been applied to induce TS ever since. Stimuli range from simple broadband noise or pure tones to specifically filtered or modulated sounds [80, 59, 20, 62, 45, 47, 67]. These acoustic stimuli share communalities and exhibit differences in various acoustic parameters, most critically the frequency dimension and the temporal dimension [52, 45, 8]. Derived insights from these studies furthermore suggest that stimulation intensity, duration, specific stimuli modulations or modifications, and especially

stimuli covering the individual tinnitus frequency [64] facilitate tinnitus suppression in a parametric fashion.

Little is known about the basic neurophysiological processes behind RI [61], especially on the cortical level in humans. Despite the prospect of acoustic tinnitus suppression or RI to better understand mechanisms behind tinnitus, there is only a handful of experimental studies which investigated brain activity during RI. Reduced (spontaneous) firing rates of neurons after acoustic stimulation in the central auditory pathway including the inferior colliculi are theorized to play a key role in RI [11, 10]. Unfortunately, these studies present animal data which lacks validation in human subjects, which currently is impossible to obtain given (non-invasive neurophysiological) measurement methods in humans as well as the translational gap between animal and human models of tinnitus. With the help of magnetoencephalography an increase in low frequency spectral power was observed during RI in a single subject [29]. Contrary to this observation, single-subject intracranial local field potential electroencephalographic recordings showed a reduction of low frequency activity in the auditory cortex during RI. These tinnitus-related low frequency oscillations also interacted with alpha, beta and gamma activity [71]. Beyond that, tinnitus intensity during RI was shown to be connected to delta, theta and gamma oscillatory activity in the auditory cortex [72]. [26] evaluated neuromagnetic activity in 10 tinnitus patients experiencing RI, defined as 50% of tinnitus loudness reduction for 30 seconds after stimulation offset. A significant reduction of delta activity in temporal areas was observed during RI, whereas the gamma band was not affected. Currently, it can be concluded that there is convergent evidence of the neural correlates of RI and that this evidence can be considered an inversion of maladaptive brain activity patterns in tinnitus [85, 86]. This consideration would thus imply that through acoustic stimulation and resulting RI chronified maladaptive tinnitus-related brain activity might be reversible, at least for the duration of the suppression. Notably, this reversal pattern has been found consistently for the delta frequency band whereas evidence for the alpha band is missing. Alpha band oscillations putatively play a cen-

tral role in tinnitus inhibition and auditory perception in general [84]. Overall, given the different study designs, measurement and analysis methods, sample sizes (often very small sample sizes and case reports), responder rates, and tinnitus heterogeneity, the evidence is not yet conclusive and generalizable. Most importantly, current research is unable to disentangle tinnitus-specific effects from unspecific effects of acoustic stimulation, which calls for large-scale, well-controlled studies comparing tinnitus patients to healthy controls. Translational aspects like suitability for treatments, be it sound therapies, neuromodulatory, or even their combination, have to be thoroughly examined [21, 69].

In the remainder of this thesis, applied methods are briefly introduced, presented original work summarized and finally discussed in respect to future directions in tinnitus research.

## **2 Methods**

### **2.1 Audiometry, tinnitometry, and acoustic stimulation**

Audiometry and tinnitometry data is mandatory to describe tinnitus populations, and even more important as a confounding factor in experimental design or data analysis of tinnitus research. Tinnitus is tightly linked to hearing loss in most cases [6]. For the research presented in this thesis, hearing loss assessment is critical to creating the acoustic stimuli, which have to be leveled regarding the sensation level at certain frequencies. Furthermore, it is also a selection criterion for study populations where 60 dB hearing loss should not be surpassed in some frequencies to be able to stimulate with e.g. 60 dB above sensation level without hitting hardware and safety limits.

Pure tone audiometry is a widely used method to check the hearing status of single frequencies, usually spaced in half-octave steps, over the whole range of the audible spectrum [23]. This method was applied in the presented studies with a calibrated au-



diometer (Madsen Midimate 622D; GN Otometrics, Denmark) and audiometry-grade Sennheiser HDA 2000 headphones (Sennheiser, Germany). In the last study, audiometry was performed with a custom-built system using Matlab (Matlab R2017a; Mathworks, USA), a modified MultiThreshold toolbox (University of Essex, United Kingdom) with a single-interval adaptive procedure [31, 12], ER-2 Insert Earphones (Etymotic Research Inc., USA) together with an external soundcard (RME Fireface UCX; Audio AG, Germany). This custom system can test audiometric frequencies above 8 kHz and perform acoustic stimulation without electromagnetic artifacts in the electroencephalography (EEG) signal.

Tinnitusometry was performed by adhering to the ‘Tinnitus Tester’ workflow [62] with some modifications in subtests and stimulus material. First, it was decided on which ear(s) the tinnitusometry should be conducted. Usually, it is assessed on the contralateral ear to the tinnitus perception or in the better hearing ear in the case of bilateral tinnitus. Second, a reference tone was set to a comfortable level and then manipulated in frequency to match the perceived tinnitus frequency. Third, the loudness was adjusted to match the perceived tinnitus loudness after the frequency matching had been completed. Finally, the resulting sound was checked for octave confusion by presenting the sound one octave above and below the tinnitus frequency. More details of this method of adjustment tinnitus pitch matching can be found in the original manuscript of study 1 [44]. Details of software and hardware (e.g., matching controller devices or headphones) partly vary between presented studies while the professional soundcard (RME Fireface UCX; Audio AG, Germany) was used in all of the studies. All systems were tested and calibrated to ensure reliable measures.

Acoustic stimulation in tinnitus can be subdivided into three major branches. Tinnitus masking [16], acoustic tinnitus suppression or RI [61], and sound therapies building on acoustic ‘neuromodulation’ (e.g., [54, 78]). As seen in the section above, the studies presented in this thesis mainly investigated short-term acoustic tinnitus suppression or RI with a prospect towards a sound therapy.

Stimuli were created with basic Matlab functions according to individual parameters (i.e., tinnitus frequency, sensation level, and filter parameters). Depending on the study, they were then presented using the respective software and hardware setups.

## 2.2 EEG neurophysiology

EEG for application in humans was invented about 100 years ago [1] and was the first non-invasive method to study the neurophysiology of the brain. EEG records an electrogram of the electrical activity with multiple electrodes on the scalp using a differential amplifier (i.e., differences in voltages of recording electrodes to a reference electrode). The recorded electrical activity reflects macroscopic activity of neuronal populations in the underlying brain tissue [42]. EEG paradigms are either event-related, measuring multiple responses to external stimuli, or resting state, recording continuous activity of the brain in the absence of any (repeated) stimulation. Recorded data can in both cases be analyzed regarding band power in defined frequency bins, namely delta, theta, alpha, beta, and gamma, which are attributed to general physiological arousal states, but also to specific functional processes. Building on biological concepts of self-organization and energy efficiency, it is theorized that these omnipresent oscillations are organized in a hierarchical interlocked oscillator array to control bodily and cerebral functions [27].

In the final study presented in this thesis, a BrainAmp DC EEG system, an EasyCap electrode cap with 64 electrodes, and Brain Vision Recorder 1.20 software (Brain Products GmbH, Germany) were used. Resting state data recorded before, during, and after acoustic stimulation was analyzed with multitaper frequency transformation 'mtmfft' in the Matlab toolbox 'Fieldtrip' [53] to create a frequency spectrum in single Hz steps covering the different frequency bands. Resulting frequency spectra were then also projected into a template brain volume to localize effects within the brain using the dynamic imaging of coherent sources approach [13]. Finally, statistics were performed

on the scalp level and the brain volume level using cluster permutation methods implemented in Fieldtrip.

### 3 Synopsis

#### 3.1 Study 1: Comparing Three Established Methods for Tinnitus Pitch Matching With Respect to Reliability, Matching Duration, and Subjective Satisfaction

*Neff, P., Langguth, B., Schecklmann, M., Hannemann, R., & Schlee, W. (2019). Trends in hearing, 23(3), 2331216519887247.*

In order to study tinnitus in general as well as specifically design stimuli for acoustic stimulation, tinnitus matching is key. To this day, no consensus on standard procedures are established and various methods are presently used in laboratory or clinical practice [17].

The aim of this study was to compare the most established matching methods with respect to reliability of tinnitus matchings, subjective satisfaction with the matched tone, and time to completion. Three methods were compared head-to-head in a between-subject design with 3 matched groups (n=59). Two methods used algorithm-driven methods (i.e., method of likeness fitting a tinnitus probability spectrum by presenting participants with random tones, which have to be rated with respect to their likeness to pitch and loudness of the perceived tinnitus [51]; two-alternative forced-choice method narrowing down a bracket of 2 differently pitched sounds converging on a final tinnitus frequency [56]), and an user-driven method of adjustment, where participants adjust the tinnitus pitch with knobs and sliders on hardware device [19]). Commercial software and hardware were used for the two-alternative forced-choice method whereas custom apparatus was developed for the other two methods. Participants in each group performed 5 runs of tinnitus matching, completed tinnitus-related questionnaires and

underwent standard pure tone audiometry.

Results showed good reliabilities for all methods in various measures, most importantly the intraclass correlation coefficient, and end points of the confidence intervals extended between fair and excellent intraclass correlation coefficient values. Looking at completion time, participants learned to perform the matching faster in the last of the five runs compared to the first in all methods. The likeness method overall resulted in longer completion times, which is mostly inherited to the applied algorithm which requires a lot of repeated ratings of a large search space. Finally, satisfaction with matching results were high (above 8 out of 10) for the likeness and adjustment method for all runs, but not for the forced-choice method. As with the limitation of the likeness method with respect to completion time, the head-to-head comparison between methods is limited here by inherent features of the matching algorithms.

Overall, tinnitus matching could be completed with good reliability, within reasonable time frames (i.e., under 1 hour with 5 runs of matching and audiometry), and with high satisfaction ratings. The sample size in this study is considerably larger compared to most previous studies, which solidifies found reliabilities and differences between methods. Given the results and insights from this study, a combined approach was developed where the search space of tinnitus pitch is reduced by stepping from pure tone audiometry to likeness method. From the latter, the most likely tinnitus pitch is selected and fine-tuned with the method of adjustment. The two-alternative forced-choice method is considered redundant in this framework, but could be added to evaluate the result of the combined approach.

### **3.2 Study 2: Comparison of Amplitude Modulated Sounds and Pure Tones at the Tinnitus Frequency: Residual Tinnitus Suppression and Stimulus Evaluation**

*Neff, P., Zielonka, L., Meyer, M., Langguth, B., Schecklmann, M., & Schlee, W. (2019). Trends in hearing, 23(1), 2331216519833841.*

Temporary tinnitus suppression following acoustic stimulation or RI has been studied for many years mostly using noise stimuli. Pure tone stimuli or modulated sounds have not been subject to these studies until very recently. Former studies tested several sounds, including pure tones and noises, with 40 Hz modulations in the amplitude and frequency domain, and showed larger suppression effect with these more complex tailored acoustic stimuli [59, 80]. Stimuli were not matched to the tinnitus frequency but were presented in several frequency bins also spanning tinnitus frequencies. In 2017, I published a study with a similar approach with the critical expansion of stimuli matched to the tinnitus frequency and the focus on 10 Hz amplitude modulated sounds [45]. In synthesis of these previous works, it was established that the most efficient suppression sounds are amplitude modulated pure tones in or at the tinnitus frequency. In consequence, this stimulus class was systematically tested in the here presented within-subject design study (n=29).

Stimuli were matched to the tinnitus frequency rendering the frequency of the stimuli to a fixed factor of the experimental manipulation. The other stimulus parameters, namely (amplitude) modulation rate and presentation level (i.e., loudness), were manipulated to test for differences between modulation and presentation level regimes. Modulation rates of 0, 10, and 40 Hz were applied with 0 Hz being the control condition. Presentation levels were manipulated with 60 dB above the sensation level at the frequency closest to the matched tinnitus frequency, 6 dB above the minimum masking level of tinnitus, and -6 dB below the sensation level serving as the inactive control stimulus. Sounds were presented for 3 minutes and the tinnitus loudness level compared to the

normal level before stimulation was rated every 30 seconds after stimulus offset. These loudness scores are the main outcome variable of the suppression whereas the valence and arousal ratings were also assessed for each of the stimuli [2].

Results partly confirmed the hypotheses, while not all statistical contrasts reached statistical significance or survived correction for multiple comparisons. This may be mostly due to a misfortunate order effect, which was present in the data even in the presence of active measures in the experimental design to counteract possible order effects. The issue was transparently reported and discussed in the article. Still, the results are in line with former findings and in essence confirm the hypothesis that 10 Hz amplitude modulated sounds at loud presentation levels surpass unmodulated sounds at the same or other presentation levels. Moreover, the hypothesized pattern of descending depth of tinnitus suppression following stimulus manipulation was also reflected by ratings of valence and arousal. The 10 Hz amplitude modulated sound was better tolerated at both presentation levels than its unmodulated pendant whereas no differences were observed in the arousal ratings. The prima facie absence of any comparable effect of the 40 Hz amplitude modulated sound is mostly explainable by the high modulation rate which is psychoacoustically close to a tone perception while 40 Hz stimuli generally generate the most pronounced neurophysiological responses in the central nervous system [57].

This was the first study to systematically investigate modulated pure tones at the tinnitus frequency regarding their suppressive potential. Theory and hypotheses were mostly supported by the data with clearly identified limitations. Most importantly, the 10 Hz sounds were rated more comfortable and suppressive than other sounds which qualifies this stimulus category to be applied to further study residual inhibition stimulus parameters but also putative therapeutic approaches. Notably, the approach has received attention and distribution in online self-help communities and was implemented into a tinnitus app <sup>1</sup> in consultation with the author of this treatise, who also supervised

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<sup>1</sup><https://apps.apple.com/us/app/tinnitusplay/id1485397051>

the implementation of tinnitus matching, hearing test, and overall scientific accuracy of the functions of the app. Following a natural progression through the parameter space of this line of acoustic stimulation research, future studies should investigate different carrier sounds (i.e., noise or natural/musical sounds) and tone frequencies. The same is true of modulation rates or even modulation types (e.g., frequency vs. amplitude modulation).

### **3.3 Study 3: Amplitude Modulated Noise for Tinnitus Suppression in Tonal and Noise-Like Tinnitus**

*Schoisswohl, S., Arnds, J., Schecklmann, M., Langguth, B., Schlee, W., & Neff, P. (2019). Audiology & Neurotology, 24(6), 309 – 321.*

As mentioned before, temporary tinnitus suppression following acoustic stimulation or RI is traditionally induced by noise stimuli [61]. Tinnitus itself mostly manifests as (pure) tones or narrow-band noise with a sharply tuned central frequency whereas fewer individuals report their tinnitus as (broadband) noise. Little is known about the efficacy of differential acoustic stimuli or carrier sounds in the latter subtype of tinnitus. The current paradigms of masking and RI in tinnitus assume broadband noise (i.e., white noise) to be most effective for the most common subtype of tonal tinnitus. No systematic investigation has been performed to test these assumptions by comparing noise stimuli on the subtypes of tonal and noise-like tinnitus. Furthermore, modulation of noise stimuli has not been studied in any of these subgroups to this day. In addition, tinnitus matching of noise-like tinnitus has not been investigated in a focused way except in a matching study not specifically targeted at the noise-like subgroup [20]. Taken together, the study was devised to address these unresolved issues, especially with respect to the efficacy of amplitude modulated noise stimuli and their efficacy in tonal vs. noise-like tinnitus. Akin to previous own studies, participants with tinnitus were recruited and underwent comprehensive audiometry, tinnitometry, and psychometry before partaking in the ac-

tual experimental procedure of acoustic stimulation (n=29). Stimuli were designed to manipulate amplitude modulation and filtering of noise whereas the presentation level was fixed at 60 dB above sensation level. In more detail, broadband noise (i.e., white noise) was amplitude modulated with 0, 10, and 40 Hz, and a second stimulus class was established with individually matched noise spectra around the center tinnitus frequency with the same modulation rates as the broadband noise stimulus class. Participants with tonal tinnitus were presented filtered noises with a one octave bandwidth whereas participants with noise-like tinnitus were presented with bandpass-filtered noise stimuli with individually matched bandwidths. All participants were additionally stimulated with the broadband stimulus class.

No differences were found between the two stimulus classes of broadband and filtered noise as well as between modulated and unmodulated stimuli. This pattern is also reflected in the valence and arousal ratings of the stimuli where no differences were found except overall better tolerance for the single control sound at lower presentation levels. On the other hand, a pronounced difference was identified between the group with tonal tinnitus vs. the group with noise-like tinnitus, especially at the time point of maximal suppression right after stimulus offset.

The absence of differences between modulated and unmodulated noise sounds came as a surprise, but has to be framed with respect to the novelty of the unstudied approach. Noise itself covers not only a wide range in the audible frequency spectrum with no frequency selectivity, it also comprises all frequencies in the modulation spectrum. Therefore, neither the manipulation of the noise bandwidth around the tinnitus frequency nor the amplitude modulation may have introduced sufficient specific signal alteration to induce expected effects. The inherent properties of noise stimuli may thus limit the line of research with modulated sounds to induce RI. Interestingly, missing differences in valence or arousal ratings of the stimuli complement the behavioral acoustic suppression results and thus are in line with the observed overlap of suppression and stimuli ratings in the former studies [45, 47]. Of special note, participants with noise-



like tinnitus could not reliably match their tinnitus or center frequency of noise which further limits the specificity of putative effects. Nevertheless, the study at hand clearly shows a preference for noise stimulation in individuals with noise-like tinnitus whereas individuals with tonal tinnitus seem to profit more from tonal stimuli as also seen in the previous own studies. This insight might transcend the current state of knowledge which upholds that noise stimulation is optimally effective for all kinds of tinnitus including the widespread tonal tinnitus. The exploratory novel line of research here calls for further iteration to both better understand the phenomenon of RI in general and to elucidate differences in the tinnitus subtypes, also with respect to future individualized treatments.

### **3.4 Study 4: Neurophysiological correlates of residual inhibition in tinnitus: Hints for trait-like EEG power spectra**

*Schoisswohl, S., Schecklmann, M., Langguth, B., Schlee, W., & Neff, P. (2021). Clinical Neurophysiology, 132 (7), 1694-1707.*

The neurophysiological underpinnings of RI or general tinnitus suppression are not well studied. Current models consider RI to be triggered by feedforward inhibition in the auditory system in or around the stimulated frequencies [61]. Based on animal data, it was further proposed that RI may be generated in the inferior colliculus where it was observed that acoustic stimulation suppresses spontaneous firing rates theorized to reflect the maladaptive hyperactivity leading to the tinnitus perception [10]. While the former theory rather focused on cortical mechanisms, the latter hypothesis can be interpreted as forward masking on a subcortical level. Given that subcortical neurophysiology is currently inaccessible with human neuroimaging techniques, research is constrained to behavioral and cortical measures or putative proxies of subcortical activity. A single study on the group level can be reported with magnetoencephalography [26] whereas RI research has not been attempted with magnetic resonance imaging (MRI) to this

day. The former study reported a decrease of low frequency oscillatory activity in the delta band during RI, which partly constitutes a reversal of the maladaptive neural signature of elevated delta activity and reduced alpha activity [85]. Single case data [29] and single case intracranial data [71] is in further support of this finding. Finally, the absence of any findings in the alpha and gamma band, central to auditory processes and possibly tinnitus inhibition in the case of the alpha band [84], is puzzling. In consequence, an increase in alpha and a decrease in gamma as well as delta band activity during RI were hypothesized for the study presented here. The aim of this study was to replicate and extend former findings with the addition of different noise stimuli, electroencephalography, and a clinical cohort of tinnitus patients (n=45) [68].

The paradigm was similar to the former studies presented here with the addition of EEG recordings before, during, and after acoustic stimulation. Besides broadband noise, bandpass-filtered and band-stop-filtered noise around the tinnitus frequency were presented to the participants at 65 dB above sensation level. This explorative stimulus manipulation was hypothesized to generate different suppression depths where the band-stop-filtered noise also exerts lateral inhibition around the tinnitus frequency in the tonotopic strip of the primary auditory cortex.

The band-stop-filtered noise surprisingly resulted in lower tinnitus suppression than the other 2 stimuli, which might have been again reflected by related valence (and partly arousal) ratings of the stimuli. The electrophysiological analysis was constraint to RI responder to non-responder contrasts in sensor (i.e., scalp electrodes) and source space within the brain (i.e., source estimation of peak effects on the sensor level). Here, it was found that alpha activity was increased and gamma activity decreased during RI in the responder group which is in line with hypotheses and theory thus constituting a possible reversal of the maladaptive neural signature of tinnitus on the cortical level.

This study is a critical contribution to the study of RI and suppression or manipulation of the tinnitus perception. It was the first study which could demonstrate the involvement of (inhibitory) cortical alpha activity in the generation and/or maintenance of tinnitus in

real-time by manipulation of tinnitus presence. Notably, effects are solid, pronounced, and stable, even though the responder analysis considerably lowered the number of participants per group. The solid effects are furthermore reflected by relatively accurate source estimation in the primary auditory cortex. This localization, even to the level of primary auditory cortex or Heschl' gyrus, further corroborates the theory that this locus is a central and first cortical *relay station* of ascending maladaptive neurophysiology in tinnitus. Change of activity in this locus may be sufficient to completely suppress tinnitus which also generates implications regarding targets or outcomes of neuromodulatory interventions. Given some limitations of this and previous studies like the absence of correlations between changes in loudness and neurophysiology, further research is warranted to replicate and extend these findings.

## 4 Conclusion and future directions

The articles presented in this cumulative thesis represent (parts of) an iterative line of research concerned with aspects of acoustic tinnitus suppression.

Looking at acoustic or sound therapies for tinnitus, the last two decades produced a manifold of approaches all of which did not produce sufficient evidence in clinical efficacy. Therefore, no recommendations for the use of any of these sound therapies currently exist from expert consensus (e.g., [4, 74]). The approaches were generally rushed and partly directly ran uncontrolled clinical trials before assessing the sound therapies' concepts and parameters in basic research experiments. More refined approaches targeted putative maladaptive neuroplastic alterations of the auditory system largely based on animal models [52]. These approaches aimed at stimulation of frequencies around the hearing loss edge or the tinnitus frequency, thus mostly focusing on the frequency domain of the acoustic parameter space. While most of suggested methods of sound therapies did not produce more than singular pilot studies, two approaches have a considerable track of research including neurophysiology and clinical

trials [54, 78]. Nevertheless, after more than 10 years of focused research, neither of these approaches could produce sufficient evidence while sound therapy parameters are constantly updated by the authors. In both cases, there are even commercialized versions available and they are widely implemented in current mobile apps [39, 38]. Besides these fundamental issues in basic and clinical research, further aspects of acoustic tinnitus suppression may help to better understand the inconclusive state of research. First, a bias for more pronounced tinnitus suppression in female participants was observed in the presented studies. This finding has been specifically analyzed in a dedicated publication [55]. It was shown that women are especially more responsive to the modulated stimuli class. Further research is warranted here to elucidate the neurophysiological mechanisms of action differentiating between sexes. Second, psychopathological aspects of tinnitus disorder could play a role in the interindividual differences of suppression patterns. In line with related own research [75], we assessed personality traits in two of the presented studies here [47, 67]. It was hypothesized that the personality trait openness may modulate tinnitus suppression positively whereas neuroticism may have a negative effect on tinnitus suppression [14]. In order to investigate if these putative effects are linked to the rating of the stimuli, statistical models were also applied to predict rating scores of valence and arousal. No effects were found for the pooled sample of  $n = 69$  participants which led to the conclusion that suppression effects may be primarily driven by biological factors. Third, the phenomenon of prolonged tinnitus suppression or RI has been anecdotally reported in previous research while it was never systematically assessed and discussed. Given the occurrence of this phenomenon throughout the studies presented here, cases from 4 studies were pooled and cases with prolonged suppression (i.e., full suppression longer than the stimulation time) [48]. Of special note, participants with prolonged suppression were excluded from the original studies given that they could not complete the study procedures. From the pool of 130 unique individuals, 6 individuals reported prolonged suppression which equals a rate between 3% and 7% of cases in each of the studies. 4 out of the 6 cases

were female which is in line with similar findings of better suppression in the female tinnitus population. Given the exclusion during the experiments, further patterns are not accessible with the current data and thus no valid statements can be produced with respect to the stimuli inducing this phenomenon (stimuli presentation was randomized for all participants and the first presented stimulus induced prolonged suppression in 4 out of the 6 cases). Furthermore, no hints were found in the audiometric, tinnitometric, and psychometric data available. The observed phenomenon of prolonged tinnitus suppression after short-term acoustic stimulation should therefore be studied systematically with individuals experiencing it, also in respect to individual treatment options. Taken together, these additional aspects of the presented line of research pave the way for further insightful research and subtypization of the heterogeneous tinnitus population. Looking ahead, I am convinced that the study of acoustic tinnitus suppression and possible sound therapies should be carefully performed in two complementary and convergent modes. First, basic research should be performed in a more rigorous, iterative, and transparent manner to ensure reliability and validity of found effects. This urge certainly also reflects ongoing concerns of replication crisis in human empirical sciences [35] and calls for open or reproducible science in general [83]. In more detail, this strategy entails careful selection of methods (e.g., [81]) and outcome measures (e.g., [7]), which should also be kept up to date with current state of the art in scientific fields involved in tinnitus research. The own line of research is continued with a focus on the critical differentiation between non-specific effects of acoustic stimulation and tinnitus-related specific effects of acoustic tinnitus suppression. Applying the established behavioral acoustic stimulation paradigm, neurophysiological EEG and structural MRI data has therefore been collected from tinnitus patients and healthy controls. The major novel aspects of this research are the inclusion of a matched control group and the deployment of polymodal neuroscientific methods to further elucidate structure and function of the brain related to RI (in prep.) Second, acoustic research in tinnitus, especially on the behavioral level, should be scaled massively and performed with contemporary technology.

Acoustic stimulation is highly mobile and can be performed on different devices with manageable efforts in development. This scaled and distributed research approach would enable researchers to surpass current limitations of resourceful lab work and small sample sizes. The latter is especially important with regards to meaningful statistics and better subtypization efforts of tinnitus (suppression). Most importantly, it would allow to test a large variety of sounds in a single framework rather than to rely on a series of effortful lab research. In this spirit, I already developed an exhaustive system of relevant sounds along the dimensions of natural vs. artificial sounds, tinnitus frequency vs. non-tinnitus frequency, spectral complexity, temporal modulation, order and disorder (i.e., entropy), and sound energy over time. Building on this system, I selected and programmed a preliminary set of 64 sounds which cover all of these dimensions <sup>2</sup>. These sounds are currently used in a large-scale multi-center clinical trial <sup>3</sup> as iOS and Android apps called 'Shades Of Noise' <sup>4</sup> <sup>5</sup>. The apps also allow for control and tracking of presentation levels as well as customizing various sounds with respect to the tinnitus frequency. Furthermore, usage tracking of app activity allows for more detailed insights in usage patterns and sound preferences which generates rich big data for in-depth analysis. In short, the proposed mode of research may render classical lab research obsolete by saving time as well as increasing the amount and depth of data considerably. It would also allow for participant selection for lab studies to discover biological phenotypes (e.g., neurophysiology) in the tinnitus population. Given the novelty of the approach and related research, current challenges or limitations still have to be identified and addressed.

Taken together, the line of research presented here, ongoing studies and analyses, and finally the future directions laid out in this final paragraph might eventually lead to major progress in the understanding and treatment of tinnitus.

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<sup>2</sup><https://tinyurl.com/2een728p>

<sup>3</sup><https://uniti.tinnitusresearch.net/>

<sup>4</sup>[https://apps.apple.com/de/app/shades-of-noise/id1506159709?platform=iphone,](https://apps.apple.com/de/app/shades-of-noise/id1506159709?platform=iphone)

<sup>5</sup><https://play.google.com/store/apps/details?id=com.dbis.haugxhaug.shadesofnoise>

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## 7 Copies of the four original articles


**Article 1:** Neff, P., Langguth, B., Schecklmann, M., Hannemann, R., & Schlee, W. (2019). Comparing Three Established Methods for Tinnitus Pitch Matching With Respect to Reliability, Matching Duration, and Subjective Satisfaction. *Trends in hearing*, 23(3), 2331216519887247.

**Article 2:** Neff, P., Zielonka, L., Meyer, M., Langguth, B., Schecklmann, M., & Schlee, W. (2019). Comparison of Amplitude Modulated Sounds and Pure Tones at the Tinnitus Frequency: Residual Tinnitus Suppression and Stimulus Evaluation. *Trends in hearing*, 23(1), 2331216519833841.

**Article 3:** Schoisswohl, S., Arnds, J., Schecklmann, M., Langguth, B., Schlee, W., & Neff, P. (2019). Amplitude Modulated Noise for Tinnitus Suppression in Tonal and Noise-Like Tinnitus. *Audiology & Neurotology*, 24(6), 309–321.

**Article 4:** Schoisswohl, S., Schecklmann, M., Langguth, B., Schlee, W., & Neff, P. (2021). Neurophysiological correlates of residual inhibition in tinnitus: Hints for trait-like EEG power spectra. *Clinical Neurophysiology*, 132 (7), 1694-1707.

