Using Brain Imaging Techniques to Find the Tinnitus Signal

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Agenda

• Brain Imaging
  – Functional Magnetic Resonance Imaging
• Measuring tinnitus severity
• Use of brain imaging in tinnitus
  – Objective biomarkers
  – Task-based, Rest-based
  – Neural Networks
    • Auditory network
    • Attention network
    • Emotion processing network
    • Default mode network
  – Replicability, robustness of measures, diagnosis
BRAIN IMAGING
Tools to study the brain: Spatial and Temporal Resolution

Gazzaniga, Ivry & Mangun, *Cognitive Neuroscience*
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
The “Scanner”
**MRI vs. fMRI**

**MRI** studies brain anatomy.

**Functional MRI** (fMRI) studies brain function.
Imaging Structure in the Brain
Imaging Function in the Brain
Stimulus to BOLD

1. Neuronal activity
   - Excitatory activity and inhibitory activity
   - Anaesthetic influence

2. Neurovascular coupling
   - Metabolic signal unknown
   - Anaesthetic influence

3. Haemodynamic response
   - Blood flow
   - Blood oxygenation level
   - Blood volume
   - Haematocrit
   - Magnetic field strength
   - TR, repetition time
   - TE, echo time
   - Spin or gradient echo EPI

4. Detection by MRI scanner

Source: Arthurs & Boniface, 2002, *Trends in Neurosciences*

BOLD = Blood oxygen-level dependent response
**BOLD Time Course**

- **Initial dip**
- **Overshoot**
- **Post stimulus undershoot**

**5-6 seconds**
Activation Statistics

Functional images

~2s

fMRI Signal (% change)

ROI Time Course

Time

Condition

Region of interest (ROI)

~ 5 min

Statistical Map superimposed on anatomical MRI image
Reminder...

NEURAL NETWORKS
Auditory Network

Ascending auditory pathways

- Auditory cortex
- Medial geniculate nucleus
- Inferior colliculus
Emotion processing network
Attention Network
TINNITUS SEVERITY
**Tinnitus** is known as the conscious perception of sound in the absence of an external source.

<table>
<thead>
<tr>
<th>Percept</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitch</td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Loudness</td>
<td>Concentration</td>
</tr>
<tr>
<td>Duration</td>
<td>Communication</td>
</tr>
<tr>
<td>Laterality</td>
<td>Stress</td>
</tr>
<tr>
<td>Masking</td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Suicidal ideation</td>
</tr>
</tbody>
</table>

Ringing - Buzzing - Humming - Roaring - Waterfall
...reaction to tinnitus

ASSESSING TINNITUS SEVERITY
Table 1. Nine widely used tinnitus questionnaires

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

\(^a\) 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.
Tinnitus Handicap Inventory

- 3 point scale; yes = 4 points, sometimes = 2 points, no = 0 points.
- Maximum score of 100 points for 25 Questions
- Higher score, greater difficulty in functioning or handicap
- 3 subscales – functional, emotional, catastrophic

- 0-16, no handicap
- 18-36, mild handicap
- 38-56, moderate handicap
- 58-100, severe handicap

Newman et al., 1996
Tinnitus Functional Index

• More sensitive to treatment effects
• 25 questions on the scale of 1-10
• Scoring: sum of all valid answers divided by number of questions with valid answers * 10 (TFI score within 0-100 range)
• 8 subscales: intrusive, sense of control, cognitive, sleep, auditory, relaxation, quality of life, emotional.
• 0-17: Not a problem
• 18-31: Small problem
• 32-53: Moderate problem
• 54-72: Big problem
• 73-100: Very big problem

Meikle et al., 2013
Table 2. Topics covered by the nine questionnaires in Table 1a

