Canadian Academy of Audiology
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Cognitive Neuroscience of Tinnitus

Speaker: Dr. Fatima T. Husain, Professor, Department of Speech and Hearing Science, University of Illinois Urbana-Champaign

Host: Stephen G. Lomber, Ph.D., Professor of Physiology at McGill University, CAA Board Member

2023-04-26

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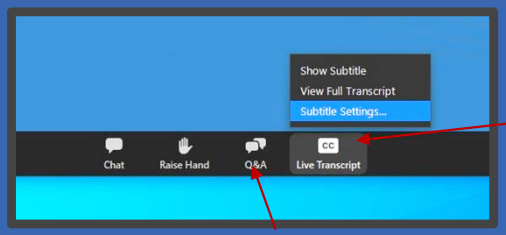

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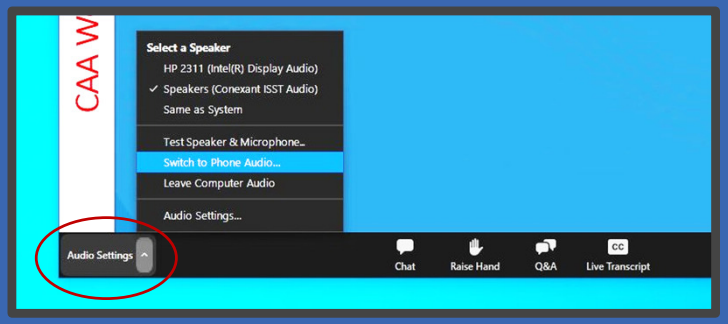

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Moderator – Stephen G. Lomber, Ph.D., Professor of Physiology at McGill University, CAA Board Member

Stephen G. Lomber, Ph.D. is a Professor of Physiology at McGill University and directs the Cerebral Systems Laboratory. Dr. Lomber is the Associate Editor of Hearing Research and Scientific Program Chair for the Annual Meeting of the Association for Research in Otolaryngology (ARO).

He is a past chair of the Gordon Research Conference on the Auditory System and the International Conference on Auditory Cortex, and a CAA Board Member.

Speaker: Dr. Fatima T. Husain, Professor in the Department of Speech and Hearing Science, University of Illinois Urbana-Champaign

Dr. Fatima T. Husain is a Professor in the Department of Speech and Hearing Science, University of Illinois Urbana-Champaign. She is also affiliated with the Neuroscience Program and the Beckman Institute for Advance Science and Technology.

Dr. Husain's research program is centered around three major themes: (1) normal audition and speech perception, (2) disorders of the auditory system, particularly hearing loss and tinnitus, and (3) effects of aging on audition and cognition.

Cognitive neuroscience of tinnitus

Fatima T. Husain, PhD
Professor
Speech and Hearing Science, Neuroscience and
Beckman Institute for Advanced Science and
Technology

UNIVERSITY OF
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URBANA-CHAMPAIGN

Agenda

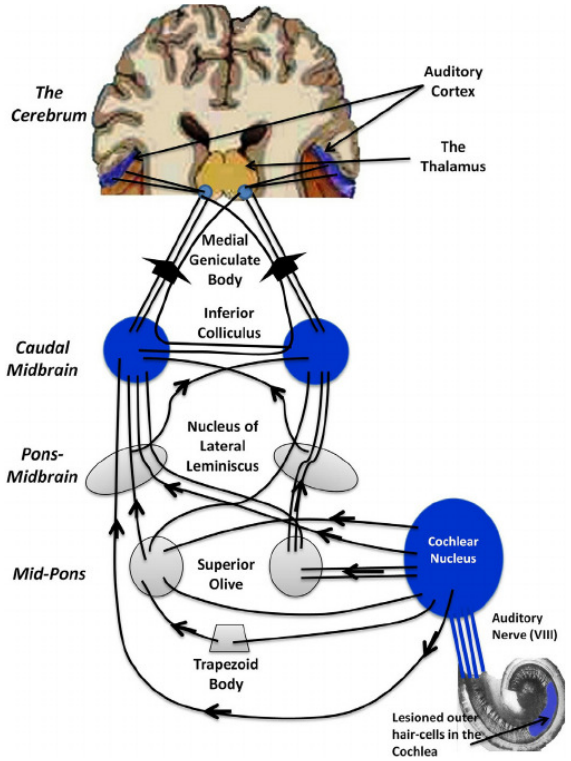
1. Tinnitus – perception and reaction
2. Brain imaging – Magnetic Resonance Imaging, neural networks
3. Alterations in neural networks due to tinnitus presence or tinnitus severity
4. Changes in neural networks due to interventions – hearing aids, mindfulness based cognitive therapy

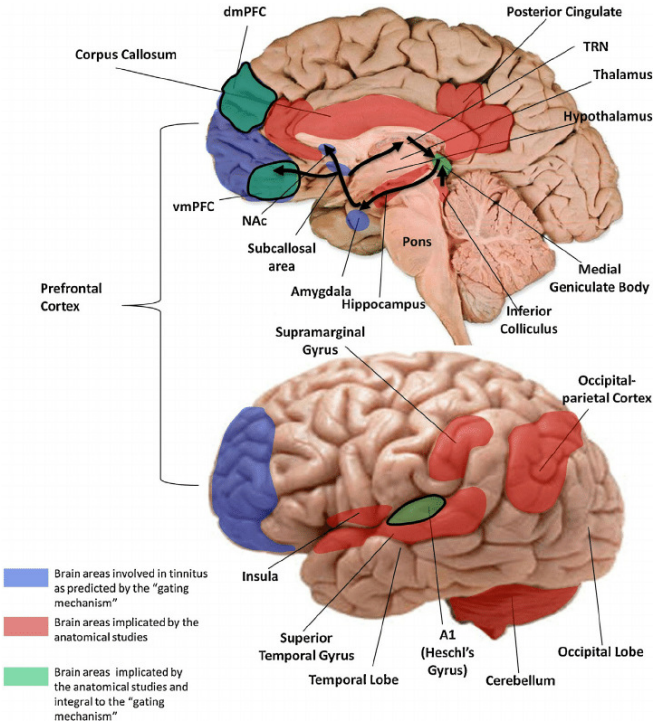
Poll

Tinnitus is known as the conscious perception of sound in the absence of an external source