# Comparing Three Established Methods for Tinnitus Pitch Matching With Respect to Reliability, Matching Duration, and Subjective Satisfaction

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## Abstract

The pitch of tinnitus sound is a key characteristic that is of importance to research and sound therapies relying on exact tinnitus pitch matches. The identification of this tinnitus pitch is a challenging task as there is no objective measurement available. During the tinnitus pitch-matching procedure, the participant identifies an external sound that is most similar to the subjective perception of the tinnitus. Several methods have been developed to perform this pitch-matching procedure with tinnitus sufferers. In this study, we aimed to compare the method of adjustment, the two-alternative forced-choice (2AFC) method, and the likeness rating (LR) with respect to reliability, matching duration, and subjective satisfaction. Fifty-nine participants with chronic tinnitus were recruited and performed five consecutive runs of tinnitus matching. The participants were randomized to the three different pitch-matching methods. The intraclass correlation coefficients were .67 for method of adjustment, .63 for 2AFC, and .69 for LR, which can be interpreted as good reliability for all the three methods. However, the 2AFC method revealed significant larger within-subject variability than the other measures. Across the five runs and the three different methods, all participants learned to perform the pitch matching faster and with better self-rated accuracy. Comparing the three pitch-matching methods, LR is more time consuming and the participants were less satisfied with the 2AFC method. Overall, the three pitch-matching methods show good reliability. However, we identified differential aspects for improvement in all methods, which are discussed in this article.

## Keywords

tinnitus, tinnitus pitch matching, likeness rating, two-alternative forced choice, method of adjustment

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## Introduction

Tinnitus is the conscious perception of a sound in the absence of any physical source. It is estimated that about 5% to 15% of the population is chronically affected by tinnitus (Hoffman & Reed, 2004). This tinnitus sound is often described as a tone or noise with specific spectral characteristics that can be unique for each individual participant. Moreover, it has been shown that the perception of tinnitus can fluctuate in various situations and environments (Probst, Pryss, Langguth, & Schlee, 2016; Schlee et al., 2016). Currently, there is no objective measurement available that can determine the individual sound characteristics of the tinnitus. The assessment of the tinnitus sound characteristics has therefore to rely on

the subjective description of the participant that matches the perceived tinnitus to an external sound as precisely as possible.

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A precise matching of the tinnitus sound is not only an important measure for the research toward a better understanding of the general and neuronal mechanisms underlying the tinnitus perception but also a key measure that enables well-adjusted individualized sound treatments to suppress or reduce tinnitus sound perception. In the recent years, research on sound therapies (for a review, see Searchfield, Durai, & Linford, 2017) and basic research on the temporary suppression of tinnitus (Fournier et al., 2018; Neff et al., 2017; Roberts, Moffat, Baumann, Ward, & Bosnyak, 2008) have steadily increased. Approaches relying on tinnitus pitch in both research branches are in need of a precise and reliable matching of the individual tinnitus pitch.

In parallel to these developments, studies on the methodology of tinnitus pitch matching have become steadily more numerous continuing to this day. Some of these studies merely applied standard audiometric methods (i.e., demonstration of hearing-relevant frequency sets) to assess tinnitus pitch—a practice which is still widespread in clinical routine and also generating data for concurrent studies (e.g., 31; Gollnast et al., 2017).

Besides and after this audiology-guided area of tinnitus pitch matching, the method of adjustment (MOA) emerged. In short, MOA methods allow for mostly user-controlled adjustment of the central parameters of tinnitus pitch and loudness. These parameters are controlled by mostly knob and slider and to a lesser degree button or graphical user interface (GUI) interaction. Instructions were mostly given beforehand or on-screen in the case of GUIs (e.g., Henry, Rheinsburg, & Ellingson, 2004b; Henry, Rheinsburg, Owens, & Ellingson, 2006; Tyler & Conrad-Armes, 1983).

Contrary to this user-guided method, other approaches have been developed where the loudness matching is taken care of algorithmically, usually precursing the tinnitus pitch matching of the predefined target frequencies. The two-alternative forced-choice method (2AFC; see Penner & Bilger, 1992) and the likeness rating (Norena, Micheyl, Chéry-Croze, & Collet, 2002; Roberts, Moffat, Baumann, Ward, & Bosnyak, 2006) approach are the most important examples for this algorithm-guided methodology. Following the principle of the 2AFC methodology, there are two sound examples presented to the participant who is then forced to pick one of the two examples, that is, more similar to the subjectively perceived tinnitus. After the participant has made the decision, a new pair of sound examples is played, and the participant has again to decide which example is more similar to the tinnitus. The sound examples are chosen in a way to narrow down the search interval to a frequency range that comes close to the individually perceived tinnitus sound with a small number of reversals. The algorithm

for defining these sound examples underwent several modifications in the following years by different research groups. In the end, optimal step size for the central frequency domain emerged to be around 100 Hz (or  $1/12$  octave = 1 semitone when adjusted for the nonlinearity of physical frequencies behind musical scales or human auditory pitch perception; e.g., 56, Wunderlich et al., 2015).

As another algorithm-guided tinnitus pitch-matching methodology, two research groups independently introduced the method of rating standard audiometric frequencies for its contribution (i.e., likeness or similarity) to the perceived tinnitus (Norena et al., 2002; Roberts et al., 2006). The rating of likeness was performed not only on a 0–10 scale in subsequent studies (Basile, Fournier, Hutchins, & Hébert, 2013; Fournier & Hébert, 2012; Hébert & Fournier, 2017) but also on a percent scale (Hoare, Edmondson-Jones, Gander, & Hall, 2014; Roberts et al., 2008). Beyond that, the rating on the percent scale almost exclusively was performed in decades (e.g., 10%, 20%, or 90%). In the study of Norena et al. (2002), LR and the absolute hearing thresholds were overlayed and the authors observed a relationship between the shapes of both curves in that regions with the most pronounced hearing loss coincide with elevated level of tinnitus pitch likeness. The advantage of the LR can be seen in its ability to depict the tinnitus pitch likeness over the whole relevant frequency spectrum, thus giving an array of probabilities, instead of narrowing down the tinnitus pitch to a single frequency as performed in MOA or 2AFC. Still, while the LR method implicates that there may be no relation between the tinnitus pitch likeness, the method could be used to narrow down the search space to identify the tinnitus pitch (Norena et al., 2002) or even extract pitch matches from the LR results (Hébert, 2018).

Evaluating the LR method, Hoare et al. (2014) repeated the procedure at different time intervals resulting in an acceptable test–retest reliability with a 2 week but not with a 3-month interval. A further study was directly comparing the LR with the 2AFC method (Hébert, 2018) with the specific aim to extract one dominant pitch and loudness matching for 2AFC and accordingly three dominant matches for LR. The matching was repeated two times at a 1-month interval. Results were indicative of a superior test–retest reliability of LR compared with 2AFC.

The aim of this study was to compare these three established methods, namely, MOA, 2AFC, and LR. For this comparison, three evaluation categories have been of particular focus: reliability, matching duration, and satisfaction. The reliability of the tinnitus pitch matching is important for basic research as well as for clinical treatments with sound therapies. The duration of the tinnitus matching is of practical importance for the

clinical routine. Since the matching of the tinnitus pitch is purely subjective, the self-rated satisfaction with the matching result is an important feedback of the tinnitus individual that can be used as an additional indicator for the precision of the matching.

## Methods

### Participants

We recruited a sample of 59 tinnitus participants from the interdisciplinary tinnitus clinic at the university hospital Regensburg with an age range spanning from 18 to 75 years. Convenience sampling was applied with the following inclusion and exclusion criteria: Primary and sole inclusion criterion was chronic, tonal tinnitus (single pitch) present for at least 6 months. Exclusion criteria were neurological or psychiatric diseases, concurrent tinnitus interventions, substance abuse, hearing aids, and finally hearing loss above 40 dB at any frequency up to 8 kHz. All participants gave written informed consent after being informed about the scope and procedural details of the study. The study was approved by the ethical review board of the University of Regensburg (approval number 17-658-101). Demographic characteristics of the participant sample are described in Table 1.

To ensure comparability between the pitch-matching methods, participants were randomly assigned to three groups with the goal of three equivalent groups matched for age, sex, hearing loss, and musicality. The resulting groups did not show any statistically significant difference with respect to age ( $t$  test,  $p > .1$ ), sex ( $\chi^2$  test,  $p > .9$ ), hearing loss ( $t$  test,  $p > .4$ ), or musicality ( $\chi^2$  test,  $p > .8$ ). Beyond these primary matching parameters, we also report nonsignificant differences in further assessed variables relevant to the study procedure ( $t$  tests), namely, educational status ( $p > .8$ ), tinnitus duration ( $p > .6$ ), self-reported subjective tinnitus loudness ( $p = .19$ ), and time aware of tinnitus ( $p > .4$ ).

### Questionnaires

Upon the actual experiment, participants filled in an online questionnaire comprising the Tinnitus Sample Case History Questionnaire for clinical and demographic data (Langguth et al., 2007), a short version of the Tinnitus Questionnaire (mini-TF, Goebel & Hiller, 1994), and the German adaption of the Tinnitus Handicap Inventory (Newman, Jacobson, & Spitzer, 1996). Questions, comments, and ratings during the experimental procedure were assessed with paper and pencil.

**Table 1.** Demographic Characteristics of the Study Population (Newman et al., 1996).

Demographic characteristics	Study population (N = 59)
Age (years)—mean $\pm$ SD	53.9 $\pm$ 9.0
Sex— $n$ (%)	
Male	38 (64.4)
Female	21 (35.6)
Average hearing loss (dB)—mean $\pm$ SD	18.4 $\pm$ 18.8
THI sumscore (0–100)—mean $\pm$ SD	55.7 $\pm$ 11.4
Musical experience— $n$ (%)	
No musical experience	44 (74.6)
HM	15 (25.4)
Musical practice hours per week (HM, hours)—mean $\pm$ SD	0.68 $\pm$ 0.48

Note. HM = hobby musician; SD = standard deviation; THI = Tinnitus Handicap Inventory.

### Audiometry

Hearing thresholds were measured in the frequency range from 125 Hz to 8 kHz in octave steps with semi-octave steps between 0.5 and 1 (i.e., 0.75 kHz), 1 and 2 (i.e., 1.5 kHz), 2 and 4 (i.e., 3 kHz), and 4 and 8 kHz (i.e., 6 kHz), respectively (Madsen Midimate 622D; GN Otometrics, Denmark) with Sennheiser HDA 2000 headphones (Sennheiser, Germany).

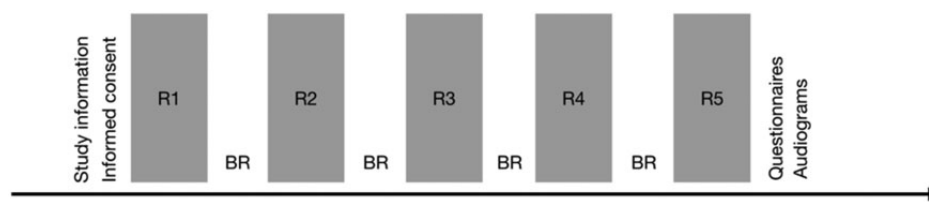
### Study Design

At the beginning of the experiment, the participants were informed about the study procedures and signed the informed consent. All participants performed five consecutive runs of tinnitus matching. Between the runs, participants had a break of at least 5 min where they could read news, solve crosswords, or sudoku for distraction. After the fifth session of the experiment, participants filled in the online survey with the questionnaires described in the earlier questionnaire section. Upon completion of the survey, participants underwent pure tone audiometry (Figure 1). Finally, participants were debriefed and dismissed. The experiment lasted about 90 min on average. No measurements had to be excluded.

### Tinnitus Pitch-Matching Methods

As a first measure, as common in tinnitus pitch matching, an ear was defined on which the matching sounds were presented (Henry & Meikle, 2000). Ideally, the ear contralateral to the tinnitus was chosen in the case of unilateral tinnitus and good hearing in the contralateral ear. In case of bilateral tinnitus with no preference to one side, the matching was performed on the better hearing ear (the ear with less average hearing loss over all tested





**Figure 1.** Flowchart of the experimental procedure. There were five consecutive runs (R1–R5) for tinnitus matching, interrupted by 5-min BR to relax and distract the participants. BR = break.

frequencies). Finally, if all of the above options failed, participants were able to choose their preferred ear for matching. Upon decision on the matching ear, all of the three methods were configured to present their sounds on the respective ear exclusively. With respect to presentation sound levels (i.e., loudness), LR was user-driven as the loudness could be adjusted for each frequency in each trial with a slider starting from a just audible level. In MOA and 2AFC, levels were adjusted to a comfortable level (see details in the following subsections).

**Method of adjustment.** After a 500 Hz tone had been adjusted to a comfortable frequency, participants were instructed to use a rotary encoder to adjust the frequency of the matching pure tone to the pitch of their tinnitus. It was emphasized and demonstrated that the rotary encoder can be used for both fast scrolling through the whole audible spectrum as well as slowly turned for fine tuning. Following this central step of pitch matching, octave confusion was tested with a respective switch. If an octave confusion was identified, participants were asked to redo the pitch-matching procedure. Finally, after successful pitch matching, the loudness of the matching sound was adjusted to match the loudness of the tinnitus.

**Two-alternative forced choice.** The 2AFC procedure was done in three steps: First, a coarse definition of the octave where tinnitus is most probably situated was defined. This was achieved by both having an eye on the audiometric profile and testing the limits of the range with probe tones. The latter was performed in our case and is comparable to the method of limits (Tyler & Conrad-Armes, 1983). The upper and lower limits of this octave then served as the extreme of the starting bracket of the double stair case (e.g., 4000 and 8000 Hz, respectively). This bracket then served for the actual tinnitus pitch matching, where the final frequency was approached on the double staircase in one-third octave steps with a maximum of seven iterations per run. Finally, as a third step, octave confusion was tested and procedure repeated, in case of actual confusion. This last step was comparable to the procedure in MOA.

**Likeness rating.** A frequency list of 11 frequencies (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 kHz according to Hoare et al., 2014) was displayed on the operators GUI and were presented in sequence from top to bottom. Upon button press of a frequency, the sound was played for 3 s. First, participants were instructed to adjust the level of the sound to the loudness of their tinnitus. Following that, participants rated the likeness of the presented sound to the subjective tinnitus on a percent scale. Upon completion, the next frequency was presented and the procedure continued until all 11 frequencies were adjusted and rated. The procedure was implemented in Matlab as a GUI application controllable via computer mouse by the operator (study personnel) and via volume fader by the participants. The set of the 11 frequencies spanning up to 12,000 Hz was pseudo-randomly generated so that no direct neighbor frequency was presented in sequence, and that the single runs did not start or end with identical frequency to counteract anchor and other learning effects. For all of the three methods, a final best matching frequency was chosen. Therefore, for LR, participants had to opt for a favorite frequency if the same LR was given for several frequencies.

### Statistical Analysis

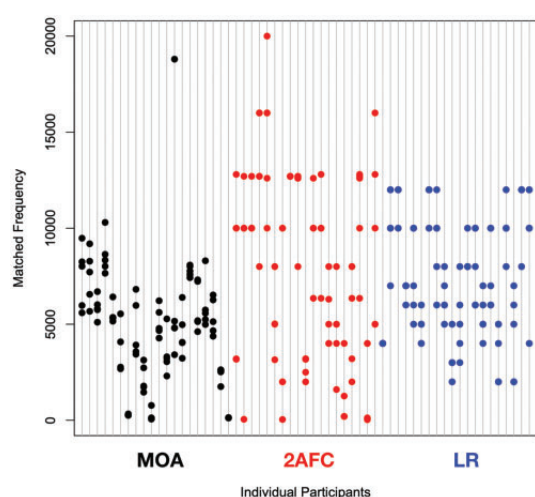
Statistical analysis was performed with R version 3.3.3 (R project, Vienna, Austria). Several measures were used to assess the reliability of the three tinnitus pitch-matching methods. The intraclass correlation (ICC) was calculated using the “irr” library (version 0.84). The coefficient of variation (CV, also known as relative standard deviation) was calculated as a ratio between the standard deviation and the mean. Furthermore, the CV compliance rate (CVCR) was calculated to identify the percentage of participants with a CV below a given cutoff value. For this cutoff value, we chose the criterion  $<0.33$ , as this is commonly interpreted as an acceptable CV (Ruhe, Fejer, & Walker, 2010). All these measures are based on a linear frequency scale, which does not respect the natural pitch perception of the human ear, which is better described as proportional to the logarithm of the frequency. Therefore, we also calculated

the difference between the matched tinnitus pitches in octaves. For each, an average difference between all matching results—measured in octaves—was calculated. Mixed-model analyses of variance (ANOVAs) were calculated with the “nlme” library (version 3.1-131) modeling a random intercept per participant.

## Results

### Tinnitus Pitch-Matching Results

Figure 2 shows the pitch-matching results for each participant and run. The CV was calculated across the five measurements for each participant, and an average CV is reported for each method in Table 2. The highest CV was found for the 2AFC method with 43.6%, which was significantly higher than for the LR (two-sample  $t$  test,  $t = 2.20$ ,  $p = .038$ ). There was no significant difference between the CV values of the MOA and the 2AFC method ( $p > .1$ ) nor between the MOA and the LR



**Figure 2.** Dot plot of the tinnitus matching results for the 59 tinnitus participants. The dots represent individual pitch-matching results. Each individual participant performed five consecutive measures of the tinnitus pitch, visualized by the five dots on the respective line. MOA measurements are shown in black, the 2AFC measurements in red, and the LR measurements in blue. MOA = method of adjustment; 2AFC = two-alternative forced choice; LR = likeness rating.

( $p > .5$ ). In addition, the CVCR compliance rate (CVCR) was calculated for each method with a cutoff criterion of  $CV < .33$  (Ruhe et al., 2010). The largest CVCR was found for the MOA with 80% of the participants showing a CV below .33. Of the participants using LR, 73.7% scored below this level, while only 55% of the participants using the 2AFC method reached such a low CV value. For each participant, the mean difference between the five pitch-matching results was calculated in octaves. The average values and standard differences for each method are reported in Table 2. The largest average was found for the 2AFC method with a mean difference of 1.07 octaves. This average was significantly higher than the average of the MOA (two-sample  $t$  test,  $t = 2.31$ ,  $p = .03$ ) and significantly higher than the LR (two-sample  $t$  test,  $t = 2.37$ ,  $p = .03$ ). There was no significant difference in the mean octave differences between the MOA and the LR ( $p > .9$ ). The average tinnitus pitch measured with the MOA was with 4,697 Hz significantly lower than the average pitch measured with the 2AFC method (two-sample  $t$  test,  $t = 2.90$ ,  $p = .007$ ) and also significantly lower than the average pitch measured with the LR (two-sample  $t$  test,  $t = 3.46$ ,  $p = .001$ ). There was no significant difference in the average pitch measures between the 2AFC method and the LR ( $p > .8$ ).

### Duration of Pitch Matching

The time duration for the performing the pitch matching was measured for each run and each tinnitus participant, and the mean durations are shown in Table 3. A mixed-model ANOVA revealed a significant main effect for the run ( $F = 144.4$ ,  $p < .0001$ ) and the method type ( $F = 12.5$ ,  $p < .0001$ ), while the interaction effect of run and method was not significant ( $p > .1$ ). Across all pitch-matching methods, the participants learned quickly to perform the pitch matching with shorter time durations. For all methods, the comparison between Run 1 and Run 5 shows much faster pitch matching for the last session (paired  $t$  tests, all  $p < .0001$ ). Post hoc analysis on the main effect for the method type showed that the LR was always the method with the longest duration. In all the five runs, the LR was the significantly slower than the fastest method (all  $p < .01$ ). Between the 2AFC

**Table 2.** Reliability Measures and Average Pitch Measures for the Three Different Pitch-Matching Methods.

Method	ICC (95% CI)	Average CV (%)	CVCR (%)	Mean OD	Mean frequency (Hz)
MOA	0.67 [0.50, 0.83]	28.4	80	$0.42 \pm 0.36$	4697
2AFC	0.63 [0.44, 0.80]	43.6	55	$1.07 \pm 1.20$	7779
LR	0.69 [0.51, 0.84]	23.4	73.7	$0.41 \pm 1.20$	7632

Note. ICC = intraclass correlation; CI = confidence interval; CV = coefficient of variation; CVCR = CV compliance rate; OD = octave difference; MOA = method of adjustment; 2AFC = two-alternative forced-choice; LR = likeness rating.

**Table 3.** Time Duration for Pitch Matching, Measured in Seconds (mean  $\pm$  SD).

Method	Run 1	Run 2	Run 3	Run 4	Run 5
MOA	385 $\pm$ 205	164 $\pm$ 73	146 $\pm$ 111	152 $\pm$ 81	131 $\pm$ 81
2AFC	327 $\pm$ 108	215 $\pm$ 89	205 $\pm$ 86	170 $\pm$ 60	161 $\pm$ 78
LR	480 $\pm$ 162	335 $\pm$ 132	256 $\pm$ 97	252 $\pm$ 77	233 $\pm$ 72

Note. MOA = method of adjustment; 2AFC = two-alternative forced choice; LR = likeness rating.

**Table 4.** Subjective Self-ratings of the Participants on the Accuracy of the Pitch Matching (mean  $\pm$  SD).

Method	Run 1	Run 2	Run 3	Run 4	Run 5
MOA	8.1 $\pm$ 0.78	8.2 $\pm$ 1.24	8.45 $\pm$ 1.23	8.45 $\pm$ 1.05	8.7 $\pm$ 1.03
2AFC	7.5 $\pm$ 1.43	6.6 $\pm$ 1.9	7.9 $\pm$ 1.12	7.35 $\pm$ 1.81	7.9 $\pm$ 1.37
LR	8.21 $\pm$ 1.23	8.79 $\pm$ 0.79	8.84 $\pm$ 1.07	8.68 $\pm$ 0.89	8.63 $\pm$ 1.11

Note. Range: 1–10, 1 = *not satisfactory at all*, 10 = *highly satisfactory*. MOA = method of adjustment; 2AFC = two-alternative forced choice; LR = likeness rating; SD = standard deviation.

method and MOA, there was no significant difference found in neither of the runs (all  $p > .05$ ).

### Subjective Satisfaction With Matching Accuracy

After each pitch matching, the participants were asked to rate the matching accuracy on a scale from 0 to 10. The mean values and standard deviation for all methods and runs are given in Table 4. A mixed-model ANOVA on these self-rating values revealed a main effect for the run ( $F = 9.6$ ,  $p = .002$ ) and the method type ( $F = 9.1$ ,  $p < .001$ ), but no significant interaction ( $p > .6$ ). The main effect for the run reflects the tendency that the satisfaction slightly increased over the five consecutive runs. However, post hoc analysis between the first and the fifth run revealed only for the MOA a significant improvement ( $t$  test,  $t = 2.07$ ,  $p = .046$ ). The main effect for the method reveals that participants using the 2AFC method always gave the lowest ratings across all runs, while the participants using the LR gave the highest ratings in four of the five runs. In Runs 2, 3, and 4, the difference between the satisfaction self-ratings of the 2AFC method and the LR reached statistical significance (all  $p < .011$ ).

### Discussion

MOA, 2AFC, and LR are three different pitch-matching methods that have been compared on 59 chronic tinnitus participants. The pitch-matching methods have been compared with respect to their retest reliability, the time duration for performing the matching procedure, and the subjective satisfaction of the participants with the matching result.

To evaluate the reliability of pitch-matching methods, we used four different measures highlighting different aspects of the retest results. The ICC was calculated as

a commonly used measure for retest reliability with multiple repeated measures. The ICC values of all the three pitch-matching methods (Table 2) can be interpreted as good reliability. End points of the confidence intervals extended between fair and excellent ICC values. Since the ICC measures resulted in wide confidence intervals, it was not possible to decide whether there is one method significantly less or more reliable than the others. Similar observations for reliability were made in several former studies where different matching methods were compared (Basile et al., 2013; Hauptmann et al., 2016; Henry, Flick, Gilbert, Ellingson, & Fausti, 2004a; Tyler & Conrad-Armes, 2009; Wunderlich et al., 2015). Conflicting results were shown in an other study demonstrating superior test–retest concordance of LR in comparison to 2AFC (Hébert, 2018). To test for differences not accessible with the ICC method, we also calculated the CV, which is a measure for the relative standard deviation of the matching results. The CVs for participants using the 2AFC method were found to be much higher than in the participants using the LR. This also reflected in the CVCR. Only 55% of the participants using the 2AFC method were able to produce a CV smaller than .33. On the other side, the CVCR for the LR reached 73.7% and the MOA 80%. A similar analysis was performed in Hauptmann et al. (2016) where the comparison of 2AFC and MOA in matching a test tone resulted in 80% of the trials within a 5% pitch interval for 2AFC and only 40% for MOA. Notably, given the specific task of matching to a fixed external sound, the results cannot be directly compared with the results in this study and are furthermore in conflict with the view of none or only minor differences in reliability between the established methods. Another important measure, for example, for the individual adjustment of sound therapies, is the mean octave difference. As some

contemporary sound therapies (e.g., the notched music therapy or the notched hearing aid) need to adjust a notch (e.g., 0.5–1 octave) around the individually measured tinnitus pitch, the average deviation is of practical importance for the clinical treatment. We found that the mean octave difference in participants using the 2AFC method is significantly higher than in participants using the MOA or the LR. This could be explained by a rather low number of reversals applied in our study (i.e., 7) or a latent, systematic bias in the 2AFC experimental group.

The evaluation of the duration for tinnitus matching revealed a strong learning effect of all participants across all pitch-matching methods. The average matching duration in Run 5 was always more than 50% faster than in Run 1. This very fast learning effect will need to be considered for designing future studies with repeated tinnitus pitch matchings. In addition, we found that the LR method consistently needed a longer time duration for pitch matching, which can be explained by the time cost of its inherent procedurality (i.e., loudness matching of all probe tones). This dependence on procedural details as well as no previous studies testing multiple runs of different matching methods in parallel obstructs a meaningful discussion of testing duration. Fittingly, Henry et al. (2004a, page 134) noted for LR that

However, note that for the Subject-Guided method, the time required to obtain thresholds and loudness matches at each frequency was not factored into the time of testing. Thus obtaining a pitch match with this method would take much longer if total testing time was combined.

Taken together, the duration of tinnitus matching lacks a proper conceptualization as details inherent to the procedure or dependencies between matching procedures or audiometric measures limit the measurement of *actual* matching duration.

To assess the subjective satisfaction of the participant with the pitch-matching result, the participants were asked to self-rate on a scale between 0 and 10 how much the matched tinnitus tone corresponds to the subjectively perceived tinnitus. We found that subjective satisfaction slightly increased from the first to the fifth run across all pitch-matching methods, especially MOA. This can be interpreted as an indicator that the participants not only learned to perform the pitch matching faster but also learned to match their tinnitus with better accuracy. A comparable slight increase overtime or certainly between the first and the subsequent session was found for MOA (Henry et al., 2004b) and for LR or 2AFC (Hébert, 2018). However, the improvement is rather small in magnitude in our data as well as in former studies. More studies will be needed to examine

the learning progress in more detail. Furthermore, the analysis revealed that the participants in the 2AFC group were on average less satisfied with matching results than the participants using the MOA or the LR. This *prima facie* contradicts our findings, but could again be explained by the latent limitations of the 2AFC method in our study. Future studies could also profit from a differential set of questions regarding satisfaction such as comprehensibility, ease of use, certainty about the result, and comfort level of the procedures (Wunderlich et al., 2015).

In our study, we presented the matching sound stimulus to the ear contralateral to the tinnitus ear according to common practice. Yet, there is conflicting evidence and recommendations. Tyler and Conrad-Arnes (1983) observed lower pitch matchings in some subjects in the contralateral matching procedure and recommend the use of ipsilateral stimulation to “avoid any effects of diplacusis.” Furthermore, this study identified seven to nine runs as the optimal number of repetitions in tinnitus pitch matching and proposed to track the variability of the results. Related to that, consistent measure over larger time intervals are needed to both identify persons with fluctuating tinnitus but also better prepare any study or treatment dependent on tinnitus pitch (Tyler, 1985). With increasing repetitions and related exposure to sounds, the effect of those sounds on the tinnitus itself but also the matching procedure have to be considered (Henry & Meikle, 2000; Tyler, 2005). Unfortunately, we cannot provide the reader with any data on such effects at this point.

Summarizing the results of this comparison, there was no pitch-matching method that is the clear winner in all categories. Future methodological studies on tinnitus pitch matching may take advantage of these results by developing a combined method melting the advantages of each method together (e.g., as proposed in Hauptmann et al., 2016). MOA was found to be a method with good reliability of the tinnitus matching, low variability of matching results, short time duration for the tinnitus matching, and high participant satisfaction. However, it has to be highlighted here that the frequencies of the matched tinnitus tones were significantly lower than the frequencies that have been matched with 2AFC or LR. With implementation that we used in this study, the participants using the MOA always started with an initial setting of 500 Hz and were asked to increase the frequency until they reach their individual tinnitus pitch. We suspect that this initially low frequency setting biased the participants toward lower frequencies and offering an anchor for their matching decision, which might have favored octave confusions toward lower frequencies. Future developments will need to address this disadvantage by better solutions for the initial setting



(e.g., starting with a random frequency). The 2AFC method was found to be a fast technique for tinnitus pitch matching. The analysis of the ICC demonstrates a good reliability. The analysis of the CV as well as the mean octave difference, however, reveals large variations of the matched frequency within repeated measures of the individuals. This is most likely due to the algorithm that forces the participants into making a series of comparative decisions. If the participant makes a wrong decision in the beginning, this leads the following decision tree into a wrong direction (Wunderlich et al., 2015). Accordingly, the subjective satisfaction of the participants remained poor compared with the other matching procedures. Pitch matching with the LR was done with good reliability and relatively low variation of pitch-matching results. The subjective satisfaction of the participants with the results was relatively high. However, the participants needed significantly more time to perform the pitch matching compared with the other methods. An important limitation of the LR is the frequency resolution of the results. In our implementation, we used 11 different frequencies for the LR. The maximum and minimum frequencies as well as the frequency resolution are dependent on these predefined frequencies. In addition, more test frequencies would prolong the matching procedure. This is an immanent trade-off of the methodology. The researcher or clinician performing the LR therefore has to decide on the needed frequency resolution and time commitment.