<table>
<thead>
<tr>
<th>Tinnitus topics or “dimensions”</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance</td>
<td>9</td>
</tr>
<tr>
<td>Intrusive, aversive nature of tinnitus</td>
<td>8</td>
</tr>
<tr>
<td>Irritability, nervousness, stress, tension</td>
<td>8</td>
</tr>
<tr>
<td>Reduced quality of life</td>
<td>8</td>
</tr>
<tr>
<td>Cognitive difficulty: problems concentrating, difficulty focusing attention, mental confusion</td>
<td>8</td>
</tr>
<tr>
<td>Difficulty relaxing: difficulty doing quiet leisure pursuits</td>
<td>7</td>
</tr>
<tr>
<td>Interference with social interactions and activities</td>
<td>6</td>
</tr>
<tr>
<td>Depression, feeling low, suicidal thoughts</td>
<td>6</td>
</tr>
<tr>
<td>Anxiety, worry, panic</td>
<td>6</td>
</tr>
<tr>
<td>Work interference</td>
<td>4</td>
</tr>
<tr>
<td>Hearing difficulties attributed to tinnitus</td>
<td>4</td>
</tr>
<tr>
<td>Anger, annoyance, frustration</td>
<td>4</td>
</tr>
<tr>
<td>Feeling uncomfortable in quiet</td>
<td>4</td>
</tr>
<tr>
<td>Reduced sense of control (feel insecure, helpless, desperate, unable to cope)</td>
<td>4</td>
</tr>
<tr>
<td>Feeling tired: ill, fatigued</td>
<td>3</td>
</tr>
<tr>
<td>Uncomfortable in noise, avoiding noise</td>
<td>3</td>
</tr>
<tr>
<td>Distress, general unhappiness</td>
<td>2</td>
</tr>
<tr>
<td>Ease of masking tinnitus by external sounds</td>
<td>2</td>
</tr>
<tr>
<td>Frequency of complaining about tinnitus</td>
<td>2</td>
</tr>
</tbody>
</table>

Omitted from list are topics mentioned in only one questionnaire: intermittency of tinnitus; worry that tinnitus may damage health; need for or use of medications for tinnitus; attitudes of others about tinnitus; tinnitus that is worse under stress; tinnitus has grown worse over years.

Meikle et al., Progress in Brain Research, 2007
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?

• No objective measurement of tinnitus severity
  => use brain imaging
• Although there might not be consensus about how exactly to measure severity, we all agree patients reaction to tinnitus varies.
  – Mild to severe spectrum
• Neural correlates may complement self-report
  – More objective
USING BRAIN IMAGING IN TINNITUS
Assessing tinnitus severity using fMRI

- Audition
- Emotion
- Attention
- Rest/sleep
Methods: Subject Groups

TIN: (mild)Tinnitus + hearing loss; bothersome tinnitus + hearing loss
HL: hearing loss without tinnitus
NH: normal hearing without tinnitus
Methods - Task based fMRI: Sparse Sampling
Methods - Rest based fMRI: Continuous Scanning

- Spontaneous fluctuations in the BOLD response
- Fluctuations can be correlated to show coherent networks
- 5-20 minute, continuous scanning with eyes open
- DMN = default mode network, DAN = dorsal attention network, AUD = auditory network

Mnatini 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: anticorrelated

- **Suppression of DMN during a task is important**
  - Correlations between the networks negatively correlated with performance on working memory task (Hampson et al., 2010, Magn Reson Imaging)

- **This relationship is disrupted outside of young healthy individuals**
  - Connectivity within DMN is also disrupted

Images from Fox et al., 2005, PNAS
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.
AUDITORY
Neural correlate of tinnitus – auditory cortex

- Is there hyperactivity in auditory cortices due to tinnitus?
  - Hyperactivity may be due to reduced inhibition and/or increased excitation
Effect of Hearing Loss

HL + TIN

HL > NH

NH > HL

Husain et al., PLoS ONE, 2011
Effect of Tinnitus

Husain et al., PLoS ONE, 2011
Effect of Tinnitus on Auditory Cortex in Attention Demanding Tasks

Husain et al., Brain Research, 2015
Processing Emotional Sounds (Mild Tinnitus)

Carpenter-Thompson et al., Brain Research, 2014

No difference
Processing Emotional Sounds (Severe Tinnitus)

Mild > Severe Tinnitus

Greater response in mild tinnitus

Carpenter-Thompson et al., 2015
Is there hyperactivity in auditory cortices?