Percept	Reaction
• Pitch • Loudness • Duration • Laterality • Masking	• Sleep disturbance • Concentration • Communication • Stress • Anxiety • Depression • Suicidal ideation

Possible tinnitus generation sites of tinnitus





Adjamian, Peyman & Hall, Deborah & Palmer, Alan & Allan, Thomas & Langers, Dave. (2014). Neuroanatomical abnormalities in chronic tinnitus in the human brain. Neuroscience and biobehavioral reviews. 45. 10.1016/j.neubiorev.2014.05.013.

Tinnitus severity -> heterogeneity

- …to help patients

Assessing tinnitus severity

Table 1. Nine widely used tinnitus questionnaires[a]

Questionnaire name	Authors and year	Number of items	Response options for each item
Tinnitus Questionnaire	Hallam et al. (1988)	34	3 levels: true, partly true, not true
Tinnitus Handicap Questionnaire	Kuk et al. (1990)	27	100 levels: 100 = strongly agree, 0 = strongly disagree
Tinnitus Severity Scale	Sweetow and Levy (1990)	15	4 levels: wording of response options varies between items
Subjective Tinnitus Severity Scale	Halford and Anderson (1991)	16	2 levels: yes/no
Tinnitus Reaction Questionnaire	Wilson et al. (1991)	26	5 levels: not at all, a little of the time, some of the time, a good deal of the time, almost all the time
Tinnitus Severity Grading	Coles et al. (1992)	9	5 levels: wording of response options varies between items
Tinnitus Severity Index	Meikle (1992) and Meikle et al. (1995)	12	5 levels[b]: never, rarely, sometimes, usually, always
Tinnitus Handicap Inventory	Newman et al. (1996)	25	3 levels: yes, sometimes, no
Intake Interview for Tinnitus Retraining Therapy	Jastreboff and Jastreboff (1999)	12	7 items: 3 levels (always, sometimes, never); 2 items: 100 levels: 0–100% of time; 3 items: 0–10 numeric scale

[a] Each of the nine questionnaires is cited in a separate bibliographic entry (see References).
[b] Original version of Tinnitus Severity Index used more complex response options: six items had three levels, six items had four levels with wording of response options varying between items.

Meikle et al., Progress in Brain Research, 2008

But there are problems…

- No single questionnaire covers every dimension—each questionnaire omitted some dimensions
- All the questionnaires differ in regard to item format, scaling, and wording
- It is difficult to compare treatment effects obtained in different clinics
- No reliable psychoacoustic test of tinnitus

Neural correlates of severity?

- Although there might not be consensus about how exactly to measure severity, we all agree patients' reactions to tinnitus vary
  - Mild to severe spectrum
- No objective measurement of tinnitus severity
- Neural correlates may complement self-report
  - use brain imaging
  - more objective

Using brain imaging in tinnitus

Brain Imaging Studies

1. Provide information about neural mechanisms subserving both tinnitus generation and persistence
2. Objective measures of a subjective disorder in a heterogeneous population
3. Estimate effect of interventions
4. Provide information necessary to develop new therapies
5. Dissociate from impact of hearing loss
6. Advance theory of tinnitus

Assessing tinnitus severity using fMRI

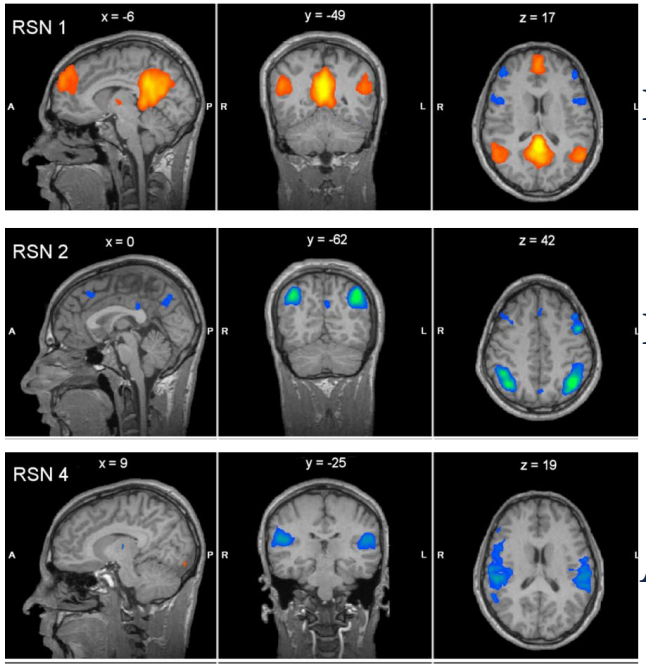
- Auditory processing network
- Emotion processing network
- Attention networks
- Default mode network
- Interaction between these networks

Brain Function: Resting state fMRI

Resting State and Tinnitus

Tinnitus is uniquely suited to being studied via the resting state than other disorders because the presence and awareness of tinnitus puts the participant in a non-resting state.