## Conclusion

Altogether, the compared methods for pitch matching show good reliability with acceptable matching durations and participant satisfaction. However, in all the aforementioned methods, we identified room for improvement. Beyond that, the meaningful combination of the three methods could improve reliability, matching duration, and satisfaction with the results. Especially in a time of emerging auditory treatments that depend on precise tinnitus pitch matching, future advancements are needed to develop methods that can be performed fast and with high reliability. This will help to improve the efficacy of the clinical treatment and also enable new insights in the scientific understanding of tinnitus.

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# Comparison of Amplitude Modulated Sounds and Pure Tones at the Tinnitus Frequency: Residual Tinnitus Suppression and Stimulus Evaluation

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## Abstract

Recent studies have compared tinnitus suppression, or residual inhibition, between amplitude- and frequency-modulated (AM) sounds and noises or pure tones (PT). Results are indicative, yet inconclusive, of stronger tinnitus suppression of modulated sounds especially near the tinnitus frequency. Systematic comparison of AM sounds at the tinnitus frequency has not yet been studied in depth. The current study therefore aims at further advancing this line of research by contrasting tinnitus suppression profiles of AM and PT sounds at the matched tinnitus frequency (i.e., 10 and 40 Hz AM vs. PT). *Participants with chronic, tonal tinnitus (n = 29)* underwent comprehensive psychometric, audiometric, tinnitus matching, and acoustic stimulation procedures. Stimuli were presented for 3 minutes in two loudness regimes (60 dB sensation level [SL], minimum masking level [MML] + 6 dB, control sound: SL –6 dB) and amplitude modulated with 0, 10, or 40 Hz. Tinnitus loudness suppression was measured after the stimulation every 30 seconds. In addition, stimuli were rated regarding their valence and arousal. Results demonstrate only trends for better tinnitus suppression for the 10 Hz modulation and presentation level of 60 dB SL compared with PT, whereas nonsignificant results are reported for 40 Hz and MML + 6 dB, respectively. Furthermore, the 10 Hz AM at 60 dB SL and the 40 Hz AM at MML + 6 dB (trend) stimuli were better tolerated as elicited by valence ratings. We conclude that 10 Hz AM sounds at the tinnitus frequency may be useful to further elucidate the phenomenon of residual inhibition.

## Keywords

tinnitus, residual inhibition, amplitude modulation, sound therapy, entrainment

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## Introduction

Subjective tinnitus is defined as the perception of a phantom sound in the absence of any external objective physical source (Eggermont & Roberts, 2004) and is defined as chronic after continuous presence for 6 months (Mazurek, Olze, Haupt, & Szczeppek, 2010). Chronic subjective tinnitus is highly prevalent with 10% to 15% of the population reporting continuous tinnitus perception and about 1% to 2% suffering immensely from the condition (Langguth, Kreuzer, Kleinjung, & De Ridder, 2013). The phenomenon is continuously gaining relevance as it coincides with a steadily aging demographic (Hoffman & Reed, 2004) and concomitant age-related hearing loss (presbycusis; Ferreira, Ramos Júnior, &

Mendes, 2009), noisy occupational or leisure time environments (Sanchez et al., 2016; Shargorodsky, Curhan, & Farwell, 2010), and stress (Mazurek, Haupt,

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& Olze, 2012). Moreover, tinnitus is not only related to altered auditory functions like speech perception (Ivansic et al., 2017; Jagoda et al., 2018), sound source localization (Hyvärinen, Mendonça, Santala, Pulkki, & Aarnisalo, 2016), auditory attention (Cuny, Norena, El Massioui, & Chéry-Croze, 2004), and emotional attention processes (Trevis, McLachlan, & Wilson, 2016), but also to affective disorders like depression or anxiety (Langguth, 2012), insomnia (Croenlein et al., 2016), and lowered quality of life (Nondahl et al., 2007; Weidt et al., 2016).

In most cases, the perception of the phantom sound seems to develop after loss of cochlear hair cells or other peripheral alterations leading to maladaptive plasticity in the auditory pathway and brain. It is still debated if and how either objective (Eggermont & Roberts, 2004; Mazurek et al., 2010; Schaette & Kempter, 2006) or “hidden” hearing loss (Adjamian, Sereda, Zobay, Hall, & Palmer, 2012; Schaette & McAlpine, 2011; Weisz, Hartmann, Dohrmann, Schlee, & Norena, 2006) contribute to tinnitus generation. Models of tinnitus generation and maintenance are still being debated (Sedley, Friston, Gander, Kumar, & Griffiths, 2016) and are limited by an underlying inherent heterogeneity of the disorder (Landgrebe et al., 2012). Yet, consensus arose that both the peripheral auditory system as well as differential brain networks are involved and correlate with differential aspects of tinnitus (Adjamian, Sereda, & Hall, 2009; De Ridder, Elgoyhen, Romo, & Langguth, 2011; De Ridder et al., 2014; Eggermont & Roberts, 2004; Elgoyhen, Langguth, De Ridder, & Vanneste, 2015; Jastreboff, 1990; Schlee, Mueller, et al., 2009).

Up to today, there is no generally applicable cure for this phantom sound perception. Established interventions aim at alleviating the tinnitus sound or accompanying symptoms (Baguley, McFerran, & Hall, 2013). Within a consensus clinical management framework (Langguth et al., 2013), three avenues of symptom-oriented interventions are suggested: First, ideally accompanying other treatment options (Baguley et al., 2013), cognitive behavioral therapy is suggested to establish coping strategies (Cima et al., 2012). A further option involves differential approaches of neuromodulation and stimulation (Hoare, Adjamian, & Sereda, 2016; Soleimani, Jalali, & Hasandokht, 2016) with concurrently increased efficacy applying multisite montages (Lehner, Scheckmann, Greenlee, Rupprecht, & Langguth, 2016), individual protocols (Kreuzer et al., 2017), and possibly combined approaches (Shekhawat, Kobayashi, & Searchfield, 2015; Teismann et al., 2014). Finally, auditory stimulation was traditionally studied and evolved to exert efficacy in suppressing tinnitus in sound therapies (Feldmann, 1971; Hazell & Wood, 2009; Henry, Rheinsburg, & Zaugg, 2004; Terry, Jones, Davis, & Slater, 1983; Vernon, 1977). Recent technical advances

and neuroscientific research could spawn some promising approaches of auditory retraining aimed at reversing maladaptive neural plasticity related to tinnitus (Adamchic et al., 2017; Okamoto, Stein, et al., 2015; Stracke, Stoll, & Pantev, 2010; Tass, Adamchic, Freund, von Stackelberg, & Hauptmann, 2012). Yet, whereas masking alongside counseling in tinnitus management has proven efficacy and may be clinically implemented (Baguley et al., 2013), there is still debate about clinical use of aforementioned retraining approaches (e.g., Wegger, Ovesen, & Larsen, 2017).

The present study joins the branch of auditory stimulation in tinnitus with a focus on residual inhibition (RI; Roberts, 2007) or, more specifically, tinnitus suppression effects with patterned (here: amplitude-modulated [AM]) sounds. Recent studies aimed to demonstrate more pronounced tinnitus suppression after stimulation with AM or frequency-modulated (FM) sounds compared with unmodulated sounds and noise with inconclusive results (Neff et al., 2017; Reavis et al., 2012; Tyler, Stocking, Secor, & Slattery, 2014). This putative effect is primarily observed with sounds in or around the tinnitus frequency (Schaette, König, Hornig, Gross, & Kempter, 2010; Roberts, Moffat, Baumann, Ward, & Bosnyak, 2008; Roberts, Moffat, & Bosnyak, 2006; Sockalingam, Dunphy, Nam, & Gulliver, 2009) while its exact mechanisms of action remain unclear. Concretely, it is not known if and how modulated sounds may produce stronger and longer tinnitus suppression or RI than constant noise or pure tone (PT) sounds. This is partly explicable by the fact that, in classical masking and RI, only unmodulated sounds and noise have been used (e.g., Roberts et al., 2006, 2008; Terry et al., 1983).

Alternatively or concomitantly, neural entrainment effects may account for normalization of tinnitus-specific neural oscillations (Neff et al., 2017; Reavis et al., 2012) and in comparable disorders (e.g., pain [Ecsy, Jones, & Brown, 2017]). Neural entrainment describes the phenomenon of synchronization of endogenous neural oscillations to patterned or rhythmic external stimuli (here: auditory [Draganova, Ross, Wollbrink, & Pantev, 2008; Picton, John, Dimitrijevic, & Purcell, 2003]). Furthermore, changes in neurophysiology (Kaltenbach & Godfrey, 2008) or chemistry (Sedley et al., 2015) throughout the auditory pathway and the brain may also play a role but would have to be specifically tested and modeled with the modulated stimulus class.

Generally, a resurrection of interest in RI is observable in tinnitus research, as echoed and welcomed in a recent study by Fournier et al. (2018). Yet, given the multitude of possible mechanisms of action, the ongoing research on causes and mechanisms, the underlying problem of heterogeneity of tinnitus, limited methods, and the gap between human and basic animal research,



it is difficult to propose an all-encompassing model of the mechanism of action of AM stimulation at this point. Beyond that, data are scarce and largely absent in the case of prolonged stimulation for possible tinnitus treatment with the modulated stimulus class. Therefore, it is deemed necessary to proceed in small steps and iterate on the immediate subjective effects of the stimulus class. Ideally, primary parameters of modulation rate, presentation level, carrier sounds or frequency (range), duration, and tolerability should be evaluated in respective study designs.

Psychological aspects, especially tolerability of tinnitus RI and therapeutic sounds, should be investigated, as they seem to be affecting tinnitus loudness perception (Durai, O'Keeffe, & Searchfield, 2017) or sound therapy treatment outcomes (Searchfield, Durai, & Linford, 2017). Furthermore, differences in general sound or specific stimuli tolerability could be mediated by personality (Searchfield et al., 2017) and are generally influenced by neurobiological interactions between auditory systems of perception and limbic systems related to valence (Kraus & Canlon, 2012). To sum up, psychological and biological factors, besides well-definable physical stimulus parameters, contribute to the perception of sounds or suppression of tinnitus and should be taken into account when studying induced tinnitus suppression. Concretely, studies should assess tolerability of tested sound stimuli to better understand the mechanisms of action in RI or sound therapy in tinnitus.

Former studies observed the potential to temporarily suppress tinnitus with 40 Hz AM and FM sounds in fixed frequency bands (Reavis et al., 2012), with 40 Hz AM pitch-matched sounds in contrast to broadband noise (Tyler et al., 2014), or with 10 Hz AM sounds at the matched tinnitus frequency in our former study (Neff et al., 2017). In more detail, our former study tested an explorative set of three 10 Hz AM with PT (at tinnitus frequency and 108 Hz) or FM sounds as carrier sounds, two 10 Hz (notch) filter modulations around tinnitus frequency with pink noise and music as carrier sounds, and two control stimuli (PT at tinnitus frequency, pink noise) in respect to RI after 3 minutes of stimulation at 60 dB SL. Post hoc contrasts between the stimuli indicated stronger RI for the AM sound at the tinnitus frequency compared with pink noise, AM at 108 Hz, and the filter modulated music, as well as stronger RI for the AM or FM sound compared with pink noise and music. The results from our former and the aforementioned previous studies were especially inconclusive when contrasting AM to PT sounds with identical carrier sounds. This contrast is deemed paramount to better understand the RI potential of AM and PT sounds as merely the modulation (i.e., AM) is manipulated while the other stimuli parameter (i.e., carrier sound and loudness) are controlled. In these previous studies, either carrier sounds

were not matched to the tinnitus frequency (Reavis et al., 2012), or the contrast was performed between PT and noise carrier sounds (Tyler et al., 2014), or a wide array of differential sounds was used with no significant difference between AM and PT sounds matched at the tinnitus frequency (Neff et al., 2017). Moreover, the modulation rate was different with 40 Hz for Reavis et al. (2012) and Tyler et al. (2014) whereas our former study applied 10 Hz. Besides that, many aspects of the designs and analysis strategies of the studies are not directly comparable further adding to the limited insights regarding differences between modulated and unmodulated PTs. Taken together, no former study was specifically designed to test this critical contrast of interest. The aim of this study is therefore to compare AM with PT sounds at the matched tinnitus frequency to further elucidate efficacy in tinnitus suppression of the AM stimulus class.

Concretely, we hypothesize that AM sounds (with 10 and 40 Hz modulation) at the tinnitus frequency may elicit better short-term tinnitus suppression than their unmodulated PT pendants. Secondly, we want to test if and how different sound levels during acoustic stimulation may influence this contrast by presenting the stimuli at SL plus 60 dB (Neff et al., 2017) compared with presentation 6 dB above individual's minimum masking level (MML). While we expect generally stronger tinnitus suppression for the SL stimuli due to the higher presentation loudness compared with the MML stimuli, we still hypothesize that the effect of better suppression of AM compared with unmodulated sound will become evident in both loudness regimes. In addition, aiming both at better understanding of RI profiles and at possible future acoustic interventions for tinnitus, subjective evaluation of tolerability of the stimuli is deemed as critical and was assessed by means of pictorial scales (manikins) of valence and arousal (Bradley & Lang, 1994). Given the broad use of these pictorial scales for emotional assessment, also for reactivity to sounds (Bradley & Lang 2000), these scales are deemed as suitable to test the tolerability of stimuli used in this study. Hence, we expect better tolerability (reflected by higher valence and lower arousal scores) for the AM compared with the PT sounds. To the best of our knowledge, the present study is the first study to directly compare AM and PT sounds matched to the tinnitus frequency (i.e., using the same PT carrier sound). Results could have implications for both the RI phenomenon as well as for possible future sound therapies.

## Methods

Methods, procedures, and sample size of the study are directly comparable to our former study (Neff et al., 2017) with some changes in the tinnitus matching

equipment and protocol. Numeric participant characteristics, tinnitus parameters, and tinnitus matching results are listed in Table 2 in the Results section.

### Participants

Twenty-nine patients (9 females, between age 18 and 75 years) with chronic bilateral tonal tinnitus (>12 months since tinnitus onset) from the Interdisciplinary Tinnitus Clinic of Regensburg were included in this study. Patients with a history or presence of any severe and relevant somatic, neurological, or mental disorders were excluded. Further exclusion criteria were ongoing intake of any psychotropic medication or substance and the participation in other tinnitus studies or treatments. The study was approved by the local ethics committee (16-101-0061). After a comprehensive explanation of the procedures, risks, and benefits, all participants gave written informed consent.

### Psychometry

Upon the actual experiment, participants filled in an online questionnaire comprising German adaptations of the Tinnitus Sample Case History Questionnaire for clinical and demographic data (Langguth et al., 2007), tinnitus questionnaire (Goebel & Hiller, 1994), tinnitus handicap inventory (Kleinjung et al., 2007), and a short version of the hyperacusis questionnaire (mini-HQ9 [Goebel, Berthold, Scheffold, & Bläsing, 2013]).

### Audiometry

Hearing thresholds were measured in the frequency range from 125 Hz to 8 kHz in octave steps with semi-octave steps between 0.5 and 1 (i.e., 0.75 kHz), 1 and 2 (i.e., 1.5 kHz), 2 and 4 (i.e., 3 kHz), and 4 and 8 kHz (i.e., 6 kHz), respectively (Madsen Midimate 622D; GN Otometrics, Denmark). Sennheiser HDA 2000 headphones (Sennheiser, Germany) were used for audiometry, subsequent tinnitus matching, and the actual acoustic stimulation procedure.

### Tinnitus Matching

Tinnitus matching was performed applying a method of adjustment approach (Henry, Rheinsburg, & Ellingson, 2004) with a custom-tailored MAX program (MAX 7; Cycling '74, USA) and a modular hardware controller (Palette Expert Kit; Palette; Canada). For the actual procedure, we adhered to the sequence of the tinnitus tester procedure (Roberts et al., 2008) without tinnitus likelihood ratings, tests for RI, and loudness matching of 1 kHz reference tones. An octave confusion test was included at the end of the procedure. Participants were

accustomed to the device and subsequently trained for the procedure. Main parameters of interest assessed by the matching procedure were tinnitus loudness (in dB), tinnitus side (on a continuum between 0 [=left ear] to 127 [=right ear] with the value of 63 representing equally distributed bilateral tinnitus) and tinnitus frequency (in Hz). The frequency dial's step size (i.e., endless dial) was slightly below a semitone, and its frequency range between 40 and 16000 Hz. During the actual matching procedure, participants self-reliantly adjusted all the parameters with no need to check with the study personnel or a computer screen (tinnitus parameters were indicated on the controller upon touching of the respective control units): First, a 500 Hz PT was set to a comfortable level. Following on that, participants proceeded with the matching of the frequency. Finally, the sound was adjusted in loudness to fit the perceived tinnitus loudness and localized in the stereo spectrum with the panning dial. Participants were then given the opportunity to rate the correspondence between matched sound and their tinnitus as well as the general usability of the matching equipment on a scale ranging from 1 to 10. The time of the self-reliant matching procedure was assessed by the study personnel, and the matching procedure was repeated after acoustic stimulation described in the next paragraph. In the case of multiple tinnitus sensations, participants were instructed to focus on their dominant tinnitus.

### Acoustic Stimulation

Five amplitude modulated sounds (10 or 40 Hz modulation rates at 60 dB SL and MML + 6 dB presentation loudness, and a single, inaudible 10 Hz stimulus 6 dB below SL) and two unmodulated sounds (PTs at 60 dB SL and MML) were prepared in MATLAB (MATLAB R2015a; Mathworks, USA) with the matched tinnitus pitch acting as the frequency of the PT carrier sounds. SL was defined by the hearing threshold at the frequency neighboring (i.e., lower) to the matched tinnitus frequency (e.g., the hearing threshold of 3 kHz when tinnitus frequency was matched to 3.2 kHz). In the remainder of the manuscript, the stimuli are termed as follows (Table 1): AM1060 refers to the AM sound modulated with 10 Hz at 60 dB SL, AM10MML to the 10 Hz AM sound at 6 dB above MML, AM4060 to the 40 Hz AM sound at 60 dB SL, AM40MML to the 40 Hz AM sound at 6 dB above MML, P60 to the PT at 60 dB SL, PMML to the PT at 6 dB above MML, and finally AM10U to the undetectable 10 Hz AM sound 6 dB below SL. The sum total of seven acoustic stimuli with 3 minutes of duration each was produced for each participant individually. Details regarding how stimuli were created are indicated in the section "Sound Stimuli" and Figure 1 of our previous publication (stimuli in the

current study correspond to the “AMTinnitus” stimulus in the former study; Neff et al., 2017). The stimuli presented were matched in peak amplitude between the PT and AM stimuli classes in both loudness regimes. As a consequence, AM stimuli had a slightly lower root mean square sound pressure level ( $<5.3$  dB root mean square for the AM sounds) compared with the PT sounds; 80 dBA (peak) was the upper limit for the sound level of all stimuli, which were presented idiotically. Participants were reminded to interrupt the procedure whenever a sound was deemed uncomfortable. No particular instruction was given to focus their attention on either the sound or tinnitus. Presentation sequence of the seven stimuli was randomized for each participant. To assess the residual tinnitus suppression of the sounds,

participants were instructed to rate the loudness of their tinnitus on a numeric rating scale in percentage, compared with the prestimulation loudness (i.e., normal or recuperated loudness), after each stimulation at time points 0, 30, 60, 90, 120, 150, and 180 seconds (Neff et al., 2017; Reavis et al., 2012). Furthermore, participants were asked to rate all stimuli in valence and arousal on pictorial manikin scales with nine steps (Bradley & Lang, 1994). Participants were thus shown scales with increasing arousal states, represented by different stages of an explosion in the manikin’s chest region, and increasing valence ratings, represented by a spectrum between sad and smiling faces. At the end of the stimulation procedure, participants again performed the tinnitus matching task and were finally dismissed.

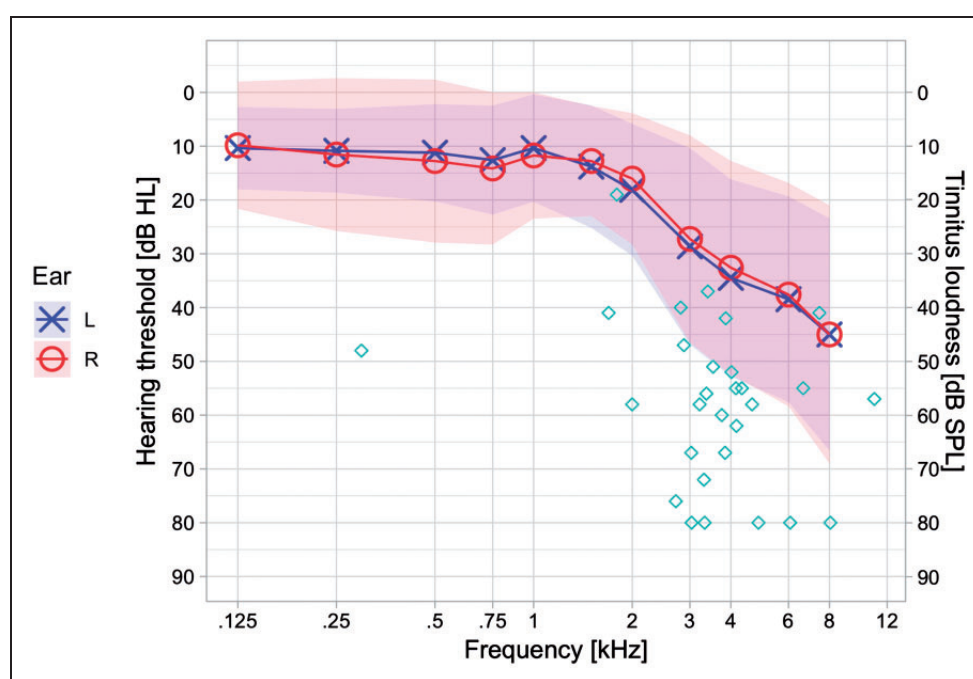
**Table 1.** Overview and Nomenclature of the Acoustic Stimuli.

Modulation rate (Hz) \ Stimulation level	60 dB SL	MML + 6 dB	SL – 6 dB
0	P60	PMML	–
10	AM1060	AM10MML	AM10U
40	AM4060	AM40MML	–

Note. SL = sensation level; MML = minimum masking level.

### Data Analysis

R (R version 3.3.3; R Foundation for Statistical Computing, Austria) was used to calculate statistics including descriptives, Pearson correlations, and paired samples *t* test to test the matching outcomes as well as the differences in evaluation of the stimuli. To investigate the main research question, namely the difference between modulated and unmodulated sounds at the tinnitus frequency, mixed effect models were computed with the nlme package (<https://cran.r-project.org/web/packages/nlme/>). After identifying an effect for position



**Figure 1.** Mean hearing thresholds and matched tinnitus of all participants. Hearing thresholds: Colored ribbons indicate one standard deviation interval for the two ears, respectively. Tinnitus matching: Cyan diamonds are indicative individual tinnitus pitch and loudness matches. Notably, 80 dB was the upper limit for tinnitus loudness matches.

(i.e., the order of the presented seven stimuli), the final model consisted of fixed effects for condition (i.e., different acoustic stimuli), random effects for time and subjects, and an added term for position as a covariate, both modeled linearly and with a polynomial term for optimal model fit. The model was fitted using the maximum likelihood method unbiased for the fixed effects and appropriate for the given sample size. A priori contrasts of interest were defined between AM and PT conditions for both stimulation level regimes (i.e., 10 and 40 Hz AM vs. PT sounds at 60 dB SL and MML).

Given the weak effects of previous work (Neff et al., 2017; Reavis et al., 2012; Tyler et al., 2014) and adherence to statistical rigor, we report the results of two-tailed tests. Both corrected (Bonferroni adjustment for the number of contrasts) and uncorrected results are reported side by side, which enables readers to draw their own conclusions from the results presented while we focus our discussion of results on significant and trending (i.e.,  $p < .1$ ) corrected results. For the exploratory analysis of valence and arousal related to the stimuli, two-tailed tests were used given the lack of a directed hypothesis. Furthermore, Bonferroni adjustment was performed for the number of contrasts.

## Results

### Participants' Characteristics and Audiometry

Participants' characteristics, questionnaire scores, and main tinnitus matching parameters are listed in

Table 2. Mean hearing thresholds did not differ between the two ears (left side: mean = 21.21,  $SD = 9.54$ ; right side: mean = 20.96,  $SD = 11.03$ ;  $t(28) = 0.36$ ,  $p = .722$ ). Eleven participants indicated their tinnitus location in both ears, three inside the head, six in both ears stronger in the left ear, four in both ears stronger in the right ear, one in the left ear, and four in the right ear.

### Tinnitus Matching

Results of the matching procedure before acoustic stimulation are listed in Table 2 and plotted in the audiogram of Figure 1. Participants' ratings of the matched sound and the matching procedure were high (matched sound: mean = 8.66,  $SD = 0.936$ ; matching procedure: mean = 8.62,  $SD = 1.237$  [range 1–10]). Notably, all participants were able to match their single (or in three cases: dominant) tonal tinnitus with subjectively satisfactory results. We double-checked the outlier matching of 298 Hz (see Table 2 and Figure 1 with the participant [i.e., with multiple upward octave shifts, oral discussion]) with no change in the resulting matched frequency. Average time spent for the first matching run was 382 seconds ( $SD = 207$ ). Moreover, there were no significant differences of matching parameters, namely tinnitus frequency, loudness, and side,  $t(\max) = -0.644$ ,  $p(\min) = .525$ , between the matching procedures before and after the actual stimulation. This further enhances confidence in the applied matching method, which is also reflected by high correlations between matching parameters of interest (tinnitus frequency:  $r = .826$ ,  $p < .001$ ; loudness:  $r = .833$ ,  $p < .001$ ; side:  $r = .937$ ,  $p < .001$ ).

**Table 2.** Participants' Characteristics and Tinnitus Parameters ( $n = 29$ ).

	Mean	SD	Median	Minimum	Maximum
Age (years)	54.72	11.26	57.00	22	73
Tinnitus duration (months)	168.97	113.92	132.00	16	420
Hearing loss (both ears, dB)	21.08	10.14	19.09	3	44
SL near tinnitus frequency (both ears, dB) <sup>a</sup>	33.45	18.67	30.00	0	70
TQ total score (0–84)	36.83	17.22	40.00	10	63
THI total score (0–100)	53.10	11.26	53.00	33	71
Mini-HQ9 (0–27)	12.38	5.39	11.00	4	24
Tinnitus awareness (%)	66.00	25.74	70.00	20	100
Tinnitus loudness (%)	59.83	21.90	60.00	20	100
VAS loudness (0–100)	50.90	2.59	50.90	1	90
MML (dB)	60.28	18.05	58.00	29	80
Tinnitus loudness (matching, dB)	57.72	15.38	56.61	19	80
Tinnitus frequency (matching, Hz)	4040.66	2122.25	3530.00	298	10965
Tinnitus side (matching, 0–127)	66.66	35.53	63.00	0	127

Note. TQ = tinnitus Questionnaire (Goebel & Hiller, 1994); THI = tinnitus handicap inventory (Newman et al., 1996); Mini-HQ9 = mini hyperacusis inventory (Goebel et al., 2013); VAS = visual analog scale; MML = minimum masking level.

<sup>a</sup>Nearest frequency of pure-tone audiometry to the matched tinnitus frequency.

