Dr. Stephanie Heike Rosemann
Department für Psychologie · Carl von Ossietzky University Oldenburg · 26111 Oldenburg
Stephanie.rosemann@uol.de

Deutsche Stiftung Tinnitus und Hören Charité
Luisenstr. 13
10117 Berlin

Datum: 30.08.2023

Bewerbung Forschungspreis Tinnitus und Hören 2023

Sehr geehrte Damen und Herren,

hiermit bewerbe ich mich für den Forschungspreis Tinnitus und Hören 2023.

Während eines Auslandsaufenthaltes an der Georgetown University (Washington DC, Arbeitsgruppe von Prof. Dr. Josef Rauschecker) habe ich eine Studie zu neuro-anatomischen und funktionellen Veränderungen in Tinnitus Patienten durchgeführt. Die zwei (bisher) publizierten Arbeiten aus dieser Studie möchte ich gerne für den Preis einreichen:

- **Rosemann, S.**, & Rauschecker, J. P. (2022). Neuroanatomical alterations in middle frontal gyrus and the precuneus related to tinnitus and tinnitus distress. *Hearing Research*
- **Rosemann, S.**, & Rauschecker, J. P. (2023). Disruptions of default mode network and precuneus connectivity associated with cognitive dysfunctions in tinnitus. *Scientific Reports*

Aktuell bin ich PI in dem von der DFG geförderten Projekt „Entschlüsselung der Höranstrengung bei altersbedingtem Hörverlust unter Einsatz von multimodaler Neuro-Bildgebung und gleichzeitiger Pupillometrie" an der Carl von Ossietzky Universität Oldenburg.

Mit freundlichen Grüßen,

St. Rosemann

____
Stephanie Rosemann

<u>Anlagen:</u>

- Ausgefülltes Formblatt zur Bewerbung
- Darstellung der eingereichten Arbeiten
- CV
- Publikationsliste
- PDFs der publizierten Arbeiten

STIFTUNG TINNITUS & HÖREN CHARITÉ

Forschen. Aufklären. Lindern.

Formblatt zur Bewerbung um den Forschungspreis Tinnitus & Hören 2023

Wir bitten Sie, dieses Formblatt auszufüllen, zu unterschreiben und als Scan Ihrer Bewerbung per E-Mail, als Kopie Ihrer Bewerbung per Post beizufügen.

1. Bestätigung exklusive Einreichung

☑ Hiermit bestätige ich, dass die für den Forschungspreis Tinnitus & Hören 2023 eingereichte wissenschaftliche Arbeit nicht für einen anderen Preis eingereicht wurde und dass bis zur Entscheidung der Preisvergabe diese Arbeit nicht für einen anderen Preis eingereicht wird.

2. Bestätigung Autor:innenschaft

An der von mir für den Forschungspreis Tinnitus & Hören 2023 eingereichten wissenschaftlichen Arbeit waren mehrere Autorinnen und Autoren beteiligt.

☑ Ja

Als Preisträger:in bewirbt sich Stephanie Rosemann (Name, Vorname)

☑ Hiermit bestätige ich, dass alle Co-Autorinnen und -Autoren der eingereichten Arbeit mit der Bewerbung um den Forschungspreis Tinnitus & Hören 2023 einverstanden sind.

☐ Nein

Oldenburg	30.8.23	Rosemann, Stephanie	S. Rosemann
Ort	Datum	Name, Vorname	Unterschrift

Dr. Stephanie Heike Rosemann – Anatomical and functional alterations related to cognition in chronic tinnitus

Neuroanatomical alterations in middle frontal gyrus and the precuneus related to tinnitus and tinnitus distress

Published in Hearing Research, 108595. https://doi.org/10.1016/j.heares.2022.108595

In this study, we investigated neuroanatomical alterations related to the tinnitus perception itself along with tinnitus distress and cognitive abilities in twenty tinnitus patients and twenty control participants matched in age, sex and hearing loss. Our results showed increased grey matter volume in the middle frontal gyrus in tinnitus patients compared to control participants. Additionally, the results demonstrated increased cortical thickness in the precuneus associated with tinnitus distress as well as a group interaction between cognitive assessment scores and cortical thickness of the middle frontal gyrus, showing higher cortical thickness with better scores in controls and lower scores in tinnitus patients (*Figure 1*). Hence, our findings demonstrated structural changes in the precuneus and middle frontal gyrus which are related to the awareness of the tinnitus perception and the annoyance by it (tinnitus distress). These neuroanatomical alterations also have implications on general cognitive abilities.

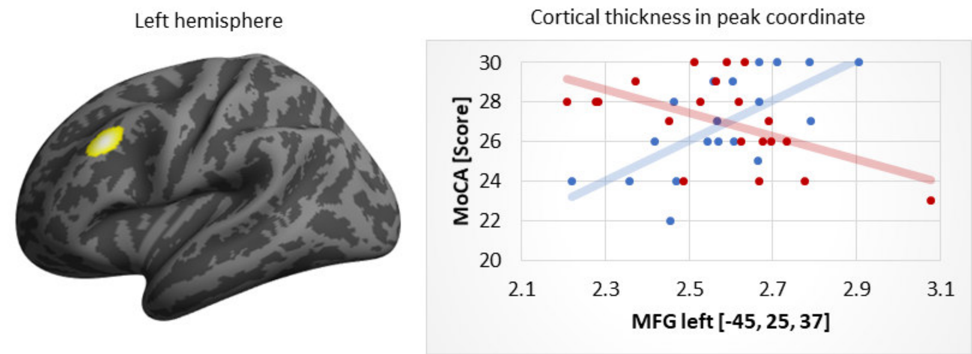

Figure 1: Summary of the most relevant results (Rosemann & Rauschecker, 2022)
Significant interaction between group and the general cognitive abilities (determined by MoCA scores) in cortical thickness of the left middle frontal gyrus (MFG); Tinnitus patients are depicted in red, control participants are depicted in blue

Disruptions of default mode network and precuneus connectivity associated with cognitive dysfunctions in tinnitus

Published in Scientific Reports 13, 5746 (2023). https://doi.org/10.1038/s41598-023-32599-0

In this paper, we present results from resting state functional connectivity in twenty tinnitus patients and twenty control participants. Even though we did not obtain significant differences in resting state functional connectivity between the two groups, our results demonstrated significant associations between general cognitive abilities and resting state functional coupling of various brain regions, such as the default mode network and the precuneus with a) the superior parietal lobule (*Figure 2*), b) orbital cortex and c) the supramarginal gyrus. Additionally, tinnitus distress correlated with resting state functional connectivity between the precuneus and the lateral occipital complex. In detail, it seems that lower cognitive scores were correlated with negative connectivity values (anticorrelation), while higher scores (indicative of normal cognitive function) were correlated with positive connectivity values. Hence, the disrupted resting state functional connectivity may be an indicator of cognitive dysfunctions in tinnitus. We hereby present the first study providing evidence of disruptions of default mode network and precuneus coupling that are related to cognitive dysfunctions in chronic tinnitus. The constant attempt to decrease the tinnitus sensation might occupy certain brain resources otherwise available for concurrent cognitive operations.

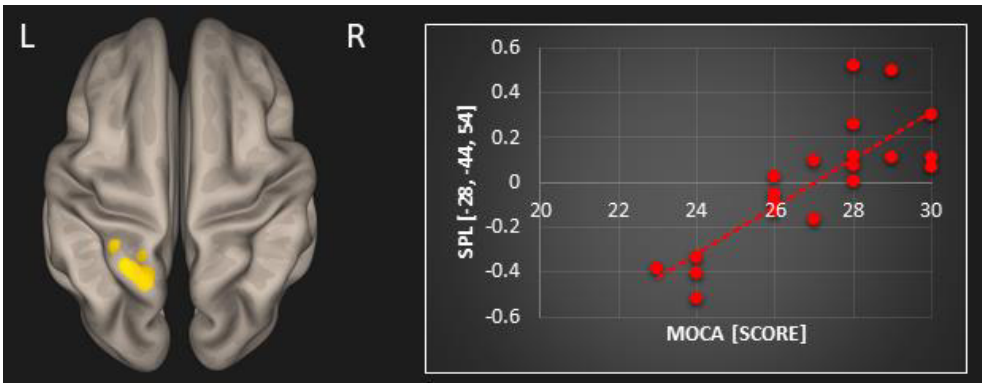

Figure 2: Summary of the most relevant results (Rosemann & Rauschecker, 2023)
Significant association between general cognitive abilities (determined by MOCA scores) and resting state functional connectivity of the default mode network and left superior parietal lobule in tinnitus patients

Significance of the submitted articles

In order to identify suitable target regions for neuromodulatory approaches or designing cognitive behavioral therapy strategies in tinnitus, understanding its pathophysiology is of crucial importance. The present findings provide novel insights into neural mechanisms in tinnitus patients related to the tinnitus perception itself along with the experienced tinnitus distress and cognitive functions. We argue that increased awareness of as well as annoyance with the tinnitus sensation is reflected in increased brain structural changes in the precuneus and middle frontal gyrus that may also have implications with regard to general cognitive abilities. Further, we suggest that disruptions of resting state functional connectivity are related to cognitive abilities in chronic tinnitus, because the affected areas are involved in decreasing the intensity of the tinnitus sensation. Hence, those resources are occupied and no longer available for concurrent cognitive operations.

In sum, we highlight the roles of the precuneus in tinnitus distress and of the middle frontal gyrus, precuneus as well as the default mode network and their relation to cognitive abilities in chronic tinnitus. Importantly, these brain regions may be of crucial importance evaluating the efficacy of tinnitus interventions but may also serve as possible target regions of neuromodulatory treatments. Additionally, cognitive behavioral therapy may assist tinnitus patients in switching away their attention from the tinnitus sensation. Thus, we want to stress the importance of including assessments of cognitive abilities in tinnitus research and to raise awareness for possible impairments on cognitive functions in tinnitus patients.

Open Science

Both articles were pre-registered on OSF (including hypotheses, study design and data analyses) and we published preprints on the OSF Preprint server. Moreover, the underlying anonymized data are shared on the OSF project repository and articles reporting the final results are published in open access journals. Hence, the results of the studies are available to everyone (researchers and public), and so are the underlying data. This enables further analyses such as meta-analyses and might foster future collaborations with other researchers.

Dr. Stephanie Heike Rosemann

Sodenstich 77 · 26131 Oldenburg · Germany
Mobile: +49 157 32634587 · Email: Stephanie.rosemann@uol.de

Work Experience

Since 10/2022	**PostDoctoral Position** Faculty of Medicine and Health Sciences, Department of Psychology, Carl von Ossietzky University Oldenburg, Germany, Lab of Prof. Dr. Christiane M. Thiel *Research focus:* *Research-based teaching, Plasticity in age-related hearing loss, eye-tracking, MR-spectroscopy, neuroimaging (anatomical and functional correlates)*
10/2020 – 09/2022	**PostDoctoral Position** Laboratory of Integrative Neuroscience and Cognition, Department of Neuroscience, Georgetown University Medical Center, Washington DC, USA, Lab of Prof. Dr. Josef Rauschecker *Research focus:* *Plasticity in chronic tinnitus, cognition, neuroimaging (anatomical and functional correlates)*
05/2016 – 03/2020	**PostDoctoral Position** Faculty of Medicine and Health Sciences and Cluster of Excellence 'Hearing4all', Department of Psychology, Carl von Ossietzky University Oldenburg, Germany, Lab of Prof. Dr. Christiane M. Thiel Research focus: *Cross-modal plasticity in hard of hearing individuals, cognition, speech processing, audiovisual abilities, hearing aid fitting, neuroimaging (anatomical and functional correlates)*
05/2013 – 04/2016	**Doctoral Program** Center for Cognitive Sciences, Department for Human Neurobiology, University of Bremen, Germany, Lab of Prof. Dr. Manfred Fahle *Research focus: Multimodal deficits after stroke, psychophysical experiments, functional neuroimaging*
01/2012 – 04/2013	**Research Assistant**, Center for Cognitive Sciences, Department for Human Neurobiology, University of Bremen, Germany, Lab of Prof. Dr. Manfred Fahle *Research focus: Deficits of visual object recognition and anatomical correlates*

Education

05/2013 – 04/2016 **Dr. rer. nat. (magna cum laude)**
Center for Cognitive Sciences, Department for Human Neurobiology, University of Bremen, Germany
Topic of doctoral thesis: *Dysfunctions of visual and auditory Gestalt perception ("amusia") after stroke: behavioral correlates and fMRI*
Supervisors: Prof. Dr. Manfred Fahle, Prof. Dr. Dr. Manfred Herrmann

10/2009 – 02/2012 **M.Sc. in Neurosciences** *(taught entirely in English)*
University of Bremen, Germany
Topic of Master's thesis: *The influence of practice, expertise and cognitive skills on sight reading – the role of the eye-hand span*
Supervisors: Prof. Dr. Manfred Fahle, Prof. Dr. Eckart Altenmüller

10/2006 – 09/2009 **B.Sc. in Cognitive Science** *(taught entirely in English)*
University of Osnabrück, Germany
Topic of Bachelor's thesis: *Currently available treatments of Parkinson's disease*
Supervisors: Prof. Dr. Gunnar Jeserich, Prof. Dr. Roland Brandt

08/2008 – 12/2008 **Study abroad,** Clinical Psychology, University of Mauritius, Mauritius

8/1997 – 07/2006 **Abitur** (University-Entrance Diploma, German equivalent to A-levels)

Teaching Experience

Summer term 2023 **Master of Neurocognitive Psychology (Universität Oldenburg)**:
- Functional MRI data analysis
- Psychological intervention within the framework of evidence-based medicine - treatment studies of selected psychiatric disorders

Zweifach Bachelor (Universität Oldenburg): Lernen, Emotionen, Sozialverhalten

Winter term 2022/23 **Master of Neurocognitive Psychology (Universität Oldenburg)**:
- Introduction to cognitive neuroscience Lecture
- Introduction to cognitive neuroscience Seminar

Biologie Bachelor (Universität Oldenburg):
- Einführung in die Neuro- und Verhaltensbiologie
- Experimente aus Neurobiologie und Verhalten

2012 – 2015 **Master of Neurosciences Program (University of Bremen)**, Module: Advanced Studies in Systemic Approaches to Brain Function

2012 – 2015	**Bachelor of Biology Program (University of Bremen)**, Module: PM3 Practice Neurobiology
Since 2012	**Supervision Bachelor's and Master's theses** (Universities of Bremen & Oldenburg)

Board and Committee Work

Since 04/2023	**Faculty council** (Fakultätsrat), Fakultät VI Medizin und Gesundheitswissenschaften, Carl von Ossietzky University Oldenburg
Since 12/2022	**Science Communication of the Department of Psychology**, Fakultät VI Medizin und Gesundheitswissenschaften, Carl von Ossietzky University Oldenburg
Since 11/2022	**PhD committee Dr. rer. nat.** (Promotionsausschuss), Fakultät VI Medizin und Gesundheitswissenschaften, Carl von Ossietzky University Oldenburg
2020 – 2021	**OHBM International Mentorship Program (mentor)**
2019 – 2020	**PhD committee Dr. rer. nat.** (Promotionsausschuss), Fakultät VI Medizin und Gesundheitswissenschaften, Carl von Ossietzky University Oldenburg
2018 – 2019	**Advisory Board for study affairs – Institute** (Studiengremium) for the Master 'Neurocognitive Psychology', Fakultät VI Medizin und Gesundheitswissenschaften, Department for Psychology, Carl von Ossietzky University Oldenburg
2017 – 2019	**Admission committee** for the Master 'Neurocognitive Psychology', Fakultät VI Medizin und Gesundheitswissenschaften, Department for Psychology, Carl von Ossietzky University Oldenburg
2017	**Appointment committee** for the W2-professorship 'Modelling and Physiology of Auditory Perception', Fakultät VI Medizin und Gesundheitswissenschaften, Carl von Ossietzky University Oldenburg
Since 2015	**Selection committee** for applicants of the German National Academic Foundation (*Studienstiftung des Deutschen Volkes*)

Scholarships

05/2013 – 04/2016	**PhD grant** from the German National Academic Foundation (*Studienstiftung des Deutschen Volkes*) – awarded for excellent academic achievement

10/2015	**Travel grant** from the German National Academic Foundation (*Studienstiftung des Deutschen Volkes*) – awarded for attending the Annual Meeting of the Society for Neuroscience, Chicago (USA)
06/2012 – 04/2013	**Stipend** from the Central Research Funding, University of Bremen, Germany – awarded to attain external funding for my PhD project

Grants

Deutsche Forschungsgemeinschaft: DFG 'Eigene Stelle' (**RO 6114/2-1**), Project: *Unravelling listening effort in age-related hearing loss using a multimodal neuroimaging approach and simultaneous pupillometry,* Carl von Ossietzky University Oldenburg, Germany, 2023-2026 (~360 k€);

Deutsche Forschungsgemeinschaft: DFG Research Fellowship for 24 months (**RO 6114/1-1**), Project: *"Tinnitus as a network problem – plasticity in anatomical and functional connectivity"*, Georgetown University, Washington DC, USA, 2020 – 2022 (~ 93 k$)

Hearing Industry Research Consortium Grant 2017: The impact of audiovisual integration on acoustic communication in hearing impaired adults, 2018 - 2020 (~ 150 k€); applicants: H. Colonius, A. Gieseler, M. Tahden, C. M. Thiel, S. Rosemann.

