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Using Brain Imaging Techniques to Find the Tinnitus Signal

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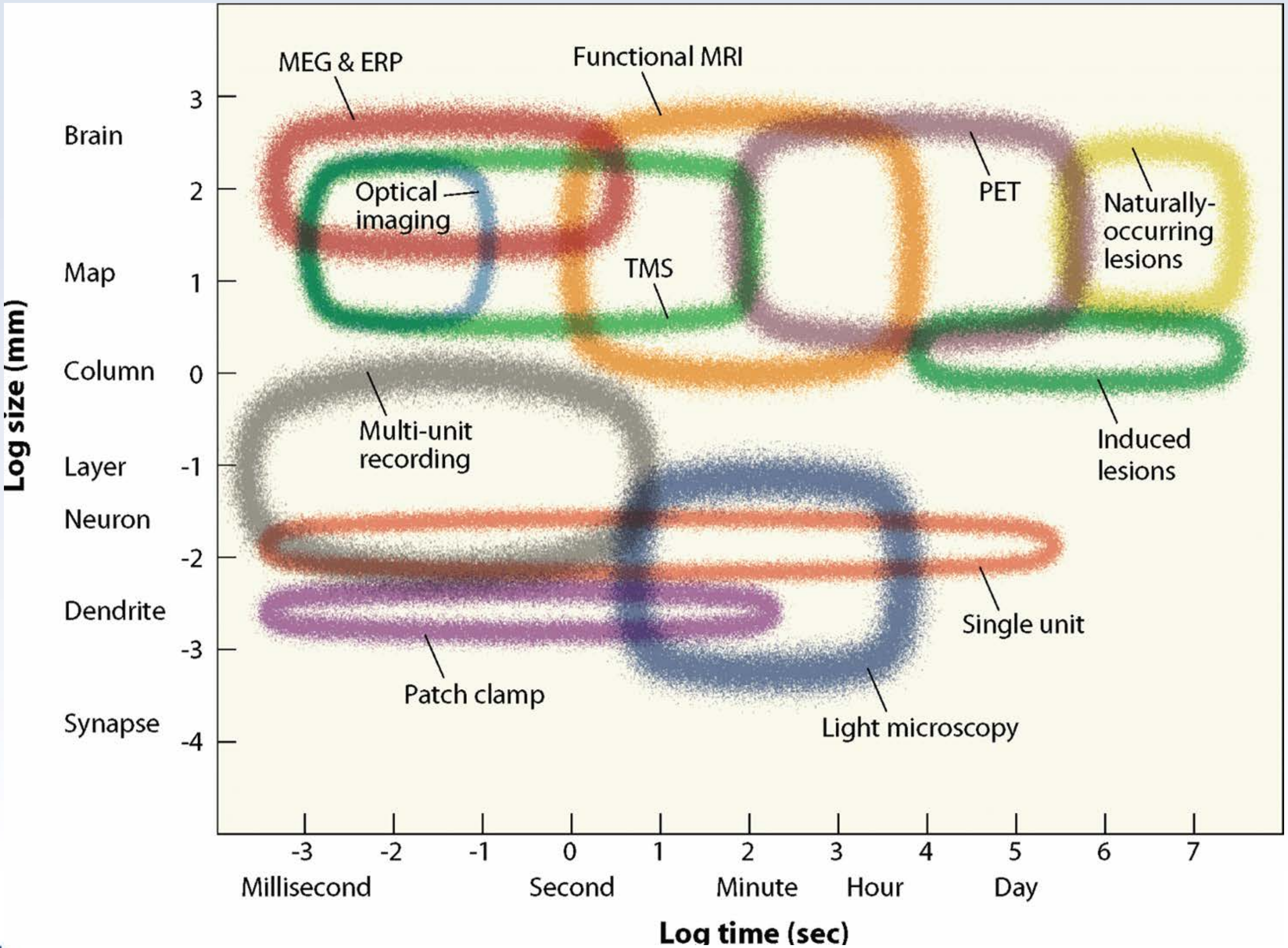
Agenda

- 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



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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

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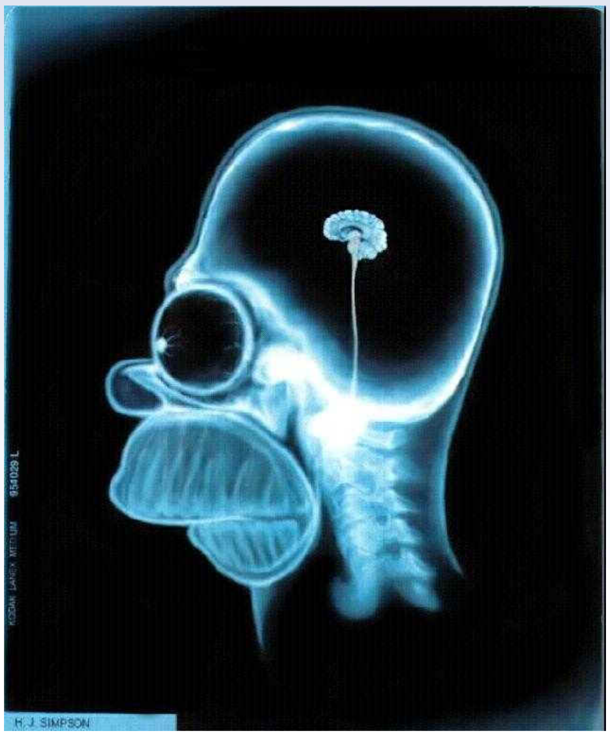
The “Scanner”

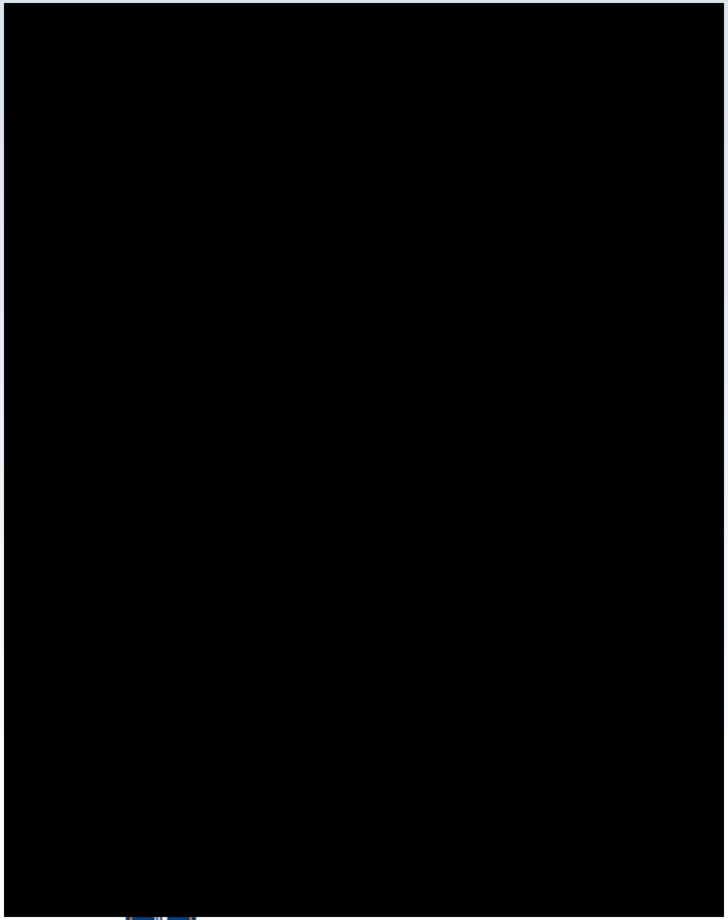
MRI vs. fMRI

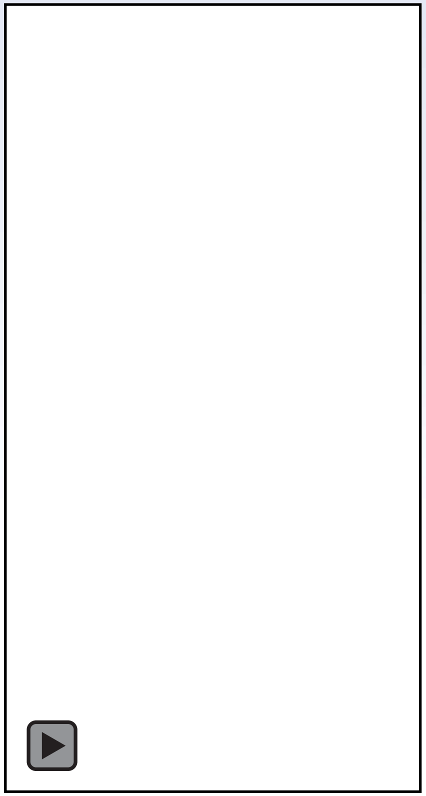
MRI studies brain **anatomy**.