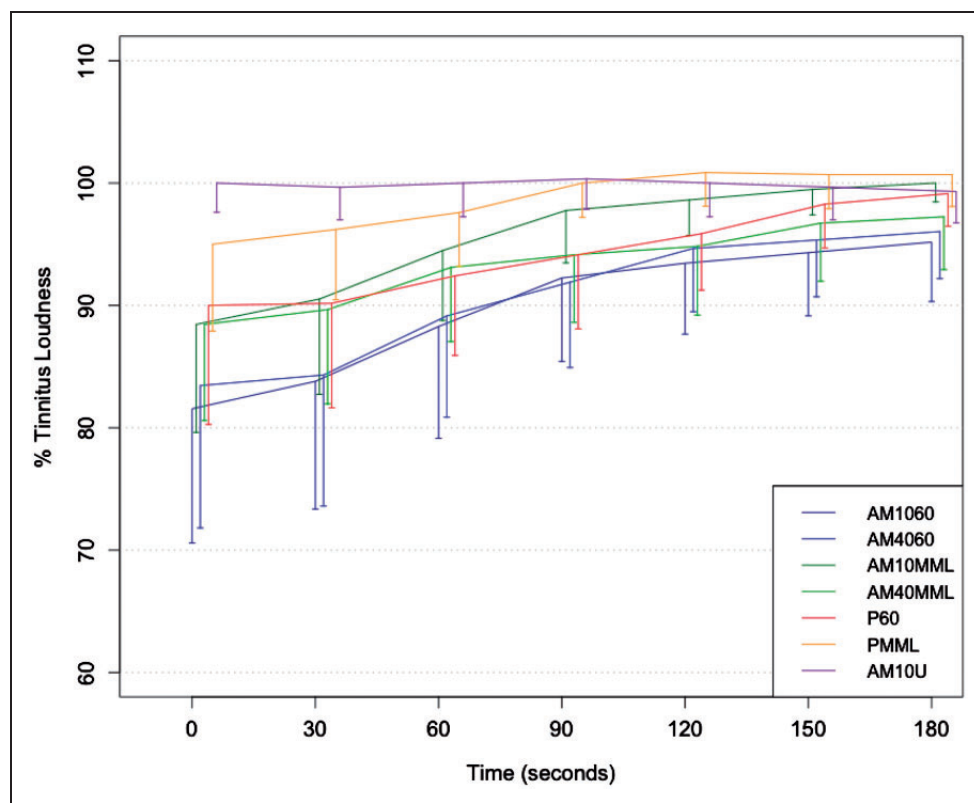
### Tinnitus Suppression

The mean tinnitus loudness suppression profile over time after stimulus offset is shown in Figure 2 and the single responses in Figure 3. Notably, tinnitus suppression is strongest 0 seconds after stimulus offset for all stimuli except AM10U and converges toward prestimulation loudness after 90 seconds toward 180 seconds. This pattern is typical for RI (Roberts, 2007), and only a few responses were indicative of temporarily increased tinnitus loudness (see Figures 3 and 4). AM sounds at 60 dB SL seem to exert the strongest suppression (AM1060 and AM4060) on average followed by their variations at MML and the PT at 60 dB SL. Finally, PMML and AM10U produced only slight or no average suppression, respectively. The results of the omnibus analysis of variance for the final model are listed in Table 3 and, in contrast to our previous study, indicative of a significant effect for position (i.e., the presentation order of the stimuli).

Within the mixed effects model, the contrasts of interest between AM1060/AM4060 and P60, and

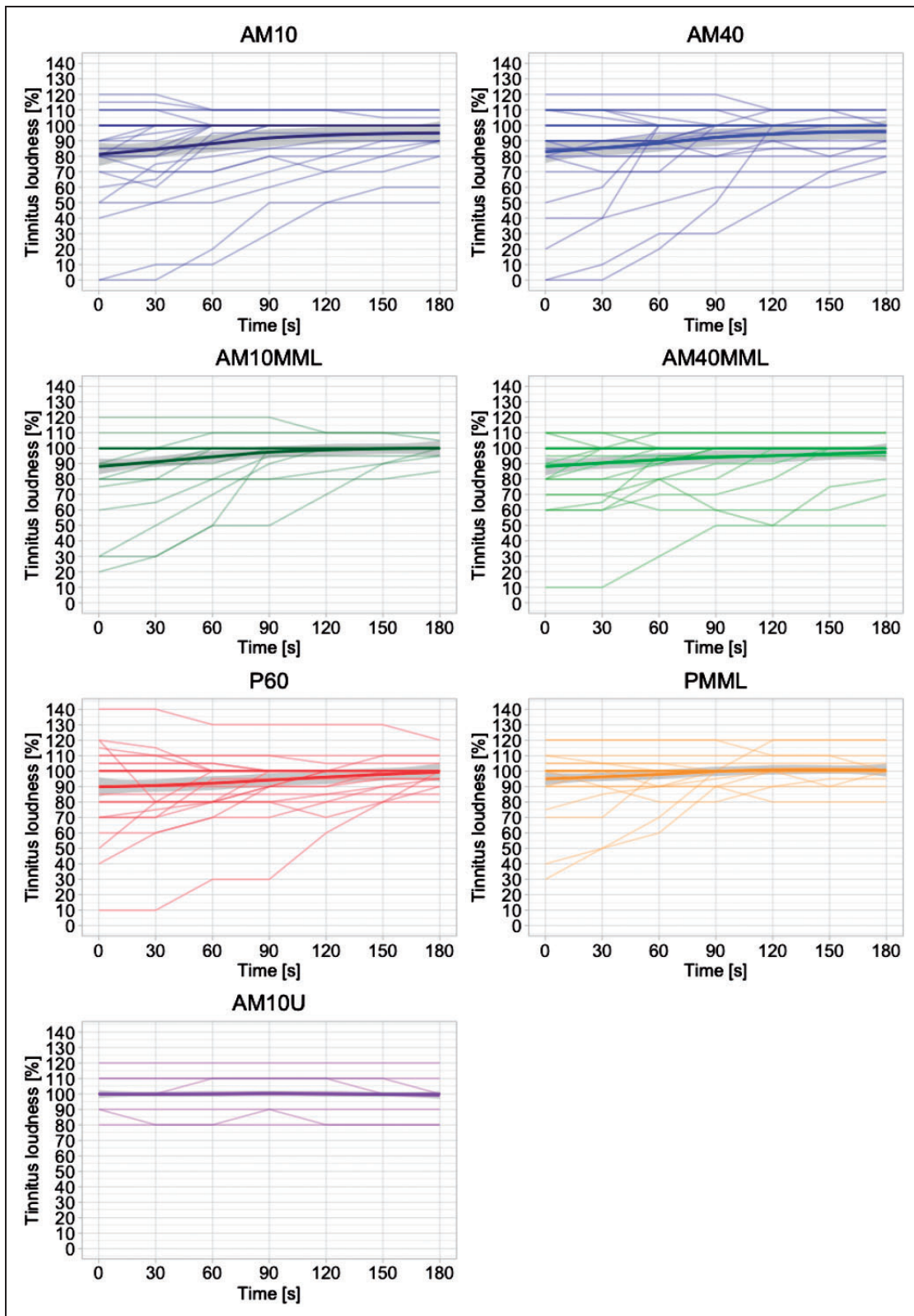
AM10MML/AM40MML and PMML, respectively, resulted in a trend for the main effect of condition of AM1060 versus P60 but not for AM4060 versus P60. This finding substantiates the observed tendencies in our previous article, partly confirms our hypotheses (trend in 1 of 4 contrasts), and is related to observations (Reavis et al., 2012; Tyler et al., 2014) that certain unmodulated sounds produce less tinnitus suppression than AM sounds. On the other hand, looking at stimulation levels near the tinnitus' actual loudness (slightly below tinnitus loudness as in [Reavis et al., 2012] and 6 dB above MML in our study), no significant results can be observed for both 10 and 40 Hz contrasts.

As we identified an effect for position, we evaluated this position effect in an ancillary model seen in Table 6 (Supplemental material) to probe possible influences on the interpretation of the main results. In consequence, and in contrast to the prima facie impression of similar suppression curves of AM1060 and AM4060 in Figure 2, this may explain the null-finding of the contrasts AM4060 versus P60 in the final model with position as a covariate.

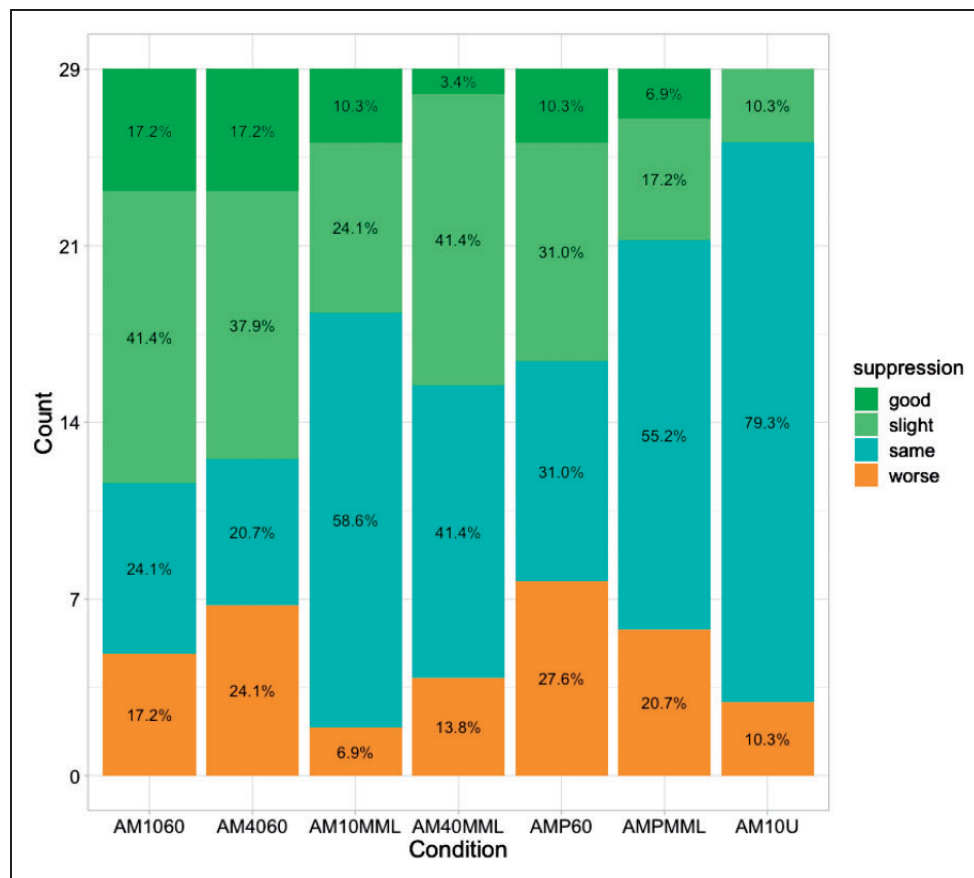


**Figure 2.** Mean tinnitus suppression after stimulus offset for all stimuli. Brackets indicate 95% confidence interval for each condition. Two-tailed tests of significance are reported (see Table 4). Generally, AM sounds tend to elicit slightly stronger or similar tinnitus suppression compared with PTs except the AM10U condition. Main contrasts of interest between AM and PT conditions for both stimulation levels show a trend toward more tinnitus suppression for AM1060 versus P60,  $t = 2.417$ ,  $p(\text{bonf}) = .064$ , Table 4. Notably, this is only true for the main effect of condition and not the interaction of Condition  $\times$  Time.





**Figure 3.** Tinnitus suppression after stimulus offset for the single stimuli. Each line is representative of a single subject's tinnitus loudness growth function after stimulus offset at 0 seconds. The mean response and the standard deviation (locally weighted scatterplot smoothing) are plotted as a thick line and a gray ribbon, respectively. Notably, the variability after stimulation offset is considerable while it converges over time as typical in RI (Roberts, 2007).



**Figure 4.** Responder profiles of tinnitus suppression for all stimuli. Initial suppression after stimulus offset ( $t_0$ ) is plotted here. Suppression of  $>50\%$  compared with prestimulus tinnitus loudness is considered “good” (green), “moderate” if  $<50\%$  and  $\geq 0\%$  (light green), “same” if  $= 0\%$ , and “worse” (i.e., residual excitation) if  $< 0\%$  (orange).

**Table 3.** Analysis of Variance of the Final Mixed Effects Model.

	numDF	F	p
Intercept	1	8452.589	<.001
Condition	6	22.495	<.001
Time	1	7.962	.005
Poly(position, 2)	2	16.155	<.001
Condition: time	6	4.721	<.001

Note. Poly = polynomial term.

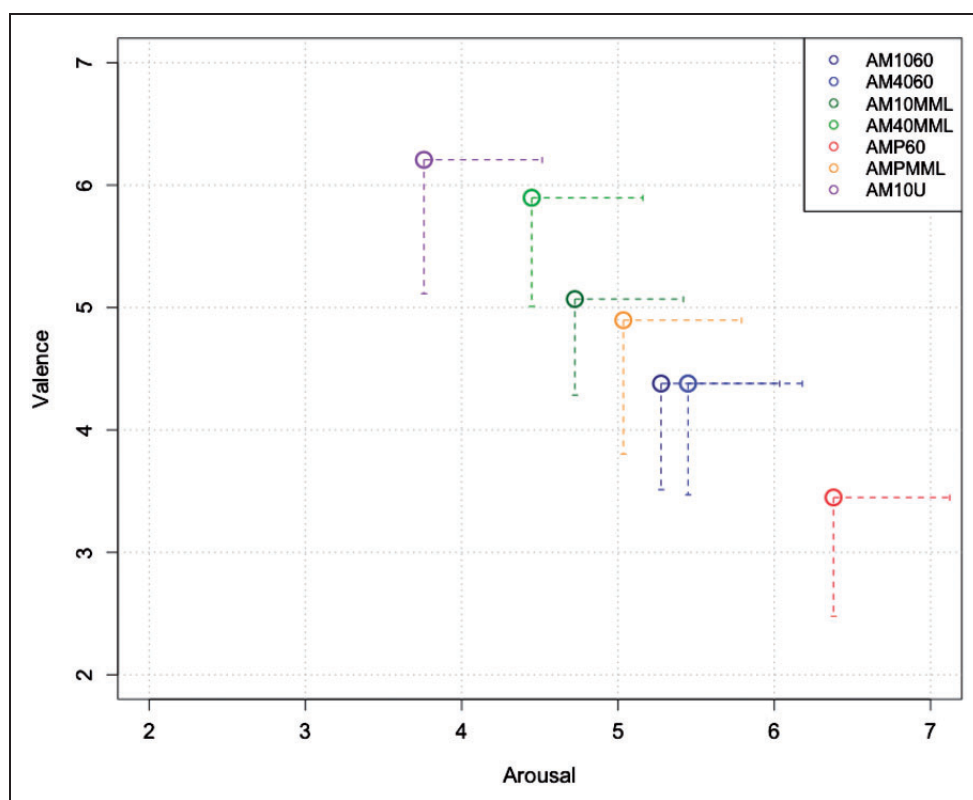
Degrees of freedom = 1,377. Notably, unlike in our previous study, an effect for position (order effect) was detected and had to be included as a covariate in the model (see Table 6 in the Supplemental Material for the interaction model). We observe significant effects for all main effects and the Interaction Condition  $\times$  Time.

Tinnitus suppression in the responder profile (Figure 4) is defined as “good” if participants rated the tinnitus loudness to be at a level of 50% or less of the initial loudness, “slight” at a level of 55% up to 95%, “same” if unchanged ( $= 100\%$ ), and “worse” if loudness

was temporarily increased at stimulation offset. Respective percentage values are plotted on the bars of each stimulus. The observed distributions further confirm that the observed tinnitus suppression, or RI potential of the AM stimulus class, is especially pronounced at high presentation levels.

### Stimulus Evaluation

Valence and arousal scores for the entire set of stimuli are plotted in Figure 5, and statistical contrasts of interest are listed in Table 5. Of particular interest and partly according to our hypotheses, valence was rated significantly higher for AM1060 versus P60,  $t = 3.480$ ,  $p(\text{bonf}) = .013$ , whereas only trends were observed AM40MML versus PMML,  $t = 2.896$ ,  $p(\text{bonf}) = .058$ . Taken together, these results may imply a slightly better tolerability of the AM sounds compared with their PT pendants, while statistical differences were only observed for two out of four contrasts and not for arousal at corrected significance levels.



**Figure 5.** Valence and arousal rating for all stimuli. Brackets indicating 95% confidence interval for valence and arousal for each condition. P60 exhibits lowest tolerability mirrored by high arousal and low valence ratings.

## Discussion

The experimental study at hand examined the difference between AM and PT sounds at the tinnitus frequency regarding temporary tinnitus suppression. Specifically, we investigated whether AM sounds with modulation rates of 10 and 40 Hz (four sounds) induce stronger tinnitus suppression after stimulation than unmodulated PTs (two sounds) within two stimulation level regimes, namely 60 dB SL and 6 dB above MML (both at the tinnitus frequency). In an additional exploratory analysis, we compared both valence and arousal of the different stimuli between the two stimuli classes. The aim of this analysis was to further evaluate if AM sounds are suitable to induce residual tinnitus suppression, or RI, and beyond that, may qualify as possible principles for tinnitus sound therapy.

The results, taking into account the effect of position (i.e., presentation order of the stimuli), could not convincingly show (i.e., only producing a trend) that 10 Hz AM sounds in the matched tinnitus frequency produce stronger tinnitus suppression on average after stimulation than unmodulated PTs in the same frequency at stimulation level 60 dB above SL. Looking at different modulation rates (i.e., 40 Hz) and stimulation levels

**Table 4.** Results of the Contrasts of Interest in the Final Mixed Effects Model.

	Value	SE	t	p	p(bonf)
Intercept	89.955	3.469	25.929	<.001	
AM1060—P60	2.840	1.175	2.417	.016	.064
AM4060—P60	1.308	1.173	1.116	.265	1
AM10MML—PMML	2.248	1.175	1.914	.056	.224
AM40MML—PMML	2.089	1.173	1.781	.075	.3

Note. SE = standard error.

Degrees of freedom = 1,377. Main contrasts of interest between AM and PT conditions for both stimulation levels show a trend of stronger tinnitus suppression for AM1060 versus P60,  $t = 2.417$ ,  $p(\text{bonf}) = .064$ .

(i.e., 6 dB above MML), we can only report nonsignificant results at the corrected level. Generally, but especially in the case of the AM4060, this may be explained by an (unfortunate) order effect (see Tables 4 and 6). The absent significant effects of the same contrasts at the lowered stimulation level 6 dB above MML may be furthermore explained by the inherent increased sound energy in the stimuli at the 60 dB SL level. Yet, given the observed statistical trend and the considerably large array of similar sound stimuli (i.e., identical regarding



their carrier frequency at the matched tinnitus frequency), these results may not come as a surprise but rather may be better elucidated in a sleeker experimental design where presentation level regimes are not mixed within one experiment or experimental block. We find this interpretation further plausible, as the narrow spectrum of different carrier sounds in the study at hand, in contrast to the wide array of carrier sounds in our former study (Neff et al., 2017), may have eased learning effects and therefore introduced the observed position effect. In conclusion, we only observed trends of better tinnitus suppression properties for 10 Hz AM sounds compared with their unmodulated pendants at 60 dB SL presentation level. These results are partly in line with previous inconclusive findings (Neff et al., 2017; Reavis et al., 2012; Tyler et al., 2014) in that they show a tendency of stronger residual tinnitus suppression than commonly used unmodulated sounds. Notably, the current study is the first one directly comparing AM and PT sounds with matched tinnitus tones as carriers.

The comparison between arousal and valence ratings between modulated and unmodulated stimuli is similar to the findings in tinnitus suppression, as AM1060 elicits significantly higher valence but not lower arousal (see Table 5). Different modulation rates and stimulation levels only produced a trend in differences of arousal and valence between conditions of interest, namely higher valence for AM40MML compared with PMML (Table 5). A former study (Terry & Jones, 1986) compared a variety of different tones and sounds. Their results did not show any specific difference between AM and PT, while filtered noises were generally less annoying than tones. As noise stimuli were not used in the current study, we cannot provide data on a contrast between tones and noise at this point.

Taken together, these results indicate that tolerability for AM sounds seems to be slightly better compared with PTs, especially in the ratings of valence. At the same

time, the high valence ratings were usually accompanied by low arousal ratings further supporting better tolerability of the AM sounds. On the other hand, it cannot be disputed that the effect is not consistent across the different stimulation levels and modulation rates and almost totally absent in the case of arousal. The latter observation may be further explained by the assumption that arousal is a concept not directly accessible to one's conscious evaluation, complicating the abstract task of judging a sound along this particular categorization system. Future studies should consider these shortcomings by elaborating on subjective evaluations of stimuli. Nevertheless, we still conclude that the stimulus class of AM sounds was well tolerated by participants, at least for the stimulation duration of 3 minutes.

A possible mechanism of action for the observed tinnitus suppression of the AM stimulus class beyond the respective body of knowledge in RI research (Roberts, 2007) may be neural (or cortical) entrainment which normalizes aberrant neural oscillations acting as putative correlates of tinnitus (Reavis et al., 2012) or other pathologies (e.g., in pain with alpha entrainment [Ecsy et al., 2017] or in schizophrenia with gamma entrainment [Voicikas, Niciute, Ruksenas, & Griskova-Bulanova, 2016]). A respective entrainment of neural oscillations may be especially relevant for specific frequency bands in tinnitus like alpha (Weisz, Moratti, Meinzer, Dohrmann, & Elbert, 2005) or gamma (Ashton et al., 2007; Sedley et al., 2012; Weisz, Dohrmann, & Elbert, 2007). Yet, the exact role of these frequency bands in the tinnitus pathology is still under debate. In any case, we agree with the considerations of Reavis et al. (2012) that modulated sounds, contrary to noise or PTs that mostly produce onset and offset auditory cortical activity, may produce sustained acoustically driven activity that may help restructure cortical firing patterns away from those that generate tinnitus. A comparable model has been postulated where prolonged tinnitus suppression or RI

**Table 5.** Paired Differences of Valence and Arousal Between Stimuli Contrasts of Interest.

	Mean difference	CI Lower	CI Upper	<i>t</i>	<i>p</i>	<i>p</i> (bonf)
V_AM1060 - V_P60	1.241	0.511	1.972	3.480	.002	.013
A_AM1060 - A_P60	-0.759	-1.503	-0.014	-2.087	.046	.369
V_AM10MML - V_PMML	0.552	-0.320	1.424	1.296	.206	.999
A_AM10MML - A_PMML	-0.138	-1.005	0.729	-0.326	.747	.999
V_AM4060 - V_P60	1.069	0.213	1.925	2.557	.016	.130
A_AM4060 - A_P60	-0.828	-1.502	-0.153	-2.512	.018	.144
V_AM40MML - V_PMML	1.310	0.384	2.237	2.896	.007	.058
A_AM40MML - A_PMML	-0.724	-1.693	-0.245	-1.530	.137	.999

Note. CI = confidence interval of 95%; V = valence; A = arousal.

Valence of AM1060 is significantly higher than P60,  $t = 3.480$ ,  $p(\text{bonf}) = .013$ , whereas a trend is reported for higher valence of AM40MML versus PMML,  $t = 2.896$ ,  $p(\text{bonf}) = .058$ .

may be explained by inhibition of central synchrony via feedforward projections (Noreña & Eggermont, 2003; Roberts et al., 2010). AM sounds in the alpha band may also have an influence on tinnitus maintenance or attentional networks through a temporary up-modulation of alpha networks driven by the auditory stimulus. This up-modulation may then reconstitute the shifted brain network homeostasis in tinnitus (e.g., the decay of wide-spread alpha networks, [related] increase of gamma networks [Schlee, Hartmann, Langguth, & Weisz, 2009]). Regarding possible alpha entrainment, we cannot rule out effects of general relaxation (Hartmann, Lorenz, Müller, Langguth, & Weisz, 2013) or mere attentional processes, as the alpha band is at the lower bound of the spectrum of entrainable oscillations (Joris, Schreiner, & Rees, 2004; Picton et al., 2003). At this point, we also embrace the possibility of similar effects produced by stimuli with modulation rates other than 10 or 40 Hz, particularly covering frequency bands higher than 40 Hz (e.g., 20–100 Hz electrical stimulation of the cochlea [Zeng et al., 2011]). Yet, with increasing modulation frequency (>40 Hz), modulated acoustic stimuli start to produce residual tones (Joris et al., 2004) and furthermore elicit less cortical entrainment (Picton et al., 2003).

Taking an all-embracing point of view given the various systems of the auditory hierarchy from the inner ear to the brain influenced by acoustic stimulation, it may be conceivable that the observed suppression effect of AM or generally modulated sounds is a conglomerate of altered activity in the auditory pathway, central auditory cortex, and widespread cortical network activation as sketched earlier. To continue this line of research, entrainment and RI effects should therefore be studied using electro- or magnetoencephalographic methods where direct causal relationships between cortical entrainment, RI, and tinnitus suppression can be tested. Beyond that, the influences of the putative entrainment mechanism and the mere RI effect of the carrier sound (here: matched tinnitus frequency) have to be differentiated to better understand the individual and joint mechanisms of action on tinnitus suppression.

### Limitations

Unfortunately, five participants did not meet the criterion of bilateral tinnitus contrary to their declaration during recruitment and the informed consent procedure. At this point, we would like to point to a possible inaptitude of tinnitus sufferers to generate valid self-reports of tinnitus characteristics (Pryss et al., 2018) and also to fluctuations of the tinnitus percept over time (Probst et al., 2017). Certainly, this issue should be considered in future studies and respective audiometric features of tinnitus specifically tested at the recruitment or informed

consent stage of the study's proceedings. In this study, all participants were consequently stimulated idiosyncratically to adhere to the study protocol.

More importantly, AM stimuli with pure-tone carriers naturally introduce sidebands alongside the carrier sound (Zwicker & Fastl, 2013), which in turn may generate off frequency patterns of activation and distortion products on the basilar membrane. These phenomena could produce a different and possibly greater afferent drive on the auditory system. The (increased) auditory input related to the sidebands may therefore explain the larger tinnitus suppression by the AM sounds in our results. As the study at hand does not allow for further insights on this issue, future studies could take this issue into account by increasing the number and range of tested modulation frequencies. In such a research design, sideband parameters could then be included and tested in statistical modeling of the tinnitus suppression as predictors or covariates.

Finally, the position effect emerging from the data and included in the final fitted model was detrimental on significance levels of the main contrasts of interest. Future studies should therefore consider smaller stimulus sets, a shorter stimulation duration per stimulus and more repetitions in a well-balanced randomized design.

### Conclusion

Despite the mentioned limitations and inconclusive results as well as mechanisms of action, we conclude that AM sounds in the matched tinnitus frequency are effective in temporarily suppressing tinnitus. This conclusion is substantiated by similar or slightly stronger tinnitus suppression or RI effects of AM compared with PT sounds and slightly better tolerability of the AM stimulus class by tinnitus sufferers. Future work should focus on understanding the neurophysiological correlates of the observed suppression effects during and after the acoustic stimulation as well as on testing long-term effects of the approach. Given the efficacy, tolerability, and simplicity of use, we furthermore propose the studied stimulus class as a suitable principle to be tested for masking or long-term tinnitus sound therapy.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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# Amplitude Modulated Noise for Tinnitus Suppression in Tonal and Noise-Like Tinnitus

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## Keywords

Tinnitus · Noise · Residual inhibition · Amplitude modulation · Bandpass filter

## Abstract

**Background:** The phenomenon of short-term tinnitus suppression by different forms of acoustic stimulation is referred to as residual inhibition (RI). RI can be triggered in the majority of tinnitus cases and was found to be depending on the used intensity, length or types of sounds. Past research already stressed the impact of noise stimulation as well as the superiority of amplitude modulated (AM) pure tones at the individual tinnitus frequency for RI in tonal tinnitus. Recently a novel approach for the determination of noise-like tinnitus characteristics was proposed. **Objectives:** The aim of the present study was to investigate whether in participants with noise-like tinnitus RI can be increased by AM noise stimuli according to the individual tinnitus frequency range. **Methods:** For this purpose the individual tinnitus characteristics (noise-like and tonal tinnitus) of 29 people affected by tinnitus (mean age = 55.59, 7 females, mean tinnitus duration = 159.97 months) were assessed via customizable noise-band matching. The objective was to generate bandpass fil-

tered stimuli according to the individual tinnitus sound (individualized bandpass filtered [IBP] sounds). Subsequently, various stimuli differing in bandpass filtering and AM were tested with respect to their potential to induce RI. Participants were acoustically stimulated with 7 different types of stimuli for 3 min each and had to rate the loudness of their tinnitus after each stimuli. **Results:** Results indicate a general efficacy of noise stimuli for the temporary suppression of tinnitus, but no significant differences between AM and unmodulated IBP. Significantly better effects were observed for the subgroup with noise-like tinnitus ( $n = 14$ ), especially directly after stimulation offset. **Conclusions:** The study at hand provides further insights in potential mechanisms behind RI for different types of tinnitus. Beyond that, derived principles may qualify for new or extend current tinnitus sound therapies.

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## Introduction

Chronic subjective tinnitus is defined as the permanent perception of a sound such as ringing or hissing in the absence of an external or internal source of noise. Ap-

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proximately 10–15% of the population in industrial countries experience this phantom sound [Langguth et al., 2013; Erlandsson and Dauman, 2013; Heller, 2003; Hall et al., 2011]. Causes for the development of tinnitus are divergent and not completely understood, though most commonly tinnitus occurs towards cochlear damages due to noise trauma [Langguth et al., 2013]. In the majority of cases, the perceived tinnitus pitch is in accordance with the frequency spectrum of hearing loss (HL) [Basile et al., 2013; Roberts et al., 2008]. As a consequence of decreased or absent auditory input and the subsequent deficiency of neural input, maladaptive pathological changes in the auditory pathway are formed, which lead to the perception of a “phantom sound” defined as tinnitus [Eggermont, 2007; Eggermont and Tass, 2015; Eggermont and Roberts, 2012]. Neurophysiological investigations of tinnitus were able to demonstrate hyperactivity in auditory brain areas [Farhadi et al., 2010; Folmer, 2007] as well as aberrant oscillatory brain activity and connectivity patterns [Schlee et al., 2009, 2014; Moazami-Goudarzi et al., 2010; Mohan et al., 2016]. Available treatment options have only limited efficacy and to date there is no cure available [Baguley et al., 2013]. Auditory stimulation is one potential treatment approach for tinnitus, but also provides insights to basic mechanisms of tinnitus [Roberts et al., 2008; Fournier et al., 2018].