Awards

Hermine Heusler-Edenhuizen Preis: awarded by the School of Medicine and Health Sciences, Carl von Ossietzky University Oldenburg (for best paper published in summer semester 2018; Rosemann & Thiel, 2018)

Additional Skills

Languages:
- German: native language
- English: nearly native
- French: basic

Computer Skills:
- Analysis Methods: SPSS, JASP, SPM, Brainvoyager, ExploreDTI, MRIcron
- Programming Languages: Presentation, Matlab
- Applications: MS Office: Word, Excel, PowerPoint; Corel, Photoshop

Full Current Clean Driving License

C2-Ausbilder im Zupforchester/Gitarrenensemble

Dr. Stephanie Heike Rosemann – Peer-reviewed publications

1. **Rosemann, S**., & Rauschecker, J. P. (2023). Disruptions of default mode network and precuneus connectivity associated with cognitive dysfunctions in tinnitus. Scientific Reports 13, 5746 (2023). https://doi.org/10.1038/s41598-023-32599-0
2. **Rosemann, S**., & Rauschecker, J. P. (2022). Neuroanatomical alterations in middle frontal gyrus and the precuneus related to tinnitus and tinnitus distress. Hearing Research, 108595. https://doi.org/10.1016/j.heares.2022.108595
3. **Rosemann, S.**, Gieseler, A., Tahden, M., Colonius, H. & Thiel, C. M. (2021). Treatment of age-related hearing loss alters audiovisual integration and resting-state functional connectivity: A randomized controlled pilot trial, ENeuro. https://doi.org/10.1523/ENEURO.0258-21.2021
4. **Rosemann, S.** & Thiel, C. M. (2021). No association between age-related hearing loss and brain age derived from structural neuroimaging data. NeuroImage: Reports, 1(2), 100020. https://doi.org/10.1016/j.ynirp.2021.100020
5. Pauquet, J., Thiel, C. M., Mathys, C. & **Rosemann, S.** (2021). Relationship between memory load and listening demands in age-related hearing impairment. Neural Plasticity, 2021, e8840452. https://doi.org/10.1155/2021/8840452
6. **Rosemann, S**., & Thiel, C. M. (2021). Rebuttal to: Neuroanatomical changes associated with age-related hearing loss and listening effort. Brain Structure & Function, 226(5), 1387–1388. https://doi.org/10.1007/s00429-021-02263-2
7. Vogelzang, M., Thiel, C. M., **Rosemann, S.**, Rieger, J. M. & Ruigendijk, E. (2021). Effects of age-related hearing loss and hearing aid experience on sentence processing. Scientific Reports, 11:5994. https://doi.org/10.1038/s41598-021-85349-5
8. Vogelzang, M., Thiel, C. M., **Rosemann, S.**, Rieger, J. M. & Ruigendijk, E. (2021). When hearing does not mean understanding: On the neural processing of syntactically complex sentences by hearing-impaired listeners. Journal of Speech, Language and Hearing Research, 64 (250-262). https://doi.org/10.1044/2020_JSLHR-20-00262
9. Schulte, A., Thiel, C. M., Gieseler, A., Tahden, M., Colonius, H. & **Rosemann, S.**, (2020). Reduced Resting State Functional Connectivity with Increasing Age-Related Hearing Loss and McGurk Susceptibility. Scientific Reports, 10:16987. https://doi.org/10.1038/s41598-020-74012-0
10. **Rosemann, S.** & Thiel, C. M. (2020). Neuroanatomical changes associated with age-related hearing loss and listening effort. Brain Structure and Function, 225(9), 2689-2700. https://doi.org/10.1007/s00429-020-02148-w
11. Vogelzang, M., Thiel, C. M., **Rosemann, S.**, Rieger, J. M. & Ruigendijk, E. (2020). Neural mechanisms underlying the processing of complex sentences: an fMRI study. Neurobiology of Language, 1(2), 226–248. https://doi.org/10.1162/nol_a_00011
12. **Rosemann, S.,** Smith, D., Dewenter, M. & Thiel, C. M. (2020). Age-related hearing loss influences functional connectivity of auditory cortex for the McGurk illusion. Cortex, 129, 266-280, https://doi.org/10.1016/j.cortex.2020.04.022
13. **Rosemann, S.** & Thiel, C. M. (2020). Neural signatures of working memory in age-related hearing loss. Neuroscience, 429, 134-142, https://doi.org/10.1016/j.neuroscience.2019.12.046

14. Puschmann S., Daeglau M., Stropahl M., Mirkovic B., **Rosemann S.**, Thiel C. M., Debener S. (2019). Hearing-impaired listeners show increased audiovisual benefit when listening to speech in noise. NeuroImage, 196, 261-268, https://doi.org/10.1016/j.neuroimage.2019.04.017
15. **Rosemann, S.** & Thiel, C. M. (2019). The effect of age-related hearing loss and listening effort on resting state connectivity. Scientific Reports, 9:2337. doi: 10.1038/s41598-019-38816-z
16. **Rosemann, S.** & Thiel, C. M. (2018). Audio-visual speech processing in age-related hearing loss: stronger integration and increased frontal lobe recruitment, NeuroImage, 175, 425-437, https://doi.org/10.1016/j.neuroimage.2018.04.023
17. **Rosemann, S.**, Gießing, C., Özyurt, J., Carroll, R., Puschmann, S., Thiel, C. M. (2017). The contribution of cognitive factors to individual differences in understanding noise-vocoded speech in young and older adults, Frontiers in Human Neuroscience, 11:294. doi: 10.3389/fnhum.2017.00294
18. **Rosemann, S.**, Wefel, I., Elis, V., Fahle, M. (2017). Audio-visual interaction in visual motion detection: Synchrony versus Asynchrony, Journal of Optometry, 10(4), 242–251. doi:10.1016/j.optom.2016.12.003.
19. **Rosemann, S.**, Brunner, F., Kastrup, A., Fahle, M. (2017). Musical, visual and cognitive deficits after middle cerebral artery infarction, eNeurologicalSci, Volume 6, 25 – 32. doi:10.1016/j.ensci.2016.11.006
20. **Rosemann, S.**, Altenmüller, E. & Fahle, M. (2015). The art of sight-reading: Influence of practice, playing tempo, complexity and cognitive skills on the eye–hand span in pianists, Psychology of Music, doi:10.1177/0305735615585398

Open Science: Pre-registrations, Open Data & Material, Preprints

Project title: The relation between grey matter metrics, resting state functional connectivity and cognition in tinnitus

- **Pre-registration**: OSF on July 20, 2021. https://osf.io/xhsm5
- **Open data**: https://osf.io/2nse8/
- **Preprint 1**: Rosemann, S. & Rauschecker, J. P. (2022, May 17). Neuroanatomical alterations in middle frontal gyrus and the precuneus related to tinnitus and tinnitus distress. https://osf.io/jdqu5
- **Preprint 2**: Rosemann, S., & Rauschecker, J. P. (2022, October 25). Disruptions of default mode network and precuneus connectivity associated with cognitive dysfunctions in tinnitus. https://osf.io/r83nw

Project title: White matter morphology in tinnitus

- **Pre-registration**: OSF on July 20, 2021. https://osf.io/scph4
- **Preprint**: Rosemann, S., & Rauschecker, J. P. (2022, December 9). Increased fiber density of the fornix in patients with chronic tinnitus revealed by diffusion-weighted MRI. https://osf.io/kebvw

Project title: Investigating white matter morphology and track-weighted functional connectivity in age-related hearing impairment

- **Pre-registration**: OSF on June 4, 2021. https://osf.io/7mgp6

Project title: Prediction of brain age in age-related hearing loss

- **Pre-registration**: OSF on June 22, 2020. https://osf.io/z7k9h
- **Preprint**: **Rosemann, S.** & Thiel, C. M. (2020, November 12). No association between age-related hearing loss and accelerated brain aging derived from structural neuroimaging data. https://osf.io/kasbt

Project title: Linking Audiovisual Integration to Audiovisual Speech-in-Noise Comprehension

- **Preprint 1**: Gieseler, A., Rosemann, S., Tahden, M., Wagener, K. C., Thiel, C. M. & Colonius, H. (2020, September 4). Linking Audiovisual Integration to Audiovisual Speech-in-Noise Comprehension. https://osf.io/46caf
- **Preprint 2**: Rosemann, S., Gieseler, A., Tahden, M., Colonius, H. & Thiel, C. M. (2021, May 28). Treatment of age-related hearing loss alters audiovisual integration and resting-state functional connectivity: A randomized controlled pilot trial. https://osf.io/48bpt

Project title: Neuroanatomical changes in age-related hearing loss

- **Pre-registration**: OSF on October 17, 2019. https://osf.io/8sz4e
- **Preprint**: Rosemann, S. & Thiel, C. M. (2020, March 31). Neuroanatomical changes associated with age-related hearing loss and listening effort. https://osf.io/qmv9j

Project title: Listening effort and cognitive load in elderly participants

- **Pre-registration**: AsPredicted.com on March 27, 2019. https://aspredicted.org/f5c4k.pdf
- **Open Data & Material**: https://osf.io/rs62e/
- **Preprint**: Pauquet, J., Thiel, C., Mathys, C., & Rosemann, S. (2020, May 6). Neural Representation of Auditory Speech Processing in Age-Related Hearing Impairment. https://osf.io/bpgr6

Project title: McGurk in age-related hearing loss

- **Open Data & Material:** https://osf.io/umypq/

Project title: nBack-Hearing

- **Open Data:** https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/OU4DC0

Hearing Research 424 (2022) 108595

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Neuroanatomical alterations in middle frontal gyrus and the precuneus related to tinnitus and tinnitus distress

Stephanie Rosemann*, Josef P. Rauschecker

Department of Neuroscience, Laboratory of Integrative Neuroscience and Cognition, Georgetown University Medical Center, 3970 Reservoir Rd NW, Washington, D.C. 20057, USA

ARTICLE INFO

Article history:
Received 17 May 2022
Revised 25 July 2022
Accepted 31 July 2022
Available online 1 August 2022

Keywords:
Tinnitus
Gray matter volume
Cortical thickness
Tinnitus distress
Cognitive abilities

ABSTRACT

Tinnitus is the phantom perception of sound when there is no external auditory input. This sound is mostly perceived as a ringing, whistling or buzzing in the ear. There is evidence of neural changes in both central auditory regions as well as other brain areas like the prefrontal cortex and the limbic system. However, brain morphological studies assessing gray matter volume and cortical thickness have shown inconsistent results. We here investigated neuroanatomical alterations in tinnitus related to the tinnitus perception along with tinnitus distress and cognitive abilities. Twenty tinnitus patients and 20 control participants matched in age, sex and hearing loss participated in the study. They underwent magnetic resonance imaging and audiometric as well as cognitive assessments. Our results demonstrate increased gray matter volume in the middle frontal gyrus and frontal pole in tinnitus compared to control participants. Moreover, we found increased cortical thickness in the precuneus associated with tinnitus distress as well as an interaction between group and cognitive assessment scores in cortical thickness of the middle frontal gyrus, indicating higher cortical thickness with better scores in controls and lower scores in tinnitus patients. These findings indicate that increased tinnitus awareness and annoyance is reflected in increased brain structural changes in the precuneus, frontal pole and middle frontal gyrus that may also have implications on general cognitive abilities.

1. Introduction

Tinnitus is the phantom perception of sound, mostly perceived as ringing, buzzing or hissing “in the ear” when there is no external stimulation. Chronic tinnitus affects approximately 10–15% of the adult population and up to 45% in the elderly population (Chang et al., 2019; Chen et al., 2021; Hu et al., 2021; Jafari et al., 2019; Knipper et al., 2020). The perception of the phantom sound significantly impacts quality of life and mental health in many tinnitus patients. General distress is increased and often comes with depression, anxiety and irritation but also problems in sleeping and concentration (Noreña, 2011; Schecklmann et al., 2014). One of the peripheral causes for tinnitus is hair cell damage followed by hearing impairment due to loud noise exposure or age-related changes (Knipper et al., 2020). The exact underlying neurophysiological mechanisms of tinnitus are however still under investigation.

At the neural level, there is compelling evidence that central auditory regions play a crucial role in tinnitus, but brain regions outside the auditory system, like prefrontal cortex and the limbic system, also contribute significantly to the tinnitus condition (Rauschecker et al., 2010). Previous studies used magnetic resonance imaging (MRI) and in particular voxel-based morphometry (VBM) to evaluate differences in volume and tissue density between tinnitus patients and controls. These studies present evidence that there are gray matter increases in the auditory thalamus (Mühlau et al., 2006), anterior cingulate and frontal cortex (Husain et al., 2011), and in the superior temporal gyri (Boyen et al., 2013). In contrast, decreases in gray matter were found in Heschl’s gyrus (Allan et al., 2016; Schneider et al., 2009), supramarginal gyrus (Leaver et al., 2012), ventromedial prefrontal cortex, including the subgenual area (Leaver et al., 2011, 2012; Mühlau et al., 2006), hypothalamus (Boyen et al., 2013; Liu et al., 2019), superior frontal gyrus (Allan et al., 2016; Boyen et al., 2013; Liu et al., 2019), and occipital lobe (Boyen et al., 2013). Differences in cortical thickness and gray matter volume in parahippocampal and cingulate gyrus have been found in subgroups of tinnitus patients with varying symptom severity (Besteher et al., 2019;

* Corresponding author.
E-mail address: Shr43@georgetown.edu (S. Rosemann).

https://doi.org/10.1016/j.heares.2022.108595

Schmidt et al., 2018). Further, tinnitus distress was related to an increase in cortical thickness in the anterior insula (Leaver et al., 2012) as well as to gray matter volume increases in hypothalamus, insula and superior frontal gyrus (Liu et al., 2019). Depression and anxiety symptoms in tinnitus patients were associated with a reduction of cortical thickness and gray matter in parahippocampal and anterior cingulate cortex (Besteher et al., 2019; Leaver et al., 2012). Altogether, these brain morphological studies show an inconsistent picture. Discrepancies seem to stem from heterogenous patient groups and the fact that some studies did not control for age and hearing loss. Hence, it is not clear which underlying anatomical changes relate to increasing age, hearing impairment, or solely to the development of chronic tinnitus.

Given that widespread neural changes are found in tinnitus patients, especially in frontal regions, accompanying cognitive impairments in addition to depression and anxiety seem to be likely. In fact, some studies already reported on cognitive deficits, such as reduced control of attention (Heeren et al., 2014; Trevis et al., 2016) and inhibition (Araneda et al., 2015a, 2015b, 2018; Trevis et al., 2016), but also a decline in general cognitive abilities like short-term memory, concentration and orientation (Wang et al. 2018). It was further shown that the performance in a Stroop task significantly correlated with brain activity in prefrontal cortex (Araneda et al., 2018). These studies suggest that tinnitus impacts cognitive abilities, specifically those of executive control of attention and inhibition (Mohamad et al., 2016; Tegg-Quinn et al., 2016). A failure of top-down cognitive control may result in a diminished ability to switch attention away from the tinnitus – leading to a maintained or even increased awareness of the tinnitus sound (Trevis et al., 2016). However, since many of the previous studies did not control for age and hearing loss, it is not entirely clear whether these findings are confounded by age- or hearing-related cognitive decline (Tegg-Quinn et al., 2016). Further, anxiety and depression have an influence on the performance in tasks that require attention and inhibitory control; hence, it is also essential to determine the role of tinnitus distress in cognitive impairments separately from cognitive deficits that arise from neuroplastic changes due to chronic tinnitus. Completing the clinical profile of tinnitus patients by assessing cognitive deficits may aid in developing or advancing patient-specific treatment options and strategies targeting their health and wellbeing (for instance cognitive training or cognitive behavioral therapy).

The aim of the present study was to examine gray matter volume and cortical thickness differences between tinnitus patients and controls (matched in age and hearing loss). We further examined general cognitive abilities and working memory performance in all participants as well as tinnitus-related distress in tinnitus patients, in order to relate any such effects to the obtained neuroanatomical measures. Our predictions were decreased gray matter volume along with decreased cortical thickness in auditory cortex, thalamic, limbic, and prefrontal brain regions (Allan et al., 2016; Boyen et al., 2013; Leaver et al., 2011, 2012; Liu et al., 2019; Mühlau et al., 2006; Schneider et al., 2009). Also, of specific interest were changes in auditory cortex, nucleus accumbens and ventromedial prefrontal cortex. Additionally, we expected decreased performance in working memory and general cognitive decline related to decreased gray matter volume in the prefrontal cortex of tinnitus patients (Araneda, 2015a, 2018; Heeren et al., 2014; Mohamad et al., 2016; Tegg-Quinn et al., 2016; Trevis et al., 2016; Wang et al., 2018). We further hypothesized that a correlation might exist between tinnitus distress and 1) increased cortical thickness in the anterior insula as well as 2) decreased cortical thickness in anterior cingulate cortex (Besteher et al., 2019; Leaver et al., 2012; Liu et al., 2019; Schmidt et al., 2018).

2. Methods

2.1. Participants

40 volunteers participated in the study. The 20 tinnitus patients and 20 control participants were matched in terms of age and sex. The mean age was 58.5 (± 9.82) years in tinnitus patients and 57.7 (± 10.7) years in the control group. Each group comprised 7 female and 13 male participants.