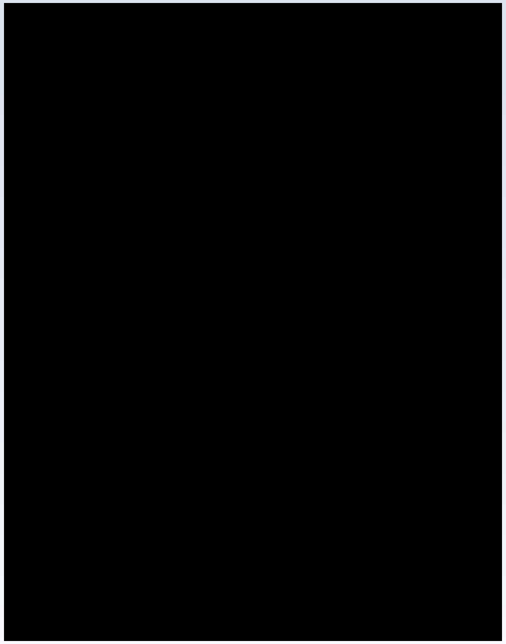
Functional MRI (fMRI) studies brain **function**.

Imaging Structure in the Brain





Imaging Function in the Brain



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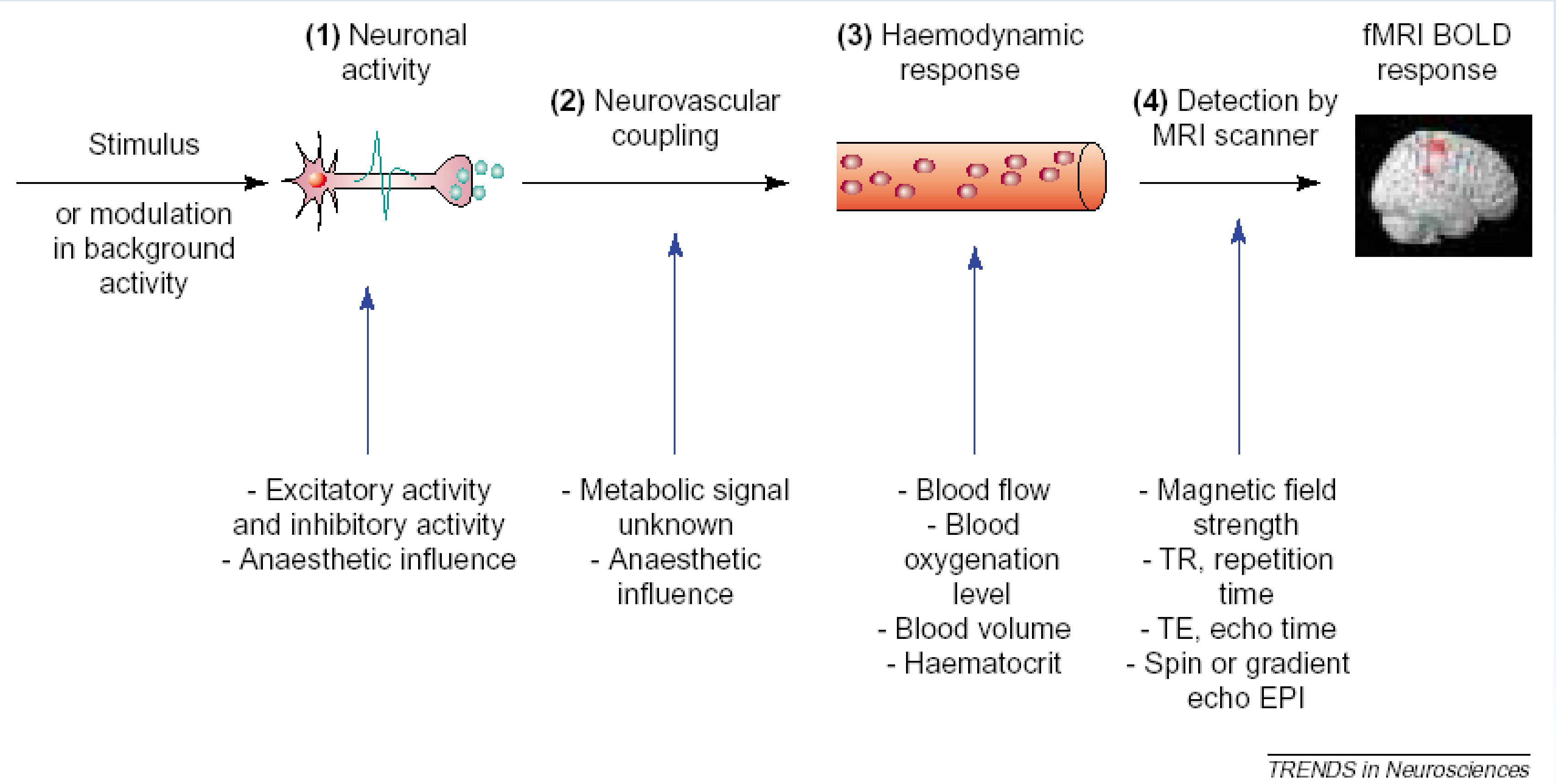
Stimulus to BOLD



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

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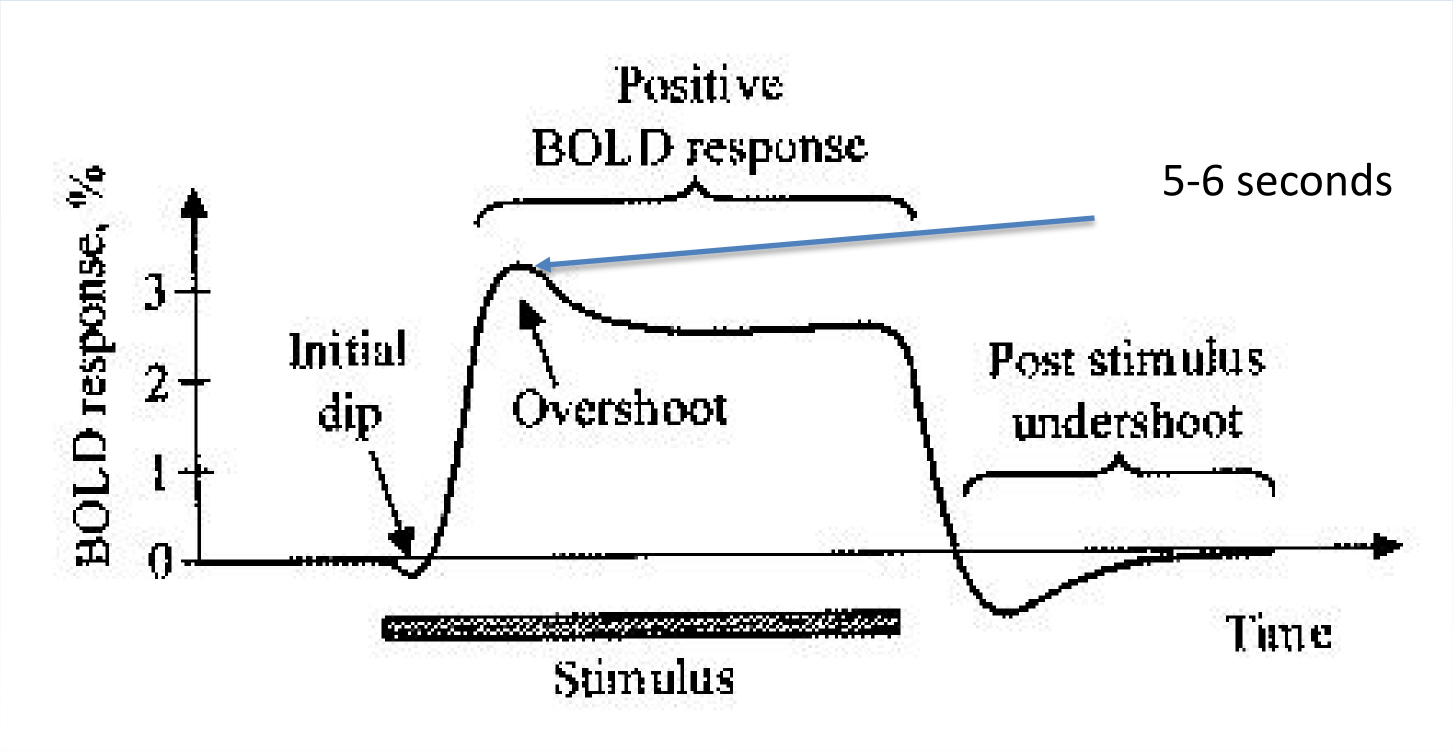
BOLD = Blood oxygen-level dependent response