Almost half a century ago, Feldmann [1971, 1983] investigated the phenomenon of short-term tinnitus suppression after sound stimulation. This temporary suppression is referred to as “residual inhibition” (RI), which manifests in individual suppression patterns (i.e., duration, depth and shape) and can be triggered in 60–80% of tinnitus cases [Roberts, 2007; Vernon and Meikle, 2003]. Various recent studies scrutinized RI in more depth. Data from several investigations suggest the effects of RI to be more prominent with sounds close or within the individual tinnitus frequency spectrum [Roberts et al., 2006, 2008; Schaette et al., 2010]. Factors including duration or intensity of the stimuli also affect RI [Terry et al., 1983; Norena et al., 2002; Vernon and Fenwick, 1984; Neff et al., 2017]. In contrast, the underlying neurophysiological mechanisms of RI are not clearly understood yet [Roberts, 2007; Galazyuk et al., 2019]. Most recent work suggests that tinnitus suppression through sound stimulation is related to reduced spontaneous firing of central auditory neurons [Galazyuk et al., 2017, 2019].

The importance of stimulation intensity and frequency was verified in a recent work from Fournier et al. [2018], who developed a novel approach for RI testing described as Minimum RI Level. Thereby, people had to

adjust the intensity of customized stimuli up to the point where their tinnitus is suppressed during a given interval after the offset of the stimulus. Results show an occurrence of RI in 86.7% of people with tinnitus by using this method [Fournier et al., 2018].

Despite noise-like tinnitus perception in many cases, to the best of our knowledge, none of the previous mentioned studies included a genuine matching for noise-like tinnitus, that is, determination of noise band-width [Roberts et al., 2006; Fournier et al., 2018].

Recently Henry et al. [2013] proposed a novel approach for tinnitus matching procedures taking into consideration the tinnitus type. In addition to the determination of the centre frequency, people with tinnitus were also able to adjust the band-width of their tinnitus [Henry et al., 2013]. Here we aim to use both frequency and band-width information to develop individualized stimuli, especially for people with noise-like tinnitus, for the investigation of RI.

Previous studies investigating the effects of differently modulated sounds on RI revealed that amplitude modulated (AM) tones near or at the individual tinnitus frequency result in larger RI [Reavis et al., 2012; Tyler et al., 2014]. Furthermore, differential results for specific amplitude modulation rates were observed [Neff et al., 2017, 2019].

The experiment aims at investigating the effects of different noise stimuli with and without AM on RI. The overarching goal is to establish new acoustic stimulation techniques for basic RI research as well as generating principles for possible future sound stimulation concepts with the AM stimulus class. For this purpose, the individual tinnitus characteristics are assessed via noise-band matching as suggested by Henry et al. [2013] in order to create personalized stimuli for RI examination.

Previous studies in the field of RI already emphasized the impact of noise stimulation on tinnitus perception in tonal tinnitus [Henry et al., 2013; Fournier et al., 2018; Roberts et al., 2006, 2008]. To the best of our knowledge, none of the existing experiments systematically investigated these noise stimulation methods, in particular the application of AM or bandpass filters (BP) to noise stimuli, in noise-like tinnitus.

According to this, the current experiment represents the first attempt to investigate the effects of an administration of individualized BP settings (IBP) and different rates of AM (10 and 40 Hz) to white noise (WN) on RI.

These stimulation methods are furthermore merged to a novel combinatory approach to apply IBP and AM to WN simultaneously and scrutinize its efficacy in RI.



Additionally, each of the used stimuli was examined with regards to induced arousal and valence as rated by the participants, since differences in stimuli evaluation could potentially affect tinnitus suppression.

Besides the assumption of the efficacy of all deployed noise stimuli in short-term tinnitus inhibition (in both noise-like and tonal tinnitus), we expect that IBP differs in its effects on RI from unadjusted WN. We hypothesized that the IBP would result in different strengths of residual tinnitus suppression compared to WN. Yet, given the lack of previous studies we are not able to define a directed hypothesis here. Furthermore, building on the insights of previous work, we hypothesize that stimulations with AM noise (filtered or unchanged) result in larger RI than their unmodulated counterparts.

## Methods

### *Participants*

The sample for this experiment consisted of 29 participants (7 female) between 18 and 75 years with noise-like ( $n = 14$ ) or tonal tinnitus ( $n = 15$ ) with a tinnitus duration of >6 months. Participants were recruited from the Interdisciplinary Tinnitus Centre in Regensburg, Germany. For detailed sample characteristics see Table 1. Primary inclusion criteria were no somatic, mental health or neurological conditions and no current intake of psychotropic medications or substances. Alike, participants were not allowed to participate in other tinnitus-related studies. The methods and the procedures used in this study were examined and approved by the local Ethics Committee of the University of Regensburg (16-101-0061). All participants were sufficiently informed about the aim, methods, and duration of the study, possible side effects, and gave written informed consent prior to the start of the experiment.

### *Psychometry*

Each participant filled in an online survey composed of German versions of the Tinnitus Handicap Inventory [Newman et al., 1994; Kleinjung et al., 2007], the Tinnitus Questionnaire (TQ) [Goebel and Hiller, 1994; Hallam et al., 1988], a brief version of the Hyperacusis Questionnaire (mini-HQ9) [Goebel et al., 2013] and the Tinnitus Sample Case History Questionnaire for tinnitus-related clinical and demographic information [Langguth et al., 2007].

### *Audiometry*

For the purpose of individual hearing threshold determination, frequencies ranging from 125 Hz to 8 kHz in octave steps including semi-octave steps between 0.5 and 1 (i.e., 0.75 kHz), 1 and 2 (i.e., 1.5 kHz), 2 and 4 (i.e., 3 kHz) and 4 and 8 kHz (i.e., 6 kHz) were quantified with a clinical audiometer (Madsen Midimate 622D; GN Otometrics, Denmark). Sennheiser HDA 2000 headphones (Sennheiser, Germany) were used for audiometric measurements, subsequent tinnitus matching and acoustic stimulation. Minimum masking level (MML) was assessed by increasing the loudness of a WN sound (Madsen Midimate 622D; GN Otometrics, Denmark) until their tinnitus was completely masked.

### *Tinnitus Matching*

In order to ascertain participants individual tinnitus pitch, the Method of Adjustment approach [Henry et al., 2013] was performed with a custom-made MAX application (MAX 7; Cycling'74, USA) together with a modular hardware controller (Palette Expert Kit; Palette, Canada). The matching procedure's steps were in accordance with the order within the Tinnitus Tester procedure [Roberts et al., 2008] with an additional test for octave confusion at the end. Prior to tinnitus matching, participants were asked to vocalize or describe their tinnitus to distinguish between noise-like and tonal tinnitus types as indicated in the recruiting process. Following on that, they were instructed and trained for the process of tinnitus matching. Parameters examined by the matching procedure were as follows: tinnitus frequency, respectively centre frequency for noise-like tinnitus (Hz), tinnitus loudness (dB) and tinnitus laterality (0 = left ear; 127 = right ear; thus a value of 63 describes a bilateral tinnitus). Control units of the matching controller were labelled accordingly. The step size of frequency dial was marginally below a semitone and ranged from 40 Hz to 16 kHz. For tonal tinnitus matching, a 3 kHz pure tone with comfortable loudness was set as a starting point, followed by an adjustment of the frequency by the participants to determine their individual tinnitus frequency. Finally, tinnitus loudness and laterality were adjusted with the matching controller to complete the matching procedure. In case of noise-like tinnitus, the starting sound was a filtered broadband noise (bandwidth: 1/3 octave of centre frequency). Participants were able to adjust the centre frequency of the noise and also the bandwidth of the filter settings according to their individual tinnitus noise. Subsequently, loudness and laterality were identified just as with the pure tone matching. Finally, participants rated the agreement of their tinnitus with the matched sound on a 1–10 scale. To assess individuals sensation level (SL), the hearing threshold of the frequency next to the individual tinnitus frequency or centre frequency was used (i.e., stepping down to the next lower frequency. For example, if the individual tinnitus frequency was 7.4 kHz, the hearing threshold at 7 kHz was investigated). The matching procedure was repeated after the acoustic stimulation block of the experiment.

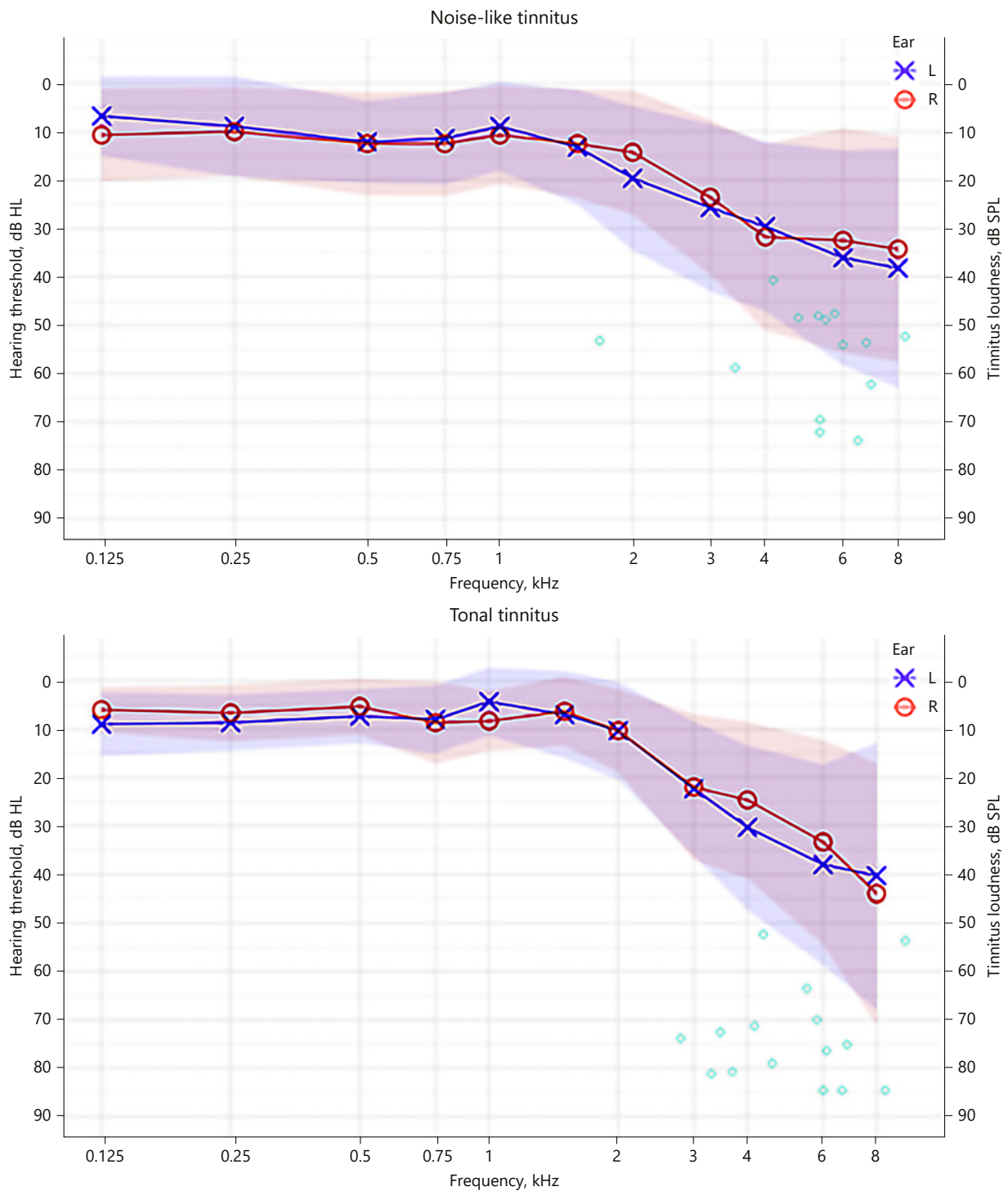
### *Acoustic Stimulation*

Seven different modified noise stimuli were created in MATLAB (Matlab R2015a; Mathworks, Natick, MA, USA) and utilised for a 3 min acoustic stimulation with an intensity of 60 dB SL. Stimuli set consisted of unmodified WN, WN with AM rates at 10 Hz (WN10) and 40 Hz (WN40), as well as a IBP with the same modulation rates (IBP, IBP10, IBP40). BP width was set according to the matching results in noise-like tinnitus participants. In participants with tonal tinnitus, the previously matched individual tinnitus pitch was used to deploy an IBP to WN with a range of one octave [Pantev et al., 2012]. Furthermore an IBP WN with 10 Hz AM rates at MML intensity (IBP10\_MML) was used for acoustic stimulation in order to contrast SL and MML. Acoustic stimulation was conducted in a randomized order for each session with a maximum loudness of 80 dB SPL diotically over the headphones. If participants experienced discomfort, they were able to stop the stimulation and experimental procedures at any time. Following a 3-minute stimulation for each stimulus, participants evaluated their tinnitus loudness (%) in comparison to prior the particular stimulation on a numeric rating scale (0% up to 140% in 10% steps) at 7 different points in time (0, 30, 60, 90, 120, 150 and 180 s after

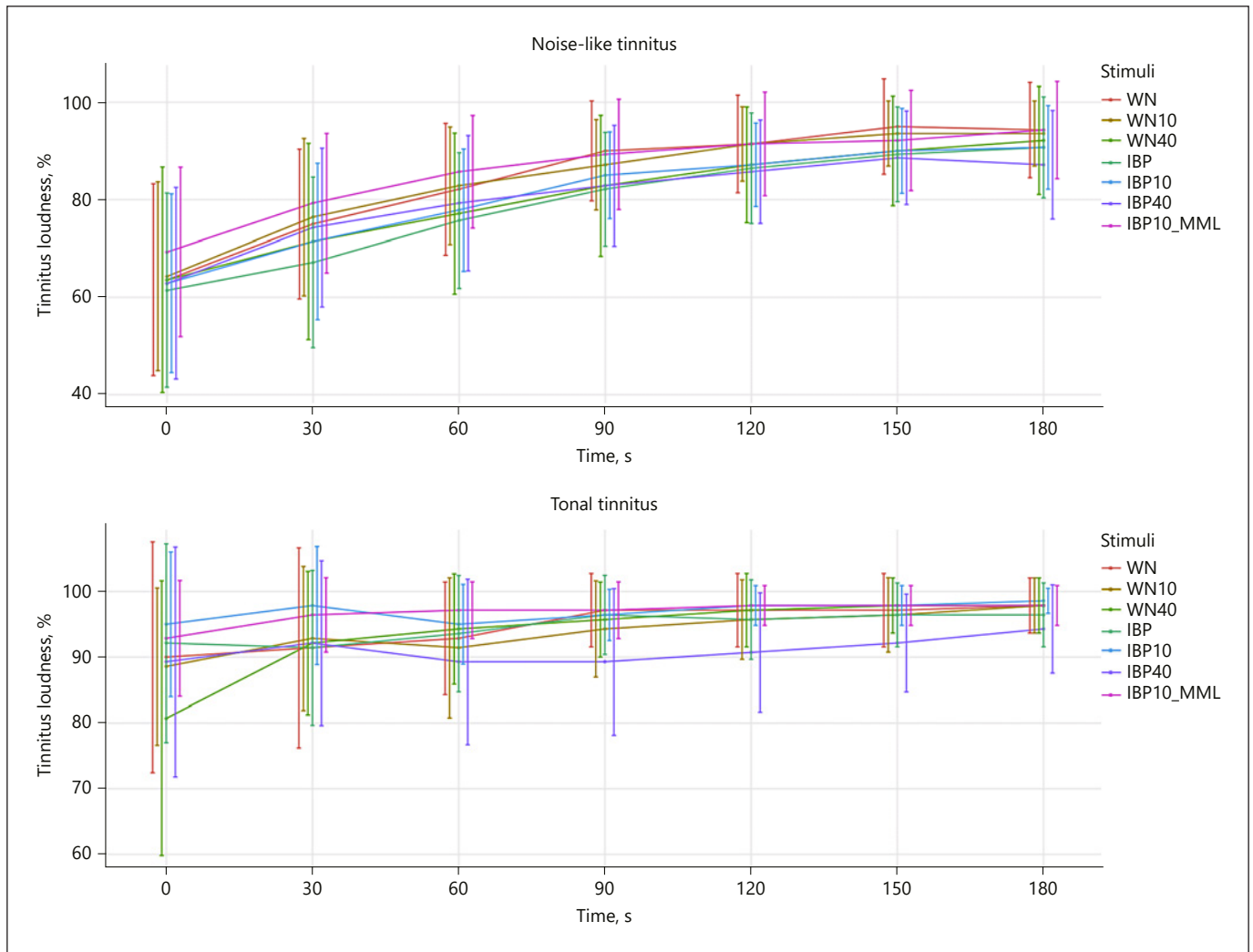
**Table 1.** Sample characteristics

	Total sample			Noise-like tinnitus				Tonal tinnitus				p value		
	Mean ± SD	Md	Min	Max	Mean ± SD	Md	Min	Max	Mean ± SD	Md	Min		Max	t (df)/U
Number (female)	29 (7)				14 (6)				15 (1)					0.03
Tinnitus laterality (left/right/both)	4/4/21				4/3/7				0/1/14					0.13
Age, years	55.59±9.51	57.00	22.00	71.00	58.50±7.81	60.00	45.00	71.00	53.07±10.44	54.00	22.00	66.00	1.59 (25.83)	0.12
Tinnitus duration, months	159.9±92.72	161.00	20.00	420.00	119.86±80.28	102.00	20.00	240.00	197.40±90.00	190.00	60.00	420.00	-2.45 (26.95)	0.02
Centre frequency (Hz) – matching 1					5,404.21±									
Centre frequency (Hz) – matching 2					1,618.94									
Tinnitus frequency (Hz) – matching 1					5,483.07±									
Tinnitus frequency (Hz) – matching 2					3,748.85									
Tinnitus loudness (dB SPL) – matching 1	65.08±13.41	69.56	40.75	84.61	55.98±10.98	53.44	40.75	73.86	5,395.27±1,893.54	5,501.00	2,796.00	9,334.00	-4.66 (26.94)	<0.01
Tinnitus loudness (dB SPL) – matching 2	63.23±14.14	63.54	36.88	84.61	53.87±11.64	51.28	36.88	76.44	5,683.73±1,980.87	5,617.00	2,471.00	9,766.00	-4.31 (26.52)	<0.01
Matching 1 length, min	11.07±4.46	11.00	4.00	19.00	13.50±3.59	15.00	6.00	17.00	8.8±4.06	8.00	4.00	19.00	170.00	<0.01
Matching 2 length, min	5.17±2.45	5.00	2.00	14.00	6.29±2.95	5.50	3.00	14.00	4.13±1.25	4.00	2.00	6.00	158.00	0.02
Hearing loss left, dB	17.98±9.99	17.27	2.73	38.64	19.16±11.45	18.64	2.73	38.64	16.88±8.67	17.27	4.09	33.18	0.60 (24.19)	0.55
Hearing loss right, dB	17.27±10.32	15.91	3.18	40.45	18.67±11.79	15.91	3.64	40.45	15.97±8.96	15.91	3.18	32.27	0.69 (24.25)	0.50
Minimum masking level, dB	54.17±16.84	55.00	20.00	80.00	47.43±17.90	40.50	20.00	76.00	60.47±13.47	57.00	41.00	80.00	-2.20 (24.12)	0.04
Sensation level (dB) (1 missing value)	32.50±19.08	35.00	5.00	70.00	31.54±21.74	35.00	5.00	70.00	33.33±17.18	35.00	5.00	55.00	-0.24 (22.79)	0.81
TQ total score (0–84)	33.28±16.97	32.00	7.00	60.00	32.07±16.03	31.00	7.00	60.00	34.40±18.28	35.00	10.00	58.00	-0.36 (26.90)	0.72
THI total score (0–100)	39.03±22.56	34.00	4.00	98.00	40.00±24.09	36.00	6.00	98.00	38.13±21.85	34.00	4.00	70.00	0.22 (26.26)	0.83
HQ9 (0–27)	11.31±5.76	11.00	1.00	24.00	11.21±4.81	11.50	5.00	20.00	11.40±6.71	8.00	1.00	24.00	-0.09 (25.28)	0.93
VAS loudness (0–100)	45.00±22.81	36.00	8.00	82.00	35.79±21.90	30.00	8.00	82.00	53.60±20.77	61.00	14.00	77.00	57.00	0.04
Md, median; Min, minimum; Max, maximum; TQ, tinnitus questionnaire; THI, tinnitus handicap inventory; Mini-HQ9, mini Hyperacusis questionnaire; VAS loudness, Visual Analog Scale tinnitus loudness.														

Md, median; Min, minimum; Max, maximum; TQ, tinnitus questionnaire; THI, tinnitus handicap inventory; Mini-HQ9, mini Hyperacusis questionnaire; VAS loudness, Visual Analog Scale tinnitus loudness.



**Fig. 1.** Audiometry and Tinnitometry. Audiometric measurement results for both ears together with individual tinnitus frequency (i.e., centre frequency of the IBP) and loudness as identified by tinnitus matching split for noise-like and tonal tinnitus. It should be noted, that tinnitus/centre frequency overlaps with the frequencies of HL. HL, hearing loss.



**Fig. 2.** Tinnitus loudness time curve split by group. For each stimulus the tinnitus loudness rating over all time points is plotted separately for noise-like and tonal tinnitus (CIs at 95% shown as brackets). Overall, each stimulus was able to suppress tinnitus loudness (cf. online suppl. Table S1). In terms of suppression averaged over time but also at T0, stimulus IBP appeared to produce the strongest

effect on loudness in the noise-like tinnitus group, whereas in the tonal group, stimulus IBP40 induced the lowest tinnitus loudness on average. However, directly after stimulation WN40 showed the strongest suppression. WN, white noise; MML, minimum masking level; IBP, individualized bandpass filtered.

stimulation offset). Moreover, participants rated the induced valence and arousal of each single stimulus with pictorial manikin scales [Bradley and Lang, 1994].

#### Statistical Analysis

All statistical analyses were performed using the statistic software R (R version 3.4.3; R Foundation for Statistical Computing, Austria) and the packages “psych,” “emmeans,” “sjstats,” and “lme4.” Tinnitus loudness and stimulus evaluation data were analysed by means of linear mixed effect models for each dependent variable denoted as response (tinnitus loudness, valence, arousal). Potential Models were compared with Likelihood Ratio Tests in a step-wise selection approach [Harrison et al., 2018]. Following

predictors as well as their interactions were tested in the model fitting procedure: condition (stimuli used; see acoustic stimulation section), group (noise-like tinnitus, tonal tinnitus), time (0, 30, 60, 90, 120, 150, 180 s after stimulation end), gender (male, female), age, tinnitus duration, tinnitus loudness (according to first tinnitus matching), MML and tinnitus distress (TQ sum score). The proportion of explained variance was identified by marginal (variance of the fixed effects) and conditional (variance of fixed and random effects)  $R^2$  [Nakagawa et al., 2017]. In any of the fitted models, the participant (id) was treated as a random effect. Fixed effects of the final model were tested via expected mean square approach. Post-hoc Tukey tests were calculated to contrast responses for condition and group. In order to test for a potential bias due to the sequence

of the stimuli used for acoustic stimulation (position effect), a median split was conducted on the positions variable and differences in means were then tested with Student *t* tests.

Analysis of descriptive group differences (noise-like vs. tonal tinnitus) for parametric variables was done by the means of two-sample *t* tests. In case of violation of normal distribution and homoscedasticity, non-parametric testing via independent sample Mann-Whitney U tests was used. Categorical data was analyzed by Fisher's exact tests, due to cell frequencies below 5 in all variables.

Reliability for the matching procedure (between first and second matching round) was assessed via Pearson correlations, or rather Spearman correlations in case of a violation of normal distribution, for tinnitus loudness and tinnitus or centre frequency. Statistical significance was defined as  $p \leq 0.05$  for all analysis.

## Results

### Participant Characteristics

Demographic and clinical characteristics for the whole study sample and for tinnitus sub-groups (noise-like and tonal tinnitus) can be found in Table 1. A Fisher's exact test was able to identify a significant association between gender and the type of tinnitus. In the group with tonal tinnitus the proportion of female participants was significantly lower ( $p = 0.03$ ). Statistical testing revealed significant differences in terms of tinnitus duration and subjective rating of tinnitus loudness (VAS loudness), with the noise-like tinnitus group showing a shorter duration of tinnitus ( $t_{[26.95]} = -2.45, p = 0.02$ ) and evaluating their tinnitus loudness lower ( $U = 57.00, p = 0.04$ ). Further, no differences were found in TQ ( $t_{[26.90]} = -0.36, p = 0.72$ ), Tinnitus Handicap Inventory ( $t_{[26.26]} = 0.22, p = 0.83$ ) or HQ9 ( $t_{[25.28]} = -0.09, p = 0.93$ ) scores among the 2 subgroups.

### Audiometry and Tinnitometry

Table 1 shows audiometric and tinnitus matching results with a significant lower tinnitus loudness (corresponding with subjective loudness rating; see the descriptives section above) for both matching procedures (matching 1:  $t_{[26.94]} = -4.66, p < 0.01$ ; matching 2:  $t_{[26.52]} = -4.31, p < 0.01$ ) and MML ( $t_{[24.12]} = -2.20, p = 0.04$ ) in the group of noise-like tinnitus. On the basis of a consolidation of these audiometric and tinnitometric findings, Figure 1 indicates an overlap of tinnitus frequency with the frequency of HL. As might be expected, the length of the first and second matching process was significantly shorter in the tonal tinnitus group (cf. Table 1). Mean HL difference for both ears were not significantly different between groups (left:  $t_{[24.19]} = 0.60, p = 0.55$ ; right:  $t_{[24.25]} = 0.69, p = 0.50$ ). In both groups, the HL was more pronounced on the left side.

**Table 2.** Fixed effect testing

	numDF	denDF	<i>F</i>	<i>p</i> value
Condition	6.00	1,392.00	3.35	<0.01
Time	6.00	1,392.00	39.84	<0.01
Group	1.00	29.00	5.04	0.03
Time $\times$ group	6.00	1,392.00	15.17	<0.01

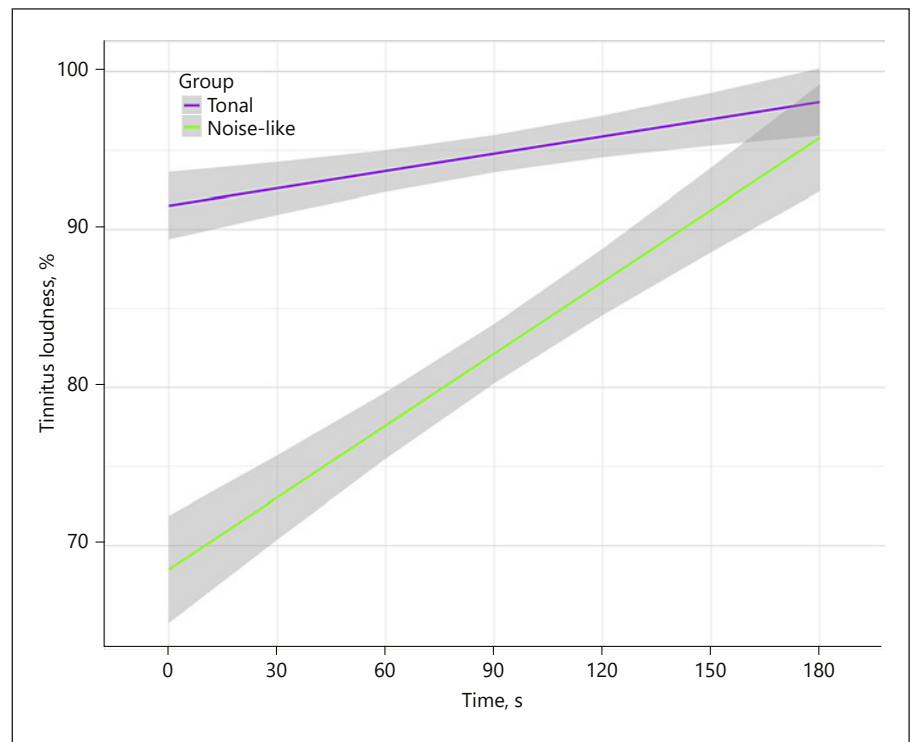
numDF, degrees of freedom numerator; denDF, degrees of freedom denominator.

There were positive significant correlations between the first and the second matching for tinnitus loudness (noise-like:  $r = 0.77, p < 0.01$ ; tonal:  $r = 0.73, p < 0.01$ ) in both groups. With respect to tinnitus/centre frequency a positive significant correlation was only observed in the tonal tinnitus group (noise-like:  $r = 0.14, p = 0.64$ ; tonal:  $r = 0.65, p < 0.01$ ).