Participants were recruited through social networks, advertisements and from our previous studies. Pediatric populations, individuals with HIV, individuals with history of seizures or other neurological disorders, with MRI-incompatible implants, with significant ear asymmetries, those with exposure to loud noise 24 h prior to testing, and pregnant women were excluded. The study was approved by the Institutional Review Board at Georgetown University and conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants gave written and informed consent and were paid for participating in this study.

2.2. Audiometric assessment

The audiometry was conducted at the Division of Audiology and Hearing Research at Medstar Georgetown University Medical Center. Pure-tone thresholds of frequencies ranging from 250 Hz to 16 kHz were assessed in a soundproof chamber. Pure-tone audiograms averaged over both ears for the two groups are depicted in Fig. 1. Hearing thresholds at 3 kHz significantly differed between both groups, as did the mean hearing loss between 250 Hz and 8 kHz ($T(38) = 2.194$, $p = 0.034$). Hearing thresholds were therefore included in the analysis (see Data analysis).

Further, tinnitus patients underwent an additional assessment to match the frequency and perceived intensity of their tinnitus. The mean frequency of the matched tinnitus pitch was 8 kHz (range 3-12.5 kHz, n=8 perceived the pitch at 8 kHz and n=7 at 10 kHz), and the mean perceived intensity was 5 dB SL. Tinnitus duration ranged from half a year to 50 years (mean duration was 15 years).

2.3. Behavioral assessment

Prior to the MRI scan, participants completed questionnaires assessing anxiety, depression and emotional distress: The Patient Health Questionnaire 9 (PHQ9; Kroenke et al., 2001), the Generalized Anxiety Disorder (GAD7; Spitzer et al., 2006), and the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983). All participants also conducted the Modified Khalfa Hyperacusis Questionnaire (Khalfa et al., 2002). Tinnitus patients further filled in the Tinnitus Handicap Inventory (THI; Newman et al., 1996), the Tinnitus Sample Case History Questionnaire (TSCHQ; Langguth et al., 2007), the Tinnitus Functional Index (TFI; Henry et al., 2016). In addition, general cognitive abilities were assessed with the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). Moreover, we used a two-back task as a typical measure of working memory. The two-back task was a self-programmed task in which participants were asked to indicate whether the current number was the same as two numbers before (two-alternative forced choice task). It was divided into five blocks and took ten minutes to complete. Stimulus presentation was controlled by Presentation® software (version 22.0; Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

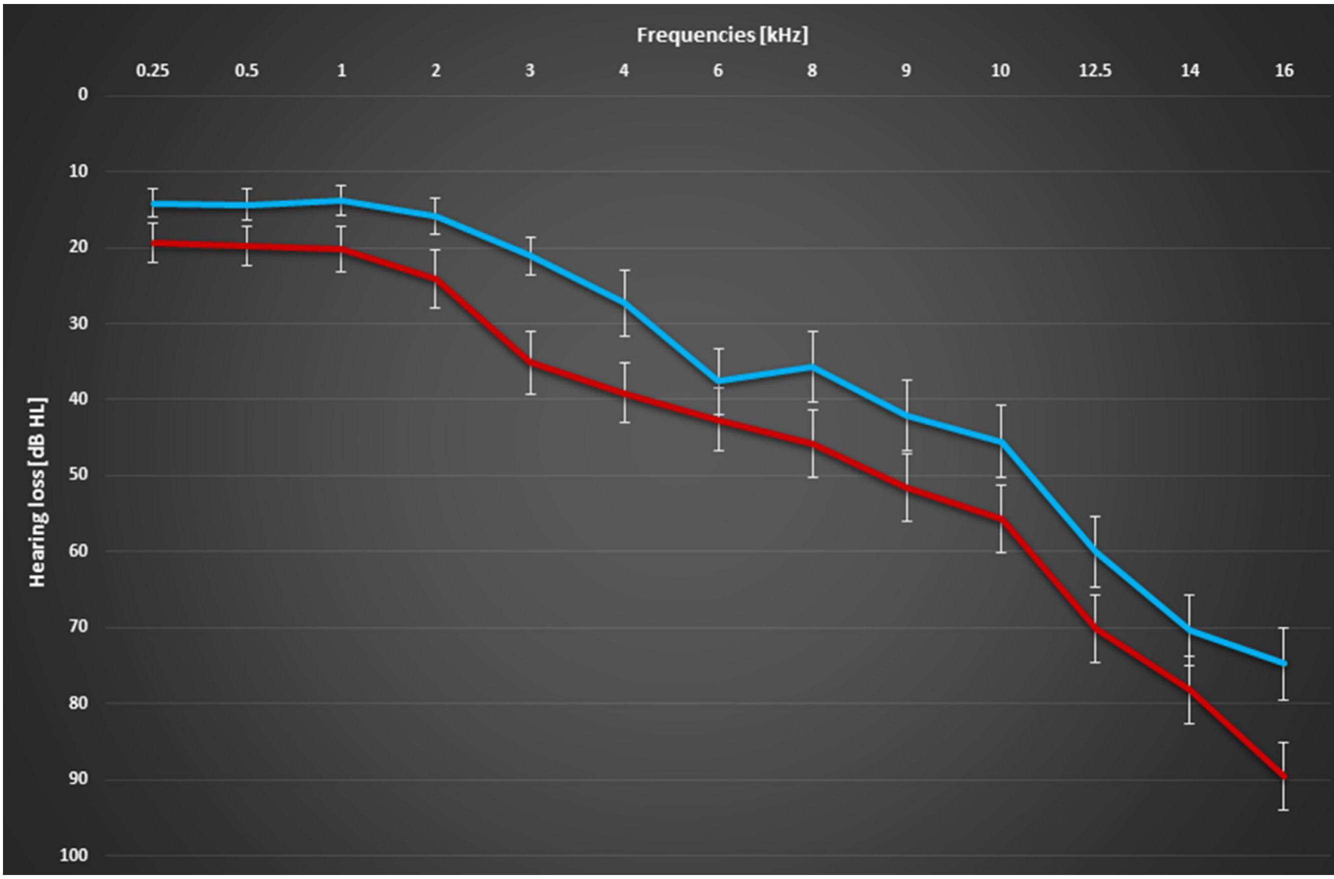

Fig. 1. Average pure tone audiograms for tinnitus patients (red) and control participants (blue) averaged over both ears. Error bars denote standard error of the mean.

2.4. Data acquisition

MRI data were acquired by a 3T whole-body Siemens Magnetom Prisma MRI scanner with a 64-channel head coil. Structural images were acquired with a 3-D T1-weighted sequence (MP-RAGE, TR = 1900 ms, TE = 2.52 ms, voxel size = 1.0 × 1.0 × 1.0 mm, flip angle 9 degrees, 160 sagittal slices).

2.5. Data analysis

Gray matter analysis was done in SPM12 and the toolbox CAT12 (Gaser et al., 2022) based on Matlab (2020b; The MathWorks, Inc., Natick, Massachusetts, United States). We performed a voxel-based morphometry (VBM) and cortical thickness analysis using the anatomical T1-weighted image. Preprocessing steps in CAT12 included normalization to the Montreal Neurological Institute (MNI) stereotactic space, segmentation into gray and white matter as well as cerebrospinal fluid and smoothing (Gaussian smoothing, full width at half maximum = 8 mm for the VBM, and full width at half maximum = 15 mm for the cortical thickness analysis). Gray matter volume and cortical thickness (using a projection-based thickness approach to estimate cortical thickness) were computed during the segmentation process. A quality check was applied between the segmentation and smoothing step. One participant (from the control group) was excluded due to inhomogeneous data. The remaining 39 participants were used in the statistical analysis. In the VBM analysis, total intracranial volume was used for global scaling. On the group level, we performed between-group comparisons (tinnitus patients versus control participants) and a linear regression analysis across tinnitus participants investigating the relation between gray matter and cortical thickness with cognitive abilities (MoCA score, two-back task performance) as well as tinnitus distress (THI and TFI scores). The linear regression analysis in the tinnitus group was controlled for age and gender because of the inhomogeneous group (age range 29–71 years; 7 female and 13 male). This was done using CAT12 for model specification and SPM12 for model estimation and statistical analysis. Mean hearing loss was entered as covariate to control for the significant difference in hearing abilities between the two groups. As an exploratory analysis, we conducted an interaction analysis (full factorial model) of group and cognitive abilities (MoCA scores and performance in the two-back task), because these were assessed in tinnitus patients and control participants (group x MoCa values; group x two-back performance). This was also done using CAT12 for model specification and SPM12 for model estimation and statistical analysis. Mean hearing loss was entered as covariate as well to control for the significant difference in hearing abilities between the two groups. For all analyses, effects were determined to be significant when passing a threshold of $p < 0.05$ (FWE cluster size inference with $p < 0.001$ cluster-forming threshold). Analyses were conducted for the whole brain and the multiple comparison problem was dealt with by using family-wise error correction based on random field theory. Peak coordinates are reported in MNI space.

Statistical analyses for the behavioral data included between-group comparisons of the cognitive tests and questionnaire scores along with correlational analyses of tinnitus characteristics, tinnitus distress and anxiety and depression scores. We also applied Bayesian independent samples t-Tests with default prior option (Cauchy distribution) to quantify the probability of the null hypothesis. This analysis was performed in JASP (JASP Team, 2020; Version 0.14.1). We report standard deviation of the mean, if not indicated otherwise.

Table 1
Overview of cognitive task performance and scores on questionnaires assessing anxiety, depression and emotional distress for each participant group [mean values ± standard deviation; t-values and BF_{10} indicating the Bayes factor in favor of H1 over H0 for between-group comparisons].

	Tinnitus patients	Control participants	t-values	BF_{10}
MoCA [score]	27.1 (± 2.14)	26.9 (± 2.37)	0.28	0.319
Two-back task [% performance]	89.7 (± 7.6)	86.6 (± 7.1)	1.328	0.618
HADS depression [score]	3.15 (± 2.35)	2.45 (± 2.72)	0.871	0.417
HADS anxiety [score]	5.1 (± 3.21)	3.75 (± 3.68)	1.236	0.564
BDI [score]	6.2 (± 4.58)	4.7 (± 5.74)	0.913	0.430
GAD [score]	1.7 (± 2.11)	1.25 (± 2.0)	0.694	0.374
PHQ [score]	2.0 (± 2.05)	2.1 (± 3.23)	-0.117	0.311
Khalfa hyperacusis [score]	13.05 (± 9.41)	9.1 (± 9.78)	1.302	0.602

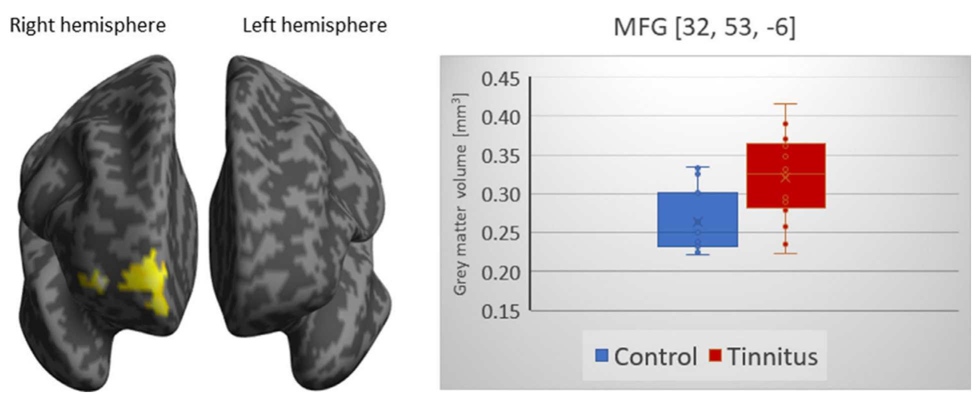

Fig. 2. Significantly higher gray matter volume in tinnitus patients compared to control participants in right middle frontal gyrus (MFG) [$p < 0.05$; FWE corrected on the cluster level].

3. Results

3.1. Behavioral assessments

Mean values (± standard deviation) for tinnitus patients and control participants for all questionnaires and cognitive tasks are displayed in Table 1. No significant differences between the two groups were obtained for any of the cognitive tasks or the questionnaires (p>0.1) and the Bayes analysis indicated favor for the null hypothesis (all $BF_{10} < 1$).

Furthermore, mean values for the tinnitus assessment questionnaires were 20 (± 11) for the THI and 49.3 (± 29.9) for the TFI. Those values were not related to depression and anxiety scores. Similarly, the values in perceived tinnitus pitch and intensity were not related to any of the depression and anxiety scores ($p > 0.1$).

Scores in general cognitive status (MoCA) and working memory (two-back task) were also not related to the THI, TFI or any values obtained in the tinnitus assessment ($p > 0.1$).

3.2. MRI data

For the VBM and cortical thickness analysis, we conducted two different analyses each: between-group comparisons (tinnitus patients versus control participants) to determine differences between both groups and a linear regression analysis across tinnitus participants investigating the relation between gray matter and cortical thickness with cognitive abilities (MoCA score, two-back task performance) as well as tinnitus distress (THI and TFI scores).

The group comparison showed a significantly higher gray matter volume in a cluster spanning the right middle frontal gyrus and frontal pole (peak MNI coordinate in MFG: $x = 32$, $y = 53$, $z = -6$; cluster size $k = 1538$, z-value $= 4.49$) in tinnitus patients compared to control participants (Fig. 2). No significant differences between groups were obtained in the cortical thickness analysis.

The regression analysis in the tinnitus group with cognitive abilities assessed by the MoCA and two-back test as well as with tinnitus distress assessed by the TFI and THI, showed two significant associations. There was a positive correlation between MoCA scores and gray matter in the cerebellum (left: MNI coordinate: $x = -17$, $y = -48$, $z = -29$; cluster size $k = 1220$, z-value $= 4.85$; right: MNI coordinate: $x = 27$, $y = -35$, $z = -23$; cluster size $k = 914$, z-value $= 4.05$). Further, there was a positive relation between cortical thickness in the right precuneus und the TFI scores (MNI coordinate: $x = 9$, $y = -74$, $z = -44$; cluster size $k = 120$, z-value $= 3.79$; Fig. 3). The correlation analysis in control participants was not significant.

As an exploratory analysis, we conducted an interaction analysis of group times the cognitive abilities, because these were assessed in tinnitus patients and control participants. We found a significant interaction of MoCA scores and group in the cortical thickness of the left middle frontal gyrus (MNI coordinate: $x = -45$, $y = -25$, $z = 37$; cluster size $k = 122$, z-value $= 4.1$; Fig. 4). No significant interaction was obtained for the two-back test.

4. Discussion

The first aim of the current study was to examine gray matter volume and cortical thickness measures between tinnitus patients and controls. The second aim was to relate neuroanatomical measures to cognitive abilities and tinnitus distress in tinnitus patients. Our hypotheses were decreased gray matter volume and cortical thickness in auditory cortex, thalamic, limbic, and prefrontal brain regions (Allan et al., 2016; Boyen et al., 2013; Leaver et al., 2011, 2012; Liu et al., 2019; Mühlau et al., 2006; Schneider et al., 2009). Moreover, we expected a correlation between 1) performance in working memory and general cognitive decline and gray matter volume in prefrontal cortex (Araneda et al., 2015a, 2018; Heeren et al., 2014; Mohamad et al., 2016; Tegg-Quinn et al., 2016; Trevis et al., 2016; Wang et al., 2018), and between tinnitus dis-

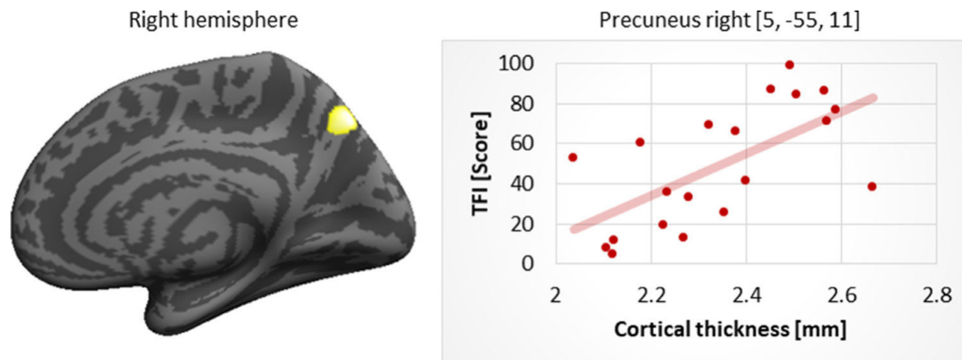

Fig. 3. Significant correlation between cortical thickness in the precuneus and the scores in the TFI in tinnitus patients [$p < 0.05$; FWE corrected on the cluster level].