BOLD Time Course



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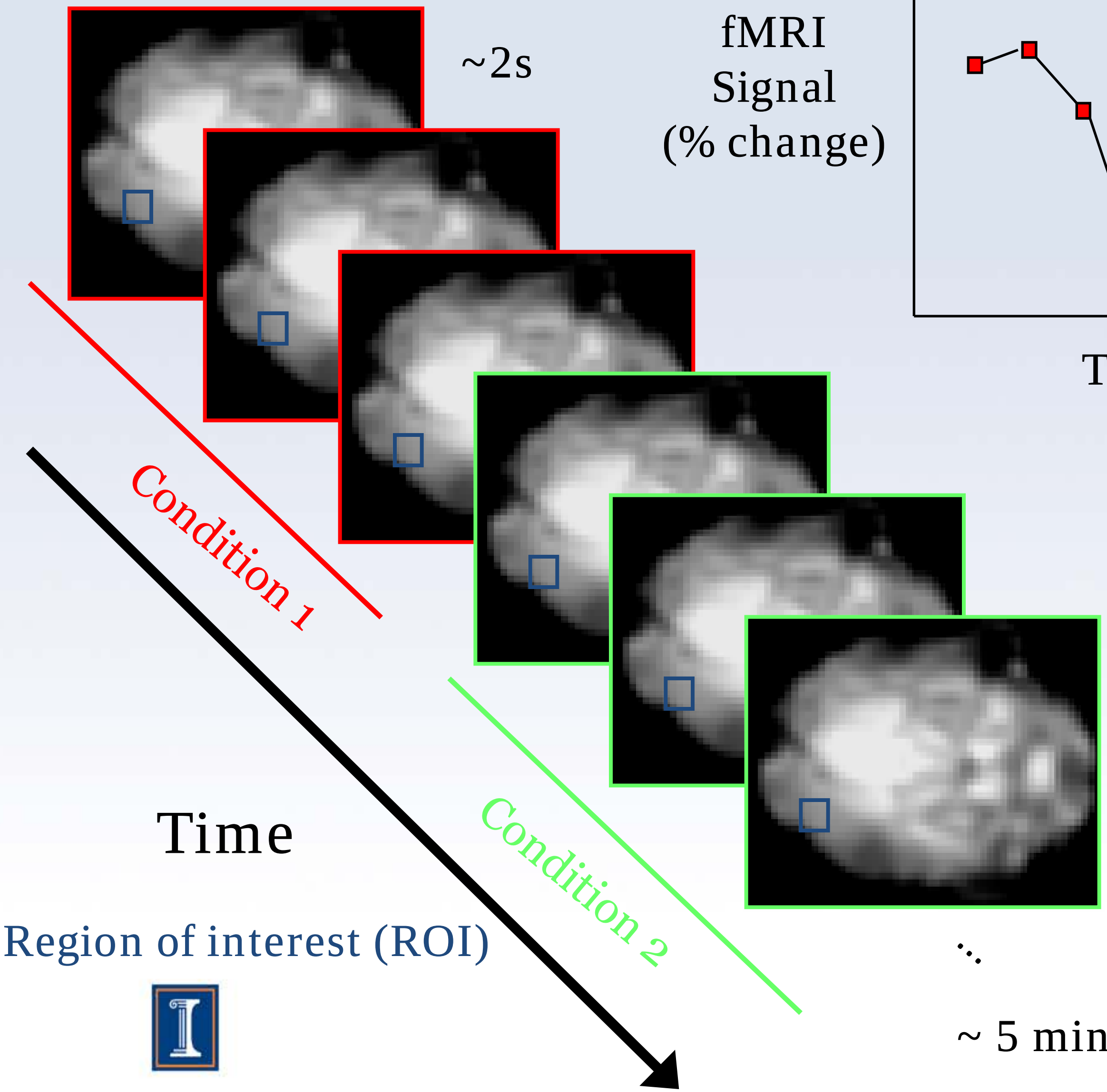
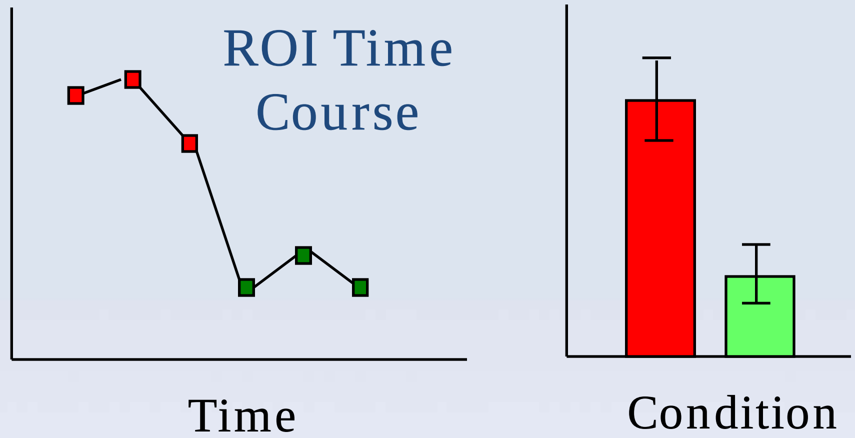
Activation Statistics

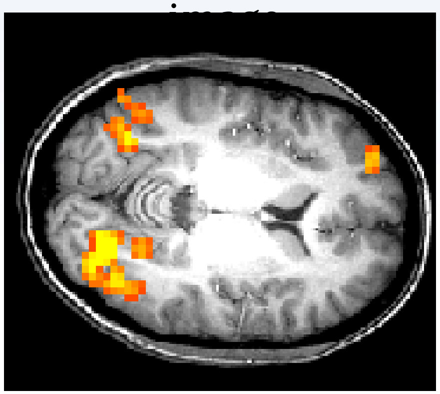
Functional images



fMRI
Signal
(% change)