### Acoustic Stimulation

Prima facie, the stimulus IBP40 appeared to produce the strongest tinnitus suppression regardless of group and time ( $M = 86.16, SD = 25.60$ ), whereas at time point T0 (immediately after stimulation offset), WN40 induced the lowest tinnitus loudness ( $M = 73.10, SD = 41.76$ ). Descriptive statistics for the 7 utilized stimuli averaged over time and for time point T0 are listed in online supplementary Table S1 (see [www.karger.com/doi/10.1159/000504593](http://www.karger.com/doi/10.1159/000504593) for all online suppl. material) for the whole sample and divided for subgroups. Figure 2 shows the time curve for all stimuli with respect to tinnitus loudness ratings, in the same manner online supplementary Figure S1 provides information about single subject responses for each stimulus. No confounding effect caused by the order of the stimuli in the stimulation sequence was detected by our analysis ( $t_{[1,215.60]} = 0.09, p = 0.93$ ) and therefore stimuli order was not entered in the final model fitting procedure. In accordance with the previous described model fitting approach (cf. section statistical analysis in methods part), we were able to identify the following model with the best fit to our data:  $response \sim condition + time \times group + (1|id)$ . Detailed results of the model fitting are outlined in online supplementary Table S2. By testing the fixed effects of the model via expected mean square approach, significant effects for condition, time, group and for the interaction time  $\times$  group on tinnitus loudness were observed (cf. Table 2). Subsequent post-hoc contrasts for condition failed to find statistically significant differences in tinnitus loudness ratings with respect to the applied stimuli (Table 3).





**Fig. 3.** Mean suppression differences between groups. Time curve of the averaged tinnitus suppression values split for tonal and noise-like tinnitus. SD for the mean suppression data of each group is plotted as a grey ribbon. Differences between the 2 subgroups were found to be significant.

**Table 3.** Post-hoc Tukey contrasts for condition

Contrast	Estimate	<i>t</i>	<i>p</i> value
IBP – IBP10	–1.53	–1.06	0.94
IBP – IBP10_MML	–4.38	–3.05	0.04
IBP – IBP40	1.08	0.75	0.99
IBP – WN	–2.76	–1.92	0.47
IBP – WN10	–2.17	–1.51	0.74
IBP – WN40	–0.34	–0.24	>0.99
IBP10 – IBP10_MML	–2.86	–1.98	0.42
IBP10 – IBP40	2.61	1.81	0.54
IBP10 – WN	–1.23	–0.86	0.98
IBP10 – WN10	–0.64	–0.44	>0.99
IBP10 – WN40	1.18	0.82	0.98
IBP10_MML – IBP40	5.47	3.80	<0.01
IBP10_MML – WN	1.63	1.13	0.92
IBP10_MML – WN10	2.22	1.54	0.72
IBP10_MML – WN40	4.04	2.81	0.08
IBP40 – WN	–3.84	–2.67	0.11
IBP40 – WN10	–3.25	–2.26	0.27
IBP40 – WN40	–1.43	–0.99	0.96
WN – WN10	0.59	0.41	>0.99
WN – WN40	2.41	1.68	0.63
WN10 – WN40	1.82	1.27	0.87

Degrees of freedom = 1,410.23; SE = 1.44. IBP, individualized bandpass filtered; MML, minimum masking level; WN, white noise.

**Table 4.** Post-hoc Tukey contrasts for group

Contrast	Estimate	<i>t</i>	<i>p</i> value
Tonal vs. noise-like	12.65	2.17	0.04
Degrees of freedom = 31.15; SE = 5.84.			

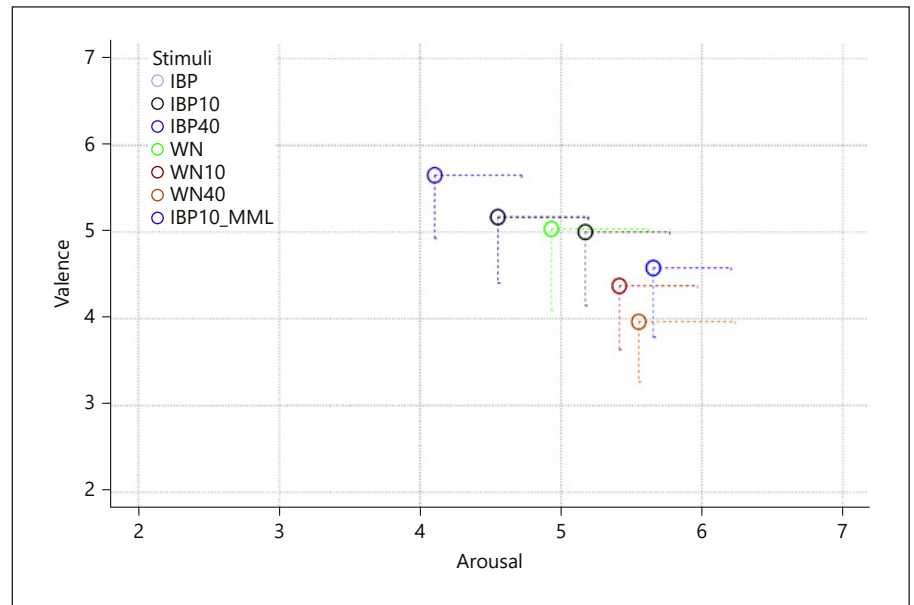
Interestingly, a significant difference in tinnitus loudness ratings between the 2 subgroups was revealed independently of condition and time as exemplified in Table 4 and Figure 3 (noise-like:  $M = 82.14$ ,  $SD = 26.68$ ; tonal:  $M = 94.79$ ,  $SD = 16.44$ ;  $t_{[31.15]} = 2.17$ ,  $p = 0.04$ ). On the basis of a significant interaction among group and time, we contrasted the mean tinnitus loudness for each group for all 7 time points after stimulation. Our results point out a significant difference between the groups only at T0 (noise-like:  $M = 63.98$ ,  $SD = 36.49$ ; tonal:  $M = 90.19$ ,  $SD = 28.01$ ;  $t_{[38.40]} = 4.27$ ,  $p < 0.01$ ; cf. Table 5).

#### Stimulus Evaluation

##### Arousal

As pointed out in online supplementary Table S3 and Figure 4, emotional stimuli evaluation for the whole group

**Fig. 4.** Valence and arousal rating per stimuli. Parentheses show 95% CI for arousal and valence ratings for all stimuli. Lowest tolerability was found in WN40 as indicated by high arousal and low valence stimulus valuation, whereas stimulus IBP10\_MML shows the highest tolerability. WN, white noise; MML, minimum masking level; IBP, individualized bandpass filtered.



**Table 5.** Post-hoc Tukey contrasts for group  $\times$  time

Contrast	Estimate	<i>t</i>	<i>p</i> value
<i>Tonal vs. noise-like</i>			
Time			
0	26.21	4.27	<0.01
30	20.05	3.27	0.10
60	13.61	2.22	0.62
90	9.91	1.62	0.93
120	7.61	1.24	>0.99
150	5.54	0.90	>0.99
180	5.59	0.91	>0.99

Degrees of freedom = 38.40; SE = 6.13.

identified the highest arousal ratings for stimulus IBP40, while IBP10\_MML expectably manifested in the lowest arousal values. Model fitting proceedings identified the subsequent model with the best fit for our arousal data: *response ~ condition + (1|id)* (cf. online suppl. Table S4). Fixed effect testing detected a significant effect for condition (cf. Table 6). Ensuing post-hoc contrasts revealed significant differences in arousal ratings for IBP versus IBP40 ( $t_{[180,21]} = -3.08$ ,  $p = 0.04$ ), IBP10 vs. IBP10\_MML ( $t_{[180,21]} = 2.98$ ,  $p = 0.05$ ), IBP10\_MML versus IBP40 ( $t_{[180,21]} = -4.33$ ,  $p < 0.01$ ), IBP10\_MML versus WN10 ( $t_{[180,21]} = -3.66$ ,  $p < 0.01$ ), and IBP10\_MML vs. WN40 ( $t_{[180,21]} = -4.04$ ,  $p < 0.01$ ). Post-hoc analysis results are reported in Table 7; relevant significant results are highlighted in bold.

**Table 6.** Fixed effect testing – arousal and valence

	numDF	denDF	<i>F</i>	<i>p</i> value
Arousal condition	6.00	174.00	5.17	<0.01
Valence condition	6.00	174.00	3.25	<0.01

numDF, degrees of freedom numerator; denDF, degrees of freedom denominator.

### Valence

In line with the descriptive arousal results, IBP10\_MML had the highest ratings for valence, whereas stimulus WN40 was evaluated with the least valence (cf. online suppl. Table S3; Fig. 4). Same model structure was fitted as for the arousal data (cf. online suppl. Table S4) and likewise a significant effect of condition was found (cf. Table 6). Post-hoc results are listed in Table 7 and demonstrate a significant difference for IBP10\_MML versus WN40 ( $t_{[180,21]} = 3.78$ ,  $p < 0.01$ ).

### Discussion

The aim of the present study was to investigate the effects of different IBP and AM noise stimuli on RI in people with tonal and noise-like tinnitus. To the best of our knowledge, no former study has systematically investigated the deployed acoustic stimulation procedures, especial-



**Table 7.** Post-hoc Tukey contrasts for condition

Contrast	Arousal			Valence		
	estimate	<i>t</i>	<i>p</i> value	estimate	<i>t</i>	<i>p</i> value
IBP – IBP10	–0.62	–1.73	0.60	0.17	0.39	>0.99
IBP – IBP10_MML	0.45	1.25	0.87	–0.48	–1.08	0.93
IBP – IBP40	–1.10	–3.08	0.04	0.59	1.31	0.85
IBP – WN	–0.38	–1.06	0.94	0.14	0.31	>0.99
IBP – WN10	–0.86	–2.41	0.20	0.79	1.77	0.57
IBP – WN40	–1.00	–2.79	0.08	1.21	2.70	0.10
IBP10 – IBP10_MML	1.07	2.98	0.05	–0.66	–1.47	0.76
IBP10 – IBP40	–0.48	–1.35	0.83	0.41	0.93	0.97
IBP10 – WN	0.24	0.67	0.99	–0.03	–0.08	>0.99
IBP10 – WN10	–0.24	–0.67	0.99	0.62	1.39	0.81
IBP10 – WN40	–0.38	–1.06	0.94	1.03	2.32	0.24
IBP10_MML – IBP40	–1.55	–4.33	<0.01	1.07	2.39	0.21
IBP10_MML – WN	–0.83	–2.31	0.25	0.62	1.39	0.81
IBP10_MML – WN10	–1.31	–3.66	0.01	1.28	2.86	0.07
IBP10_MML – WN40	–1.45	–4.04	<0.01	1.69	3.78	<0.01
IBP40 – WN	0.72	2.02	0.41	–0.45	–1.00	0.95
IBP40 – WN10	0.24	0.67	0.99	0.21	0.46	>0.99
IBP40 – WN40	0.10	0.29	>0.99	0.62	1.39	0.81
WN – WN10	–0.48	–1.35	0.83	0.66	1.47	0.76
WN – WN40	–0.62	–1.73	0.60	1.07	2.39	0.21
WN10 – WN40	–0.14	–0.38	>0.99	0.41	0.93	0.97

Arousal: Degrees of freedom = 180.21; SE = 0.36; Valence: Degrees of freedom = 180.21; SE = 0.45. IBP, individualized bandpass filtered; WN, white noise; MML, minimum masking level.

ly neither AM nor IBP sounds, in noise-like tinnitus cases. A parametric noise-band matching approach was applied in order to personalize BP settings in accordance with the tinnitus characteristics in the group with noise-like tinnitus, whereas the group with tonal tinnitus matched their tinnitus via the centre frequency of a fixed filter bandwidth. Taken together, all these aspects constitute novel lines of investigation within tinnitus research. Omnibus results of our experiment emphasize the ability of all used noise stimuli in inducing RI (cf. Table 2). The time courses and different suppression patterns for each stimuli appear in a similar manner as in previous studies, in that they generally converge over time after an initial maximum of suppression [Feldmann, 1983; Roberts et al., 2008; Neff et al., 2017, 2019; Vernon and Meikle, 2003; Roberts, 2007].

Contrary to our hypotheses, no statistically significant differences between the various stimuli and their impact on tinnitus perception respectively RI was observed. In more detail, neither the customization of the noise bands nor the AM resulted in significant differences between the conditions (i.e., stimuli). This outcome is in conflict with findings of earlier studies, which have suggested advantages of AM pure tones for RI [Neff et al., 2017, 2019;

Reavis et al., 2012; Tyler et al., 2014]. Yet, looking at these studies, pure tones were only compared to AM pendants with the exception of Tyler et al. [2014], who contrasted AM pure tones with unmodulated broadband noise.

A potential explanation for the lack of advantage of AM stimuli could be attributed to the circumstances, that noise is inherently composed of a wide spectrum of frequencies and signal-inherent amplitude modulation rates. These may cover up or neutralize the potential effects of certain AM rates for RI.

To the best of our knowledge, no former study specifically tested RI or sound therapies in entities with noise-like tinnitus. Of special interest, our analysis revealed statistical differences in RI for the subgroups noise-like and tonal tinnitus, with the noise-like group demonstrating larger RI than the tonal group. These significant differences were only observed immediately after the stimulation, suggesting a time-limited advantage of noise stimuli for RI in noise-like tinnitus. The reason for this group-difference is not clear, and a possible rationale may be due to physiological differences between these 2 groups with a supposed additional contribution of the extralemniscal system in noise-like tinnitus [Møller, 2006].

A further potential confounding factor for this group effect might be the fact that tinnitus loudness as elicited by MML, tinnitus matching and also in subjective ratings via VAS scales was found to be significant higher in the tonal subgroup. On the other hand, with no meaningful difference in HL between the groups and in consequence similar SLs, the putative confounding influence of these measures may play a negligible role. An in-depth analysis of the noise-like tinnitus group exclusively, demonstrated no statistical differences in tinnitus loudness ratings with respect to the used stimuli in a similar fashion as the analysis of the whole study sample.

However, since the bandwidth of BP filter settings in participants with tonal tinnitus was set to a range of one octave around the individual tinnitus frequency, whereas participants with noise-like tinnitus were able to individually adjust the BP filter settings, the differences in the subgroups may also derive from discrepancies in stimuli creation.

It was expected that a stimulation with noise is more pleasant or tolerable than a stimulation with pure tones. Unlike this assumption, our findings reveal a similar tolerability pattern for AM noise stimuli as Neff et al. [2019] on the basis of AM pure tones (cf. Fig. 4). The analysis conducted also show, that AM might lead to more arousal as indicated on a descriptive level as well as the significant difference between IBP and IBP40 (cf. Table 7). As must be expected, the lower intensity stimulus (IBP10\_MML) had the lowest arousal and highest valence ratings.

Our results indicate that the used matching method is feasible for determining tinnitus characteristics. In detail there was good consistency for both tinnitus loudness and frequency for both matching trials in noise-like and tonal tinnitus groups. These findings are in line with Henry et al. [2013], who already reported test-retest reliability for noise-band tinnitus matching.

### *Limitations*

The generalizability of these results is subject to certain limitations. As already discussed above, the significantly lower tinnitus loudness in the group of noise-like tinnitus could weaken our findings of subgroup differences in short-term tinnitus suppression.

However, as no difference in HL and equality in SL were observed, this may not play a significant role.

Likewise, the sample size of this experiment is rather small and gender ratio in the subgroups is unbalanced. One main issue is the impossibility to control for potential participant-related failures in noise-band matching. But for all of that, unavailable validation of the quantifica-

tion of peoples' tinnitus characteristics represents a common problem in tinnitus matching approaches, as it is a subjective phenomenon. Future studies should strive for new possibilities in verifying tinnitus matching results, as well as optimization of given methodological approaches.

Since we did not compare tonal and noise stimuli, it is not possible to make a statement about a general superiority of noise stimuli in short-term tinnitus suppression in noise-like tinnitus.

## **Conclusion**

The current study demonstrates a general efficacy of noise stimuli with different AM rates and filtering strategies for RI. Contrary to our expectations, no differences between the types of stimuli were observed. There were differences in RI among the subgroups of noise-like and tonal tinnitus, with better performance directly after the stimulation in the noise-like tinnitus group, were observed. Although, no stable rationale for the group differences can be provided, the findings may provide insights in the mechanism of RI for different tinnitus types. Future studies with larger sample sizes, improved matching/audiometry procedures and more acoustic stimulation repetitions per stimuli are needed to investigate these potential differences in more detail in order to enhance our understanding of the effects of acoustic stimulation on tinnitus perception.

Taken together these results illustrate the potential of noise-stimuli in short-term tinnitus suppression, especially in entities with noise-like tinnitus.

## **Acknowledgement**

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## **Statement of Ethics**

This study was approved by the Ethics Committee of the University of Regensburg, Germany (16-101-0061).

## **Disclosure Statement**

The authors have no conflicts of interest to disclose.

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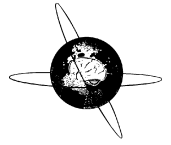
## Author Contributions

The authors P.N., W.S., and S.S. designed the study. J.A. collected the data. S.S. and P.N. analysed the data and wrote the main manuscript. All authors contributed to and reviewed the manuscript.

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# Neurophysiological correlates of residual inhibition in tinnitus: Hints for trait-like EEG power spectra



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## HIGHLIGHTS

- Trait-specific forms of oscillatory signatures related to residual inhibition.
- Alpha activity in auditory areas increased during residual inhibition.
- Lack of behavioral and neural correlations hamper conclusive interpretations

## ABSTRACT

**Objective:** To investigate oscillatory brain activity changes following acoustic stimulation in tinnitus and whether these changes are associated with behavioral measures of tinnitus loudness. Moreover, differences in ongoing brain activity between individuals with and without residual inhibition (RI) are examined (responders vs. non-responders).

**Methods:** Three different types of noise stimuli were administered for acoustic stimulation in 45 tinnitus patients. Subjects resting state brain activity was recorded before and after stimulation via EEG alongside with subjective measurements of tinnitus loudness.

**Results:** Delta, theta and gamma band power increased, whereas alpha and beta power decreased from pre to post stimulation. Acoustic stimulation responders exhibited reduced gamma and a trend for enhanced alpha activity with the latter localized in the right inferior temporal gyrus. Post stimulation, individuals experiencing RI showed higher theta, alpha and beta power with a peak power difference in the alpha band localized in the right superior temporal gyrus. Neither correlations with behavioral tinnitus measures nor stimulus-specific changes in EEG activity were present.

**Conclusions:** Our observations might be indicative of trait-specific forms of oscillatory signatures in different subsets of the tinnitus population related to acoustic tinnitus suppression.

**Significance:** Results and insights are not only useful to understand basic neural mechanisms behind RI but are also valuable for general neural models of tinnitus.

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## 1. Introduction

Subjective tinnitus is defined as the perception of a ringing or hissing without the presence of a corresponding internal or external source of sound. If this phantom sound perception is present over a period of at least six months, it is considered as chronic (Mazurek et al., 2010). About 10–15% of the global population suffers from tinnitus, whereas in 1–2% it represents a severe burden (Langguth et al., 2013; Heller, 2003; Erlandsson and Dauman,

2013) with comorbidities such as depression, anxiety disorder, sleep disorder or reduced quality of life (Croenlein et al., 2016; Nondahl et al., 2007; Weidt et al., 2016; Trevis et al., 2016).

Currently there is no treatment option for tinnitus available. A major challenge towards an identification of a treatment is related to heterogeneity in tinnitus phenotypes (Hesse, 2016; Kleinjung and Langguth, 2020; Cederroth et al., 2019; Zenner et al., 2017). Up to now, cognitive behavioral therapy represents the treatment option with the best available evidence for tinnitus (Landry et al., 2020; Cima et al., 2012; Li et al., 2019; Fuller et al., 2020).

In the majority of cases, tinnitus develops as a consequence of cochlear damages subsequent to noise trauma or hearing loss (HL) (Langguth et al., 2013). Typically, the perceived tinnitus pitch

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corresponds to the frequency range of maximum HL (Basile et al., 2013; Roberts et al., 2008; Norena et al., 2002; Schecklmann et al., 2012). Theories about the generation of tinnitus commonly suggest that the reduced or missing auditory input triggers maladaptive alterations along the auditory pathway and the central auditory system, which may lead to the sensation of a phantom sound in the frequencies of the peripheral HL (Eggermont, 2007; Eggermont and Roberts, 2012; Eggermont and Tass, 2015; Adjajian et al., 2009).

On a macroscopic level tinnitus was associated with anomalous oscillatory brain activity patterns such as enhanced activity in the delta and gamma frequency range alongside with reduced alpha activity over temporal regions (Weisz et al., 2005; Weisz et al., 2007). As observed in several neurophysiological investigations, this delta increase and alpha decrease appears to be closely linked to tinnitus perception as well as tinnitus distress (Weisz et al., 2005; Schlee et al., 2014; Adjajian et al., 2012; Moazami-Goudarzi et al., 2010; Balkenhol et al., 2013). Due to relations with tinnitus loudness as defined via tinnitus pitch matching (Balkenhol et al., 2013), subjective tinnitus loudness (van der Loo et al., 2009; De Ridder et al., 2015) or tinnitus-specific increased activity in the auditory cortex (Ashton et al., 2007; Vanneste et al., 2011), high gamma activity was proposed to represent the oscillatory signature of tinnitus perception per se (Weisz et al., 2007). These tinnitus-specific spontaneous brain activity patterns were subsumed under the framework of the thalamo-cortical dysrhythmia model (TCD) (Llinás et al., 1999; Llinás et al., 2005; De Ridder et al., 2015), which was further expanded to the “Synchronization-by-Loss-of-Inhibition-Model” (SLIM) (Weisz et al., 2007).

Conversely, some studies neither observed altered delta and alpha activity in tinnitus (Ashton et al., 2007), any power spectra differences compared to healthy controls (Zobay et al., 2015) nor correlations between electrophysiology and psychoacoustic or psychosocial tinnitus measures (Pierzycki et al., 2016). In the same vein, further studies report higher alpha activity in tinnitus (Moazami-Goudarzi et al., 2010), a relationship of enhanced alpha and tinnitus intensity (Meyer et al., 2014) or emphasize the relevance of other frequency bands like beta and theta in neural activity related to tinnitus (Meyer et al., 2014; Moazami-Goudarzi et al., 2010; Balkenhol et al., 2013). Considering these observations, assumptions about abnormal tinnitus-specific respectively tinnitus-related spontaneous brain activity are not so conclusive as presumed initially.

The phenomenon of short-term tinnitus suppression following acoustic stimulation was first studied almost 50 years ago (Feldmann, 1971; Feldmann, 1983). This phenomenon was defined as “residual inhibition” (RI) and can be observed in 60–80% of tinnitus sufferers, whereby depth and duration of suppression patterns vary among individuals (Roberts et al., 2006; Roberts, 2007; Vernon and Meikle, 2003). Since that time several experiments already examined the impact of various auditory stimulation techniques on RI. These vary from simple white noise (WN) or pure tones, to the application of specific filters or modulation rates, up to the combination of both modulation techniques applied to WN (Henry et al., 2013; Fournier et al., 2018; Roberts et al., 2008; Roberts et al., 2006; Tyler et al., 2014; Neff et al., 2017; Neff et al., 2019; Reavis et al., 2012; Schoisswohl et al., 2019). It has been suggested that stimulation intensity, duration, specific modulations as well as stimuli including the individual tinnitus frequency (ITF) facilitate short-term acoustic tinnitus suppression.

Another approach to reduce subjective tinnitus loudness for a longer period of time is provided via long-term stimulation with notch filtered music (individual tinnitus pitch is removed from the signal), referred to as “tailor-made notched music training” (TMNMT). The supposed underlying physiological effect behind

TMNMT takes place through an inhibition of frequencies within the notch filter called lateral inhibition. By means of long term applications, maladaptive pathological reorganization of the auditory cortex in tinnitus may be reversed (Pantev et al., 2012; Okamoto et al., 2010).

Nevertheless, little is known about the basic neurophysiological processes behind RI (Roberts, 2007). Reduced firing rates of neurons in the central auditory pathway are theorized to play a key role in RI (Galazyuk et al., 2017; Galazyuk et al., 2019), which covers subcortical structures of the auditory system. There is a paucity in experimental studies examining oscillatory brain activity after acoustic stimulation or rather during RI. With the help of neuro-magnetic measures in one tinnitus subject Kristeva-Feige et al. (1995) observed an increase in low frequency (2–8 Hz) spectral power during RI. Contrary to this observation, single-subject intracranial recordings showed a reduction of low frequency (delta: 1–4 Hz; theta: 4–8 Hz) activity in the auditory cortex during RI (Sedley et al., 2015). These tinnitus-related low frequency oscillations also interacted with alpha (8–12 Hz), beta (20–28 Hz) and gamma (>30 Hz) activity (Sedley et al., 2015). Beyond that, tinnitus intensity during RI was identified to be connected to delta (1.5–4 Hz), theta (4–8 Hz) and gamma (30–150 Hz) oscillatory activity in the auditory cortex by the use of single patient measurements of neuromagnetic brain activity (Sedley et al., 2012). The relevance of auditory gamma band activity for RI respectively tinnitus perception could be further corroborated by means of an inverse correlation with tinnitus intensity exclusively in tinnitus subjects experiencing residual excitation (Sedley et al., 2012). Kahlbrock and Weisz (2008) evaluated neuromagnetic activity in 10 tinnitus patients experiencing RI, defined as 50% of tinnitus loudness reduction for 30 s after stimulation offset. A reduction of delta (1.3–4 Hz) activity in temporal areas was observed during RI, whereas the gamma band (low: 30.5–49 Hz; high: 50.3–70.2 Hz) was not affected. The authors conclude that during a short-term reduction of tinnitus intensity, tinnitus-related abnormal oscillatory activities are temporary reversed resulting in a restored balance of neural inhibitory and excitatory processes. A recent study from King et al. (2021) investigated ongoing electrophysiological brain activity of 30 tinnitus subjects following broad band noise stimulation. 17 participants were able to experience RI, whereby a comparison of RI with a control auditory stimulation condition without the ability to induce RI revealed differences with respect to ongoing brain activity. In detail, the authors report higher power in the alpha and gamma frequency bands over the course of RI compared to the control condition.

To the best of our knowledge, the above mentioned five studies (Kristeva-Feige et al., 1995; Sedley et al., 2015; Sedley et al., 2012; Kahlbrock and Weisz, 2008; King et al., 2021) represent the only attempts to investigate resting state oscillatory brain activity in the context of RI. The fact that available findings are inconsistent and that merely two experiments - one utilizing Magnetoencephalography (MEG) and one Electroencephalography (EEG) - analyzed spontaneous brain activity during RI on a group level indicates an urgent need for respective research whether it is by means of MEG or EEG. Besides single subject analysis, group level analysis represent a basic pillar in science in order to make more general statements about the investigated population e.g., ongoing brain activity associated with RI.

Previous research utilizing neurophysiological measurements, used only one type of non-personalized sound and did not compare participants with and without RI. In the course of this study we are employing an extended set of modified and personalized noise stimuli targeting putatively differential neural mechanisms (i.e., RI and lateral inhibition). Thus the main purpose of this EEG experiment was to examine oscillatory brain activity changes during RI (pre vs. post) following a stimulation with different types of noise.

Moreover we aimed to investigate, whether these changes are related to subjective tinnitus loudness ratings. Since RI is a phenomenon which cannot be induced in all people with tinnitus, differences in spontaneous brain activity between people who reported RI and those who didn't were analyzed (responders vs. non-responders).

Apart from the efficacy of each used stimulus type in short-term tinnitus suppression on a group level, we hypothesize that filtered noise would result in stronger suppression patterns compared to unfiltered noise. In detail, bandstop-filtered noise is assumed to produce the strongest effect via a potentially suppression of neurons reacting to frequencies within the filter range as already shown in long-term applications via TMNMT (Pantev et al., 2012; Okamoto et al., 2010).

Due to the lack of past research in this field, we have no direct stimulus-specific a priori hypothesis about the types of changes from pre to post auditory stimulation in ongoing brain activity. However, we assume that potential changes in spontaneous brain activity can be associated with subjective tinnitus loudness ratings after stimulation. In accordance to Kahlbrock and Weisz (2008) we expect a decrease in delta and gamma activity as well as an increase in alpha activity from pre to post auditory stimulation in tinnitus cases experiencing RI (responders). Further we anticipate spectral power differences in the respective frequency bands between acoustic stimulation responders and non-responders. In order to link these differences to auditory cortical activation, source localization of the EEG data was performed.

## 2. Methods

### 2.1. Participants

In the course of this study, N = 45 (14 female) patients with chronic subjective tinnitus (> 6 months tinnitus duration) were recruited from the Interdisciplinary Tinnitus Centre Regensburg, Germany. For participation, patients had to fulfill the following primary inclusion criteria: age between 18 and 75 years; absence of other causes for tinnitus e.g., Meniere's disease, otosclerosis or acoustic neurinoma; no infection of the oropharynx; no present somatic, neurological or psychiatric disorder; no intake of psychoactive medication (e.g., antidepressants or anticonvulsant drugs), respectively substance or alcohol abuse at least 12 weeks before the start of the experiment; no hypersensitivity to sound; no tinnitus frequency < 1 kHz; no concurrent participation in other tinnitus-related studies or start of any other tinnitus-related treatment in the last three months prior study start.