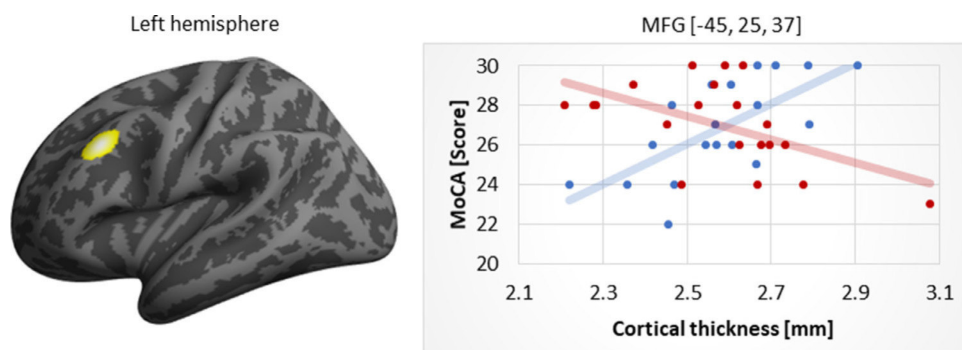

Fig. 4. Significant interaction between group and the MoCA scores in cortical thickness of the left middle frontal gyrus (MFG), tinnitus patients are depicted in red, control participants are depicted in blue [$p < 0.05$; FWE corrected on the cluster level].

tress and 2) increased cortical thickness in the anterior insula as well as 3) decreased cortical thickness in anterior cingulate cortex (Besteher et al., 2019; Leaver et al., 2012; Liu et al., 2019; Schmidt et al., 2018). Our results showed significantly higher gray matter volume in the right middle frontal gyrus and frontal pole in tinnitus patients compared to control participants. Further, we obtained a significant positive association between MoCA values and gray matter volume in the cerebellum as well as between tinnitus distress assessed by the TFI and cortical thickness in the precuneus. Our interaction analysis showed a significant interaction of group and MoCA scores in cortical thickness of the left middle frontal gyrus.

4.1. Increased gray matter volume in the frontal cortex of tinnitus patients

Our group comparison revealed significantly higher gray matter volume in the right middle frontal gyrus and frontal pole in tinnitus patients compared to control participants. Increased neural responses during emotional sound stimulation were observed in bilateral middle frontal gyri in patients with longer duration of tinnitus compared to recently diagnosed tinnitus patients or relative to control participants not experiencing tinnitus (Carpenter-Thompson et al., 2014, 2015; Husain, 2016). Further, increased activity in middle frontal gyrus was found in highly distressed tinnitus patients compared to individuals with low level tinnitus distress (Golm et al., 2013). The increased response is supposed to indicate a control mechanism in order to decrease awareness and annoyance of the tinnitus sensation especially developed after a longer duration of tinnitus (Carpenter-Thompson et al., 2015). The right middle frontal gyrus was also found to be involved in interference conditions such as the Stroop effect in tinnitus patients compared to control participants (Araneda et al., 2018). The authors argued that the increased activity might be a tinnitus related interference during the task. In line with this argumentation is a previous study demonstrating a correlation between middle frontal gyrus activity and tinnitus loudness ratings on the day of testing (Seydell-Greenwald et al., 2012). Hence, neural activity of the middle frontal gyrus has been linked to emotional processing in tinnitus as well as tinnitus distress, and the middle frontal region was also suggested as target region for neuromodulatory approaches (De Ridder et al., 2012; Golm et al., 2013; Vanneste et al., 2013). Recently, the middle frontal gyrus was found to be one of the regions whose gray matter volume effectively differentiated patients with tinnitus from healthy subjects (Liu et al., 2019). Similarly, activity in medial frontal gyrus/frontal pole was observed as a condition effect between pleasant, unpleasant and neutral sounds (Carpenter-Thompson et al., 2014). Recent resting-state functional connectivity studies found increased connectivity between left posterior cerebellum and the left frontal pole in tinnitus patients (Hinkley et al., 2022) as well as increased alpha-band power in the frontal pole (Li et al., 2022). Those studies suggest that frontal pole activity and connectivity might be an indicator of modulating and evaluating the emotional valence of the tinnitus sensation (Carpenter-Thompson et al., 2014; Hinkley et al., 2022; Li et al., 2022). The frontal pole is supposed to engage in cognitive flexibility, problem-solving and multitasking (Koechlin, 2011). Hence, the role of the frontal pole in tinnitus might be related to internal evaluation of the tinnitus sensation and cognitive flexibility regarding its modulation and suppresion. Thus, our results support the idea that not only neural activity but also gray matter volume of the middle frontal gyrus as well as frontal pole is involved in chronic tinnitus. Importantly, our results were not confounded by age or hearing loss and may trigger future research on elucidating the role of the middle frontal gyrus and frontal pole in tinnitus and its possible relation to tinnitus distress. It is not clear whether structural changes contribute to the onset of tinnitus or whether they are a result of the chronic tinnitus sensation. Longitudinal studies may help to shed light on this issue.

4.2. Gray matter volume in the cerebellum associated with general cognitive abilities in tinnitus patients

Our results revealed a positive correlation between MoCA scores and gray matter volume in the left and right cerebellum in tinnitus patients indicating higher cognitive status with increased gray matter volume. Although mostly studied in animals (Brozoski et al., 2013; Chen et al., 2015), the cerebellum has recently gained interest in tinnitus research in humans. Increased cerebellar gray matter volume was demonstrated in tinnitus patients compared to controls (Koops et al., 2020). Further, a recent resting-state functional connectivity study found increased connectivity between the posterior cerebellum and the frontal pole in tinnitus patients (Hinkley et al., 2022). Increased neural activity in the cerebellum was also associated with presentation of deviant tones in tinnitus patients compared to control participants (Zenke et al., 2021). Hence, it was suggested that the cerebellum contributes to central auditory processing and that its neural activity in challenging auditory situations might be altered in tinnitus patients. A different line of research demonstrated that tinnitus distress was correlated with gray matter volume of the left and right flocculus in patients after unilateral cerebellopontine angle surgery (Mennink et al., 2018). Since both the flocculus and paraflocculus receive auditory input, it was suggested that there is a feedback loop between those areas of the cerebellum and the auditory cortex which might play a role in modulating tinnitus severity (Mennink et al., 2020). Hence, the accessory paraflocculus was also proposed as a potential target region for tinnitus treatment such as deep brain stimulation or local pharmaceutical intervention (Mennink et al., 2020). Moreover, the cerebellum was suggested to play a role in cognitive deficits in aging and dementia (Rapoport et al., 2000). Further, cerebellar hypometabolism (Ishii et al., 1997) and brain atrophy (Barclay and Brady, 1992) were detected in Alzheimer's patients. Thus, decreased functioning of the cerebellum is supposed to be related to decreased cognitive abilities and dementia. We here found a similar connection between gray matter volume of the cerebellum and cognitive abilities that was however only significant in tinnitus patients and not in control participants. It is probable that cognitive functioning of the cerebellum plays only a significant role in patient populations such as tinnitus patients or patients with Alzheimer's disease and not in healthy participants. However, it is difficult to draw firm conclusions because we did not find cognitive deficits in the tinnitus group (please see discussion below). Future studies are needed to elaborate on the function of the cerebellum in cognitive abilities as well as its role in chronic tinnitus.

4.3. Cortical thickness in precuneus associated with tinnitus distress

Our results showed a significant positive association between scores in the TFI and cortical thickness in the right precuneus. Previous work showed decreased cortical thickness in the precuneus of tinnitus patients compared to controls (Allan et al., 2016; Besteher et al., 2019). Similarly, resting-state studies have demonstrated decreased functional connectivity between the precuneus and the dorsal attention network (Schmidt et al., 2017) as well as decreased resting-state perfusion of the precuneus in tinnitus compared to control participants (Zimmerman et al., 2021). Indeed, the precuneus seems to be one of the key brain regions in tinnitus with anatomical as well as functional measures being diminished compared to individuals not suffering from tinnitus. In contrast, we here show *higher* cortical thickness in the precuneus with increased tinnitus distress. Increased gray matter volume has also been found in early-onset depressive disorder patients who experience more depressive episodes than adult-onset major depressive disorder patients (Blank et al., 2022). Further, increased myelination of axons in the brain's gray matter regions that are usually only lightly myelinated were associated with anxiety and post-traumatic stress disorder in rats and humans (Long et al., 2021). The increased myelin was suggested to speed communication between brain regions and making those connections hyperresponsive to memories of trauma. Another study showed that patients with social anxiety disorder showed larger gray matter volume in the precuneus compared to controls (Wang et al., 2018). The increased gray matter volume was suggested to reflect the increased effort to cope with and regulate emotions and anxiety in social situations, i.e., compensatory structural alterations in response to increased anxiety. Increased tinnitus distress comes along with an increased conscious awareness of the tinnitus perception and thus with an increased effort to reduce it. Hence, our results may suggest that the increased annoyance and awareness of the tinnitus is reflected in an increased cortical thickness of the precuneus that might be seen as a compensatory structural alteration resulting from a constant attempt to decrease the tinnitus sensation. This might highlight the role of the precuneus in attenuating or ignoring the tinnitus sensation.

Unfortunately, we were not able to replicate previous findings about neuroanatomical changes in other limbic areas associated with tinnitus distress. This was surprising given consistent results from a number of independent studies particularly mentioning the insula and the subcallosal anterior cingulate cortex (Besteher et al., 2019; Leaver et al., 2012; Liu et al., 2019; Mühlau et al., 2006; Schmidt et al., 2018). There are also classical findings for an involvement of the subcallosal/subgenual area in clinical depression (Drevets et al., 1997; Mayberg, 1997) and in the perception of sounds with negative valence (Blood et al., 1999). Potential reasons for the absence of these effects in the present study might be the use of different toolboxes (Leaver et al., 2011, 2012; Liu et al., 2019; Mühlau et al., 2006), more lenient thresholds (Besteher et al., 2019; Leaver et al., 2011, 2012), but also a higher number of participants (Besteher et al., 2019; Liu et al., 2019; Mühlau et al., 2006) in prior tinnitus studies. Additionally, patient characteristics such as extent of hearing loss, tinnitus duration or severity of tinnitus distress may be different across studies (Husain and Schmidt, 2014; Kleinjung and Langguth, 2020). Limbic regions such as the insula and parahippocampus may only be involved in mild forms of tinnitus or in patients that successfully habituated to the tinnitus signal and hence reflect lower levels of tinnitus distress (Husain, 2016; Liu et al., 2019). In contrast, engagement of the amygdala seems to be related to severe forms of tinnitus (Husain, 2016). Our sample covers a range from slight to catastrophic distress with the mean being in the moderate range (based on TFI and THI scores). Therefore, it is possible that anatomical changes in some of the above regions were not detected.

4.4. General cognitive abilities differently associated with frontal cortical thickness in tinnitus and controls

The interaction analysis showed a significant interaction between group and thickness in the left middle frontal cortex associated with MoCA scores. Tinnitus patients had lower cortical thickness with higher MoCA scores (negative correlation) while control participants showed higher cortical thickness with higher MoCA scores (positive correlation). Previous work demonstrated cognitive deficits in tinnitus affecting attention, inhibition, concentration and short-term memory (Araneda et al., 2015a, 2015b, 2018; Heeren et al., 2014; Trevis et al., 2016; Wang et al., 2018). Those declines in cognitive abilities may be related to a diminished ability to switch attention away from the tinnitus that may lead to a maintained or even increased awareness of the tinnitus sound (Trevis et al., 2016). In our study, we did not find differences between MoCA scores or performance in the working memory task between tinnitus and control participants, but lower cognitive abilities were associated with increased cortical thickness in tinnitus patients and with decreased cortical thickness in control participants. It is possible that tinnitus patients with higher cortical thickness exhibit problems in cognitive tasks because their frontal areas are employed by attenuating and ignoring the tinnitus and thereby decreasing the tinnitus distress (Carpenter-Thompson et al., 2014, 2015; Husain, 2016). Individuals not experiencing tinnitus that show better performance with higher cortical thickness seem to have more resources to complete tasks requiring cognitive abilities such as concentration, attention and short-term memory. In tinnitus patients, on the other hand, increased annoyance and awareness of the tinnitus may be reflected in increased neuroanatomical measures in the middle frontal gyrus. The middle frontal gyrus is also recruited in effortful listening conditions in order to increase cognitive control, memory processes and facilitate the listening process in young as well as older adults (Erb and Obleser, 2013; Pauquet et al., 2021; Rosemann and Thiel, 2018). Similarly, the middle frontal gyrus might be recruited in tinnitus patients in order to direct attention away from the tinnitus signal. This increase in cognitive control to attenuate the tinnitus might interfere with cognitive resources available for other cognitive tasks such as general cognitive abilities assessed by the MoCA (Leaver et al., 2016; Trevis et al., 2016).

However, future research is needed to further investigate the association between cognitive abilities and neural correlates in tinnitus patients. As mentioned, previous research provided evidence of cognitive deficits, primarily reporting reduced control of attention (Heeren et al., 2014; Trevis et al., 2016) and inhibitory control (Araneda et al., 2015a, 2015b, 2018; Trevis et al., 2016). Our study included the MoCa – a cognitive screening tool for the detection of mild cognitive impairment – and a two-back task – a measure of working memory. We did not obtain significant differences between the groups which was also confirmed by Bayesian statistics favoring the null hypothesis. It is probable, that both measures were not targeting the affected cognitive processes and it might be beneficial to include assessments of attention and attention-switching such as the Attention Network Test (Heeren et al., 2014), a go/no-go task (Araneda et al., 2015a) or a Stroop task (Araneda et al., 2018) in the future. A crucial next step may also be the systematic evaluation of a variety of cognitive abilities in tinnitus patients as well as their relation to neural correlates such as gray matter volume and cortical thickness.

Interestingly, high functional connectivity between left middle frontal gyrus and the precuneus was found in patients with high tinnitus distress (Golm et al., 2013). Hence, both areas individually, but also their functional connectivity with each other, seem to play an important role in tinnitus distress. We showed increased gray matter in middle frontal gyrus in tinnitus patients compared to controls. Further, we demonstrated that higher cortical thickness in the precuneus is related to higher distress, whereas higher cortical thickness in the middle frontal cortex is associated with lower cognitive abilities in tinnitus patients. These results suggest that plastic changes in frontal and parietal brain structures of tinnitus patients appear to mediate the tinnitus sensation with possible cognitive control of attention. Additionally, increased cognitive control to attenuate and ignore the tinnitus may also interfere with general cognitive abilities executed in those regions (Araneda et al., 2018; Heeren et al., 2014; Trevis et al., 2016). Future studies should therefore consider investigating structural as well as functional connectivity between middle frontal gyrus and the precuneus and their relation to tinnitus distress but also cognitive abilities. These brain regions may be of crucial importance evaluating the efficacy of tinnitus interventions but may also serve as possible target regions of neuromodulatory treatments (Kleinjung and Langguth, 2020).

4.5. Conclusion

Our study demonstrates increased gray matter volume in in the middle frontal gyrus and frontal pole in tinnitus patients compared to control participants. Moreover, our results reveal increased cortical thickness in the precuneus associated with tinnitus distress, as well as a group interaction between MoCA scores and cortical thickness of the middle frontal gyrus, due to higher cortical thickness with higher scores in controls and lower scores in tinnitus patients. In sum, these results indicate that an increased awareness of as well as annoyance with the tinnitus sensation is reflected in increased brain structural changes in the precuneus and middle frontal gyrus that may have implications with regard to general cognitive abilities. The present findings, therefore, provide useful insights into neuroanatomical alterations in tinnitus patients related to tinnitus distress and cognitive function.

Preregistration

The study was preregistered on OSF on July 20th 2021 and can be found at https://osf.io/xhsm5.

A preprint version of this manuscript was published on OSF on May 17th 2022 and can be found at https://osf.io/jdqu5.

Funding

SR is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; RO6114/1-1).

Declaration of Competing Interest

The authors declare no competing interest.

CRediT authorship contribution statement

Stephanie Rosemann: Conceptualization, Methodology, Formal analysis, Visualization, Data curation, Writing – original draft. **Josef P. Rauschecker:** Conceptualization, Supervision, Writing – review & editing.

Acknowledgments

The authors wish to thank Anjul Bhangu for assistance in behavioral data curation and Melanie Spindler for valuable input on data analysis.

References

Allan, T.W., Besle, J., Langers, D.R.M., Davies, J., Hall, D.A., Palmer, A.R., Adjamian, P., 2016. Neuroanatomical alterations in tinnitus assessed with magnetic resonance imaging. Front. Aging Neurosci. 8. doi:10.3389/fnagi.2016.00221.

Araneda, R., De Volder, A.G., Deggouj, N., Philippot, P., Heeren, A., Lacroix, E., Decat, M., Rombaux, P., Renier, L., 2015a. Altered top-down cognitive control and auditory processing in tinnitus: evidences from auditory and visual spatial stroop. Restor. Neurol. Neurosci. 33 (1), 67–80. doi:10.3233/RNN-140433.

Araneda, R., De Volder, A.G., Deggouj, N., Renier, L., 2015b. Altered inhibitory control and increased sensitivity to cross-modal interference in tinnitus during auditory and visual tasks. PLoS One 10 (3), e0120387. doi:10.1371/journal.pone.0120387.

Araneda, R., Renier, L., Dricot, L., Decat, M., Ebner-Karestinos, D., Deggouj, N., De Volder, A.G, 2018. A key role of the prefrontal cortex in the maintenance of chronic tinnitus: an fMRI study using a Stroop task. NeuroImage Clin. 17, 325–334. doi:10.1016/j.nicl.2017.10.029.

Barclay, L.L., Brady, P.A., 1992. Cerebellar atrophy as a CT marker for mixed dementia. Biol. Psychiatry 31 (5), 520–524. doi:10.1016/0006-3223(92)90263-Y.