Statistical Map
superimposed on
anatomical MRI



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Reminder…

NEURAL NETWORKS

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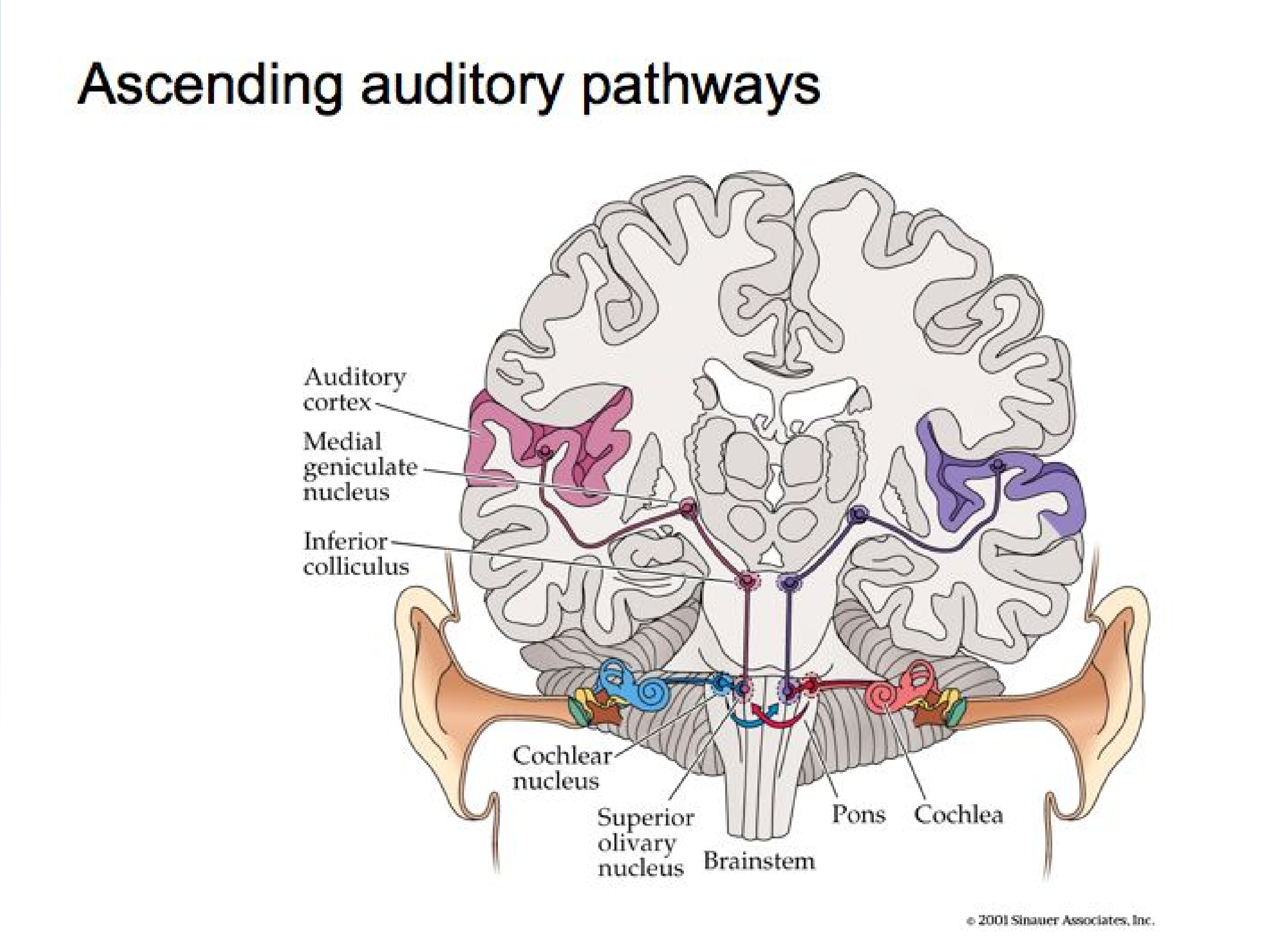
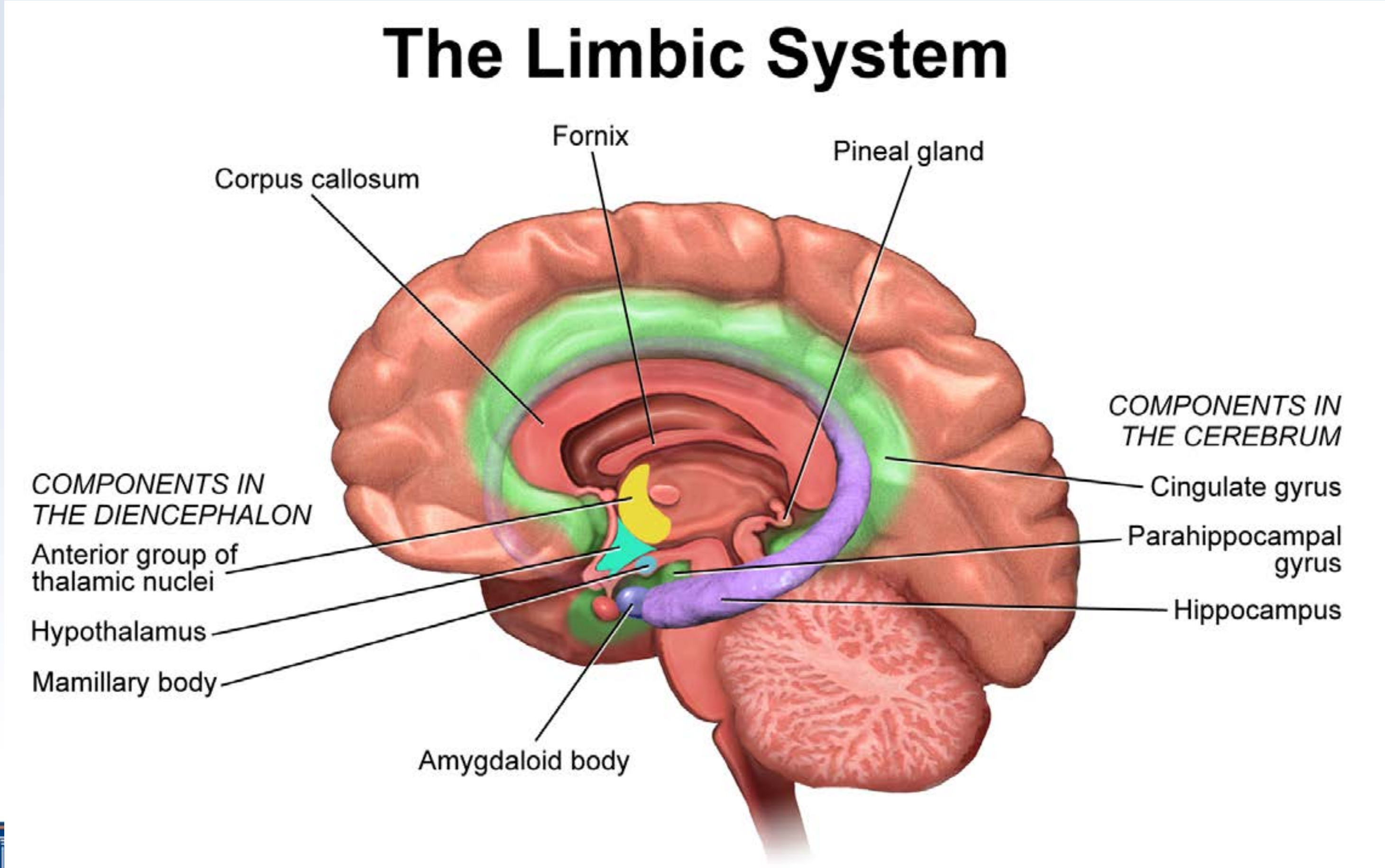
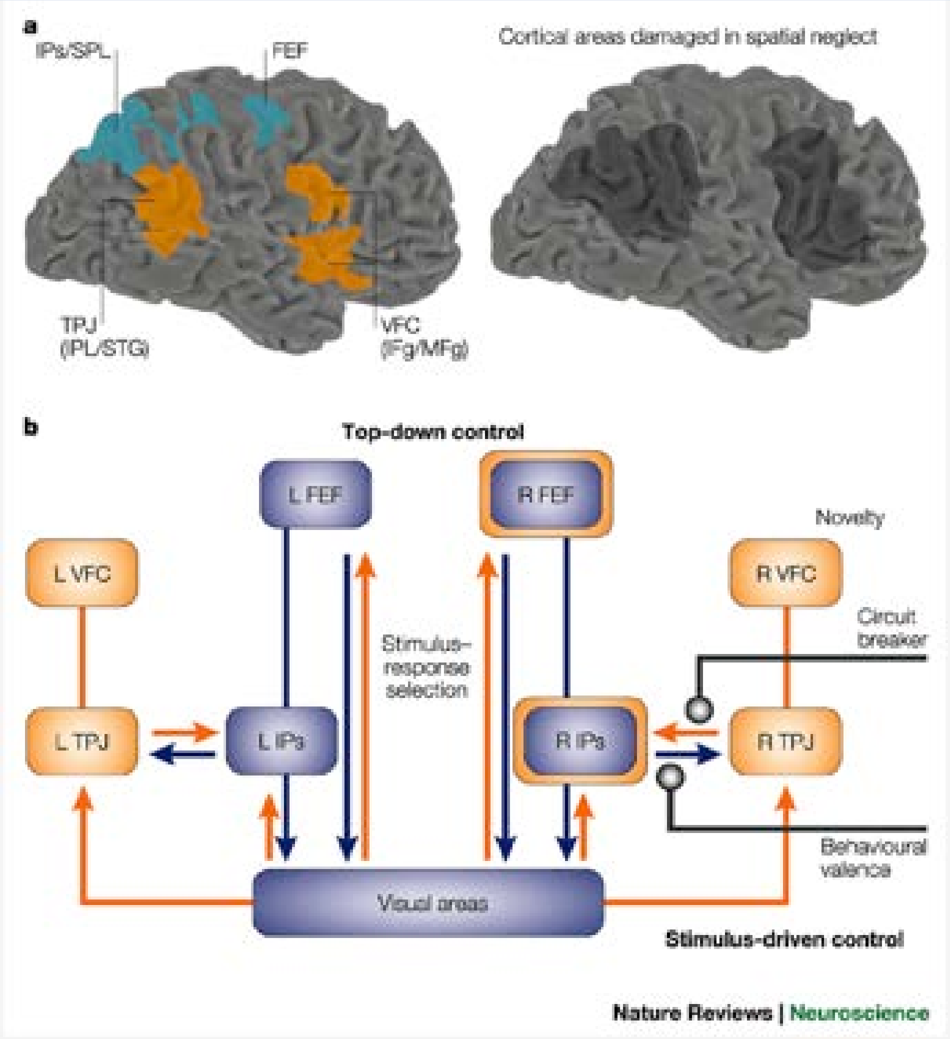
Auditory Network