Networks revealed



DMN

DAN

AUD

- Spontaneous fluctuations in the fMRI response
- Fluctuations can be correlated to show coherent networks

- DMN= default mode network, DAN = dorsal attention network, AUD = auditory network

Mantini et al.,. 2007

Default Mode Network function

- **"Sentinel hypothesis"**
  - Monitor external environment
- **"Internal mentation hypothesis"**
  - Self-reflective actions—envisioning the future, theory of mind, autobiographical memory

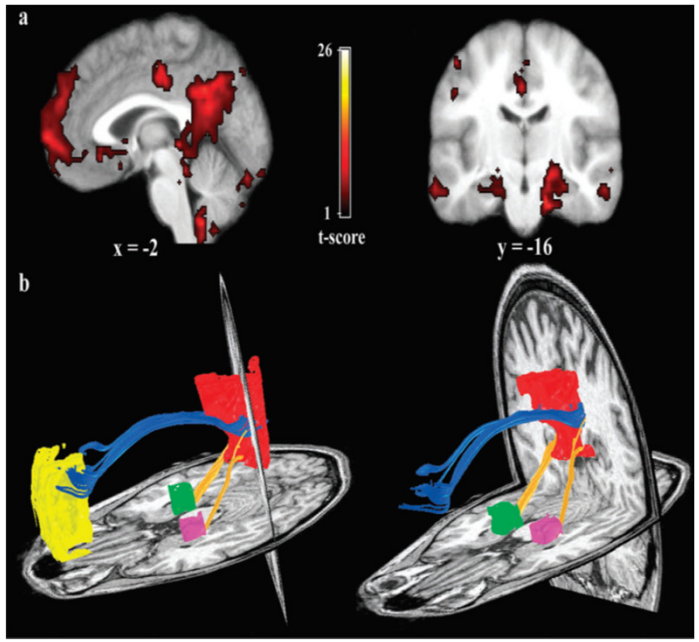
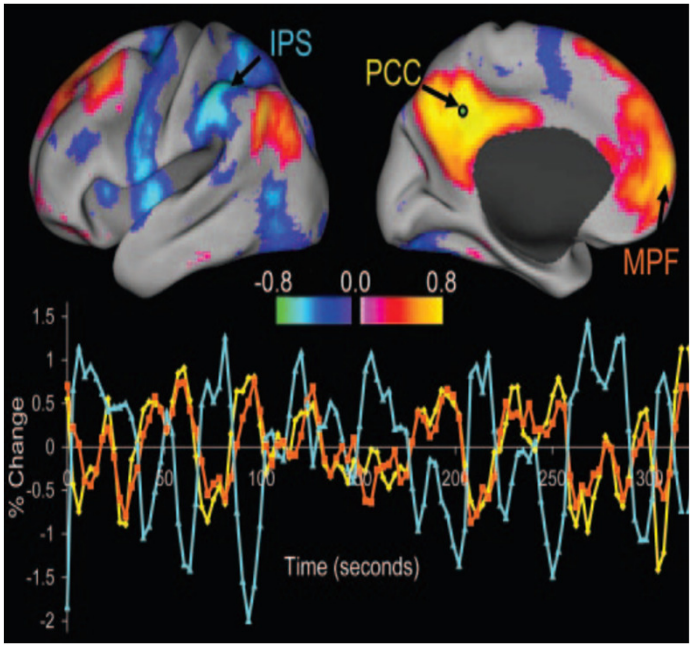


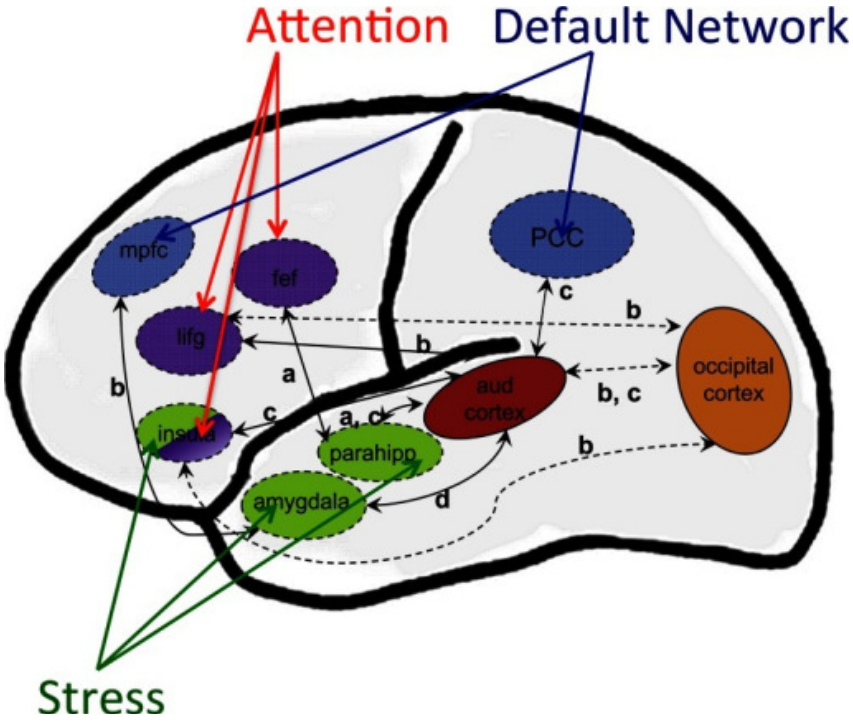
Image from Greicius et al., 2009, Cerebral Cortex

Default mode and attention networks: anti-correlated

- **Suppression of DMN during a task is important**
- **This relationship is disrupted outside of young healthy individuals**



Summary of the first 6 studies



Eggermont and Roberts, Cell Tissue Res, 2014
Tinnitus: animal models and findings in humans.

Summary of ~100 studies

Some commonalities but vastly heterogeneous results

So what's going on here?

- **Why is there little consensus?**
- **Is it the heterogeneity, i.e. different tinnitus subgroups?**
  - Age? Severity? Lateralization? Time/cause of onset? Depression/anxiety? Genetics? Other comorbid factors?