Besteher, B., Gaser, C., Ivanšić, D., Guntinas-Lichius, O., Dobel, C., Nenadić, I., 2019. Chronic tinnitus and the limbic system: reappraising brain structural effects of distress and affective symptoms. NeuroImage Clin. 24, 101976. doi:10.1016/j.nicl.2019.101976.
Blank, T.S., Meyer, B.M., Wieser, M.K., Rabl, U., Schögl, P., Pezawas, L., 2022. Brain morphometry and connectivity differs between adolescent- and adult-onset major depressive disorder. Depress. Anxiety 39 (5), 387–396. doi:10.1002/da.23254.
Blood, A.J., Zatorre, R.J., Bermudez, P., Evans, A.C., 1999. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nat. Neurosci. 2 (4), 382–387. doi:10.1038/7299.
Boyen, K., Langers, D.R.M., de Kleine, E., van Dijk, P., 2013. Gray matter in the brain: differences associated with tinnitus and hearing loss. Hear. Res. 295, 67–78. doi:10.1016/j.heares.2012.02.010.
Brozoski, T.J., Wisner, K.W., Odintsov, B., Bauer, C.A., 2013. Local NMDA receptor blockade attenuates chronic tinnitus and associated brain activity in an animal model. PLoS One 8 (10), e77674. doi:10.1371/journal.pone.0077674.
Carpenter-Thompson, J.R., Akrofi, K., Schmidt, S.A., Dolcos, F., Husain, F.T., 2014. Alterations of the emotional processing system may underlie preserved rapid reaction time in tinnitus. Brain Res. 1567, 28–41. doi:10.1016/j.brainres.2014.04.024.
Carpenter-Thompson, J.R., Schmidt, S.A., Husain, F.T., 2015. Neural plasticity of mild tinnitus: an fMRI investigation comparing those recently diagnosed with tinnitus to those that had tinnitus for a long period of time. Neural Plast. 2015, 161478. doi:10.1155/2015/161478.
Chang, N.C., Dai, C.Y., Lin, W.Y., Yang, H.L., Wang, H.M., Chien, C.Y., Ho, K.Y., 2019. Prevalence of persistent tinnitus and dizziness in an elderly population in Southern Taiwan. J. Int. Adv. Otol. 15 (1), 99–105. doi:10.5152/iao.2019.6257.
Chen, Q., Lv, H., Chen, Y.C., Song, J.J., Wang, Z., 2021. Editorial: neuroimaging approaches to the study of tinnitus and hyperacusis. Front. Neurosci. 15, 700670. doi:10.3389/fnins.2021.700670.
Chen, Y.C., Li, X., Liu, L., Wang, J., Lu, C.Q., Yang, M., Jiao, Y., Zang, F.C., Radziwon, K., Chen, G.D., Sun, W., Krishnan Muthaiah, V.P., Salvi, R., Teng, G.J., 2015. Tinnitus and hyperacusis involve hyperactivity and enhanced connectivity in auditory-limbic-arousal-cerebellar network. ELife 4, e06576. doi:10.7554/eLife.06576.
De Ridder, D., Vanneste, S., Plazier, M., Menovsky, T., van de Heyning, P., Kovacs, S., Sunaert, S., 2012. Dorsolateral prefrontal cortex transcranial magnetic stimulation and electrode implant for intractable tinnitus. World Neurosurg. 77 (5), 778–784. doi:10.1016/j.wneu.2011.09.009.
Drevets, W.C., Price, J.L., Simpson, J.R., Todd, R.D., Reich, T., Vannier, M., Raichle, M.E., 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386 (6627), 824–827. doi:10.1038/386824a0.
Erb, J., Obleser, J., 2013. Upregulation of cognitive control networks in older adults' speech comprehension. Front. Syst. Neurosci. 7. doi:10.3389/fnsys.2013.00116.
Gaser, C., Dahnke, R., Thompson, P.M., Kurth, F., Luders, E., 2022. CAT - A Computational Anatomy Toolbox for the Analysis of Structural MRI Data. BioRxiv, 2022.06.11.495736 doi:10.1101/2022.06.11.495736.
Golm, D., Schmidt-Samoa, C., Dechent, P., Kröner-Herwig, B., 2013. Neural correlates of tinnitus related distress: an fMRI-study. Hear. Res. 295, 87–99. doi:10.1016/j.heares.2012.03.003.
Heeren, A., Maurage, P., Perrot, H., De Volder, A., Renier, L., Araneda, R., Lacroix, E., Decat, M., Deggouj, N., Philippot, P., 2014. Tinnitus specifically alters the top-down executive control sub-component of attention: evidence from the attention network task. Behav. Brain Res. 269, 147–154. doi:10.1016/j.bbr.2014.04.043.
Henry, J.A., Griest, S., Thielman, E., McMillan, G., Kaelin, C., Carlson, K.F., 2016. Tinnitus functional index: development, validation, outcomes research, and clinical application. Hear. Res. 334, 58–64. doi:10.1016/j.heares.2015.06.004.
Hinkley, L.B.N., Larson, P.S., Henderson Sabes, J., Mizuiri, D., Demopoulos, C., Adams, M.E., Neylan, T.C., Hess, C.P., Nagarajan, S.S., Cheung, S.W., 2022. Striatal networks for tinnitus treatment targeting. Hum. Brain Mapp. 43 (2), 633–646. doi:10.1002/hbm.25676.
Hu, J., Cui, J., Xu, J.J., Yin, X., Wu, Y., Qi, J., 2021. The neural mechanisms of tinnitus: a perspective from functional magnetic resonance imaging. Front. Neurosci. 15, 621145. doi:10.3389/fnins.2021.621145.
Husain, F.T., 2016. Neural networks of tinnitus in humans: Elucidating severity and habituation. Hear. Res. 334, 37–48. doi:10.1016/j.heares.2015.09.010.
Husain, F.T., Medina, R.E., Davis, C.W., Szymko-Bennett, Y., Simonyan, K., Pajor, N.M., Horwitz, B., 2011. Neuroanatomical changes due to hearing loss and chronic tinnitus: a combined VBM and DTI study. Brain Res. 1369, 74–88. doi:10.1016/j.brainres.2010.10.095.
Husain, F.T., Schmidt, S.A., 2014. Using resting state functional connectivity to unravel networks of tinnitus. Hear. Res. 307, 153–162. doi:10.1016/j.heares.2013.07.010.
Ishii, K., Sasaki, M., Kitagaki, H., Yamaji, S., Sakamoto, S., Matsuda, K., Mori, E., 1997. Reduction of cerebellar glucose metabolism in advanced Alzheimer's disease. J. Nucl. Med. 38 (6), 925–928.
Jafari, Z., Kolb, B.E., Mohajerani, M.H., 2019. Age-related hearing loss and tinnitus, dementia risk, and auditory amplification outcomes. Ageing Res. Rev. 56, 100963. doi:10.1016/j.arr.2019.100963.
Khalfa, S., Dubal, S., Veuillet, E., Perez-Diaz, F., Jouvent, R., Collet, L., 2002. Psychometric normalization of a hyperacusis questionnaire. ORL 64 (6), 436–442. doi:10.1159/000067570.
Kleinjung, T., Langguth, B., 2020. Avenue for future tinnitus treatments. Otolaryngol. Clin. N. Am. 53 (4), 667–683. doi:10.1016/j.otc.2020.03.013.
Knipper, M., van Dijk, P., Schulze, H., Mazurek, B., Krauss, P., Scheper, V., Warnecke, A., Schlee, W., Schwabe, K., Singer, W., Braun, C., Delano, P.H., Fallgatter, A.J., Ehlis, A.C., Searchfield, G.D., Munk, M.H.J., Baguley, D.M., Rüttiger, L., 2020. The neural bases of tinnitus: lessons from deafness and cochlear implants. J. Neurosci. 40 (38), 7190–7202. doi:10.1523/JNEUROSCI.1314-19.2020.
Koechlin, E., 2011. Frontal pole function: what is specifically human? Trends Cogn. Sci. 15 (6), 241. doi:10.1016/j.tics.2011.04.005.
Koops, E.A., de Kleine, E., van Dijk, P., 2020. Gray matter declines with age and hearing loss, but is partially maintained in tinnitus. Sci. Rep. 10 (1), 21801. doi:10.1038/s41598-020-78571-0.
Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: Validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613. doi:10.1046/j.1525-1497.2001.016009606.x.
Langguth, B., Goodey, R., Azevedo, A., Bjorne, A., Cacace, A., Crocetti, A., Del Bo, L., De Ridder, D., Diges, I., Elbert, T., Flor, H., Herraiz, C., Ganz Sanchez, T., Eichhammer, P., Figueiredo, R., Hajak, G., Kleinjung, T., Landgrebe, M., Londero, A., … Vergara, R., 2007. Consensus for tinnitus patient assessment and treatment outcome measurement: tinnitus research initiative meeting, regensburg, July 2006. Prog. Brain Res. 166, 525–536. doi:10.1016/S0079-6123(07)66050-6.
Leaver, A.M., Renier, L., Chevillet, M.A., Morgan, S., Kim, H.J., Rauschecker, J.P., 2011. Dysregulation of limbic and auditory networks in tinnitus. Neuron 69 (1), 33–43. doi:10.1016/j.neuron.2010.12.002.
Leaver, A.M., Seydell-Greenwald, A., Rauschecker, J.P., 2016. Auditory–limbic interactions in chronic tinnitus: challenges for neuroimaging research. Hear. Res. 334, 49–57. doi:10.1016/j.heares.2015.08.005.
Leaver, A.M., Seydell-Greenwald, A., Turesky, T.K., Morgan, S., Kim, H.J., Rauschecker, J.P., 2012. Cortico-limbic morphology separates tinnitus from tinnitus distress. Front. Syst. Neurosci. 6. doi:10.3389/fnsys.2012.00021.
Li, Y.H., Chi, T.S., Shiao, A.S., Li, L.P.H, Hsieh, J.C., 2022. Pros and cons in tinnitus brain: enhancement of global connectivity for alpha and delta waves. Prog. Neuropsychopharmacol. Biol. Psychiatry 115, 110497. doi:10.1016/j.pnpbp.2021.110497.
Liu, Y., Niu, H., Zhu, J., Zhao, P., Yin, H., Ding, H., Gong, S., Yang, Z., Lv, H., Wang, Z., 2019. Morphological neuroimaging biomarkers for tinnitus: evidence obtained by applying machine learning. Neural Plast. 2019, 1712342. doi:10.1155/2019/1712342.
Long, K.L.P., Chao, L.L., Kazama, Y., An, A., Hu, K.Y., Peretz, L., Muller, D.C.Y., Roan, V.D., Misra, R., Toth, C.E., Breton, J.M., Casazza, W., Mostafavi, S., Huber, B.R., Woodward, S.H., Neylan, T.C., Kaufer, D., 2021. Regional gray matter oligodendrocyte- and myelin-related measures are associated with differential susceptibility to stress-induced behavior in rats and humans. Transl. Psychiatry 11 (1), 1–15. doi:10.1038/s41398-021-01745-5.
Mayberg, H.S., 1997. Limbic-cortical dysregulation: a proposed model of depression. J. Neuropsychiatry Clin. Neurosci. 9 (3), 471–481. doi:10.1176/jnp.9.3.471.
Mennink, L.M., Van Dijk, J.M.C., Van Der Laan, B.F.A.M., Metzemaekers, J.D.M., Van Laar, P.J., Van Dijk, P., 2018. The relation between flocculus volume and tinnitus after cerebellopontine angle tumor surgery. Hear. Res. 361, 113–120. doi:10.1016/j.heares.2018.01.009.
Mennink, L.M., van Dijk, J.M.C., van Dijk, P., 2020. The cerebellar (para)flocculus: a review on its auditory function and a possible role in tinnitus. Hear. Res. 398, 108081. doi:10.1016/j.heares.2020.108081.
Mohamad, N., Hoare, D.J., Hall, D.A., 2016. The consequences of tinnitus and tinnitus severity on cognition: a review of the behavioural evidence. Hear. Res. 332, 199–209. doi:10.1016/j.heares.2015.10.001.
Mühlau, M., Rauschecker, J.P., Oestreicher, E., Gaser, C., Röttinger, M., Wohlschläger, A.M., Simon, F., Etgen, T., Conrad, B., Sander, D., 2006. Structural brain changes in tinnitus. Cereb. Cortex 16 (9), 1283–1288. doi:10.1093/cercor/bhj070.
Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53 (4), 695–699. doi:10.1111/j.1532-5415.2005.53221x.
Newman, C.W., Jacobson, G.P., Spitzer, J.B., 1996. Development of the tinnitus handicap inventory. Arch. Otolaryngol. Head Neck Surg. 122 (2), 143–148. doi:10.1001/archotol.1996.01890140029007.
Noreña, A.J., 2011. An integrative model of tinnitus based on a central gain controlling neural sensitivity. Neurosci. Biobehav. Rev. 35 (5), 1089–1109. doi:10.1016/j.neubiorev.2010.11.003.
Pauquet, J., Thiel, C.M., Mathys, C., Rosemann, S., 2021. Relationship between memory load and listening demands in age-related hearing impairment. Neural Plast. 2021, e8840452. doi:10.1155/2021/8840452.
Rapoport, M., van Reekum, R., Mayberg, H., 2000. The role of the cerebellum in cognition and behavior. J. Neuropsychiatry Clin. Neurosci. 12 (2), 193–198. doi:10.1176/jnp.12.2.193.
Rauschecker, J.P., Leaver, A.M., Mühlau, M., 2010. Tuning out the noise: limbic-auditory interactions in tinnitus. Neuron 66 (6), 819–826. doi:10.1016/j.neuron.2010.04.032.
Rosemann, S., Thiel, C.M., 2018. Audio-visual speech processing in age-related hearing loss: stronger integration and increased frontal lobe recruitment. NeuroImage 175, 425–437. doi:10.1016/j.neuroimage.2018.04.023.
Schecklmann, M., Landgrebe, M., Langguth, B., 2014. Phenotypic characteristics of hyperacusis in tinnitus. PLoS One 9 (1), e86944. doi:10.1371/journal.pone.0086944.
Schmidt, S.A., Carpenter-Thompson, J.R., Husain, F., 2017. Connectivity of precuneus to the default mode and dorsal attention networks: a possible invariant marker of long-term tinnitus. NeuroImage Clin. doi:10.1016/j.nicl.2017.07.015.

Schmidt, S.A., Zimmerman, B., Bido Medina, R.O., Carpenter-Thompson, J.R., Husain, F.T., 2018. Changes in gray and white matter in subgroups within the tinnitus population. Brain Res. 1679, 64–74. doi:10.1016/j.brainres.2017.11.012.

Schneider, P., Andermann, M., Wengenroth, M., Goebel, R., Flor, H., Rupp, A., Diesch, E., 2009. Reduced volume of Heschl's gyrus in tinnitus. Neuroimage 45 (3), 927–939. doi:10.1016/j.neuroimage.2008.12.045.

Seydell-Greenwald, A., Leaver, A.M., Turesky, T.K., Morgan, S., Kim, H.J., Rauschecker, J.P., 2012. Functional MRI evidence for a role of ventral prefrontal cortex in tinnitus. Brain Res. 1485, 22–39. doi:10.1016/j.brainres.2012.08.052.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166 (10), 1092–1097. doi:10.1001/archinte.166.10.1092.

Tegg-Quinn, S., Bennett, R.J., Eikelboom, R.H., Baguley, D.M., 2016. The impact of tinnitus upon cognition in adults: a systematic review. Int. J. Audiol. 55 (10), 533–540. doi:10.1080/14992027.2016.1185168.

Trevis, K.J., McLachlan, N.M., Wilson, S.J., 2016. Cognitive mechanisms in chronic tinnitus: psychological markers of a failure to switch attention. Front. Psychology 7, 1262. doi:10.3389/fpsyg.2016.01262.

Vanneste, S., Walsh, V., Van De Heyning, P., De Ridder, D., 2013. Comparing immediate transient tinnitus suppression using tACS and tDCS: a placebo-controlled study. Exp. Brain Res. 226 (1), 25–31. doi:10.1007/s00221-013-3406-7.

Wang, X., Cheng, B., Luo, Q., Qiu, L., Wang, S., 2018. Gray matter structural alterations in social anxiety disorder: a voxel-based meta-analysis. Front. Psychiatry 9, 449. doi:10.3389/fpsyt.2018.00449.

Wang, Y., Zhang, J., Hu, W., Li, J., Zhou, J., Zhang, J., Shi, G., He, P., Li, Z., Li, M., 2018. The characteristics of cognitive impairment in subjective chronic tinnitus. Brain Behav. 8 (3), e00918. doi:10.1002/brb3.918.

Zenke, J.K., Rahman, S., Guo, Q., Leung, A.W.S., Gomaa, N.A., 2021. Central processing in tinnitus: FMRI study outlining patterns of activation using an auditory discrimination task in normal versus tinnitus patients. Otol. Neurotol. 42 (8), e1170. doi:10.1097/MAO.0000000000003194.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67 (6), 361–370. doi:10.1111/j.1600-0447.1983.tb09716.x.