Emotion processing network



Attention Network



TINNITUS SEVERITY

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

Ringing

Buzzing

Humming

Roaring

Waterfall

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

...reaction to tinnitus

ASSESSING TINNITUS SEVERITY

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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, 2007

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

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Table 2. Topics covered by the nine questionnaires in Table 1[a]

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

[a]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

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USING BRAIN IMAGING IN TINNITUS

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Assessing tinnitus severity using fMRI

- Audition
- Emotion
- Attention
- Rest/sleep

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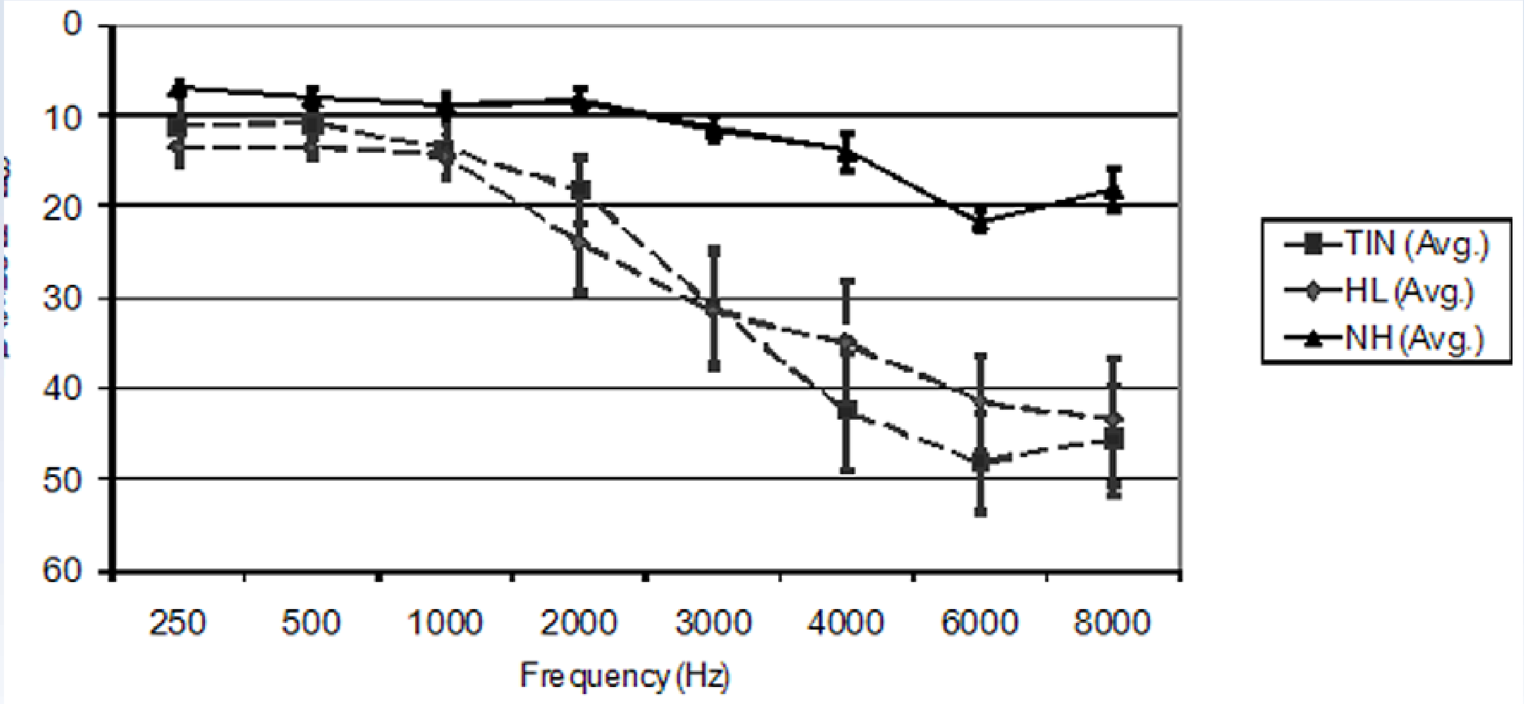
Methods: Subject Groups



TIN: (mild)Tinnitus + hearing loss; bothersome tinnitus + hearing loss
HL: hearing loss without tinnitus
NH: normal hearing without tinnitus

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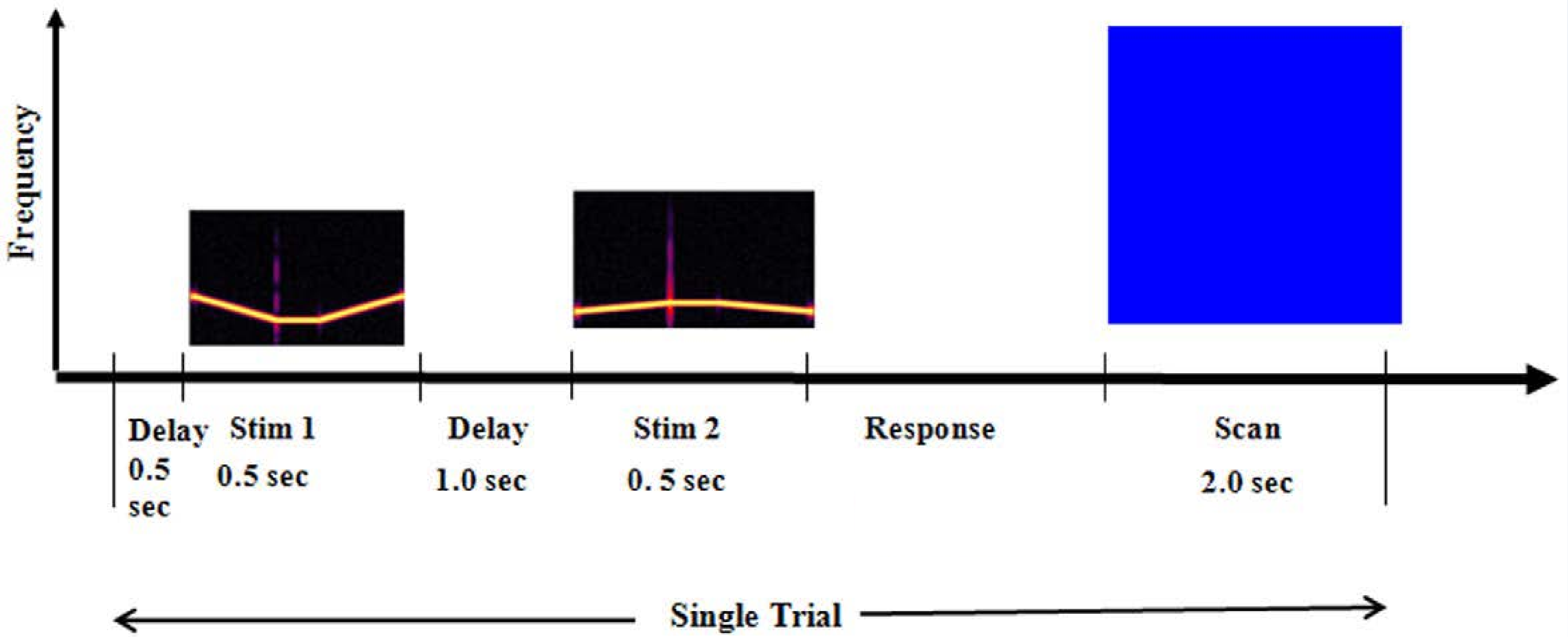
Methods -Task based fMRI: Sparse Sampling