- **Or is it the tool?**
  - Even when using the same tool (e.g., fMRI) different data collection and analytical techniques

Replication in a heterogeneous patient population

- Replication crisis
- Reliability of a tool

Solution 1:

- **Compare functional connectivity across tinnitus subgroups to identify potential biomarkers of tinnitus**
  - Data pooled from a series of small studies
  - Keep acquisition same as much as possible, same analytical technique

Demographics

Recent onset tinnitus

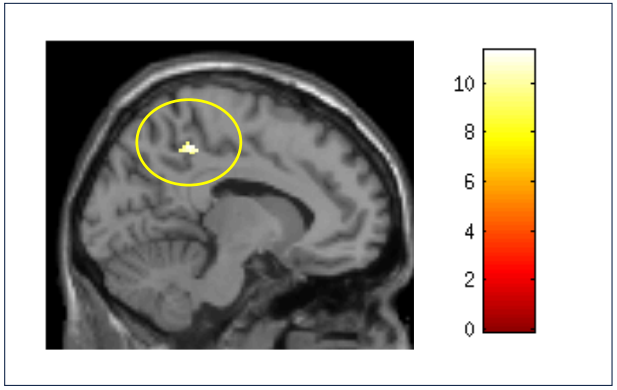
Long term tinnitus

	NH	HL	MLTIN1	MRTIN	MLTIN 2	BLTIN
# Subjects	15	13	12	13	18	16
3T Siemens Magnet	Allegra	Allegra	Allegra	Allegra	Trio	Trio
TIN severity (THI score)	N/A	N/A	8.3 ±6.8	15.7 ±10.2	10.8±6	33.4 ±9.1
TIN duration	N/A	N/A	>1 year	>6 months, < 1 year	>1 year	>1 year
Relevant Publication(s)	Schmidt et al., 2013	Schmidt et al., 2013	Schmidt et al., 2013; Carpenter-Thomspon et al., 2015	Carpenter-Thomspon et al., 2015	Schmidt et al., 2017	Schmidt et al., 2017

Mild tinnitus

Moderate tinnitus

ANOVA results

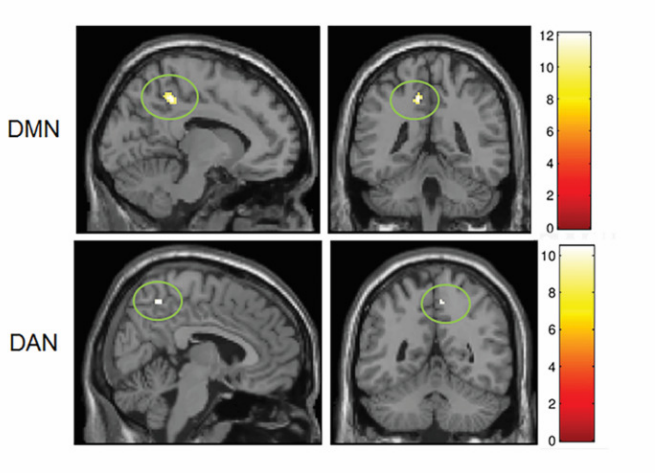


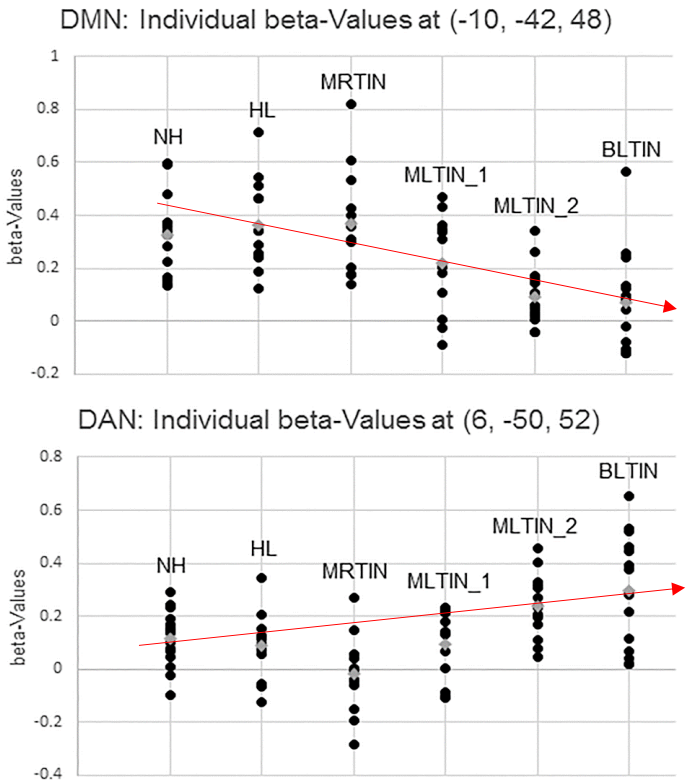
One area of significance at $p<0.05$ FWE corrected:

precuneus

episodic memory, consciousness, visuospatial memory, reflections on self

Precuneus





Schmidt, S. A., Carpenter-Thompson, J., & Husain, F. T. (2017). Connectivity of precuneus to the default mode and dorsal attention networks: A possible invariant marker of long-term tinnitus. NeuroImage. Clinical, 16, 196–204.