Ethical clearance with respect to methodological approach and design was sought from the ethics committee of the University of Regensburg, Germany before commencing the experiment (ethical approval number: 17–819-101). For a detailed descriptive overview and clinical characteristics of the sample see Table 1. All participants received detailed information about objective, methods, duration and potential side effects of the study. Every participant gave written informed consent before the start of the study and received an appropriate expense allowance after completion of the experiment.

### 2.2. Psychometry

Prior to the start of the experiment, participants were requested to answer a set of questionnaires compiled of German versions of the Tinnitus Handicap Inventory (THI) (Newman et al., 1994; Kleinjung et al., 2007), the Tinnitus Questionnaire (TQ) (Goebel and Hiller, 1994; Hallam et al., 1988), the Tinnitus Sample Case History Questionnaire (TSCHQ) (Langguth et al., 2007), visual ana-

log scales (VAS, %) for tinnitus awareness, loudness and bothersome, as well as the Questionnaire on Hypersensitivity to Sound (GUF) (Blaesing et al., 2010) (participants with a score of > 23, which constitutes a very severe impairment, were excluded from our analysis). The survey was performed with SoSci Survey (Leiner, 2016).

### 2.3. Audiometry

Participants hearing thresholds were examined with the toolbox MultiThreshold (University of Essex, United Kingdom) using the implemented paradigm absolute threshold (absThreshold) in Matlab (Matlab R2017a; Mathworks, USA). This paradigm is an implementation of the two-alternatives forced-choice threshold estimation algorithm by Green (1993). Sine tones (0.5 s) were used to test participants hearing level for frequencies from 250 up to 8000 Hz on an octave scale for each ear separately. Starting loudness level was 30 dB SPL, which was increased by 10 dB steps until the participants were able to perceive the sound. The loudness level was raised by 2 dB steps between trials. ER-2 Insert Earphones (Etymotic Research Inc., USA) together with an external soundcard (RME Fireface UCX; Audio AG, Germany) were used for hearing assessment, subsequent matching of the ITF, definition of the sensation level (SL), minimum masking level (MML) (compare Section 2.4) as well as the proper auditory stimulation.

### 2.4. Tinnitusometry

Individual tinnitus pitch matching was carried out using a Method of Adjustment approach modified from Henry et al. (2013) and Roberts et al. (2008) and implemented in a custom software tool (MAX 7; Cycling'74, USA). A custom-built hardware controller was used comprising a Teensy 3.2 USB-based microcontroller (PJRC, USA) and industrial-grade rotating knobs, switches and motor faders. Detailed information about the used tinnitus matching procedure is described in Neff et al. (2019). The starting frequency was defined as one frequency group below the frequency with the highest HL and a start loudness of 10 dB above the particular hearing threshold. Participants tried to match their tinnitus four times as good as possible and rated the accordance of the matched sound with their perceived tinnitus on a 1–10 scale (1 = no accordance; 10 = perfect accordance) after each attempt. The tinnitus matching trial with the highest rating was subsequently defined as the participants ITF. If participants rated different matching attempts similarly, the frequency closest to the mean frequency of the four attempts was chosen. The ITF was then used for the evaluation of further audiometric parameters. Similarly, the MML was defined by increasing the loudness of WN to the point of complete tinnitus masking. Assessment of the loudness discomfort level (LDL) of participants ITF was executed with the discomfort paradigm of the MultiThreshold toolbox with Sennheiser HDA 2000 headphones (Sennheiser, Germany).

### 2.5. Acoustic stimulation

Three different types of noise stimuli with a duration of three minutes each were created in Matlab (Matlab R2017a; Mathworks, USA) with an intensity of 65 dB SL (defined as the loudness level of participants first-time tinnitus pitch perception; maximum loudness of 85 dB SPL) for acoustic stimulation. For this purpose a genuine WN was used to produce individualized noise stimuli through the implementation of bandpass (IBP) and bandstop (IBS) filters with one octave width around the ITF (Pantev et al., 2012). Each stimuli was composed of a 1000 ms linear fade-in and fade-out phase and underwent a root-mean-square correction to balance levels between stimuli. Diotic acoustic stimulation was performed



**Table 1**

**Sample characteristics.** M = mean; SD = standard deviation; Md = median; Min = minimum; Max = maximum; LDL = Loudness Discomfort Level (missings in LDL are due to values over 90 dB); TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; VAS = Visual Analog Scale; GUF = Questionnaire on Hypersensitivity to Sound.

N (female)	45 (14)			
Tinnitus side (left/ right/ bilateral)	(5/ 8/ 32)			
Tinnitus loudness fluctuation (yes/ no)	(24/ 21)			
Tinnitus maskability (yes/ no/ don't know)	(31/ 5/ 9)			
Musician (yes/ no)	(4/ 41)			
	M ± SD	Md	Min	Max
Age (years)	52.29 ± 11.81	55.00	23.00	69.00
Tinnitus duration (months)	111.04 ± 72.90	96.00	18.00	280.00
Tinnitus frequency (Hz)	6251.09 ± 2811.38	5887.00	1020.00	15524.00
Tinnitus loudness (dB SPL)	51.38 ± 16.05	50.00	27.00	85.00
Hearing loss left (dB)	17.26 ± 13.61	14.69	−5.72	55.00
Hearing loss right (dB)	17.48 ± 11.52	17.43	−8.71	45.87
LDL left (dB) (25 missing values)	86.25 ± 3.21	85.50	81.00	90.00
LDL right (dB) (28 missing values)	85.06 ± 3.96	87.00	78.00	90.00
Minimum masking level (dB)	63.82 ± 14.60	60.00	37.00	90.00
Sensation Level (dB)	47.58 ± 17.49	45.00	21.00	86.00
TQ total score (0–84)	40.73 ± 15.70	40.00	17.00	71.00
THI total score (0–100)	35.91 ± 21.38	34.00	4.00	80.00
VAS awareness (%)	64.62 ± 29.62	70.00	8.00	100.00
VAS loudness (%)	61.11 ± 24.19	65.00	15.00	100.00
VAS bothersome (%)	38.20 ± 29.29	30.00	0	100.00
GUF total score (0–45)	10.73 ± 6.45	10.00	0	23.00

at a maximum loudness of 85 dB SPL and each stimuli was presented only once. The presentation sequence of the stimuli was randomized.

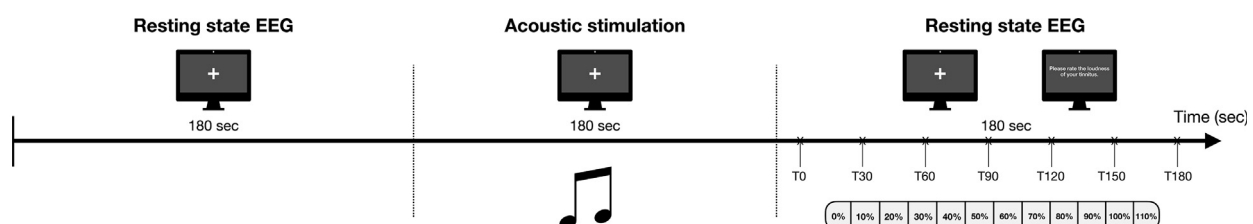
Before and after the presentation of each stimuli (3 min), participants were requested to sit quietly, focus on a white fixation cross on a black screen and avoid extensive eye-blinks and movements while their brain activity was recorded via EEG for three minutes respectively (compare Section 2.7).

After the presentation of each noise stimulus, patients had to rate the loudness of their tinnitus at seven different time points (0sec, 30sec, 60sec, 90sec, 120sec, 150sec and 180sec after stimulation offset) on a customized keyboard strip (X-Key-Stick-16-USB, XK-0981-UCK16-R; P.I. Engineering, USA) with a numeric rating scale from 0% to 110%, whereas 100% signified no tinnitus loudness changes, 0% a total absence of tinnitus and 110% an tinnitus loudness increase by 10 %. For an illustration of the acoustic stimulation procedure please see Fig. 1. The whole experimental stimulation procedure was implemented with the Psychophysics Toolbox Version 3 (Brainard, 1997; Kleiner et al., 2007) in Matlab (Matlab R2017a; Mathworks, USA) and double-blinded. At the end of the experiment, the three stimuli were again presented in a randomized order for 10 s each and participants were requested to rate the valence and the arousal of each stimuli via pictorial manikin scales (Bradley and Lang, 1994) on a 9-point Likert Scale, whereas the value 0 indicated a neutral stimulus evaluation (Valence: −4 unpleasant, 4 pleasant; Arousal: −4 relaxing, 4 upsetting).

## 2.6. Behavioral analysis

Behavioral data was analyzed with the statistic software R (R version 3.4.2; R Foundation for Statistical Computing, Austria) and the packages "psych", "emmeans", "sjstats" and "lme4". Linear mixed effect models were used to analyze tinnitus loudness ratings and stimuli evaluation (valence, arousal) separately. The following predictors were tested for the model fitting procedure of tinnitus loudness ratings: condition (stimuli, compare Section 2.5), time (0sec, 30sec, 60sec, 90sec, 120sec, 150sec, 180sec towards stimulation offset), tinnitus bilaterality (yes/no), sex (male/female), tinnitus duration and stimuli position in the auditory stimulation sequence. The predictors condition, gender and tinnitus duration were tested for the model fitting procedure of stimuli evaluation data.

Other potential predictors such as tinnitus loudness (dB), MML, SL or HL were not included in the model fitting procedure, since they were experimentally controlled e.g., by the creation of tailored stimuli. Participant (id) was considered as a random effect in all model fitting procedures. In order to identify the model with the best fit for the data, the step function of the lme4 package was deployed. Thereby, a backward elimination of non significant predictors as well as a forward addition of significant predictors is conducted by comparing the models with Likelihood Ratio Tests (Harrison et al., 2018). Marginal (variance of the predictors) and conditional (variance of predictor and random effect)  $R^2$  were



**Fig. 1. Acoustic stimulation procedure.** Prior and post of acoustic stimulation (3 min), participants resting state brain activity was recorded via EEG (3 min). Participants were instructed accordingly and requested to focus on a white fixation cross on a black screen during the whole experiment. Following acoustic stimulation, participants were requested to rate the current loudness of their tinnitus ("Please rate the loudness of your tinnitus.") at seven points in time (0, 30, 60, 90, 120, 150 and 180 s towards stimulation offset) on a numeric rating scale from 0% to 110% (0% - total absence of tinnitus; 100% - no tinnitus loudness changes; 110% - 10% tinnitus loudness increase). This acoustic stimulation procedure was repeated for each of the three used types of noise stimuli (white noise, individualized bandpass filtered white noise, individualized bandstop filtered white noise).

computed to provide the amount of the explained variance of the respective model (Nakagawa et al., 2017). For each final model, fixed effects were examined via Expected Mean Square Approach. Potential differences in tinnitus loudness and stimuli evaluation within predictors were analyzed with post hoc Tukey-tests. Analysis of descriptive differences between HL and LDL between the left and right ear were tested by the means of two-sample t-tests. Normal distribution (Shapiro–Wilk-Test) and homoscedasticity (F-test) were examined and if violated, non-parametric testing with independent sample Mann–Whitney U-tests were conducted. To evaluate effect size of significant differences, Cohen's d was calculated. The level of statistical significance was set to  $p \leq .05$  for all analyses.

## 2.7. Electrophysiological data acquisition and analysis

### 2.7.1. EEG recording

EEG data was recorded with a BrainAmp DC system, EasyCap electrode cap with 64 electrodes, and Brain Vision Recorder 1.20 software (Brain Products GmbH, Germany). The sampling rate was 500 Hz and electrodes were referenced to FCz during recording. Impedances were kept below 10 k $\Omega$ .

### 2.7.2. Preprocessing

Raw EEG data was preprocessed with a custom-built semi-automatic pipeline using the Fieldtrip toolbox (Oostenveld et al., 2011) in Matlab (Matlab R2017a; Mathworks, USA). EEG data was filtered between 0.5 Hz and 45 Hz with a 4th order Butterworth bandpass filter.

Hereafter, an independent component analysis (ICA, fastICA <http://research.ics.aalto.fi/ica/fastica/index.shtml>) was used to identify and remove components with horizontal and vertical eye movement. Noisy or aberrant channels were interpolated using weighted neighbors. Neighboring channels were defined via a triangulation of 2D sensor position projection and channels identified for interpolation were replaced with the mean of neighboring sensors. In a next step, average referencing was performed and the recording reference electrode FCz was added as a data channel. In order to control for noisy channels introduced by the rating procedure of the post stimulation conditions, posterior (Iz, TP9, TP10) as well as frontal channels (FPz, FP1, FP2, AF3, AF4, AF7, AF8) were discarded from subsequent analyses steps. Data was then segmented into 2 s segments. All segments during which participants rated the loudness of their tinnitus were rejected. Additionally, one segment before and after the rating was excluded as well. Segments with remaining artifacts were rejected with combined automatic identification via a z-score ( $\mu V$ ) threshold of  $-2/+2$  and visual inspection in a final step. Average number of valid segments was different ( $U = 1970.50$ ,  $p = .001$ ) between pre ( $M = 78.93$ ,  $SD = 6.48$ ) and post ( $M = 60.37$ ,  $SD = 6.19$ ) acoustic stimulation.

### 2.7.3. EEG analysis

**Power analysis - whole group** Frequency power spectra of pre and post auditory stimulation datasets per subject and condition (compare 2.5) were calculated using multitaper frequency transformation (mtmfft) and a hanning window with a spectral smoothing of 1 Hz. Next, grand averages were created for pre and post stimulation datasets per condition by computing power spectra averages across all valid segments and all subjects.

Potential changes in EEG power spectra were analyzed with a 2 x 3 repeated measurement ANOVA and the within subject factors time (pre, post) and condition (WN, IBP, IBS), which was implemented in Fieldtrip. The main effects for time and condition were tested with paired two-sided t-tests via non-parametric cluster-based permutation tests with 10,000 iterations. In order to test for an interaction effect of time and condition, a dependent sam-

ples multivariate ANOVA was conducted using a non-parametric cluster-based permutation test with 10,000 iterations as well. We were primarily interested in an interaction effect of time and condition. In case of a significant time x condition interaction, effects were followed up using post hoc contrasts. Pre vs. post contrast per condition were analyzed with dependent samples t-tests, whereas potential differences in stimuli-induced power spectra changes from pre to post stimulation as well as post stimulation differences (inter-stimulus contrasts), were contrasted via independent samples t-tests using non-parametric cluster-based permutation test as described above.

Additionally, Pearson correlations between post stimulation power spectra and pre-post power spectra differences with averaged tinnitus loudness ratings (over all 7 time points) as well as directly after stimulation offset (T0) were computed via cluster-based permutation tests. Significance level was set to  $p \leq .05$  for all EEG analyses and  $p < 0.1$  was defined as a statistical trend. Significant clusters were defined as a minimum of two significant neighboring channels for all analysis. For the purpose of interpretation, EEG frequency bands were defined as follows: delta 1–4 Hz, theta 5–7 Hz, alpha 8–12 Hz, beta 13–29 Hz, gamma 30–45 Hz.

**Power analysis - responder** Furthermore, we compared frequency power spectra of participants who exhibited RI with those who did not experience RI after auditory stimulation. For this purpose RI was defined as  $\leq 50\%$  of tinnitus loudness directly after stimulation offset resulting in a subset of  $n = 12$  further indicated as responders. Within this subgroup of responders,  $n = 5$  participants each, responded to a stimulation with WN or IBP, whereas only  $n = 2$  participants reported RI after a stimulation with IBS. A second subgroup of participants without RI (non-responders) were matched to responders according to the following criteria: gender; mean HL; age and absence of RI (tinnitus loudness of  $\geq 100\%$  after stimulation offset) in the same stimulus type as matched patient exhibited RI in responders group. Sample characteristics for both subgroups can be seen from Table 2. Associations of categorical variables with stimulation response (responder or non-responder) were analyzed with  $\chi^2$ -tests or Fisher's exact tests if cell frequencies were below 5. Differences in numerical variables between the two subgroups were analyzed by two-sample t-tests. In case of violated statistical assumptions, Mann–Whitney U-tests were performed. Significance levels were set to  $p \leq .05$  and a statistical trend was defined as  $p < 0.1$ .

Power spectra for pre and post auditory stimulation EEG datasets were averaged over all subjects within the respective subgroup (responders and non-responders). Analysis were conducted using normalized EEG datasets by dividing power spectra for each single frequency through the total power of the entire frequency spectrum according to the formula:

$$W(f)_{\text{norm}} = \frac{W(f)}{\int_{f_{-1}}^{f_{+5}} W(f) df}$$

Illustrated power spectra per frequency were transformed according to  $10 * \log_{10}(x)$ . EEG power spectra were analyzed with a 2 x 2 repeated measures ANOVA and the factors time (pre, post) and group (responders, non-responders). The main effects for time and group were evaluated with dependent sample respectively independent sample t-tests according to the same approach as already described in the power analysis section for the whole group. Likewise, a potential interaction effect of time and group was analyzed with an independent samples t-test.

In the case of a significant interaction effect, post hoc dependent samples t-tests for pre vs. post within subgroup contrast and independent samples t-tests for between subgroup contrast (responders vs. non-responders) separated for pre and post stimulation

measurements are conducted. Regardless of an observed interaction effect, an exploratory contrast of post stimulation power spectra differences between responders and non-responders is performed. Equal to the whole group analysis, Pearson correlations were calculated with cluster-based permutation tests for post stimulation power spectra and pre-post power spectra differences with averaged tinnitus loudness ratings or rather directly after stimulation offset (T0). Additionally, a correlation of post stimulation power spectra and pre-post power spectra differences with tinnitus loudness rated via VAS (%) was computed.

In order to explore differences in cortical alpha variability between responders and non-responders a coefficient of variance was calculated by dividing the standard deviation of the alpha frequency power (8–12 Hz) by its mean power.

**Source space analysis** Source localization of frequency data was performed using a standard boundary element headmodel (Oostenveld et al., 2003) and the dynamic imaging of coherent sources algorithm optimized for EEG frequency data (Dynamical Imaging of Coherent Sources, (Groß et al., 2001)). First, cross-spectral density was calculated for each electrode using 'mtmfft' with the 'powandcsd' option and a hanning window with 1 Hz spectral smoothing in the peak frequency extracted from the scalp analysis. Second, a standard boundary element headmodel including the tissues of scalp, skull, and brain was used ('standard\_bem'). Details of the segmentation and the conductivity models are described in Oostenveld et al. (2003, 2002). An adapted standard electrode layout was used ('standard\_1020') where the noisy channels described above were dropped. Electrode alignment was then checked visually and alignment optimized so that the electrodes were correctly positioned over the scalp and not part of any tissue of the headmodel. Finally, the leadfield was calculated with the headmodel and the aligned electrodes. Notably, a single headmodel, electrode, and leadfield template was created for source analysis of all participants given the absence of individual MRIs and electrode positions.

Inter-subgroup source contrasts (responders vs. non-responders; responders vs. non-responders post stimulation) of peak frequencies derived from the respective sensor-level cluster analysis (maximum value; please see Section 3.5 under the sub-heading for responder) were analyzed via non-parametric cluster-based permutation tests with 10,000 iterations using normalized EEG datasets. Normalization procedure was identical to the sensor level analysis.

### 3. Results

#### 3.1. Sample characteristics

Table 1 summarizes the descriptive statistics and tinnitus-related questionnaire scores of the present sample. In the majority of participants, tinnitus was perceived bilaterally ( $n = 32$ ) and featured loudness fluctuations ( $n = 24$ ). The possibility to mask their perceived tinnitus was reported by  $n = 31$  participants. Moreover,  $n = 4$  participants claimed to be musicians and the average duration of tinnitus perception was 111.04 months ( $SD = 72.90$ ).

Stimulation with either WN, IBP and IBS resulted in  $n = 12$  responders, who showed RI with at least one stimulus type.

A weak association of stimulation response (responders or non-responders) and tinnitus maskability (yes, no, don't know) was found with the group of responders exhibiting no participant who reported an absence of tinnitus maskability (cf. Table 2). Statistical testing for differences between the subgroups of responders and non-responders revealed differences in terms of tinnitus duration, MML and questionnaire data with the group of responders showing shorter tinnitus duration ( $U = 26.00$ ,  $p = .008$ ,  $d = 1.135$ ),

**Table 2**  
**Sample characteristics - responders vs. non-responders.** M = mean; SD = standard deviation; Md = median; Min = minimum; Max = maximum; df = degrees of freedom; LDL = Loudness Discomfort Level (missings in LDL are due to values over 90 dB); TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; VAS = Visual Analog Scale; GUF = Questionnaire on Hypersensitivity to Sound.

	Responders					Non-responders					p	
	11 (1)					11 (1)						
N (female)	(0/5/7)					(3/2/7)						.189
Tinnitus side (left/ right/ bilateral)	(7/5)					(6/6)						.682
Tinnitus loudness fluctuation (yes/ no)	(7/0/5)					(7/2/3)						.063
Tinnitus maskability (yes/ no/ don't know)	(3/9)					(1/11)						.590
Musician (yes/ no)	M ± SD					M ± SD						
Age (years)	54.17 ± 12.14					54.38 ± 6.98						.540
Tinnitus duration (months)	77.00 ± 69.48					159.58 ± 75.91						.008
Tinnitus frequency (Hz)	5271.58 ± 1985.77					6661.75 ± 2451.11						.142
Tinnitus loudness (dB SPL)	53.25 ± 14.70					53.92 ± 12.30						.905
Hearing loss left (dB)	19.75 ± 14.78					20.61 ± 11.17						.729
Hearing loss right (dB)	19.89 ± 7.89					19.95 ± 11.25						.988
LDL left (dB) (5 missing values/ 11 missing values)	85.71 ± 2.93					90.00						.302
LDL right (dB) (7 missing values/ 8 missing values)	83.04 ± 6.15					86.25 ± 3.77						.422
Minimum masking level (dB)	56.33 ± 13.15					72.92 ± 15.19						.012
Sensation level (dB)	46.00 ± 15.85					52.58 ± 8.84						.225
TQ total score (0–84)	28.00 ± 10.87					49.00 ± 15.20						<.001
THI total score (0–100)	22.83 ± 16.37					48.00 ± 23.34						.004
VAS awareness (%)	50.00 ± 28.92					80.83 ± 25.75						.008
VAS loudness (%)	48.75 ± 16.25					73.33 ± 16.65						.004
VAS bothersome (%)	21.33 ± 21.98					45.83 ± 29.99						.029
GUF total score (0–45)	6.00 ± 5.48					12.17 ± 5.37						.012

lower MML ( $U = 28.00$ ,  $p = .012$ ,  $d = 1.168$ ) as well as lower sum scores in TQ ( $U = 14.50$ ,  $p < .001$ ,  $d = 1.159$ ), THI ( $t_{(19,71)} = -3.30$ ,  $p = .004$ ,  $d = 1.249$ ) and GUF ( $U = 28.50$ ,  $p = .012$ ,  $d = 1.137$ ). Likewise, responders reported lower values in subjective measurements of tinnitus awareness ( $U = 26.50$ ,  $p = .008$ ,  $d = 1.126$ ), loudness ( $U = 22.50$ ,  $p = .004$ ,  $d = 1.494$ ) and bothersome ( $U = 34.00$ ,  $p = .029$ ,  $d = .931$ ) as indicated by VAS (in %). Detailed sample characteristics and statistical comparisons for the two subgroups are shown in Table 2.

### 3.2. Audiometry and Tinnitometry

Results from audiometric assessment and tinnitus matching are outlined in Table 1 as well as illustrated in Fig. S1. The investigated sample featured a mean tinnitus frequency of 6251.09 Hz ( $SD = 2811.38$ ), whereas the average tinnitus loudness was 51.38 dB SPL ( $SD = 16.05$ ). Initial perception of the individual tinnitus pitch (SL) appeared at a mean volume level of 47.58 dB ( $SD = 17.49$ ). Mann–Whitney U-tests found no differences with respect to HL ( $U = 941.50$ ,  $p = .569$ ) and LDL ( $U = 199.50$ ,  $p = .361$ ) between the left and the right ear.

### 3.3. Acoustic Stimulation

Table S1 lists the descriptive statistics for tinnitus loudness ratings for each stimuli on average as well as time point T0. Tinnitus suppression time curves, including all seven time points, are illustrated in Fig. 2 for each stimuli.

Model fitting procedure of behavioural data was able to identify the following model with the best fit for the data:  $response \sim condition + (1|id)$ . Table S3 lists detailed results of the model fitting proceeding. A significant effect of condition was

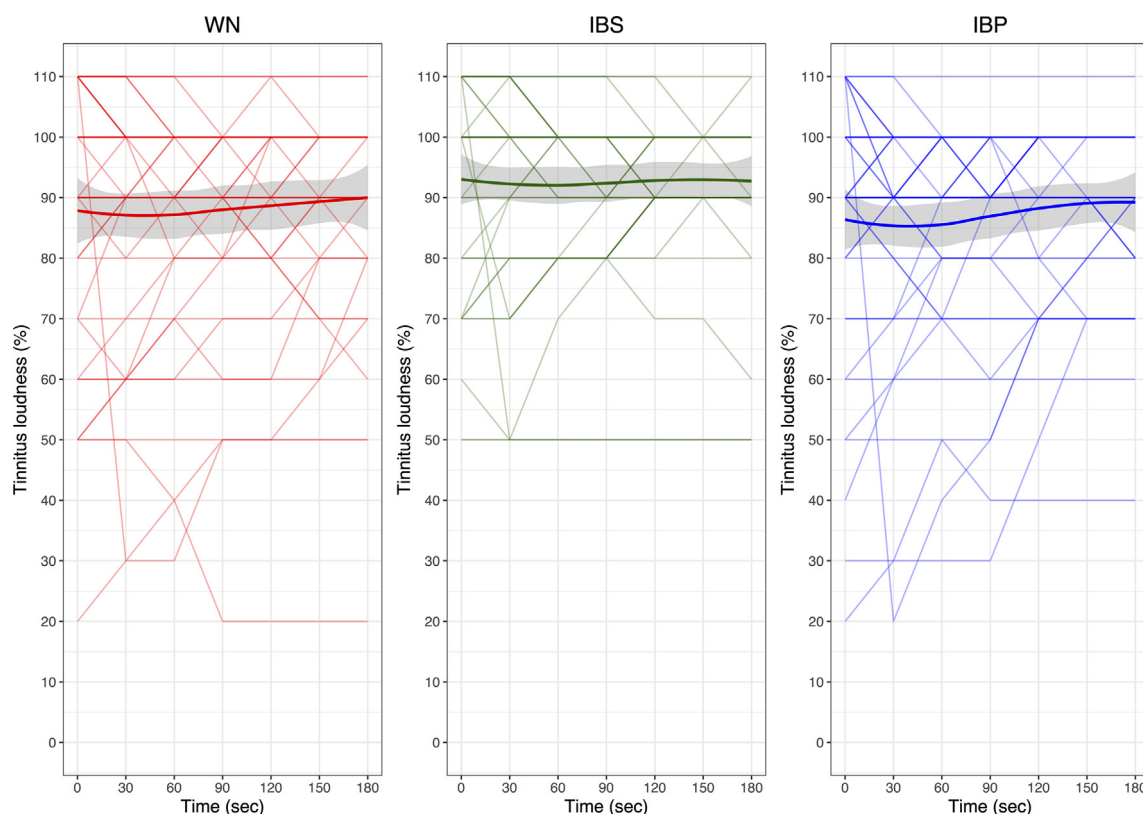
observed (cf. Table S3). Succeeding post hoc contrasts found differences between stimulus WN vs. IBS, as well as IBP vs. IBS (cf. Table 3). A potential confounding caused by the position of the stimuli in the acoustic stimulation sequence could be excluded, since position did not appear as a significant predictor in the final model.

### 3.4. Stimulus evaluation

Stimulus evaluation outcomes in terms of valence and arousal can be seen from Table S4 and Fig. S2. Model  $response \sim condition + (1|id)$  was identified to have the best fit for the valence data with condition as a significant fixed effect (cf. Tables S5 and S6). Post hoc tests were able to reveal differences for valence evaluations of stimuli WN vs. IBS and also IBP vs. IBS as can be seen from Table S7. Subsequent model was identified by our model fitting approach for arousal data:  $response \sim condition + gender + (1|id)$  (cf. Table S5). Fixed effect testing revealed significant effects for condition and gender (cf. Table S6). Post hoc analysis showed differences between stimuli IBP and IBS as well as male and female participants (cf. Table S7).

### 3.5. Electrophysiology

**Whole group** Results of whole sample EEG power spectra analysis are outlined in Table 4. A significant main effect of time was observed, indicating higher spectral power for 1–7 Hz and 26–45 Hz plus lower spectral power for 7–28 Hz after auditory stimulation. Further, a significant interaction of condition and time was found in the frequency spectra 1–7 Hz and 36–45 Hz. Succeeding post hoc contrasts revealed higher power in lower frequencies towards stimulation across all stimuli (WN: 1–7 Hz; IBP: 1–6 Hz;



**Fig. 2. Tinnitus loudness time curve per condition.** WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise. Tinnitus loudness ratings are illustrated on a single participant level for all rating timepoints separated for each stimuli. Thick lines show the mean tinnitus loudness (%) per stimulus, standard deviations are illustrated as grey ribbons.



**Table 3**

**Post hoc tukey contrasts for condition.** WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise; degrees of freedom = 902.00; standard error =.87.