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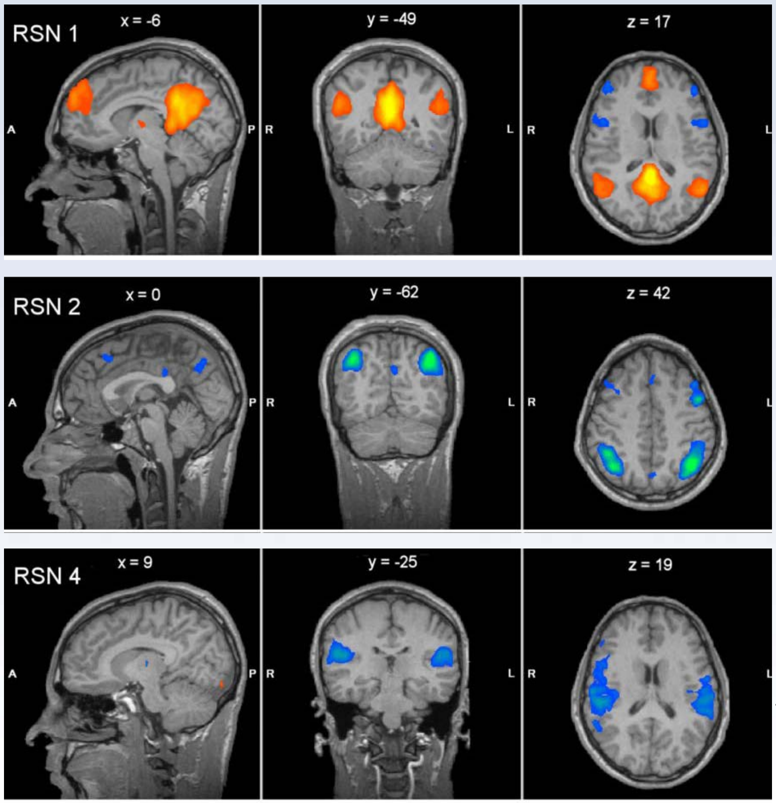
Methods - Rest based fMRI: Continuous Scanning



DMN

DAN

AUD

- 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

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Default Mode Network function

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

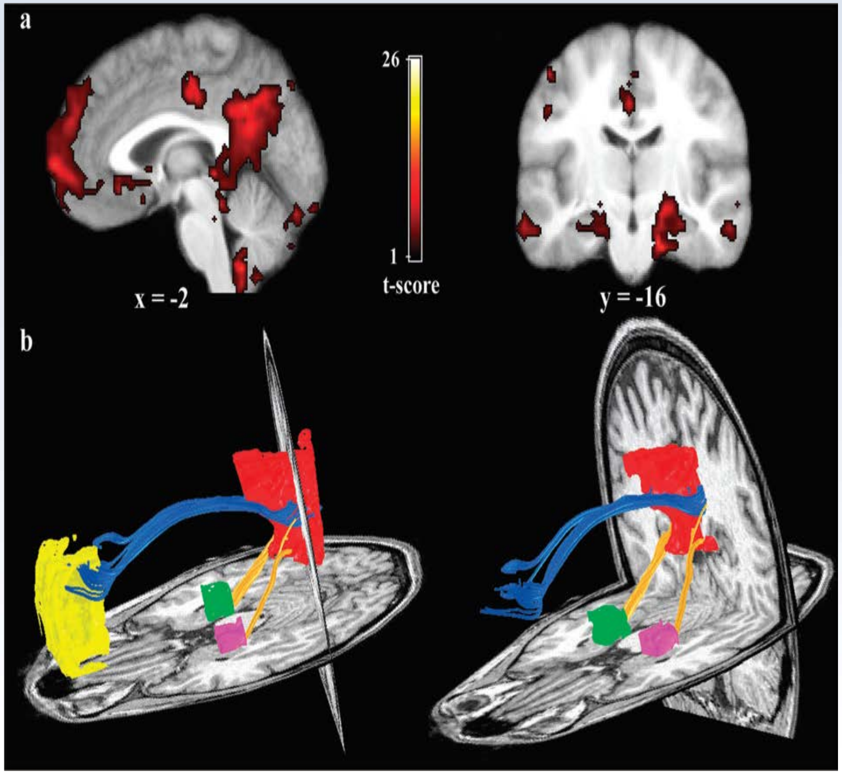

Image from Greicius et al., 2009, Cerebral Cortex

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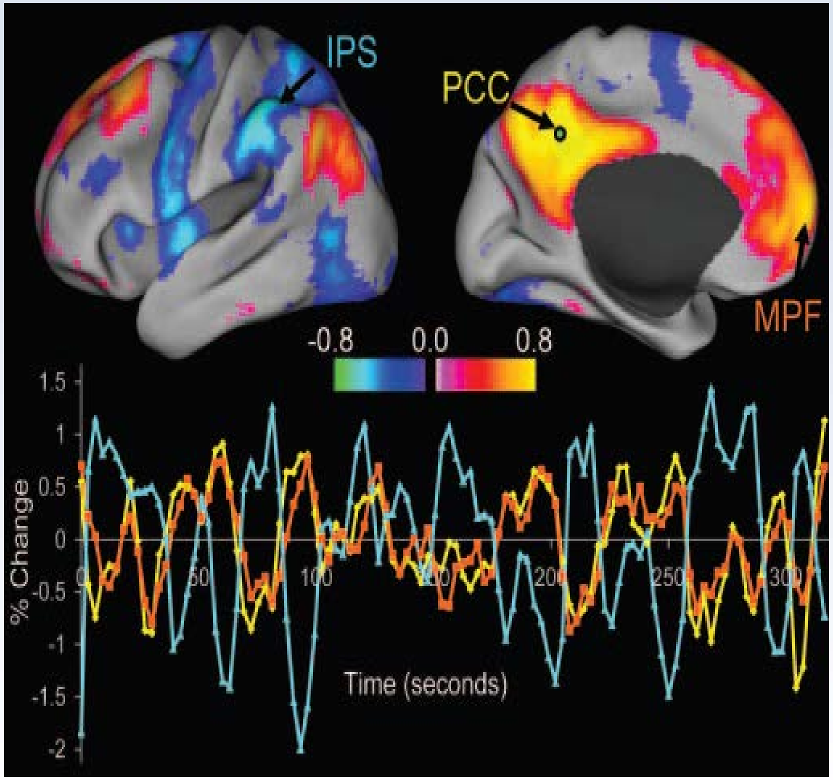
Default mode and attention networks: anticorrelated

- **Suppression of DMN during a task is important**
  - Better suppression linked to better memory formation (Whitfield-Gabrieli and Ford, 2012, Annu Rev Clin Psychol)
  - 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