Zimmerman, B.J., Schmidt, S.A., Khan, R.A., Tai, Y., Shahsavarani, S., Husain, F.T., 2021. Decreased resting perfusion in precuneus and posterior cingulate cortex predicts tinnitus severity. Curr. Res. Neurobiol. 2, 100010. doi:10.1016/j.crneur.2021.100010.

scientific reports

OPEN

Disruptions of default mode network and precuneus connectivity associated with cognitive dysfunctions in tinnitus

Stephanie Rosemann✉ & Josef P. Rauschecker

Tinnitus is the perception of a ringing, buzzing or hissing sound "in the ear" without external stimulation. Previous research has demonstrated changes in resting-state functional connectivity in tinnitus, but findings do not overlap and are even contradictory. Furthermore, how altered functional connectivity in tinnitus is related to cognitive abilities is currently unknown. Here we investigated resting-state functional connectivity differences between 20 patients with chronic tinnitus and 20 control participants matched in age, sex and hearing loss. All participants underwent functional magnetic resonance imaging, audiometric and cognitive assessments, and filled in questionnaires targeting anxiety and depression. Significant differences in functional connectivity between tinnitus patients and control participants were not obtained. However, we did find significant associations between cognitive scores and functional coupling of the default mode network and the precuneus with the superior parietal lobule, supramarginal gyrus, and orbitofrontal cortex. Further, tinnitus distress correlated with connectivity between the precuneus and the lateral occipital complex. This is the first study providing evidence for disruptions of default mode network and precuneus coupling that are related to cognitive dysfunctions in tinnitus. The constant attempt to decrease the tinnitus sensation might occupy certain brain resources otherwise available for concurrent cognitive operations.

Tinnitus is mostly perceived as ringing, buzzing or hissing "in the ear" without external stimulation and affects 10 to 25% of the adult population and as many as 45% of the elderly population[1–4]. Chronic tinnitus significantly impacts quality of life and mental health as it comes with increased distress, fatigue, depression and anxiety, and may also result in problems with sleeping and concentration[5,6].

Previous studies have applied resting-state functional magnetic resonance imaging [fMRI] to explore functional abnormalities in tinnitus patients. During a resting-state measurement, participants do not perform a specific task, but their brains are scanned while they are in a so-called 'resting-state'. Thereby spontaneous low frequency fluctuations (< 0.1 Hz) in the BOLD signal are assessed to identify resting-state networks[7]. This enables the analysis of functional connectivity—the temporal correlation of the BOLD response time courses of two brain regions that may be anatomically separate but are functionally related. Resting-state functional connectivity is particularly interesting within the framework of tinnitus because the perception of tinnitus can potentially be better determined without a distracting task. Up to 85% of chronic tinnitus patients perceive the tinnitus sensation permanently [though possibly at varying strength] and, therefore, resting-state fMRI measurements seem suitable to capture this perception[8].

Although there are some studies on changes in resting-state functional connectivity in tinnitus patients, findings are scarce and vary in their outcomes. Briefly, these studies show that tinnitus is related to an atypical functional network comprising auditory and non-auditory brain regions[9]. Further, tinnitus is associated with decreases as well as increases in functional connectivity in frontal, parietal, cerebellar, auditory and limbic regions[9–14]. Similarly, typical resting-state networks, like default mode and dorsal attention networks, as well as their connections with the precuneus, are affected by tinnitus[15–18]. Additionally, tinnitus distress correlated with decreased functional connectivity between middle temporal gyrus and middle frontal gyrus[19] and with increased

Laboratory of Integrative Neuroscience and Cognition, Department of Neuroscience, Georgetown University Medical Center, 3970 Reservoir Rd NW, Washington, DC 20057, USA. ✉email: Shr43@georgetown.edu

functional connectivity between middle frontal gyrus and the precuneus[20]. A recent meta-analysis identified consistently increased resting-state functional connectivity in the insula, middle temporal gyrus, inferior and superior frontal gyri, parahippocampal gyrus and cerebellum, as well as decreased resting-state connectivity in the cuneus und thalamus[21]. Although presenting a relatively heterogeneous picture, these studies suggest an interaction of multiple brain areas and networks that are involved in tinnitus perception, and relate differently to tinnitus distress such as anxiety or depression.

Along alterations in resting-state functional connectivity, previous research provided evidence for cognitive deficits, such as reduced control of attention[22–24], altered inhibitory control[24–26], and a decline in general cognitive abilities like short-term memory, concentration and orientation[27]. Hence, it seems that tinnitus affects specifically those cognitive abilities that require executive control of attention and inhibition[28,29]. A failure in top-down cognitive control may result in a diminished ability to switch attention away from the tinnitus signal, and therefore the awareness of the tinnitus signal is maintained or even increased[24]. However, how cognitive abilities are associated with changes in resting-state functional connectivity in tinnitus has not been investigated. A complicating factor in previous research is that many studies did not control for age and hearing loss and thus it is not clear which underlying functional connectivity changes relate to increasing age, hearing impairment or solely to development of chronic tinnitus. Hence, the question of which pathophysiological mechanisms in the human brain are involved in tinnitus, still needs to be answered. Completing the clinical profile of tinnitus patients by investigating cognitive abilities and their relationship to functional brain alterations may play a crucial role in evaluating and advancing tinnitus interventions and treatment options.

The aim of the current study was to investigate resting-state functional connectivity changes associated with the tinnitus signal but also in relation to tinnitus distress and general cognitive abilities. Based on the above results, we hypothesized that tinnitus would disrupt functional resting-state connectivity in auditory cortex, thalamic, limbic, and prefrontal brain regions[9–13] as well as in typical resting-state networks, like default-mode and dorsal attention networks, as well as their connections with the precuneus[15–18]. Further, we expected that tinnitus patients exhibit deficits in working memory and may also present with general cognitive decline[22–25,27,29,30]. These decreased cognitive abilities may be reflected in decreased resting-state connectivity between the default mode and dorsal attention networks[16,24]. Moreover, we hypothesized that tinnitus distress is related to *decreased* functional resting-state connectivity between right middle temporal gyrus and middle frontal gyrus[19] and with *increased* functional connectivity between middle frontal gyrus and the precuneus[20].

Results

Behavioral assessments. Mean values for the MoCA were 27.1 (± 2.14) for the tinnitus patients and 26.9 (± 2.37) for the control participants. The mean performance in the two-back task was 89.7 (± 7.6) % in the tinnitus group and 86.6 (± 7.1) % in the control participants. No significant differences between the groups were obtained for any of the cognitive tasks or in anxiety or depression scores ($p > 0.1$).

The mean values obtained for the tinnitus assessment questionnaires were 20 (± 11) for the THI and 123 (± 74.7) for the TFI. The mean perceived pitch frequency of the tinnitus was 8 kHz (range 3–12,5 kHz, $n = 8$ perceived the pitch at 8 kHz and $n = 7$ at 10 kHz) and the mean perceived tinnitus intensity was 5 dB SL. There was no significant correlation in our sample between tinnitus assessment questionnaires and depression or anxiety scores. Similarly, the values in perceived tinnitus pitch and intensity were not related to any of the depression and anxiety scores ($p > 0.1$) in our sample. Tinnitus duration ranged from half a year to 50 years (mean duration was 15 years) and did not significantly correlate with any of the behavioral scores. Three patients reported a pulsatile tinnitus, the others reported no pulsation. Four patients indicated their tinnitus sounded like wide-band, high-frequency noise; the others indicated they perceived it as a tone. Four tinnitus patients reported unilateral tinnitus, all others reported a bilateral tinnitus sensation.

Resting-state functional connectivity. For the resting-state functional connectivity analysis, two different analyses were conducted. First, a between-group comparison was computed to determine differences between tinnitus patients and control participants. Second, a linear regression analysis across tinnitus participants investigating the relation between resting-state functional connectivity and cognitive abilities (MoCA score, two-back task performance) as well as tinnitus distress (THI and TFI scores) was conducted.

In the between-group comparison, we did not obtain a significant difference in resting-state functional connectivity between tinnitus patients and control participants.

The subsequent multiple regression analysis in the tinnitus group showed several positive associations between resting-state functional connectivity and MoCA scores as well as TFI scores. An overview including peak coordinates is given in Table 1. First, we obtained a significant positive association between MoCA scores and resting-state functional connectivity of the default mode network and (1) left superior parietal lobule ($r = 0.809$; $p < 0.001$) and (2) orbitofrontal cortex ($r = 0.825$; $p < 0.001$) in tinnitus patients (Fig. 1). Second, a positive correlation between MoCA scores and resting-state functional connectivity of the precuneus and (1) left ($r = 0.754$; $p < 0.001$) and (2) right superior parietal lobule ($r = 0.755$; $p < 0.001$), (3) orbitofrontal cortex ($r = 0.847$; $p < 0.001$), and (4) supramarginal gyrus ($r = 0.749$; $p < 0.001$) was found in tinnitus patients (Fig. 2). Lastly, a significant positive relation between TFI scores and resting-state functional connectivity of the precuneus and the right lateral occipital cortex was apparent in the tinnitus group ($r = 0.69$; $p < 0.001$; Fig. 3).

When correcting for multiple comparisons (Bonferroni correction), only three correlations survived: The correlation between the MoCA and resting-state functional connectivity of (1) the default mode network with the superior parietal lobule and of the precuneus with (2) the orbitofrontal cortex, and (3) with the right superior parietal lobule (this is also indicated in Table 1).

Test	Seed region	Peak coordinates (x, y, z)	Z-score	Cluster size	Brain region
MoCA	Default mode network	**– 28, – 44, 54**	**4.04**	**154**	**Superior parietal lobule L**
		20, 12, – 22	4.34	136	Orbitofrontal cortex R
	Precuneus	**20, 8, – 18**	**4.46**	**167**	**Orbitofrontal cortex R**
		30, – 46, 62	**4.14**	**147**	**Superior parietal lobule R**
		– 26, – 50, 62	4.22	136	Superior parietal lobule L
		– 68, – 26, 24	4.26	102	Supramarginal gyrus L
TFI	Precuneus	40, – 92, – 8	3.92	144	Lateral occipital cortex R

Table 1. Resulting clusters of multiple regression within the tinnitus group controlled for age and sex (significant clusters that survive Bonferroni correction are displayed in bold).

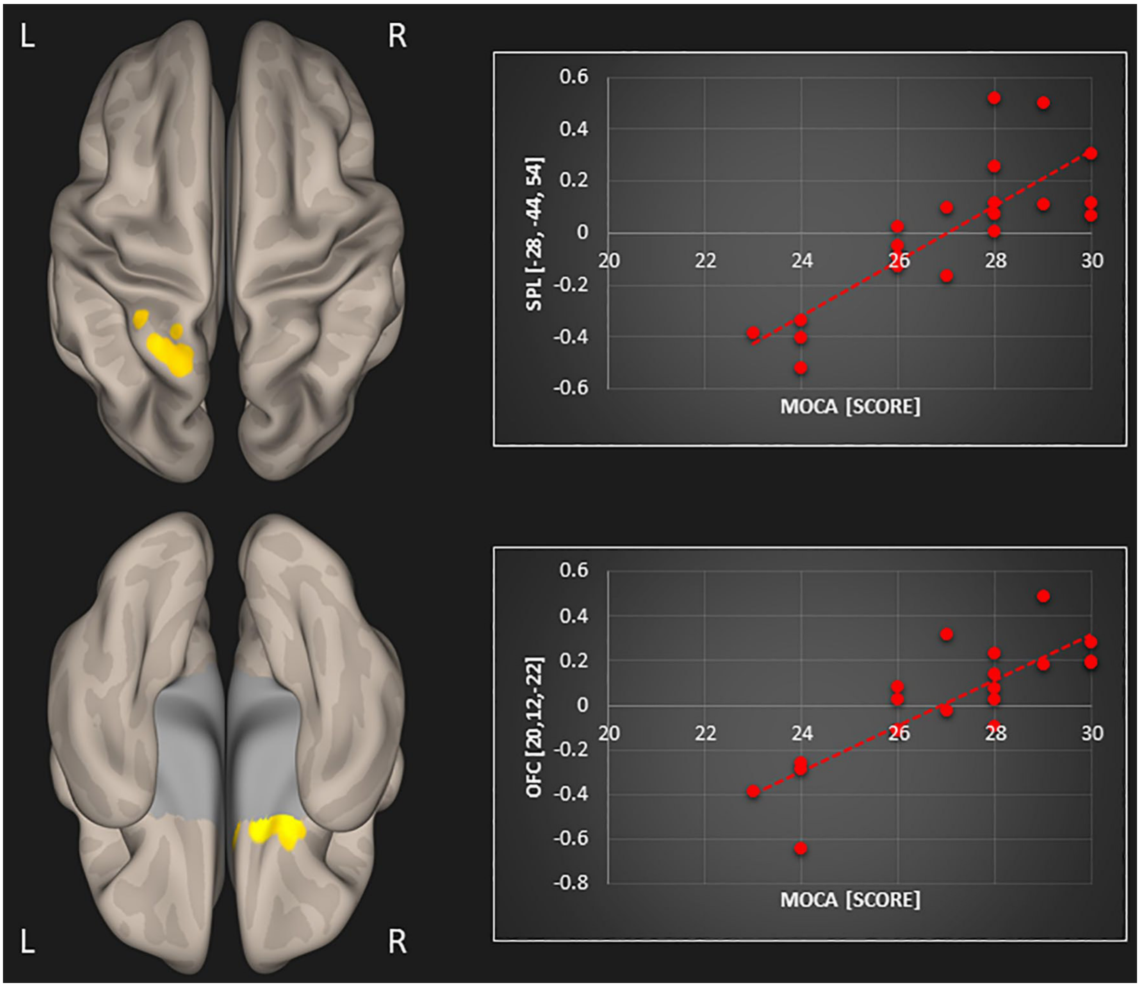

Figure 1. Significant association between MoCA scores and resting-state functional connectivity of the default mode network with the left superior parietal lobule (SPL; top row) and the right orbitofrontal cortex (OFC; bottom row) in tinnitus patients [$p < 0.05$; FWE cluster-corrected threshold]. Significant brain areas were displayed on an inflated brain by CONN version 20b[31].

We also computed correlations between cognitive scores and resting-state functional connectivity for the control group. However, no significant correlations were obtained. In order to assess any significant differences between the correlation coefficients of the tinnitus patients and the control participants, we conducted Fisher r-to-z transformations. This analysis demonstrated that correlation coefficients for control participants and tinnitus patients were significantly different from each other for associations of MoCa scores and functional connectivity (all $p < 0.05$).

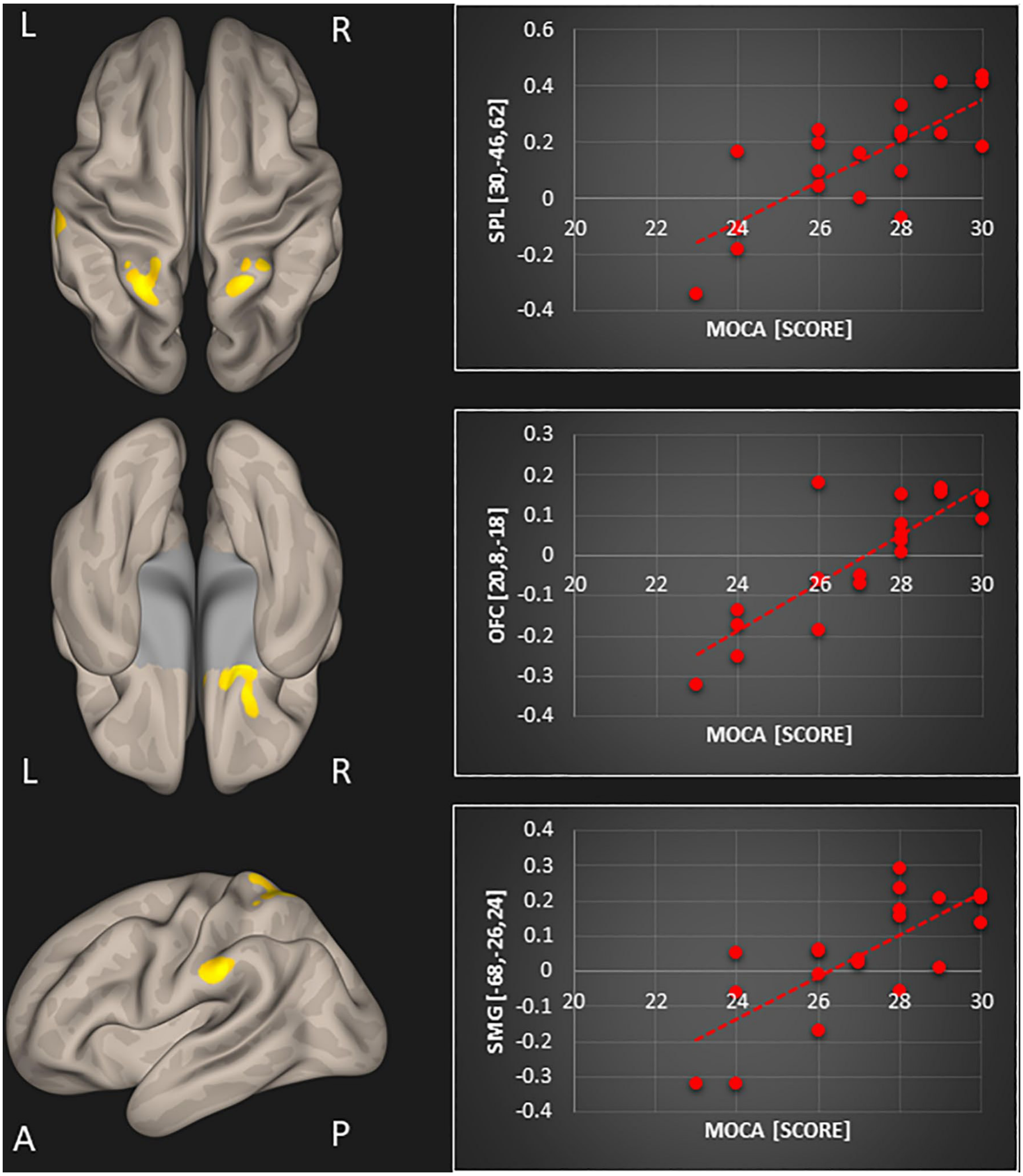

Figure 2. Significant association between MoCA scores and resting-state functional connectivity of the precuneus with the left and right superior parietal lobules (SPL; top row), the right orbitofrontal cortex (OFC; middle row), and the left supramarginal gyrus (SMG; bottom row) in tinnitus patients [$p < 0.05$; FWE cluster-corrected threshold]. Significant brain areas were displayed on an inflated brain by CONN version 20b[31].