Conclusions

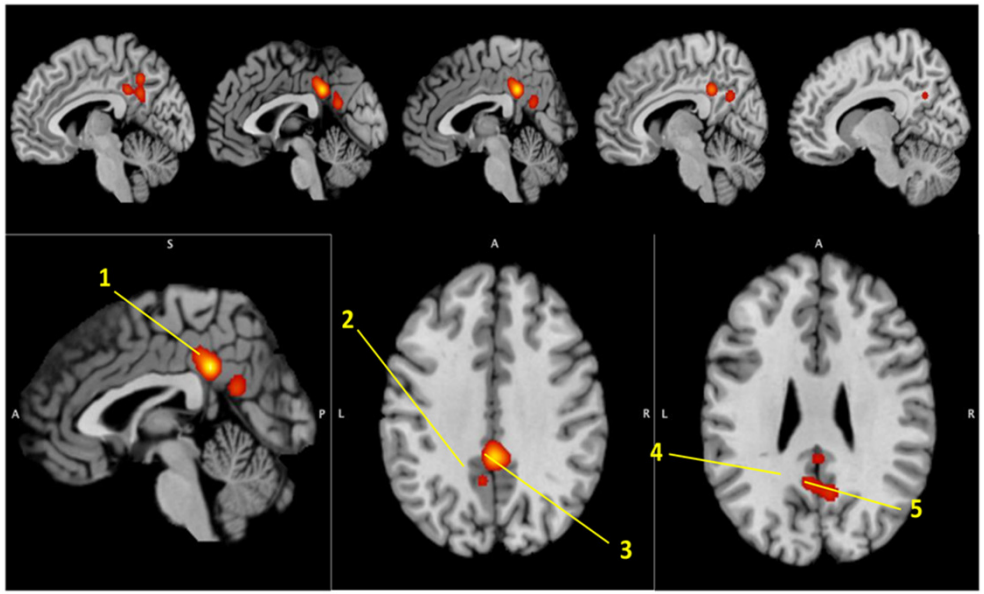
Reduced correlation between the default mode network and the precuneus may indicate the presence of tinnitus

- Tinnitus must be long-term (> 1 year) for this to manifest
- Tinnitus severity may mediate the strength of this reduction

Solution 1A:

- **Compare functional connectivity across tinnitus subgroups to identify potential biomarkers of tinnitus**
  - Data pooled from a series of small studies
  - ~~Keep acquisition same as much as possible, same analytical technique~~
  - ➔ Meta-analysis

Quantitative meta-analysis of resting state and gray matter studies



17 resting-state fMRI and 8 VBM reports of tinnitus-associated regional alterations were meta-analyzed using activation likelihood estimation (ALE).

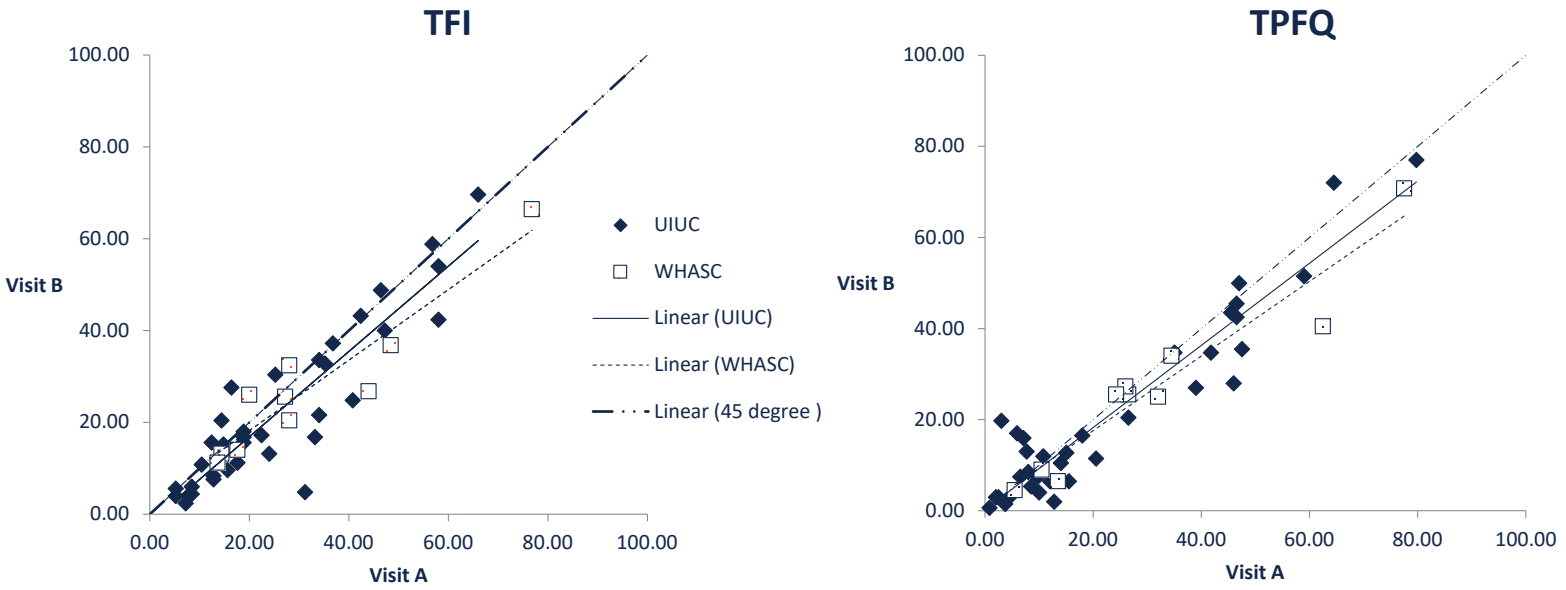
Moring, J. C., Husain, F. T., Gray, J., Franklin, C., Peterson, A. L., Resick, P. A., ... & Fox, P. T. (2022). Invariant structural and functional brain regions associated with tinnitus: A meta-analysis. PloS one, 17(10), e0276140

1 = Cingulate Gyrus; 2 = Precuneus; 3 = Cingulate Gyrus/Precuneus; 4 = Posterior Cingulate/Precuneus; 5 = Posterior Cingulate/Precuneus.