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Resting State and Tinnitus

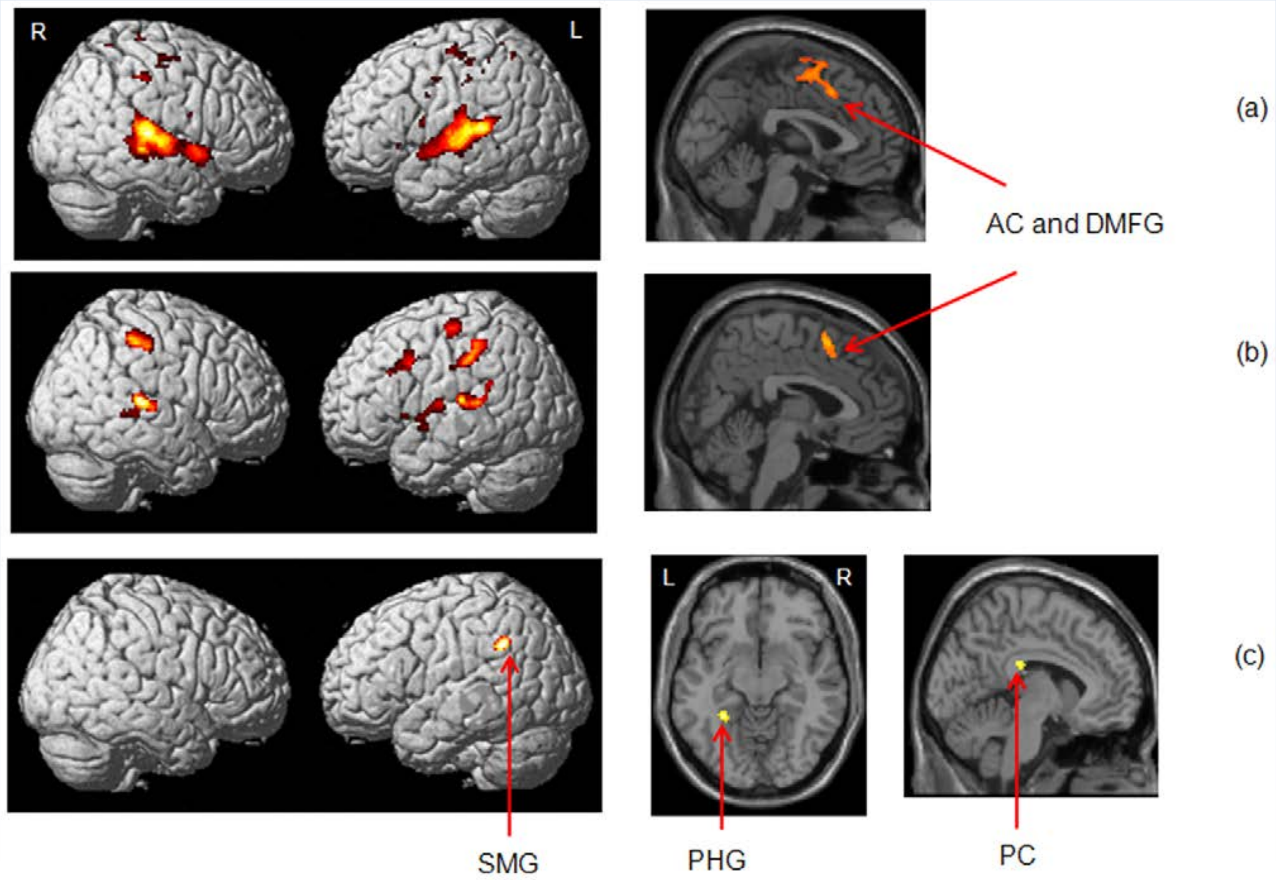
- Tinnitus is uniquely suited to being studied via the resting state than other disorders because the presence and awareness of tinnitus puts the participant in a non-resting state.

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

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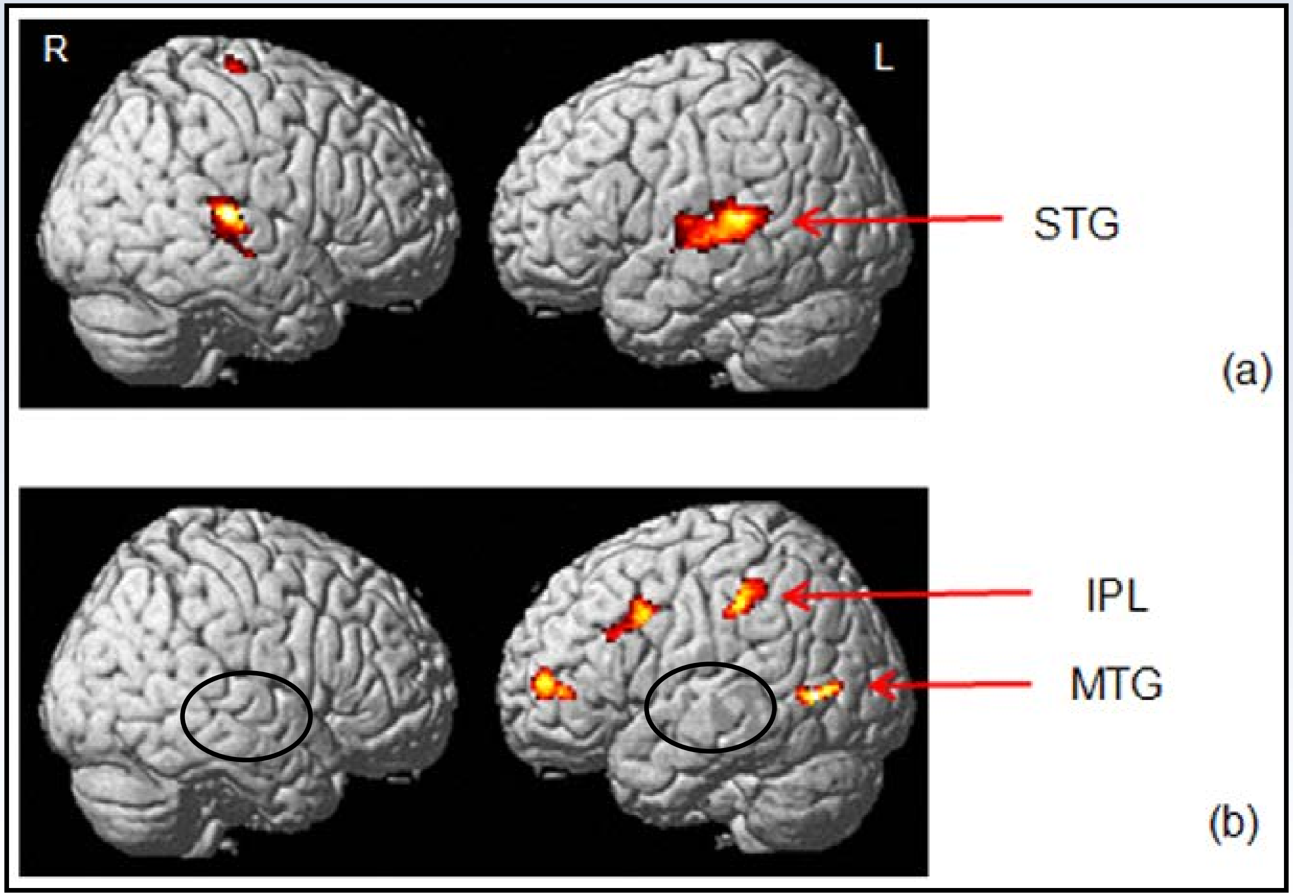
Effect of Tinnitus



TIN > NH
(no NH>TIN)

HL > TIN
(no TIN>HL)

Husain et al., PLoS ONE, 2011

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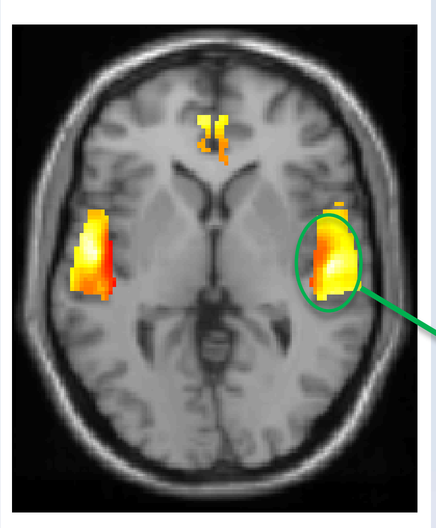
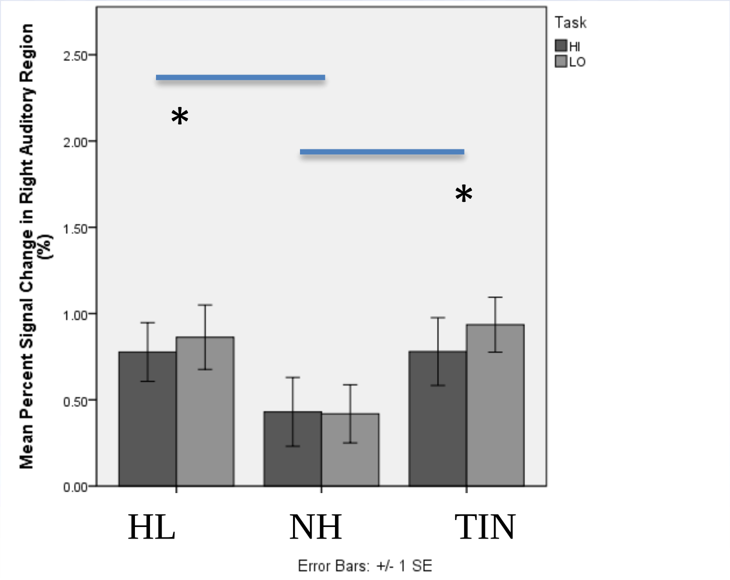