• It’s complicated
• No difference when comparing mild tinnitus to HL controls when discriminating sounds
• In those with mild tinnitus, greater activity in the auditory cortex when responding to affective sounds compared to neutral sounds (relative to severe tinnitus).
• Change in functional connectivity from auditory cortex to right parahippocampal gyrus
ATTENTION
Neural correlates of Tinnitus - attention network

- Does tinnitus cause deficits in behavior?
- Does tinnitus causes changes in attention network response?
- Are these changes modality specific?
Brain When Attending to Sounds – Differences in Neural Response, But Not in Behavior

Normal Hearing

Hearing Loss

Hearing Loss + Tinnitus

Frontal Cortex

Parietal Cortex

Husain et al., PLoS ONE, 2011
No Behavioral Differences in Auditory or Visual tasks, Varying in Difficulty

Lo = easy task
Hi = more demanding task

Husain et al., Brain Research, 2015
**AUDITORY TASKS: Neural Response**

- Intraparietal sulcus
  - Left
  - Right
Intraparietal sulcus

Left

Right

No significant difference

VISUAL TASKS: Neural Response
Dorsomedial Frontal gyrus

Right Auditory Cortex

VISUAL TASKS: Neural Response
Neural correlates of attention

• Does tinnitus cause deficits in behavior?
  – Not for mild tinnitus for discrimination tasks

• Does tinnitus cause changes in attention network response?
  – Yes!

• Do these changes alter with task difficulty?
  • Yes

• Are these changes modality specific?
  – Yes

• Implications for treatments
EMOTION
Where does emotion processing happen?

- Periphery and central auditory pathways
- Limbic system
- Frontal cortex
Tinnitus and emotion processing...

Jastreboff, 1990
Neural correlates of emotion processing

• Does tinnitus cause deficits in emotional behavior?
• Does tinnitus cause changes in emotion network response?
• Are these changes only in the auditory modality or are they domain general?
Behavior in Mild Tinnitus

Task: Classify sounds as **Pleasant, Unpleasant, Neutral**

Carpenter-Thompson et al., Brain Research, 2014
Behavior in Mild & Severe tinnitus

The only behavioral difference was that the Mild group responded significantly faster to Pleasant sounds compared to the Severe group.
Processing Emotional Sounds: Auditory cortex

Mild>Severe Tinnitus

Greater response in mild tinnitus

Carpenter-Thompson et al., 2016
Mild Tinnitus, Processing emotional sounds: Right Amygdala

Carpenter-Thompson et al., Brain Research, 2014
Response to emotional Sounds — Varies with Tinnitus Severity

Hyper-response of the amygdala in those with severe tinnitus and more engagement of the frontal cortex in those with mild tinnitus

Carpenter-Thompson et al., Brain Research, 2014
Carpenter-Thompson et al., PLoS ONE, 2015
Neural correlates of emotional processing

- **Does tinnitus cause changes in behavior?**
  - Not in classification, but in response times – may vary with severity
- **Does tinnitus cause changes in emotion network response?**
  - Yes
  - Response varies with severity
- **Are these changes only in the auditory modality or are they domain general?**
  - Current study only about sounds
  - Golm et al., 2013 showed that reading sentences with tinnitus-related (compared to neutral) content affected response of limbic and frontal regions.
REST
Resting State Functional Connectivity (RS-FC)

Spontaneous fluctuations in the BOLD response that can be organized into coherent, spatially-correlated networks

Default mode network

Dorsal attention network

Auditory network

Images from Mantini et al, 2007
Decreased connectivity between seeds in Dorsal Attention and Default mode networks and attention-related regions in mild tinnitus.
Interaction with Emotion

- Increased connection to limbic/emotion regions was seen in both auditory and attention networks in tinnitus.