Solution 2:

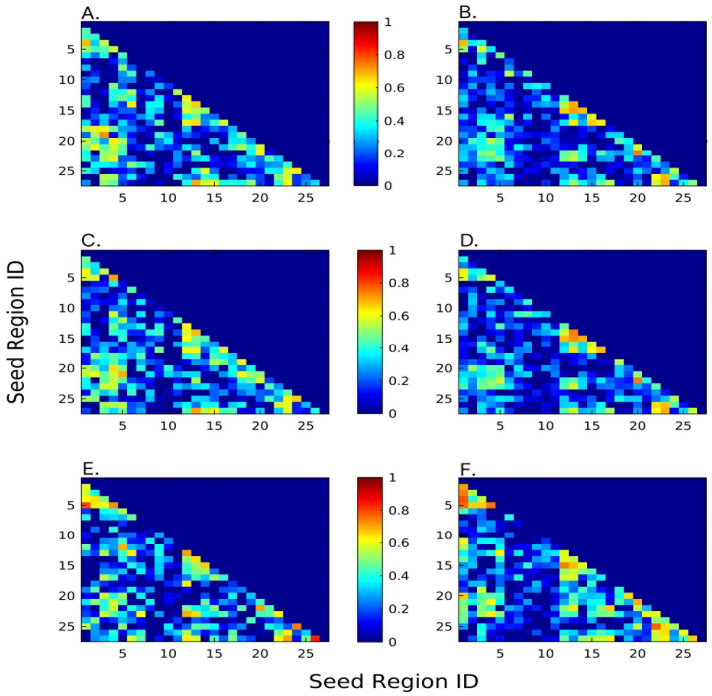
- Test the tool
- Collect data in same individuals, a week apart. Two sites: military (San Antonio, WHASC), civilian, Veteran (Illinois, UIUC)

Funding: Department of Defense



Scatterplot of tinnitus-related handicap values for visits A and B, plotted for each site. TFI: Tinnitus Functional Index, TPFQ: Tinnitus Primary Function Index. Linear trend lines, including a 45 degree line, are also plotted. If the values would be replicable across visits A and B, they would fall on the 45 degree line.

Replication at two Sites: 150 participants



Inter-class correlation values for correlations between all examined seed regions. Each panel represents a different subject group or analysis technique. In general, ICC scores for seed pairs across all subject groups (tinnitus or controls) are consistent, with warm colors appearing in the same areas of the matrices.

Summary

- Resting state functional connectivity appears to be replicable for both controls and participants reporting tinnitus
- Reliable and useful tool to objectively measure impact of tinnitus in the brain
  - Some networks (attention, default) more reliable than others (auditory)
- Over multiple studies and now multiple sites, we are beginning to understand the functional connections and disconnections in the neural networks underlying tinnitus

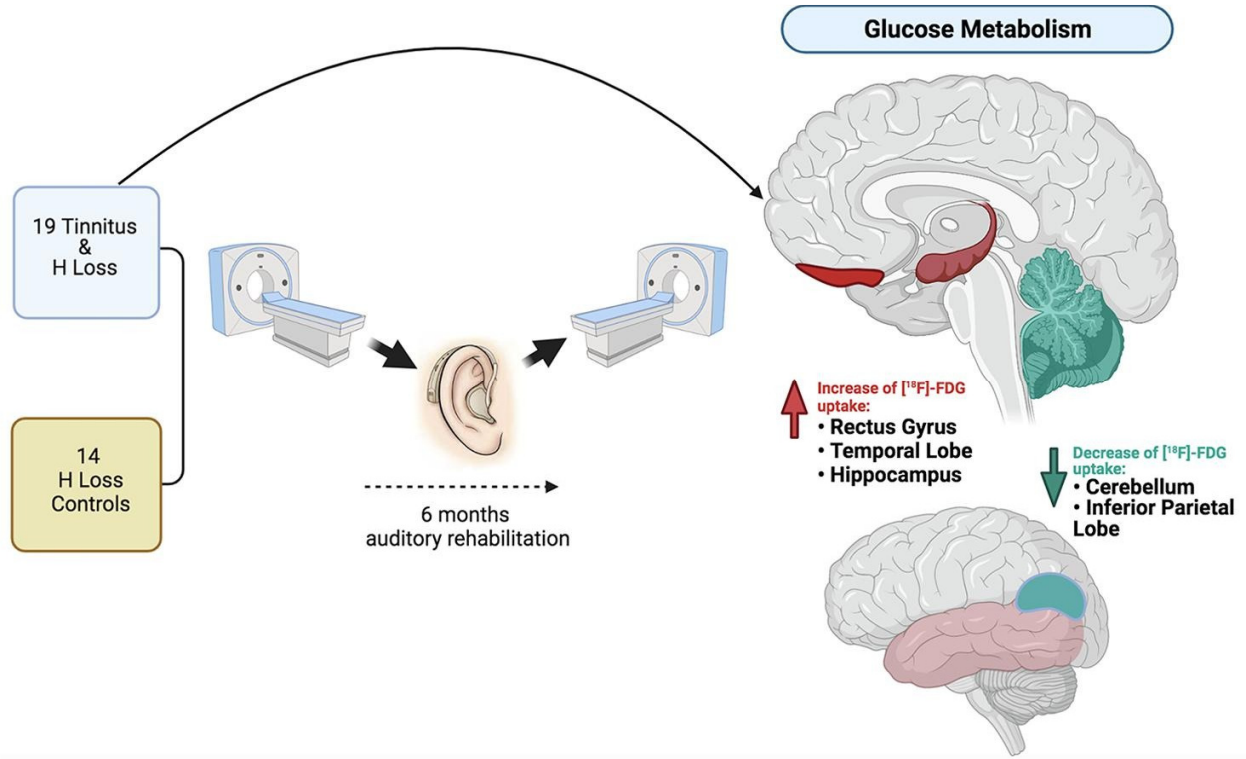
Summary II

- Existence of possible invariant neural signatures of tinnitus
  - Varying across subgroups
  - Use a variety of imaging techniques (~30 papers from our group; meta-analysis)
- Develop automated programs to differentiate patients with tinnitus from controls
  - See Zimmerman et al., 2018; Shahsavarani et al., 2020
  - Husain et al., 2021 PATENT
- Develop new theoretical models
  - See Husain, 2016; 2021 (book chapter); Khan and Husain (2020)
- Evaluate interventions -- Husain et al., 2019; Zimmerman et al. 2019, Simonetti et a., 2021