Discussion

The aims of this study were threefold: (1) to assess resting-state functional connectivity changes in tinnitus patients compared to control participants, and to investigate resting-state functional connectivity in relation to (2) the patients' cognitive abilities and to (3) their tinnitus distress. Based on prior work, our expectations were to find disrupted functional resting-state connectivity in tinnitus patients in the following brain regions: auditory cortex, thalamus, limbic, and prefrontal areas[9–13], as well as in typical resting-state networks, such as the default mode and dorsal attention networks, along with their connections to the precuneus[15–18]. Further, we assumed that tinnitus patients may exhibit deficits in working memory and general cognitive abilities[22–25,27,29,30], which may be reflected in decreased resting-state connectivity between the default mode and dorsal attention networks[16,24]. Moreover, we hypothesized that tinnitus distress is correlated with *decreased* functional resting-state connectivity between right middle temporal gyrus and middle frontal gyrus[19] along with *increased* connectivity between middle frontal gyrus and the precuneus[20]. Indeed, regarding cognitive abilities assessed by the MoCA

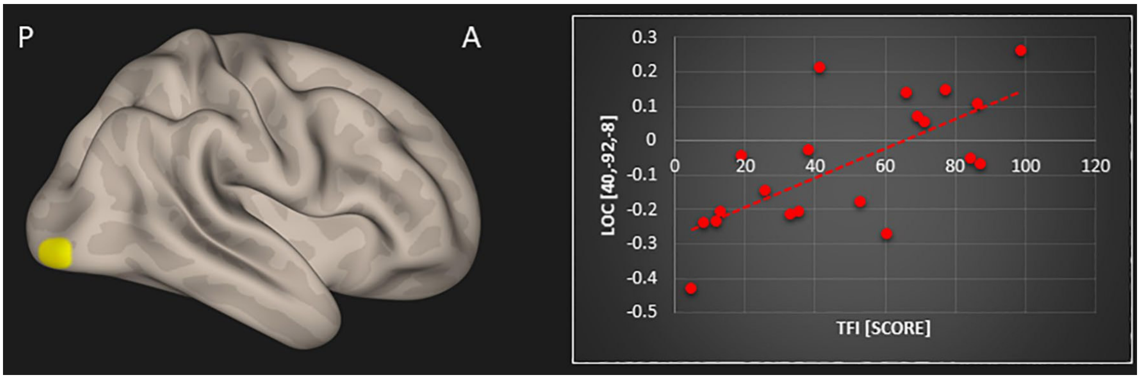

Figure 3. Significant association between TFI scores and resting-state functional connectivity of the precuneus with the right lateral occipital cortex (LOC) in tinnitus patients [$p < 0.05$; cluster-corrected threshold]. Significant brain areas were displayed on an inflated brain by CONN version 20b[31].

and tinnitus distress assessed by the TFI, our results showed some positive associations with resting-state functional connectivity in the tinnitus group which were not observed in the control group. We obtained significant positive relations between MoCA scores and resting-state functional connectivity of the default mode network with (1) the left superior parietal lobule and (2) orbitofrontal cortex; and of the precuneus with (3) left and (4) right superior parietal lobule, (5) orbitofrontal cortex and (6) supramarginal gyrus. Further, we were able to demonstrate a significant positive correlation between TFI scores and resting-state functional connectivity of the precuneus and the right lateral occipital cortex in tinnitus patients.

No differences in resting-state functional connectivity between tinnitus and control participants. Our resting-state functional connectivity analysis did not show any significant differences between tinnitus patients and the control group. This is a surprising finding considering the research that has demonstrated disrupted functional resting-state connectivity in auditory cortex, thalamic, limbic, and prefrontal brain regions as well as in default mode and dorsal attention networks[9–13,15–18]. Possible reasons for the absence of these effects might be a difference in seed regions[10,15], a higher number of participants in other studies[10,11,15], groups with unilateral tinnitus (12,16), but also control groups that were not matched for age and hearing loss[9,11,13]. Another possibility is that different analysis methods [seed-to-voxel, ROI-to-ROI, or independent component analysis] may have yielded differing results. In addition, some studies used an "eyes-open" paradigm and others used an "eyes-closed" paradigm for the resting-state acquisition, which might explain some of the heterogeneous findings[32]. It has been previously demonstrated that the choice of paradigm significantly impacts resting-state functional connectivity of visual, auditory and sensorimotor networks[33]. We employed an "eyes-open" approach and our groups were matched in terms of age, sex and hearing loss. However, other patient characteristics, such as extent of hearing loss, tinnitus duration, or severity of tinnitus distress vary across studies[32,33]. The co-occurrence of hyperacusis might play a relevant role as well[34]. A recent study on the Human Connectome Project data showed that functional connectivity of the auditory cortex decreases with age and that tinnitus patients presented even less auditory cortex connectivity than their age-matched controls[35]. Hence, it is essential to carefully match the control groups in future tinnitus research. Another suggestion for future studies might be to include a larger sample size enabling the analysis of specific subtypes of patient groups (for instance, groups with high versus low tinnitus distress). A recent meta-analysis reached a similar conclusion[36]. Furthermore, using similar acquisition paradigms, seed regions and analysis methods across studies to allow comparability and reproducibility would be beneficial.

General cognitive abilities associated with resting-state functional connectivity of the default mode network and the precuneus. Importantly, we obtained several positive associations between general cognitive abilities assessed by the MoCA and resting-state functional connectivity of the default mode network and the precuneus in tinnitus patients that were not observed in the control participants. The correlations were similar for the default mode network and the precuneus, whose functional connectivity to both orbitofrontal cortex and the superior parietal lobule were associated with general cognitive abilities. Furthermore, resting-state functional connectivity between precuneus and supramarginal gyrus correlated with MoCA values. All of these brain areas have been mentioned in previous tinnitus research. The superior parietal lobule shows less beta activity[37], reduced connectivity[38], and altered BOLD responses for visual and auditory attentional tasks in tinnitus patients[39]. Moreover, increased brain activity in the superior parietal lobule has been demonstrated during auditory interference conditions with cognitive conflict in tinnitus patients[26]. The orbitofrontal cortex is a nexus for sensory integration, modulation of autonomic reactions, as well as emotional and reward-related behaviors[40]. It functions as part of a network that includes regions of the medial prefrontal cortex, amygdala, insula, and the dopaminergic midbrain projecting to the ventral and dorsal striatum[40,41]. Thus, this network hub, which is controlled by the orbitofrontal cortex, houses the frontostriatal gating mechanism that has been proposed to reduce the intensity of tinnitus and chronic pain, if it is intact, but enables or exacerbates tinnitus, if it is broken[42,43]. Other studies have demonstrated increased functional connectivity of the orbitofrontal cortex[11,13] and even found an atypical resting-state network involving the orbitofrontal cortex in tinnitus patients[44]. Moreover, a magnetoencephalographic study revealed differences in global resting-state networks that covered prefrontal, orbitofrontal and parieto-occipital cortex when comparing tinnitus patients to controls[45]. The supramarginal gyrus has been associated with increased responses in an emotional task in chronic tinnitus compared to tinnitus patients with recent onset[46,47] along with increased regional homogeneity in chronic tinnitus patients[48,49]. Taken together, previous research has suggested that the orbitofrontal cortex, together with the superior parietal lobule and the supramarginal gyrus, might be engaged in compensatory processes attenuating the tinnitus signal. The present study is the first to show a positive relationship between cognitive abilities and changes in resting-state functional connectivity of the default mode network and precuneus to orbitofrontal cortex, superior parietal lobule, and supramarginal gyrus in chronic tinnitus. Decreased coupling was related to lower cognitive scores while tinnitus patients did not show cognitive deficits as a group (mean MoCA score was 27; see "Discussion" below). However, taking a closer look at the correlation between MoCa scores and connectivity, it seems that lower MoCa scores (< 26) are correlated with negative connectivity values (anticorrelation), while higher scores (> 26 indicative of normal cognitive function) are correlated with positive connectivity values. Hence, disruptions of default mode network and precuneus coupling may indeed be related to cognitive dysfunctions in bilateral tinnitus. It is probable, that the constant effort to decrease the tinnitus signal is associated with changes in resting-state functional connectivity. Those resources might no longer be available for other cognitive operations leading to diminished cognitive abilities. Because previous resting-state functional connectivity studies did not assess cognitive abilities, it is unclear whether their findings can be merely attributed to the chronic tinnitus perception or may also be intertwined with cognitive abilities. Further, it was recently shown that there is a bidirectional relationship between tinnitus sensation and cognitive control[22]. Thus, we want to stress the importance of including assessments of cognitive abilities in tinnitus research in the future.

Contrary to our expectations, tinnitus patients did *not* exhibit deficits in working memory or general cognitive abilities as a group, although some tinnitus patients showed decreased general cognitive status indicated by a MoCa score < 26[23–25,27,29,30]. Scores from the attention subtests in the MoCa showed a similar pattern (no impairment, no significant differences from control participants). Unfortunately, the abbreviated form of the trail making test which is included in the MoCa does not include the assessment of processing speed. It is probable, that the complete MoCA score or attention subscores as well as the two-back performance that were used in our study were not targeting the affected cognitive processes in our tinnitus sample. Thus, future research should consider including detailed assessments of attention and attention-switching such as the trail making test, specifically subtests 1 and 5[16], digit span task[16], Attention Network Test[23], a go/no-go task[25], or a Stroop task[26]. The systematic evaluation of cognitive abilities and clinical characteristics in tinnitus patients along with their association to functional brain changes might also aid in developing or improving treatment options that target their health and wellbeing[50]. Cognitive training or cognitive behavioral therapy might assist tinnitus patients in switching their attention away from the tinnitus sensation and hence reduce tinnitus distress[29,51]. In summary, these results provide a first detailed analysis about the relationship between resting-state functional connectivity of default mode network and precuneus with general cognitive abilities in chronic bilateral tinnitus. The mentioned brain areas should also be considered in neuromodulatory therapies that may aid in restoring functional connectivity of the default mode network and specifically the precuneus.

Tinnitus distress related to resting-state functional connectivity of the precuneus. Additionally, our results demonstrate a positive relationship between tinnitus distress assessed by the TFI and resting-state functional connectivity between the precuneus and the lateral occipital cortex. Previous research has suggested that *decreased* resting-state functional connectivity of the precuneus may interfere with its underlying functioning and anticorrelation with the dorsal attention network[18]. By contrast, other research has provided evidence of *increased* resting-state functional coupling of the precuneus in chronic tinnitus patients compared to controls[24] and to patients with high compared to low tinnitus distress[20]. Here we also demonstrate *increased* resting-state functional connectivity between the precuneus and the lateral occipital cortex (a higher-order visual region) with increased tinnitus distress. Similarly, we showed in a previous study that increased cortical thickness in the precuneus is correlated with increased tinnitus distress[52]. Hence, neuroanatomical as well as functional changes in the precuneus might be primarily related to increased distress from tinnitus and thereby an increased effort to decrease it. The precuneus, a medial parietal region with widespread cortical and subcortical connections, plays a central role in the modulation of conscious processes and has been found to be activated during various forms of imagery[53]. Enhanced coupling could be a sign of cross-modal plasticity (similar to that seen in deaf or blind patients) attempting to reduce the gain of the tinnitus sensation (as part of a 'noise cancellation system' suggested previously[42]). Visual brain regions might be responding to the internal sensation of the tinnitus signal[15] by trying to reduce involuntary attention to it[21,54]. Alterations in the visual network are, therefore, mostly thought of as effects of the tinnitus rather than a cause of it[33]. Indeed, various other studies have shown cross-modal effects with involvement of visual brain areas in chronic tinnitus[13,15,19,21,38,45,54]. Some studies even suggest that tinnitus can be triggered or modulated by inputs from other sensory modalities or sensorimotor systems such as the visuo-motor system[55,56]. Hence, visual areas may also serve as potential target areas for interventions, for instance neuromodulatory therapies. Possible intervention strategies may also involve attention-demanding visual tasks such as video games since those may aid in alleviating concentration difficulties and reducing tinnitus distress[39]. However, additional research is needed to clarify the role of visual areas in chronic tinnitus.

Limitations of the study
There are some limitations of the study. First of all, it is relevant to note that in resting-state fMRI studies, the data are collected during continuous scanning, i.e. there is constant scanner noise. This scanner noise might have interfered with the tinnitus perception, as it could have either masked or exacerbated the tinnitus sensation. In addition, stress and anxiety are known to modulate tinnitus loudness and distress. However, we did not assess these possible effects, which could start well in advance of the actual study. To further assess stress and distress levels of the patients, measuring physiological data such as heart rate variability, blood pressure, or respiratory indicators might provide additional information. Moreover, it is unclear whether the observed alterations reflect underlying changes contributing to the cause of tinnitus or whether they arise as a consequence of tinnitus[33]. An answer to this question is difficult to determine solely on the basis of correlational analyses. Further, tinnitus involves a complex interaction of hearing abilities, age, distress, and cognitive components[22]. Longitudinal studies may aid in disentangling this complexity as well as making inferences about causality of neural alterations in chronic tinnitus.

Conclusion
This is the first study providing evidence of associations between general cognitive abilities assessed by the MoCa and resting-state functional connectivity of the default mode network and the precuneus in tinnitus patients. Decreased coupling of the default mode network and precuneus (a medial parietal region) was observed with the superior parietal lobule, the supramarginal gyrus (in the inferior parietal lobule), and the orbitofrontal cortex, with decreasing MoCa values. Further, tinnitus distress correlated positively with resting-state functional connectivity between precuneus and lateral occipital complex. The orbitofrontal cortex, together with the superior parietal lobule and the supramarginal gyrus, is thought to be engaged in compensatory processes attenuating the tinnitus signal. We argue that disruptions of its resting-state connectivity are related to cognitive abilities in chronic tinnitus, because the affected areas are involved in decreasing the intensity of the tinnitus sensation. Hence, those resources are occupied and no longer available for concurrent cognitive operations. Further, the increased coupling of the precuneus with increased tinnitus distress might be a sign of compensatory mechanisms attempting to decrease the tinnitus sensation (as part of a 'noise cancellation system'). Based on our results, we want to stress the importance of including assessments of cognitive abilities in tinnitus research in the future. Furthermore, future studies should aim at replicating previous findings by using similar acquisition paradigms, seed regions and analysis methods across studies, which might help in identifying possible biomarkers for tinnitus. This is of crucial importance in order to advance treatment options for tinnitus or evaluating the efficacy of tinnitus interventions.

Methods
Participants. 20 tinnitus patients and 20 control participants volunteered in the study. The tinnitus patients and control participants were matched in terms of age and sex. Each group comprised 7 female and 13 male participants. The mean age in tinnitus patients was 58.5 ($\pm$9.82) years and the mean age in the control group was 57.7 ($\pm$10.7) years.

The participants were recruited from previous studies in our lab as well as through social networks and local advertisements. The following groups were excluded: pediatric populations, individuals with HIV, individuals with history of seizures or other neurological disorders, with MRI-incompatible implants, with significant ear asymmetries, those with exposure to loud noise 24 h prior to testing, and pregnant women.

Ethics declarations. The approval for the study was obtained by the Institutional Review Board at Georgetown University, and the study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants gave written and informed consent and were paid for participating in this study.

Audiometric assessment. Pure-tone thresholds of the frequencies ranging from 250 Hz to 16 kHz were assessed in a soundproof chamber at the Division of Audiology and Hearing Research at Medstar Georgetown University Medical Center. Pure-tone audiograms averaged over both ears for the two groups are depicted in Fig. 4. Hearing thresholds at 3 kHz and 4 kHz as well as the mean hearing loss between 250 Hz and 8 kHz ($T(38) = 2.194$, $p = 0.034$) differed significantly between tinnitus patients and control subjects. Hearing thresholds were therefore included in the between-group analysis (see "Data analysis").

Behavioral assessment. All participants filled in questionnaires assessing anxiety, depression and emotional distress: The Patient Health Questionnaire 9 [PHQ9][57], the Generalized Anxiety Disorder Questionnaire [GAD7][58], and the Hospital Anxiety and Depression Scale [HADS][59]. Every participant conducted the Modified Khalfa Hyperacusis Questionnaire as well[60]. Moreover, tinnitus patients completed the Tinnitus Handicap Inventory [THI][61], the Tinnitus Sample Case History Questionnaire [TSCHQ][62], and the Tinnitus Functional Index [TFI][63]. In addition, general cognitive abilities were assessed with the Montreal Cognitive Assessment [MoCA][64], and a two-back task was conducted as a measure of working memory (including numbers, duration: 10 min).