Images from Schmidt et al., PLoS One, 2013
Default Mode Network

• The default mode network is disrupted in tinnitus

Images from Schmidt et al., PLoS One, 2013
RS-FC findings in tinnitus

From Husain and Schmidt, 2014

Blue: default mode network
Green: limbic
Red: auditory network
Orange: visual network
Purple: attention

a: Schmidt et al, 2013
b: Burton et al., 2012
c: Maudoux et al, 2012a
d: Kim et al, 2012
Eggermont and Roberts, Cell Tissue Res, 2014
Tinnitus: animal models and findings in humans.
RS-FC in tinnitus across studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al, 2012</td>
<td>Group ICA to extract auditory network, ROIs within auditory component</td>
</tr>
<tr>
<td>Burton et al, 2012</td>
<td>Seed-based analysis (seed-to-seed, seed-to-voxel)</td>
</tr>
<tr>
<td>Wineland et al, 2012</td>
<td>Seed-based analysis (seed-to-seed, seed-to-voxel)</td>
</tr>
<tr>
<td>Maudoux et al, 2012a</td>
<td>Connectivity graph analysis of auditory component from group ICA</td>
</tr>
<tr>
<td>Maudoux et al, 2012b</td>
<td></td>
</tr>
<tr>
<td>Schmidt et al, 2013</td>
<td>Seed-based analysis (seed-to-voxel)</td>
</tr>
<tr>
<td>Ueyama et al, 2013</td>
<td>Regional mean functional connectivity strength (with and without effect autocorrelation coefficient)</td>
</tr>
<tr>
<td>Davies et al, 2014</td>
<td>Group ICA to extract auditory network, ROIs within auditory component</td>
</tr>
<tr>
<td>Chen et al, 2014</td>
<td>Amplitude of low frequency fluctuations (spontaneous neural activity)</td>
</tr>
<tr>
<td>Chen et al, 2015a</td>
<td>Voxel-mirrored homotopic connectivity (interhemispheric functional connectivity)</td>
</tr>
<tr>
<td>Chen et al, 2015b</td>
<td>Regional homogeneity, region of interest (connectivity)</td>
</tr>
<tr>
<td>Zhang et al, 2015</td>
<td>Seed-based analysis (in left and right thalamus)</td>
</tr>
</tbody>
</table>
## RS-FC in tinnitus across studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Severity</th>
<th>Clinical hearing loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al, 2012</td>
<td>3.14 ± 4.60 years (0.5-10)</td>
<td>????</td>
<td>normal hearing within tested frequencies</td>
</tr>
<tr>
<td>Burton et al, 2012</td>
<td>8.3 ± 1.9 SEM years (0.5-30)</td>
<td>53.5 ± 14.8 (38-76) (THI)</td>
<td>variable, normal to moderate-severe (normal controls)</td>
</tr>
<tr>
<td>Wineland et al, 2012</td>
<td>10.8 ± 10.1 years (1-35)</td>
<td>9.58 ± 6.41 (0-24) (THI)</td>
<td>variable, normal to moderate-severe (normal controls)</td>
</tr>
<tr>
<td>Maudoux et al, 2012a, 2012b</td>
<td>7.64 ± 9.16 years (1.75-33)</td>
<td>43.5 ± 20.4, 16-84 (THI)</td>
<td>variable, normal, most mild to moderate</td>
</tr>
<tr>
<td>Schmidt et al, 2013</td>
<td>16.83 ± 15.1 years (1.5-40)</td>
<td>8.33 ± 6.76 (0-22) (THI)</td>
<td>mild to moderately severe, matched HL controls</td>
</tr>
<tr>
<td>Ueyama et al, 2013</td>
<td>50.8 ± 102.9 months (3-400)</td>
<td>60.3 ± 27.8, 4-100 (THI)</td>
<td>variable, 13 normal, 11 mild to moderate</td>
</tr>
<tr>
<td>Davies et al, 2014</td>
<td>15.5 ± 20.4 years (2-70)</td>
<td>43.7 ± 1.32 (18.7-68.4) (THQ)</td>
<td>mild to moderately severe, matched HL controls</td>
</tr>
<tr>
<td>Chen et al, 2014</td>
<td>41 ± 36.2 months (6-120)</td>
<td>100.6 ± 73.4 (17.41-278.15) (THQ)</td>
<td>normal hearing</td>
</tr>
<tr>
<td>Chen et al, 2015a</td>
<td>34.3 ± 34.2 months (6-120)</td>
<td>41.3 ± 18.2 (THQ)</td>
<td>normal hearing</td>
</tr>
<tr>
<td>Chen et al, 2015b</td>
<td>39.5 ± 33.7 months</td>
<td>103.5 ± 74.4 (THQ)</td>
<td>normal hearing</td>
</tr>
<tr>
<td>Zhang et al, 2015</td>
<td>42.6 ± 41.4 months</td>
<td>41.4 ± 19.7 (THQ)</td>
<td>normal hearing</td>
</tr>
</tbody>
</table>
So what’s going on here?