⇒Develop new interventions

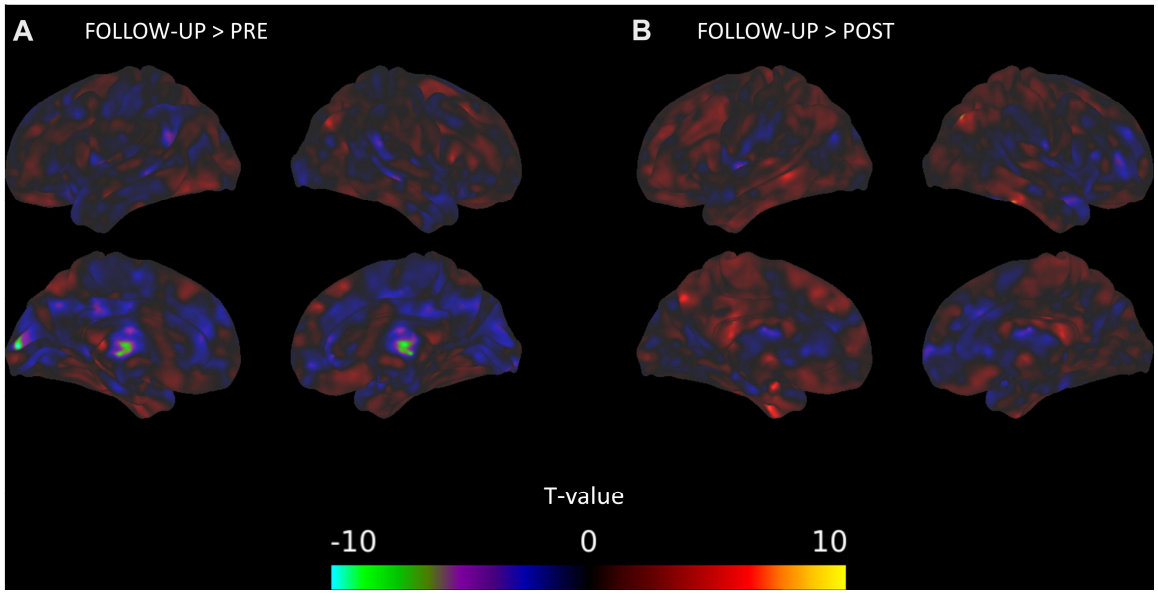
Changes in brain networks due to interventions

Intervention: Hearing Aids



Simonetti, P., Ono, C. R., Godoi Carneiro, C., Ali Khan, R., Shahsavarani, S., Husain, F. T., & Oiticica, J. (2022). Evaluating the efficacy of hearing aids for tinnitus therapy - A Positron emission tomography study. Brain research, 1775, 147728.

Intervention: Mindfulness Based Cognitive Therapy



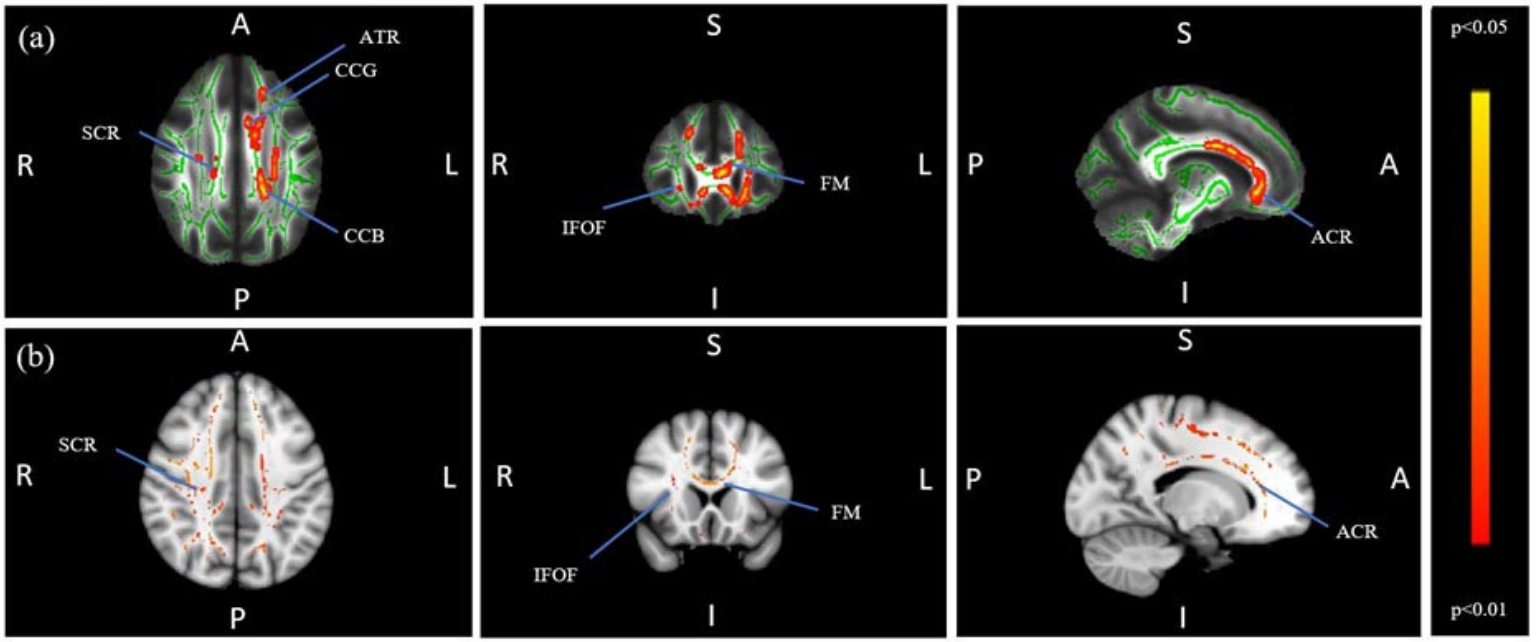
(A) Connectivity between the default mode network (DMN) and clusters in the right thalamus and visual cortex significantly decreases from the pre-intervention session to the follow-up session. (B) Connectivity between the DMN and a cluster in the right angular gyrus significantly increases from the post-intervention session to the follow-up session.