Contrast	Estimate	t	p	d
<b>Total sample</b>				
WN - IBP	1.05	1.20	.451	.057
WN - IBS	−4.32	−4.96	<.001	.251
IBP - IBS	5.37	−6.17	<.001	.328

IBS: 1–6 Hz) as well as higher gamma activity after a stimulation with IBP (32–45 Hz) and IBS (37–45 Hz). A power decrease following IBS stimulation was found for the frequency cluster 11–19 Hz. In addition, statistical trends towards power reductions in the frequency clusters 10–12 Hz and 14–19 Hz were observed for pre-post comparisons of stimulus WN. Differences between the applied types of stimuli with respect to pre-post power spectra changes or post stimulation power spectra were not detected.

Electrodes within frequency clusters as outlined in Table 4 can be found in the supplemental material in Table S8 grouped by brain areas.

No correlations were found on the cluster level for post stimulation EEG power or pre-post power spectra changes with averaged tinnitus loudness ratings or rather tinnitus loudness ratings immediately after stimulation end (T0) for any of the used stimuli.

**Responder** Table 5 provides the results obtained from the responder EEG power spectra analysis (compare Section 2.7.3). A significant main effect of time was observed, indicating a power reduction from pre to post stimulation in the frequency cluster 6–32 Hz for responders as well as non-responders. Likewise, a significant effect of group demonstrates lower power in higher frequency ranges (22–45 Hz;  $t(\max) = -4.06$ , over electrode P5 at 31 Hz; cf. Fig. 3 A and B) as well as a statistical trend towards higher power in the alpha frequency range (7–12 Hz;  $t(\max) = 4.35$ , over electrode F4 at 9 Hz; cf. Fig. 3 A and B) for the subgroup of responders. There was no significant interaction of time and group. Electrodes within frequency cluster presented in Table 5 can be found in Table S9 in the supplemental material.

Subsequent exploratory analysis of post stimulation power spectra differences between responders and non-responders, exhibited increased activity in the frequency cluster 5–17 Hz in the subgroup of responders ( $t(\max) = 4.94$ , over electrode F4 at 9 Hz; cf. Table 5 and Fig. 4 A and B).

Correlations of EEG power post stimulation or pre-post power spectra changes on the cluster level with subjective tinnitus ratings for the group of responders showed no significant results for mean tinnitus loudness or tinnitus loudness at T0. Further no correlation with tinnitus loudness rated via VAS (%) was observed.

Coefficient of variance calculation exclusively for the alpha frequency band (8–12 Hz) exposed a higher variation in frequency

**Table 4**

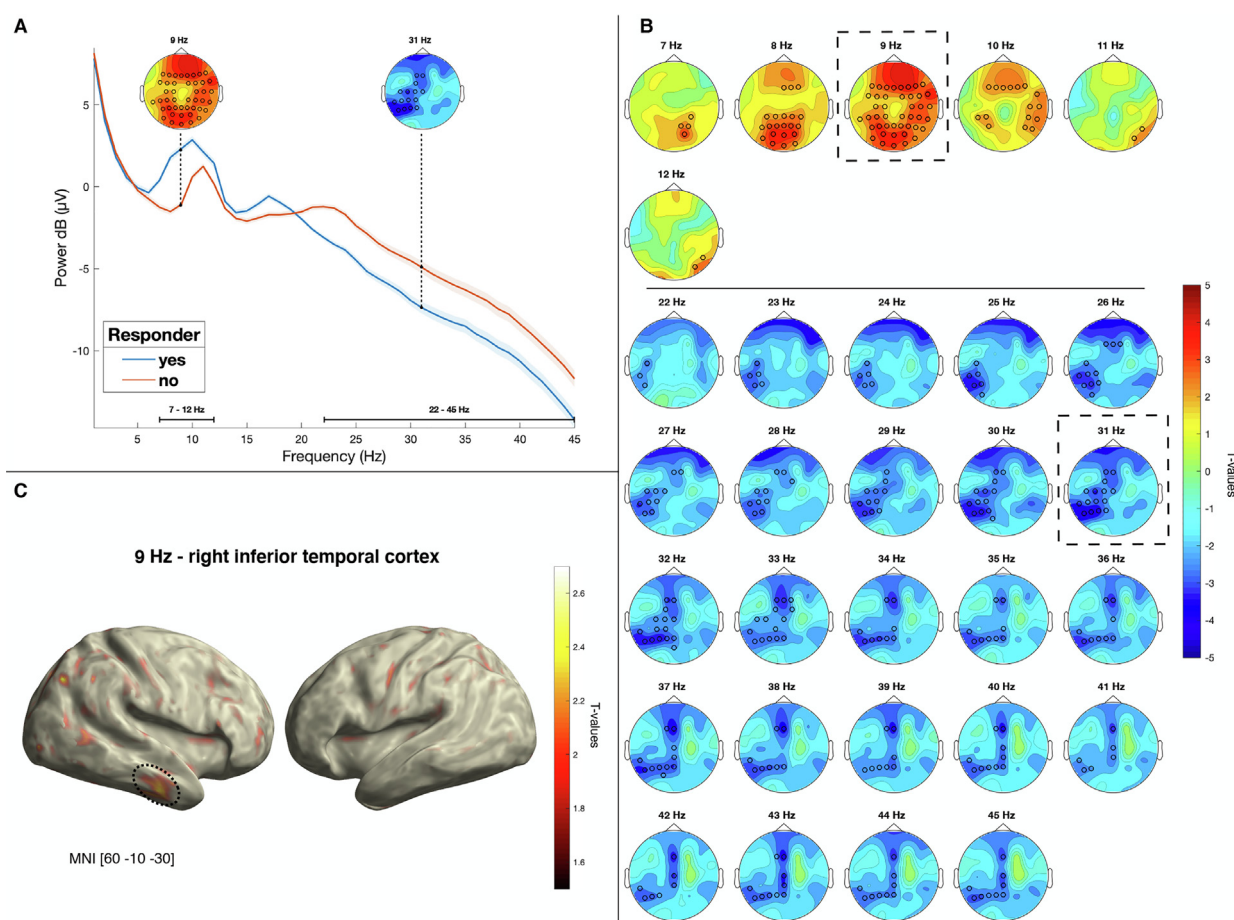
**Electrophysiology - results of cluster-based permutation test for the total sample analysis.** WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise; df = degrees of freedom; Max = maximum. Positive clusters indicate increased power spectra whereas negative clusters indicate decreased power spectra from pre to post stimulation, in the respective frequency ranges. Peak frequency (Hz) and peak electrode represent the particular frequency and electrode featuring the maximum value obtained from cluster statistics.

	Frequency (Hz)	Cluster statistic (df)	p	Peak frequency (Hz)	Peak electrode	Max. statistic
<b>Time</b>						
Positive cluster	1–7	$t(134) = 1047.88$	<.001	4	P08	7.68
Positive cluster	26–45	$t(134) = 893.13$	<.001	41	P0z	4.89
Negative cluster	7–28	$t(134) = -1150.64$	<.001	12	T8	−5.33
<b>Condition x Time</b>						
Positive cluster	1–7	$F(5,40) = 3437.77$	.002	4	P08	51.28
Positive cluster	36–45	$F(5,40) = 2783.52$	.002	42	F6	34.09
<b>Post hoc - pre vs. post stimulation per stimulus</b>						
<b>Positive cluster</b>						
WN	1–7	$t(44) = 482.28$	.006	5	O1	4.81
IBP	1–6	$t(44) = 696.17$	.002	3	O1	5.90
IBP	32–45	$t(44) = 460.98$	.007	41	F3	4.44
IBS	1–6	$t(44) = 398.13$	.006	3	O2	4.20
IBS	37–45	$t(44) = 199.09$	.026	45	P2	3.54
<b>Negative cluster</b>						
WN	10–12	$t(44) = -132.92$	.058	11	T8	−4.24
WN	14–19	$t(44) = -123.90$	.064	19	C3	−3.95
IBS	11–19	$t(44) = -242.31$	.016	13	T8	−4.20

**Table 5**

**Electrophysiology - results of cluster-based permutation test for the responder analysis.** df = degrees of freedom; Max = maximum. Positive clusters indicate increased power spectra, whereas negative clusters indicate decreased power spectra for responders compared to non-responders respectively from pre to post stimulation (effect of time) in the respective frequency ranges. Peak frequency (Hz) and peak electrode represent the particular frequency and electrode featuring the maximum value obtained from cluster statistics.

	Frequency (Hz)	Cluster statistic (df)	p	Peak frequency (Hz)	Peak electrode	Max. statistic
<b>Time</b>						
Negative cluster	6–32	$t(11) = -1539.00$	<.001	18	TP7	−6.77
<b>Group</b>						
Positive cluster	7–12	$t(22) = 246.27$	.082	9	F4	4.35
Negative cluster	22–45	$t(22) = -573.34$	.024	31	P5	−4.06
<b>Exploratory post hoc contrast - responders vs. non-responders post stimulation</b>						
Positive cluster	5–17	$t(22) = 549.39$	.035	9	F4	4.94



**Fig. 3. Responders vs. non-responders - contrast of power spectra at the sensor and source level.** **A:** Whole scalp power spectra differences for responders and non-responders for the frequencies 1–45 Hz. Significant positive cluster 5–17 Hz and negative cluster 22–45 Hz as well as the respective peak frequencies (9 Hz and 31 Hz) are highlighted. Grey ribbons represent the standard deviation for each subgroup. **B:** Cluster statistic results (t-values) of power spectra contrasts between responders and non-responders are presented as topographic plots per frequency for a positive cluster of 7–12 Hz and a negative cluster of 22–45 Hz. Significant cluster electrodes are accentuated in bold per frequency. Peak frequencies of 9 Hz and 31 Hz, representing the maximum values obtained from the cluster statistics, are highlighted with dashed line rectangles. **C:** Source localization of 9 Hz EEG power peaking in the right inferior temporal gyrus (BA 20).

band power for the subgroup of responders (responders: 61.04%; non-responders: 50.03%)

**Source localization** Projecting peak frequencies of sensor-level power differences of responders and non-responders contrasts in source space exposed differences solely for 9 Hz ( $t(\text{cluster}) = 13.07$ ,  $p = .004$ ) with maximum differences ( $t(\text{max}) = 2.70$ ) localized in the right inferior temporal gyrus (MNI: 60 –10 –30) shown in Fig. 3C). However, no difference at the peak frequency 31 Hz could be observed in source space. Source localization of the peak frequency received from sensor-level contrast between responders and non-responders post acoustic stimulation exhibited differences at the frequency of 9 Hz ( $t(\text{cluster}) = 31.95$ ,  $p = .032$ ) localized in the right superior temporal gyrus (MNI: 40 –30 10) presented in Fig. 4C.

#### 4. Discussion

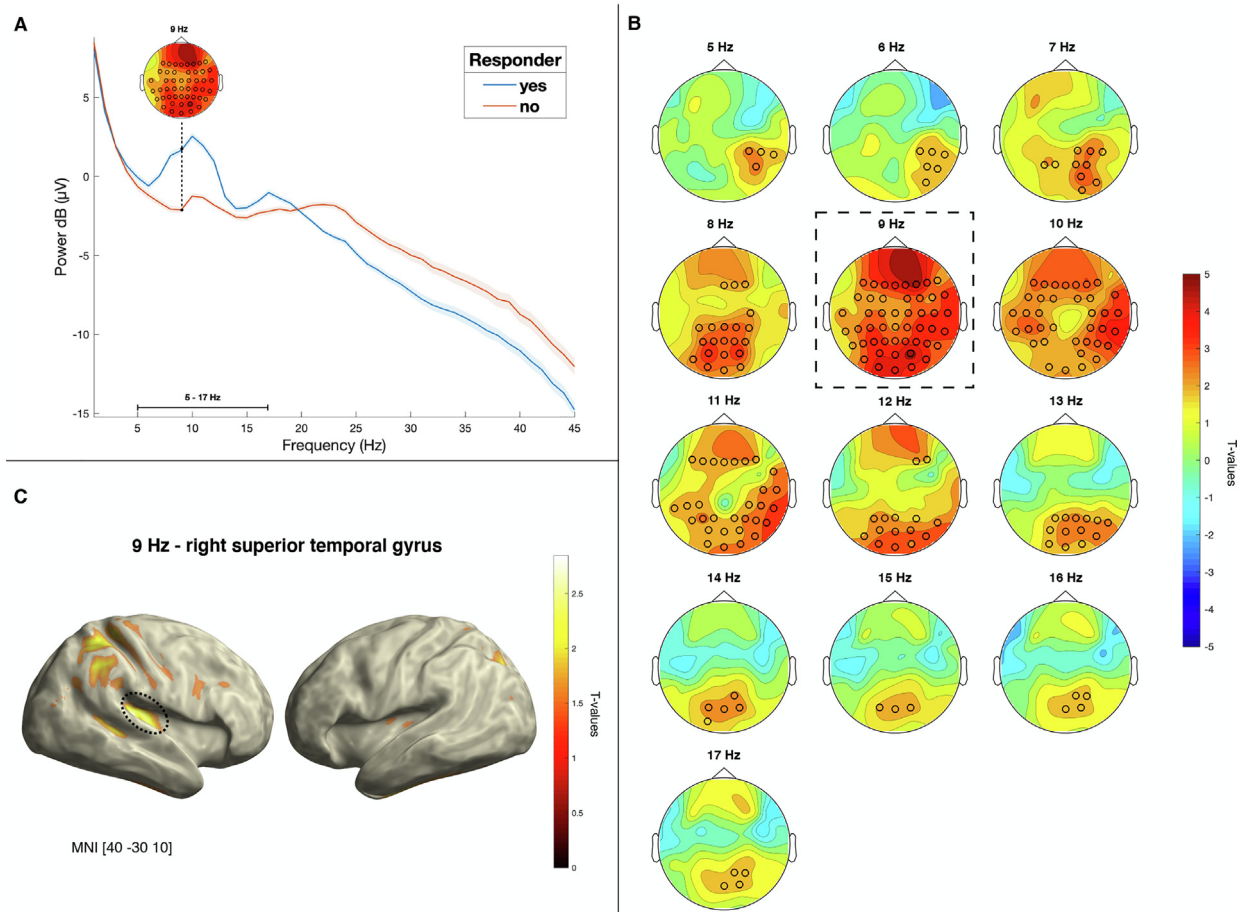
The main objective of the present study was to investigate the effect of different types of noise stimuli on short-term tinnitus suppression and corresponding electrophysiological brain activity. Moreover, we wanted to elucidate if electrophysiological changes are a function of tinnitus loudness ratings and if differential activation patterns arise from the different stimuli putatively triggering RI or lateral inhibition, respectively. Finally, we aimed at examin-

ing potential differences in ongoing brain activity between responders and non-responders. To the best of our knowledge, this presentation of notch- and bandpass-filtered WN sounds is novel in its application in tinnitus research. Similarly, we are the first group which elucidated neurophysiological differences between acoustic stimulation responders and non-responders. In the following, the results of our study are thus critically discussed in the light of current knowledge and with respect to future research outlook.

##### 4.1. Behavioral results

The behavioral analysis demonstrate similar suppression patterns as past studies in this field with only a subset of the study population reporting a considerable tinnitus loudness reduction after acoustic stimulation. On a group level all of the used stimuli induced short-term tinnitus suppression. Contrary to our hypothesis IBS appeared to produce the fewest reduction in tinnitus loudness rating, whereas IBP resulted in the strongest suppression pattern.

A potential explanation for this difference might derive from the ability of IBP/ WN in stimulating a broader range of frequencies around the ITF leading to a reduction of neural response gain and tinnitus-related hyperactivity and as a result facilitating short-term tinnitus suppression (cf. Schaette et al. (2010)), whereas sup-



**Fig. 4. Responders vs. non-responders - exploratory post stimulation power spectra contrasts at the sensor and source level.** **A:** Whole scalp power spectra differences for responders and non-responders towards acoustic stimulation for the frequencies 1–45 Hz. Significant positive cluster 5–17 Hz with the respective peak frequency of 9 Hz is highlighted. Grey ribbons represent the standard deviation for each subgroup. **B:** Results of cluster statistics (t-values) of power spectra contrasts between responders and non-responders following acoustic stimulation are presented as topographic plots per frequency for a positive cluster comprised of 5–17 Hz. Significant cluster electrodes are accentuated in bold per frequency. Peak frequency of 9 Hz is highlighted with a dashed line rectangle. **C:** Source localization of 9 Hz EEG power peaking in the right superior temporal gyrus (BA 41).

pressing effects of IBS via lateral inhibition might only appear after long-term application.

However, it is also possible that so called feed-forward inhibition is responsible for the superiority of stimuli containing signal in frequency ranges affected by hearing loss (cf. Roberts (2007, 2010)).

These explanations remain highly speculative and currently we are not able to provide a suitable explanation for these observed differences. Interestingly, stimulus IBP was evaluated with the lowest tolerability as indicated by the highest arousal and lowest valence ratings. This finding is contrary to one of our previous experiments which reports low arousal and high valence ratings for IBP (Schoiswohl et al., 2019).

Generally, about 50 to 90% of the studied individuals report some level of tinnitus suppression after acoustic stimulation (e.g., (Neff et al., 2017; Schoiswohl et al., 2019; Fournier et al., 2018; Kahlbrock and Weisz, 2008; Sedley et al., 2012)). Given the skewed distribution of RI responses on the group level in previous and this study as well as the need for a reliable threshold for strong tinnitus suppression, we opted to define a reduction in tinnitus of 50% after acoustic stimulation as the threshold for the responder classification akin to (Kahlbrock and Weisz, 2008). Applying this threshold, we can report an absolute number of 12 responders (with any stimulus type) out of 45 participants (26.67% responder rate) which is comparable to relative numbers reported by Kahlbrock and Weisz (2008) (26% responder rate), but below the quantity

of responders reported by King et al. (2021) (56.67% responder rate; the threshold for RI in this study is currently unknown due to publication status).

#### 4.2. Electrophysiology

Since only a handful of studies evaluated neural activity during RI, no specific hypotheses were generated about oscillatory changes from pre to post stimulation. In light of past neurophysiological research and the assumptions that tinnitus is accompanied by abnormal delta, alpha and gamma activity (Weisz et al., 2005; Weisz et al., 2007; Adjajian et al., 2012; Moazami-Goudarzi et al., 2010; Balkenhol et al., 2013; van der Loo et al., 2009; Ashton et al., 2007) as well as a putative brief inversion of altered spontaneous brain activity during RI (Kahlbrock and Weisz, 2008), it can be supposed that observed group-level changes in tinnitus loudness (RI) are also reflected in electrophysiological measures. Namely, a reduction in delta and gamma and an increase in alpha power spectra from pre to post stimulation is to be expected given these assumptions.

#### 4.3. Whole group analysis

Analysis of whole group pre-post stimulation changes in ongoing brain activity revealed increases in the delta, theta and gamma frequency range as well as decreases in alpha and beta



frequency bands. This increase in low frequency activity is in direct contrast to past observations, which report a reduction of delta and theta power spectra during RI in accordance with the current neurophysiological models for tinnitus (Kahlbrock and Weisz, 2008; Sedley et al., 2012; Sedley et al., 2015). In contrast, an earlier study using neuromagnetic measures in a single subject during short-term tinnitus suppression likewise reports an enhancement of low frequency activity (Kristeva-Feige et al., 1995).

Gamma band activity was suggested to represent a spontaneous brain activity pattern related to the actual tinnitus perception (Weisz et al., 2007), therefore it is assumed that during a potential suppression of tinnitus after acoustic stimulation, activity in the gamma band will be suppressed. The current findings revealed an increase in gamma power after auditory stimulation, similar to findings from (King et al., 2021; Sedley et al., 2012, 2015), who observed an increase in gamma band activity during RI. Consistent with the current literature, we observed a decrease in alpha frequency band power from pre to post stimulation (Kahlbrock and Weisz, 2008; Sedley et al., 2015). However, a recent study was able to demonstrate an increase in alpha frequency band power during RI in accordance with the given neurophysiological models in tinnitus (King et al., 2021).

No relationship of pre-post power spectra changes, neither with tinnitus loudness ratings averaged over all time points nor directly after stimulation offset was observed in our data. Past neurophysiological research was not able to produce consistent findings in terms of correlations with behavioral measures of tinnitus respectively RI (e.g., intensity, loudness). Besides observed positive correlations of low and high frequency activity (Sedley et al., 2012; Balkenhol et al., 2013; van der Loo et al., 2009) or alpha activity with tinnitus intensity (Sedley et al., 2015; Meyer et al., 2014), the current findings are in accordance with other studies which report an absence of any relationship (Adjajian et al., 2012; Pierzycki et al., 2016; Kahlbrock and Weisz, 2008). In consideration of missing correlations as well as power spectra changes in conflict with current neurophysiological models for tinnitus, we suggest that the present findings do not indicate oscillatory patterns related to tinnitus loudness suppression, rather constitute a tinnitus-unspecific neurophysiological reaction to an external acoustic stimulus.

Oscillatory activity in the alpha frequency range is supposed to be relevant for inhibitory processes of the brain (Klimesch et al., 2007), thus a sound stimulation exceeding the individual tinnitus loudness level produces excitation and consequently alpha decreases. It has already been shown, that spontaneous activity in the alpha (6–12 Hz) and beta (20 Hz) frequency bands desynchronize after sound stimulation (for an overview see Weisz et al. (2011)). Likewise, gamma band activity (30–45 Hz; 80–100 Hz), which is associated with cortical activation like attention or perception, was observed to be enhanced after the presentation of sound stimuli (Crone et al., 2001; Joliot et al., 1994) comparable to the present and recent findings (King et al., 2021).

In order to distinguish spontaneous brain activity related to tinnitus suppression from tinnitus-unspecific neurophysiological consequences to a sound stimulation, future research should not only compare acoustic stimulation responders and non-responders (RI vs. absence of RI) but also strive for a comparison with healthy control groups.

#### 4.4. Responder analysis

Another objective of this study was to compare acoustic stimulation responders with non-responders, in order to point out potential differences in regards to ongoing brain activity. To the

best of our knowledge this is the first study, which compares oscillatory activity of acoustic stimulation responders and non-responders.

Interestingly, we observed reduced gamma band activity and a trend for enhanced alpha activity (peak frequency of 9 Hz localized in the right inferior temporal gyrus; BA 20) for the group of responders in contrast to non-responders. This result may corroborate the premise that gamma might be related to tinnitus perception (van der Loo et al., 2009; De Ridder et al., 2015; Ashton et al., 2007; Weisz et al., 2007). Given the fact, that responders generally reported their perceived tinnitus loudness level lower than non-responders, the question arises if the perceived tinnitus loudness rated via VAS can be associated with ongoing brain activity e.g., lower tinnitus loudness related to reduced gamma power or enhanced alpha. Yet, a respective correlation analysis failed to show an association.

As already shown by Schlee et al. (2014) tinnitus sufferers exhibited a blunted alpha peak and more importantly reduced alpha variability (8–10 Hz). This finding could be reflected by our data in a similar way as non-responders had a lower alpha peak and lower alpha variability (8–12 Hz). In further support for this argumentation, the data of the former study as well as our present findings show longer tinnitus duration for subjects with reduced alpha power, whereas we assume that these insights from case-control contrasts can be applied to the responder analysis at hand.

The observed reduction in gamma power may be interpreted along similar veins as the findings in alpha power by applying insights from case-control studies. Responders with a less chronicized and intense tinnitus in our study are thus comparable to healthy controls in some case-control designs with reported lower gamma power values (Ashton et al., 2007; Vanneste et al., 2011). In further analogy, our findings of diminished gamma band activity together with a decrease in tinnitus loudness for the subgroup of responders can be linked to observations of past studies, namely a positive correlation of gamma with tinnitus loudness (van der Loo et al., 2009; De Ridder et al., 2015; Balkenhol et al., 2013).

We theorize that this trend for blunted alpha as well as lower gamma activity may be indicative of a trait as a consequence of tinnitus chronification.

A related observation was made by Neff et al. (2019) where active listening to tinnitus and consequential increase in tinnitus intensity did not lead to any neural alterations, which fits the reasoning about a trait-like neural representation of chronicized tinnitus.

However, it is also possible that this pattern of reduced gamma and enhanced alpha activity represent a genuine neural trait related to acoustic stimulation response more specifically the possibility to induce RI in tinnitus sufferers.

Our exploratory analysis of post acoustic stimulation contrasts revealed higher spectral power in the theta, alpha and beta frequency range with a peak in the alpha band (9 Hz) localized in the right superior temporal gyrus (BA 41) in acoustic stimulation responders.

This increased alpha in auditory fields is in line with our hypothesis of a brief inversion of altered oscillatory power during RI and is consistent with past research examining disparities between tinnitus and healthy controls (compare Section 1). Notably, this supports our assumptions about responders and related trait-like neural signatures of tinnitus in that it surmises that only responders can exhibit neural responses which are specific to RI induced by acoustic stimulation.

Finally, a lack of correlations between loudness ratings and ongoing brain activity in the present study does not allow for a conclusive interpretation with regards to tinnitus. Past studies examining correlates of tinnitus suppression and neural activity have been able to demonstrate a relationship of low and high frequency activity with tinnitus intensity (Sedley et al., 2012, 2015).

Nevertheless [Kahlbrock and Weisz \(2008\)](#) were not able to demonstrate a correlation of tinnitus suppression and ongoing neural activity in agreement with the present findings.

To further investigate these observed differences it is recommended to optimize future study designs with respect to a parametric analysis of tinnitus duration and RI-related neural activity.

#### 4.5. Limitations

Our study has several limitations which might be informative for future research in the specific subfield of acoustic stimulation and general research in tinnitus.

The use of a standard boundary element headmodel as well as electrode positions hampers the accuracy of the source-level data in this study. Unfortunately, we could neither acquire individual structural MRIs nor register individual electrode positions for any of our participants.

No correlations between neurophysiological changes and changes in behaviorally assessed self-report tinnitus loudness were found in our data. Given the narrow and skewed distribution of the behavioral data and the consequential arbitrary choice of a RI threshold of 50% for the responder group contrast, correlation analysis might neither way be informative with the current data. This negative result is in line with the former study of [Kahlbrock and Weisz \(2008\)](#). Moreover, full and prolonged RI could only be studied in a small subset of the participants. Finally, heterogeneity of tinnitus loudness suppression curves between participants and the general low reliability and validity of tinnitus self-report data may further contribute to these absent findings.

As in many previous studies, it is challenging to recruit a large enough study sample from the locally available tinnitus population for the extensive experimental procedures. Additionally, tinnitus suppression responses, especially the parameters of RI depth as well as duration, can not be properly assessed in established screening procedures. This selection bias is hard to come by and potentially distorts results. Future studies could thus profit from internet-based or on-site pre-screenings in regards to the ability to (fully) suppress participants tinnitus acoustically (i.e., induce RI) in order to generate a larger sample of responders, facilitating valid statements about oscillatory markers of RI. Beyond that, multi-center studies could help to further increase the validity of results aside from increasing the sample size.

#### 5. Conclusions

The main goal of the current study was to unveil the oscillatory signature of RI and see how this relates to established neurophysiological models of tinnitus. In contrast to former studies, we used an extended set of modified noise stimuli targeting putatively differential neural mechanisms (i.e., RI and lateral inhibition). Furthermore, we explicitly investigated responder profiles of RI. Similar to former studies, merely a quarter of tested participants exhibited pronounced RI.

Looking at the oscillatory signature of acoustic stimulation responders and non-responders, results are indicative of decreased gamma and increased alpha power for responders. These findings are in line with both the proposed models of SLIM and TCD, respectively. This observations might be indicative of trait-specific forms of oscillatory signatures in different subsets of the tinnitus population possibly related to acoustic tinnitus suppression. In agreement with a potential transient reversal of tinnitus-specific abnormal ongoing brain activity over the course of tinnitus suppression, alpha power was enhanced in the group of responders after stimulation similarly compared to non-responders. Source localization of the sensor-level differences emphasizes the involvement of

auditory cortical systems. Given the lack of correlations between tinnitus loudness and oscillatory power in this study, which was also reported by former studies, results do not allow for a conclusive interpretation with respect to these models.

The identified tinnitus patient profile experiencing RI, which mainly features less tinnitus chronification, could serve as a selection criterion to identify individuals for successful acoustic tinnitus suppression and putatively for acoustic treatments (e.g., treatment start in early stages of chronification).

Further research examining oscillatory activity during RI should strive for a healthy control group as well as control sounds not inducing RI in order to separate the neural signature of tinnitus suppression from tinnitus-unspecific neurophysiological effects.

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#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.clinph.2021.03.038>.

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We kindly ask you to fill in as well as sign this form and to attach a scan of your application to your e-mail or include a copy of your application with your letter.

## 1. Confirmation of exclusive submission

☐ I hereby confirm that the scientific work submitted for the Research Prize Tinnitus & Hearing 2024 has not been submitted for any other prize and that this work will not be submitted for any other prize until the decision on the award of the prize has been made.

## 2. Confirmation of authorship

The scientific work submitted by me for the Research Prize Tinnitus & Hearing 2024 involved several authors:

☐ Yes ☐ No

The following person is applying for the award (surname, first name)

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I hereby confirm that all authors and co-authors of the submitted work agree to the application for the Research Prize Tinnitus & Hearing 2024.

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