- How does RS-FC differ in other tinnitus subgroups? Identify objective biomarkers of tinnitus subgroups?
  - Age? Severity? Lateralization? Time/cause of onset?
  - Depression/anxiety? Genetics? Other comorbid factors?
Solution:

• Compare connectivity in the default mode network across tinnitus subgroups to identify potential biomarkers of tinnitus
  – Subgroups include tinnitus groups from previous work
  – Subgroups also include two additional groups with mild and moderate tinnitus from Carpenter-Thompson et al., 2015 (PLoS One)
  – Keep acquisition same as much as possible, same analytical technique
# Demographics

<table>
<thead>
<tr>
<th></th>
<th>NH</th>
<th>HL</th>
<th>MLTIN1</th>
<th>MRTIN</th>
<th>MLTIN2</th>
<th>BLTIN</th>
</tr>
</thead>
<tbody>
<tr>
<td># Subjects</td>
<td>15</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>3T Siemens Magnet</td>
<td>Allegra</td>
<td>Allegra</td>
<td>Allegra</td>
<td>Allegra</td>
<td>Trio</td>
<td>Trio</td>
</tr>
<tr>
<td>TIN severity (THI score)</td>
<td>N/A</td>
<td>N/A</td>
<td>8.3 ±6.8</td>
<td>15.7 ±10.2</td>
<td>10.8±6</td>
<td>33.4 ±9.1</td>
</tr>
<tr>
<td>TIN duration</td>
<td>N/A</td>
<td>N/A</td>
<td>&gt;1 year</td>
<td>&gt;6 months, &lt; 1 year</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>Relevant Publication(s)</td>
<td>Schmidt et al., 2013</td>
<td>Schmidt et al., 2013</td>
<td>Schmidt et al., 2013; Carpenter-Thomson et al., 2015</td>
<td>Carpenter-Thomson et al., 2015</td>
<td>Schmidt et al., 2017</td>
<td>Schmidt et al., 2017</td>
</tr>
</tbody>
</table>

**Recent onset tinnitus**

**Long term tinnitus**

**Mild tinnitus**

**Moderate tinnitus**
ANOVA results

One area of significance at p<0.05 FWE corrected: the precuneus.

episodic memory, consciousness, visuospatial memory, reflections on self
RS-FC connectivity across subgroups

ANOVA Results

DMN: Individual beta-Values at (-10, -42, 48)

DAN: Individual beta-Values at (6, -50, 52)
DMN: Individual beta-Values at (-10, -42, 48)

DAN: Individual beta-Values at (6, -50, 52)
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
Putting it all together...

What does it all mean?
Model of Severity & Habituation: Neural Response

Figure 1a: Effect of tinnitus on neural response during emotional processing

- **Superior FG**
- **Middle FG**
- **Inferior FG**
- **Insula**
- **Auditory Cortex**
- **Amygdala**
- **Parahipp**

Legend:
- Severe TIN > mild
- Mild TIN > severe
- RTIN > LTIN
- LTIN > RTIN
- Mild TIN > controls

Husain, Hearing Research, 2016
Model of Severity & Habituation: Functional Connectivity

Figure 1b: Effect of mild tinnitus on resting state functional connections compared to non-tinnitus conditions.