Zimmerman, B., Finnegan, M., Paul, S., Schmidt, S., Tai, Y., Roth, K., Chen, Y., & Husain, F. T. (2019). Functional Brain Changes During Mindfulness-Based Cognitive Therapy Associated With Tinnitus Severity. Frontiers in neuroscience, 13, 747.

Recent advances

- Brain Function
- Brain anatomy
  - Gray matter
  - White matter
  - Blood-flow measures
  - Neurotransmitters

Tracing anatomical and functional connectivity



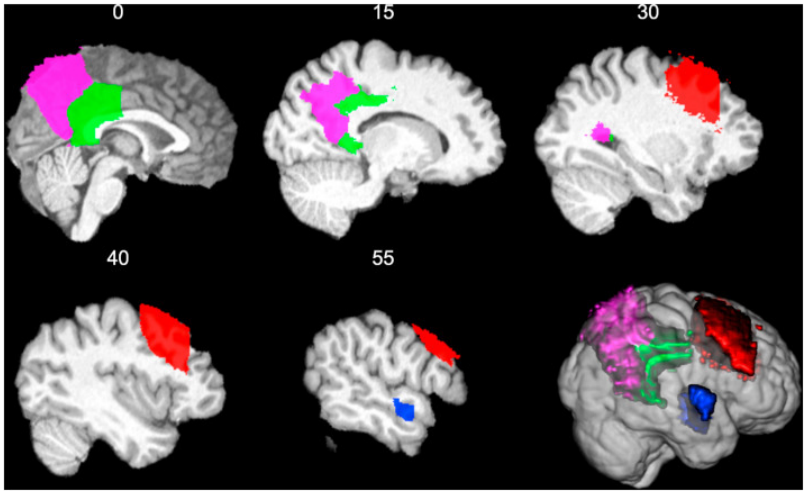
Con > Tin

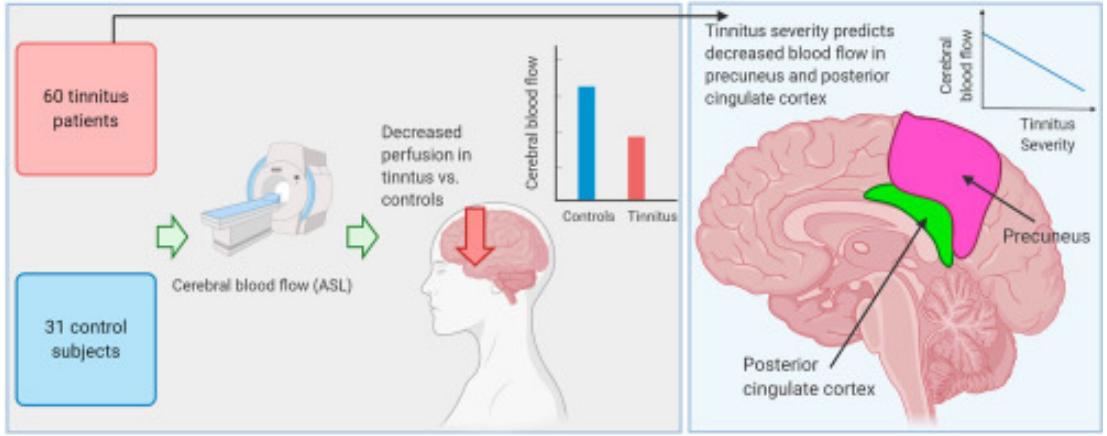
Tin > Con

Khan, R. A., Sutton, B. P., Tai, Y., Schmidt, S. A., Shahsavarani, S., & Husain, F. T. (2021). A large-scale diffusion imaging study of tinnitus and hearing loss. *Scientific reports*, *11*(1), 1-12.

corpus callosum, left anterior thalamic radiation (ATR), bilateral superior longitudinal fasciculus and left inferior longitudinal fasciculus

Arterial Spin Labeling, perfusion data





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. *Current Research in Neurobiology*, *2*, 100010.

Poll

Take home message: Peripheral, Central, One, Several

- Old wisdom: Source of tinnitus is peripheral
- Current wisdom: Source of tinnitus is in central auditory pathways
- Old wisdom: One region generates tinnitus
- Current wisdom: Tinnitus generation and persistence is due to several large-scale neural networks

- Unanswered questions: What causes persistence? How do we separate generation from persistence?
- Partially answered question: What are the neural correlates of the impact of tinnitus (severity)?

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- Support
  - UIUC- AHS/CHAD, Campus Research Board
  - Charitable Organizations: Tinnitus Research Consortium, American Tinnitus Association
  - US Federal Agencies – NIH, DoD

- Members of the Auditory Cognitive Neuroscience Lab
- Collaborators – NIH, UIUC, U. of Iowa, Hearing Center Excellence, Wilford Hall Ambulatory and Surgical Center
- Volunteers!

Questions?

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