Data acquisition. MRI data were acquired by a 3 T whole-body Siemens Magnetom Prisma MRI machine with a 64-channel head coil. Resting-state data were recorded from all participants while fixating a black dot presented centrally on a grey screen. T_2*-weighted images were acquired with a gradient echo planar imaging (EPI)

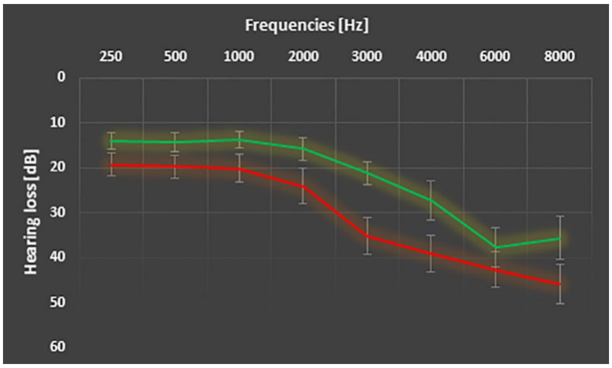

Figure 4. Average pure-tone audiograms for tinnitus patients (red) and control subjects (green) averaged over both ears. Error bars denote standard error of the mean.

sequence (530 volumes, TR = 1430 ms, TE = 35 ms, voxel size = 2.0 × 2.0 × 1.8 mm, flip angle 30 degrees, 68 slices). Structural images were acquired with a 3-D T1-weighted sequence (MP-RAGE, TR = 1900 ms, TE = 2.52 ms, voxel size = 1.0 × 1.0 × 1.0 mm^3, flip angle 9 degrees, 160 sagittal slices).

Data analysis. Resting-state functional connectivity analyses were done in SPM12 and CONN version 20b[31] based on Matlab 2020b. Preprocessing in SPM included spatial realignment estimation, slice-time correction, co-registration, normalization to the Montreal Neurological Institute space using parameters obtained from segmentation of the anatomical T1-weighted image and smoothing (full-width-at-half-maximum = 8 mm). This was followed by preprocessing in CONN including detrending, band-pass filtering (0.008–0.09 Hz), functional outlier detection (Artifact detection tools-based scrubbing[65]) and nuisance regression (motion, mean white matter and cerebrospinal fluid). To ensure data quality, a threshold of 30% of invalid/outlier scans detected with ART was set as exclusion criterion. No subject was excluded (mean 0.009 ± 0.015% outlier scans).

For the group analysis, each subject's seed-to-voxel connectivity maps of a specific seed to the whole brain (Fisher-transformed correlation coefficients) were entered into a second-level analysis. On the group level, between-subject comparisons (tinnitus patients versus control participants) were performed (corrected for hearing loss). Further, a multiple linear regression analysis with values from the cognitive tasks (MOCA and two-back task) and for tinnitus distress (THI and TFI) within the tinnitus group was conducted. This analysis was controlled for age and sex because of the inhomogeneous tinnitus group (age range 29–71 years; 7 female and 13 male).

Seed regions included the auditory cortex and the precuneus as well as the default mode network, salience network, and dorsal attention network. For the correlation analysis with tinnitus distress, we further used the right middle temporal gyrus as a seed. The seed areas for the auditory cortex (left and right Brodmann areas 41 and 42) and the right middle temporal gyrus were defined using the Automated Anatomical Labeling (AAL) ROI-Library within the Wake Forest University (WFU) PickAtlas[66–68]. Masks of the default mode, salience and dorsal attention network seeds as well as the precuneus were provided by the atlas implemented in CONN (the FSL Harvard–Oxford atlas was used for cortical and subcortical areas).

All nodes of a network were equally weighted, contributing jointly to the seed network's connectivity. Effects were determined to be significant when passing a threshold of $p < 0.05$ (FWE cluster size inference with $p < 0.001$ cluster-forming threshold). Bonferroni-correction was applied to correct for multiple comparisons (i.e. five seeds; for tinnitus distress six seeds). Peak coordinates are reported in MNI space.

Data availability

The datasets for this study can be found in the OSF project "Tinnitus as a network problem – plasticity in anatomical and functional connectivity": https://osf.io/2nse8/. Data analysis was preregistered on OSF on July 20, 2021 and can be found at https://osf.io/xhsm5. A preprint version of this manuscript was published on OSF on https://osf.io/r83nw.

Received: 25 October 2022; Accepted: 29 March 2023
Published online: 07 April 2023

References

1. Bauer, C. A. Tinnitus. *N. Engl. J. Med.* **378**, 1224–1231 (2018).
2. Chang, N. C. *et al.* Prevalence of persistent tinnitus and dizziness in an elderly population in southern Taiwan. *J. Int. Adv. Otol.* **15**, 99–105 (2019).
3. Chen, Q., Lv, H., Chen, Y.-C., Song, J.-J. & Wang, Z. Editorial: Neuroimaging approaches to the study of tinnitus and hyperacusis. *Front. Neurosci.* **15**, 700670 (2021).
4. Knipper, M. *et al.* The neural bases of tinnitus: Lessons from deafness and cochlear implants. *J. Neurosci.* **40**, 7190–7202 (2020).
5. Brueggemann, P. *et al.* Dimensions of tinnitus-related distress. *Brain Sci.* **12**, 275 (2022).

6. Noreña, A. J. An integrative model of tinnitus based on a central gain controlling neural sensitivity. *Neurosci. Biobehav. Rev.* **35**, 1089–1109 (2011).
7. Lee, M. H., Smyser, C. D. & Shimony, J. S. Resting-state fMRI: A review of methods and clinical applications. *AJNR Am. J. Neuroradiol.* **34**, 1866–1872 (2013).
8. Schecklmann, M., Landgrebe, M. & Langguth, B. Phenotypic characteristics of hyperacusis in tinnitus. *PLoS ONE* **9**, e86944 (2014).
9. Leaver, A. M., Seydell-Greenwald, A. & Rauschecker, J. P. Auditory–limbic interactions in chronic tinnitus: Challenges for neuroimaging research. *Hear. Res.* **334**, 49–57 (2016).
10. Feng, Y. *et al.* Increased resting-state cerebellar-cerebral functional connectivity underlying chronic tinnitus. *Front. Aging Neurosci.* **10**, 59 (2018).
11. Hullfish, J., Abenes, I., Yoo, H. B., De Ridder, D. & Vanneste, S. Frontostriatal network dysfunction as a domain-general mechanism underlying phantom perception. *Hum. Brain Mapp.* **40**, 2241–2251 (2019).
12. Lanting, C. P., de Kleine, E., Langers, D. R. M. & van Dijk, P. Unilateral tinnitus: Changes in connectivity and response lateralization measured with FMRI. *PLoS ONE* **9**, e110704 (2014).
13. Maudoux, A. *et al.* Auditory resting-state network connectivity in tinnitus: A functional MRI study. *PLoS ONE* **7**, e36222 (2012).
14. Xu, J.-J. *et al.* Chronic tinnitus exhibits bidirectional functional dysconnectivity in frontostriatal circuit. *Front. Neurosci.* **13**, 1299 (2019).
15. Chen, Y.-C. *et al.* Abnormal resting-state functional connectivity of the anterior cingulate cortex in unilateral chronic tinnitus patients. *Front. Neurosci.* **12**, 9 (2018).
16. Chen, Y.-C. *et al.* Alterations of the default mode network and cognitive impairment in patients with unilateral chronic tinnitus. *Quant. Imaging Med. Surg.* **8**, 1020–1029 (2018).
17. Husain, F. T. & Schmidt, S. A. Using resting state functional connectivity to unravel networks of tinnitus. *Hear. Res.* **307**, 153–162 (2014).
18. Schmidt, S. A., Carpenter-Thompson, J. R. & Husain, F. Connectivity of precuneus to the default mode and dorsal attention networks: A possible invariant marker of long-term tinnitus. *NeuroImage Clin.* https://doi.org/10.1016/j.nicl.2017.07.015 (2017).
19. Han, Q. *et al.* Disrupted local neural activity and functional connectivity in subjective tinnitus patients: Evidence from resting-state fMRI study. *Neuroradiology* **60**, 1193–1201 (2018).
20. Golm, D., Schmidt-Samoa, C., Dechent, P. & Kröner-Herwig, B. Neural correlates of tinnitus related distress: An fMRI-study. *Hear. Res.* **295**, 87–99 (2013).
21. Chen, Y.-C. *et al.* Resting-state brain abnormalities in chronic subjective tinnitus: A meta-analysis. *Front. Hum. Neurosci.* **11**, 22 (2017).
22. Brueggemann, P. *et al.* On the relationship between tinnitus distress, cognitive performance and aging. *Prog. Brain Res* **262**, 263–285 (2021).
23. Heeren, A. *et al.* Tinnitus specifically alters the top-down executive control sub-component of attention: Evidence from the attention network task. *Behav. Brain Res.* **269**, 147–154 (2014).
24. Trevis, K. J., McLachlan, N. M. & Wilson, S. J. Cognitive mechanisms in chronic tinnitus: Psychological markers of a failure to switch attention. *Front. Psychol.* **7**, 1262 (2016).
25. Araneda, R. *et al.* Altered top-down cognitive control and auditory processing in tinnitus: Evidences from auditory and visual spatial stroop. *Restor. Neurol. Neurosci.* **33**, 67–80 (2015).
26. Araneda, R. *et al.* A key role of the prefrontal cortex in the maintenance of chronic tinnitus: An fMRI study using a Stroop task. *Neuroimage Clin.* **17**, 325–334 (2018).
27. Wang, Y. *et al.* The characteristics of cognitive impairment in subjective chronic tinnitus. *Brain Behav.* **8**, e00918 (2018).
28. Mohamad, N., Hoare, D. J. & Hall, D. A. The consequences of tinnitus and tinnitus severity on cognition: A review of the behavioural evidence. *Hear. Res.* **332**, 199–209 (2016).
29. Tegg-Quinn, S., Bennett, R. J., Eikelboom, R. H. & Baguley, D. M. The impact of tinnitus upon cognition in adults: A systematic review. *Int. J. Audiol.* **55**, 533–540 (2016).
30. Araneda, R., De Volder, A. G., Deggouj, N. & Renier, L. Altered inhibitory control and increased sensitivity to cross-modal interference in tinnitus during auditory and visual tasks. *PLoS ONE* **10**, e0120387 (2015).
31. Whitfield-Gabrieli, S. & Nieto-Castanon, A. Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* **2**, 125–141 (2012).
32. Agcaoglu, O., Wilson, T. W., Wang, Y.-P., Stephen, J. & Calhoun, V. D. Resting state connectivity differences in eyes open versus eyes closed conditions. *Hum. Brain Mapp.* **40**, 2488–2498 (2019).
33. Kok, T. E. *et al.* Resting-state networks in tinnitus: A scoping review. *Clin. Neuroradiol.* https://doi.org/10.1007/s00062-022-01170-1 (2022).
34. Kleinjung, T. & Langguth, B. Avenue for future tinnitus treatments. *Otolaryngol. Clin. N. Am.* **53**, 667–683 (2020).
35. Refat, F. *et al.* Co-occurrence of hyperacusis accelerates with tinnitus burden over time and requires medical care. *Front. Neurol.* **12**, 627522 (2021).
36. Minami, S. B., Oishi, N., Watabe, T., Wasano, K. & Ogawa, K. Age-related change of auditory functional connectivity in Human Connectome Project data and tinnitus patients. *Laryngoscope Investig. Otolaryngol.* **5**, 132–136 (2020).
37. De Ridder, D. *et al.* In *Tinnitus—An Interdisciplinary Approach Towards Individualized Treatment* (eds. Schlee, W. *et al.*) 1–25 (Elsevier B.V., 2021) https://doi.org/10.1016/bs.pbr.2020.12.002.
38. Song, J.-J., De Ridder, D., Schlee, W., Van de Heyning, P. & Vanneste, S. "Distressed aging": The differences in brain activity between early- and late-onset tinnitus. *Neurobiol. Aging* **34**, 1853–1863 (2013).
39. Han, L. *et al.* Abnormal baseline brain activity in patients with pulsatile tinnitus: A resting-state fMRI study. *Neural Plast.* **2014**, e549162 (2014).
40. Husain, F. T., Akrofi, K., Carpenter-Thompson, J. R. & Schmidt, S. A. Alterations to the attention system in adults with tinnitus are modality specific. *Brain Res.* **1620**, 81–97 (2015).
41. Kringelbach, M. L. The human orbitofrontal cortex: Linking reward to hedonic experience. *Nat. Rev. Neurosci.* **6**, 691–702 (2005).
42. Rolls, E. T. The neuroscience of emotional disorders. *Handb. Clin. Neurol.* **183**, 1–26 (2021).
43. Rauschecker, J. P., Leaver, A. M. & Mühlau, M. Tuning out the noise: Limbic-auditory interactions in tinnitus. *Neuron* **66**, 819–826 (2010).
44. Rauschecker, J. P., May, E. S., Maudoux, A. & Ploner, M. Frontostriatal gating of tinnitus and chronic pain. *Trends Cogn. Sci.* **19**, 567–578 (2015).
45. Leaver, A. M. *et al.* Intrinsic network activity in tinnitus investigated using functional MRI: Intrinsic Networks in Tinnitus. *Hum. Brain Mapp.* **37**, 2717–2735 (2016).
46. Schlee, W. *et al.* Mapping cortical hubs in tinnitus. *BMC Biol.* **7**, 80 (2009).
47. Carpenter-Thompson, J. R., Schmidt, S. A. & Husain, F. T. Neural plasticity of mild tinnitus: An fMRI investigation comparing those recently diagnosed with tinnitus to those that had tinnitus for a long period of time. *Neural Plast.* **2015**, 161478 (2015).
48. Carpenter-Thompson, J. R., Schmidt, S., McAuley, E. & Husain, F. T. Increased frontal response may underlie decreased tinnitus severity. *PLoS ONE* **10**, e0144419 (2015).
49. Chen, Y.-C. *et al.* Altered intra- and interregional synchronization in resting-state cerebral networks associated with chronic tinnitus. *Neural Plast.* **2015**, 475382 (2015).

50. Gentil, A. *et al.* Alterations in regional homogeneity in patients with unilateral chronic tinnitus. *Trends Hear.* **23**, 2331216519830237 (2019).
51. Knipper, M., Mazurek, B., van Dijk, P. & Schulze, H. Too blind to see the elephant? Why neuroscientists ought to be interested in tinnitus. *J. Assoc. Res. Otolaryngol.* **22**, 609–621 (2021).
52. Chen, Y.-C. *et al.* Tinnitus distress is associated with enhanced resting-state functional connectivity within the default mode network. *Neuropsychiatr. Dis. Treat.* **14**, 1919–1927 (2018).
53. Rosemann, S. & Rauschecker, J. P. Neuroanatomical alterations in middle frontal gyrus and the precuneus related to tinnitus and tinnitus distress. *Hear. Res.* https://doi.org/10.1016/j.heares.2022.108595 (2022).
54. Cavanna, A. E. & Trimble, M. R. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain* **129**, 564–583 (2006).
55. Burton, H. *et al.* Altered networks in bothersome tinnitus: A functional connectivity study. *BMC Neurosci.* **13**, 3 (2012).
56. Cacace, A. T. Expanding the biological basis of tinnitus: Crossmodal origins and the role of neuroplasticity. *Hear. Res.* **175**, 112–132 (2003).
57. Kroenke, K., Spitzer, R. L. & Williams, J. B. The PHQ-9: Validity of a brief depression severity measure. *J. Gen. Intern. Med.* **16**, 606–613 (2001).
58. Spitzer, R. L., Kroenke, K., Williams, J. B. W. & Löwe, B. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch. Intern. Med.* **166**, 1092–1097 (2006).
59. Zigmond, A. S. & Snaith, R. P. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* **67**, 361–370 (1983).
60. Khalfa, S. *et al.* Psychometric normalization of a hyperacusis questionnaire. *ORL* **64**, 436–442 (2002).
61. Newman, C. W., Jacobson, G. P. & Spitzer, J. B. Development of the tinnitus handicap inventory. *Arch. Otolaryngol. Head Neck Surg.* **122**, 143–148 (1996).
62. Langguth, B. *et al.* Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006. *Prog. Brain Res.* **166**, 525–536 (2007).
63. Henry, J. A. *et al.* Tinnitus Functional Index: Development, validation, outcomes research, and clinical application. *Hear. Res.* **334**, 58–64 (2016).
64. Nasreddine, Z. S. *et al.* The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* **53**, 695–699 (2005).
65. Whitfield-Gabrieli, S., Nieto-Castanon, A. & Ghosh, S. Artifact detection tools (ART). *Cambridge, MA. Release Version* vol. 7, 11 (2011).
66. Maldjian, J. A., Laurienti, P. J. & Burdette, J. H. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *Neuroimage* **21**, 450–455 (2004).
67. Maldjian, J. A., Laurienti, P. J., Kraft, R. A. & Burdette, J. H. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19**, 1233–1239 (2003).
68. Tzourio-Mazoyer, N. *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**, 273–289 (2002).

Acknowledgements

The authors wish to thank Anjul Bhangu for assistance in behavioral data curation.

Author contributions

S.R. designed the study, was involved in data acquisition, analyzed the data and wrote the manuscript. J.P.R. designed the study, was involved in interpretation of the results and revised the manuscript. Both authors approved the final version of the manuscript.

Funding

SR is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; RO6114/1-1).

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to S.R.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.