- Increased connectivity
- Decreased connectivity

Brain regions: FEF, Precentral gyrus, PCC/precuneus, Supramarginal gyrus, Auditory Cortex, Parahipp, Cerebellum.
Cognitive Control of Emotion: Model of Severity & Habituation

Figure 1c: Proposed model of emotional processing in habituated and non-habituated tinnitus and proposed connections

- Superior/middle/inferior frontal
- Insula
- Amygdala
- Auditory Cortex
- Parahipp

Legend:
- Red: Without habituation
- Green: With habituation
- Enhancement
- Suppression
- Connection

Husain, Hearing Research, 2016
Cognitive Control of Emotion

Image from “An information theory account of cognitive control”, Fan, 2016
Model of Severity & Habituation

1. **In those habituated to tinnitus:**
   A. Frontal cortex (attention network) suppresses pre-potent response of amygdala (limbic network) and re-routes salience/emotional processing via insula and parahippocampus gyrus
   B. Default mode network is more coherent, but still not as intact as in those without tinnitus.

2. **In those with more bothersome tinnitus:**
   A. Amygdala is more responsive
   B. Default mode network is less coherent – brain not at true rest
   C. Hypoactivity in auditory cortex

Husain, Hearing Research, 2015
But are results replicable? Robust enough to be used as a diagnostic and prognostic tool?

REPLICATION AND DIAGNOSIS
Military and Civilian groups

Identify objective functional biomarkers of tinnitus severity using resting state functional connectivity and

Determine tinnitus subgroups using automated cluster analysis of resting state data and associate the subgroups with a set of behavioral and neural correlates
Replication of Default Mode Network Connectivity: Controls

Controls: Visit comparison of connectivity between the posterior cingulate and medial prefrontal cortex

Beta values Visit B vs. Beta values Visit A for UIUC (blue) and WHASC (red) groups.

Source: illinois.edu
Replication of Default Mode
Network Connectivity: Tinnitus

Tinnitus Patients: Visit comparison of connectivity between the left posterior cingulate and medial prefrontal cortex

Schmidt et al., in prep
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
• Over multiple studies and now multiple sites, we are beginning to understand the functional connections and disconnections in the neural networks underlying tinnitus
Objective diagnostic biomarkers of tinnitus

DIFFERENTIATING PATIENTS VS. CONTROLS
Cyclicity of fMRI data

- From the cyclicity analysis, it is possible to generate a matrix that defines ‘leader-follower’ relationships between two signals.
- A different way to look at “functional connectivity”
Certain ROIs have consistently strong leader-follower relationships, but did not differ between groups. Different patterns for patients and controls.
# Classification

## Partial Least Squares Discriminant Analysis

**Method:** PLS-DA (20 components)  
**Accuracy:** 78 %  
**Unclassified:** 135

<table>
<thead>
<tr>
<th>True Group</th>
<th>Predicted Group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Hearing</td>
<td>Tinnitus</td>
<td></td>
</tr>
<tr>
<td>Normal Hearing</td>
<td>73.0%</td>
<td>27.0%</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>17.4%</td>
<td>82.6%</td>
<td></td>
</tr>
</tbody>
</table>

- First such endeavor in tinnitus
- Both sensitivity and specificity
- Generalize to other conditions, traits

Zimmerman, Thomas, Baryshnikov, Husain, *in prep*
Conclusions...

• Finding invariant neural signatures of tinnitus
  – Varying across subgroups
• Validate the reliability of these signatures
• Develop automated programs to differentiate patients with subjective disorder and controls
  – Apply this to other conditions and states within subjects
⇒ Evaluate interventions
⇒ Develop new interventions
www.acnlab.com

- Support
  - UIUC- AHS/CHAD, Campus Research Board
  - Charitable Organizations: Tinnitus Research Consortium, American Tinnitus Association
  - 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!