Right Auditory Cortex

Effect of Tinnitus on Auditory Cortex in Attention Demanding Tasks



Husain et al., Brain Research, 2015

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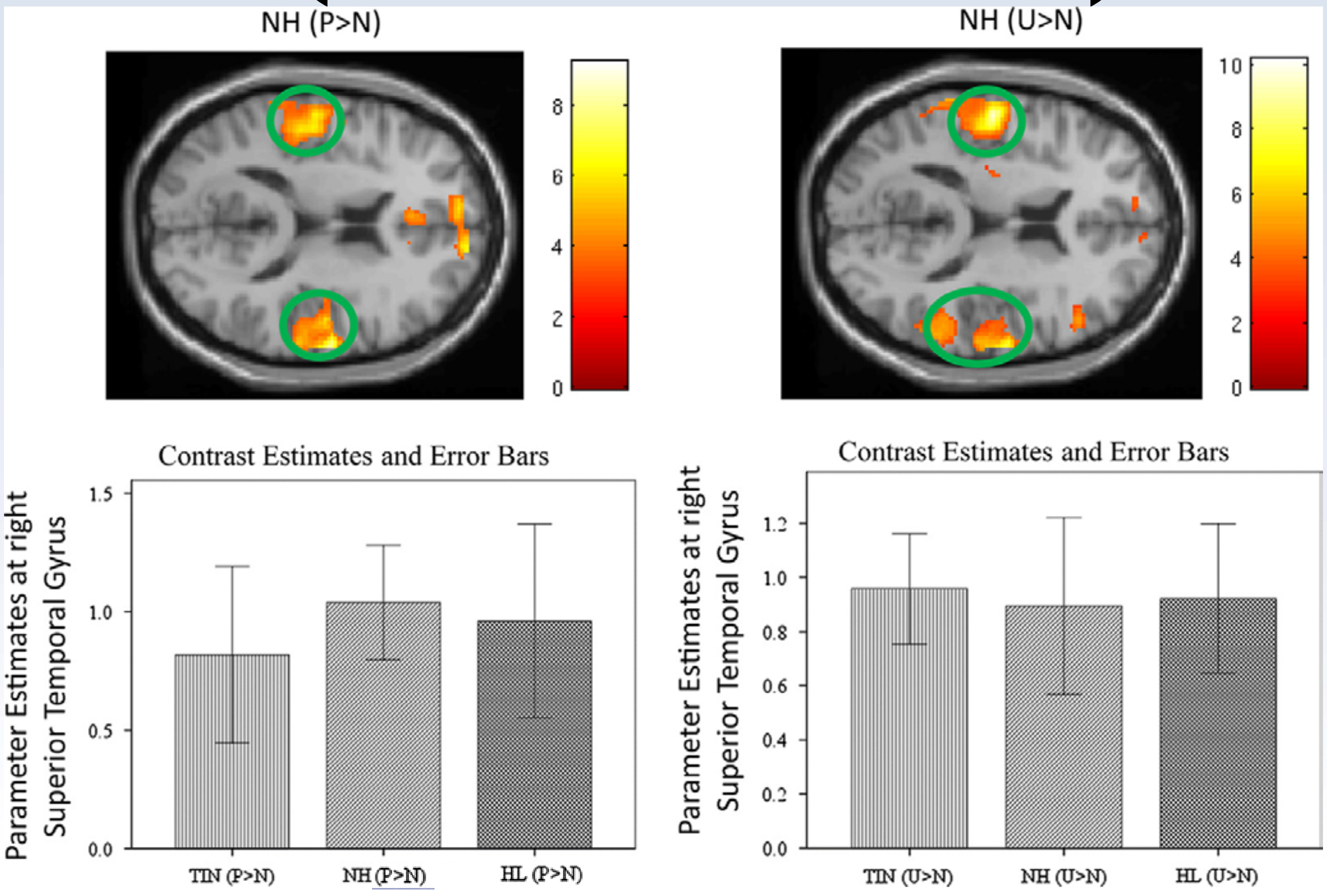
Processing Emotional Sounds (Mild Tinnitus)



No difference

Carpenter-Thompson et al., Brain Research, 2014

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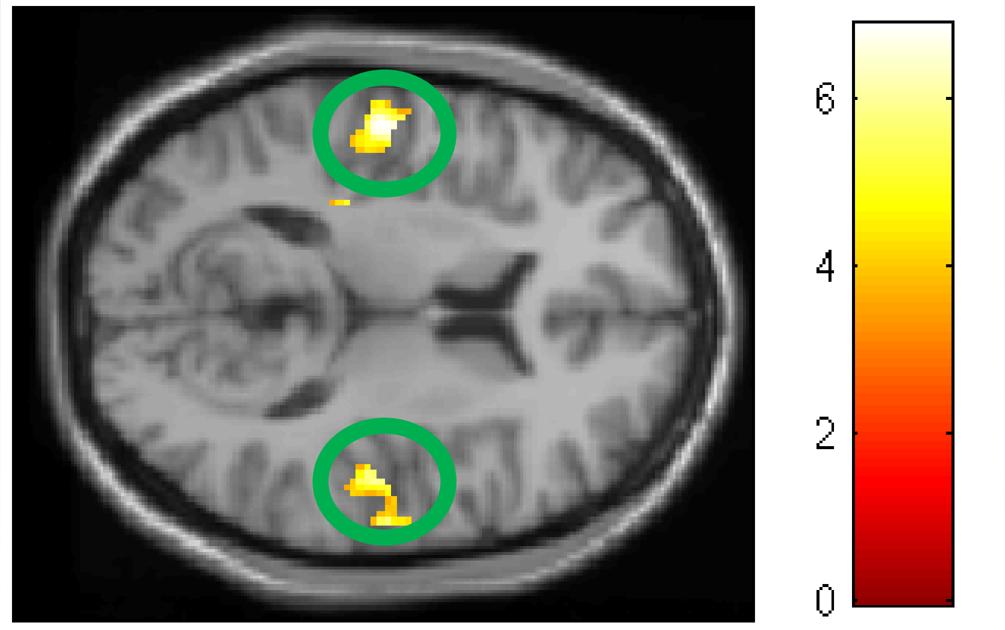
Processing Emotional Sounds (Severe Tinnitus)

Mild>Severe Tinnitus



Greater response
In mild tinnitus

Carpenter-Thompson et al., 2015

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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

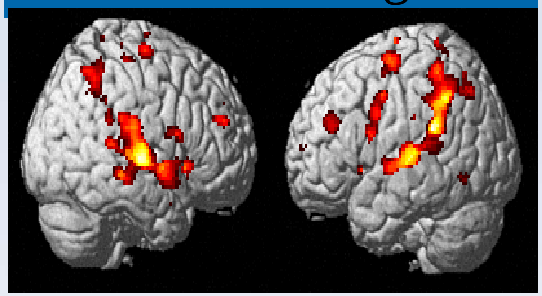
ATTENTION

Neural correlates of Tinnitus - attention network

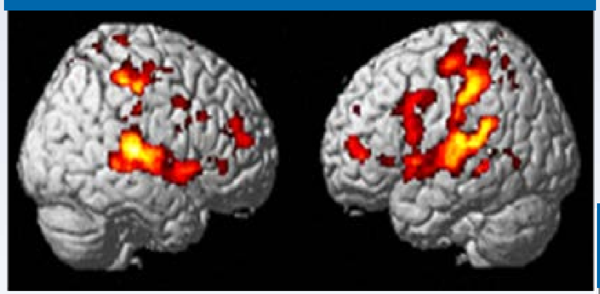
- Does tinnitus cause deficits in behavior?
- Does tinnitus causes changes in attention network response?
- Are these changes modality specific?

Brain When Attending to Sounds – Differences in Neural Response, But Not in Behavior

Normal Hearing

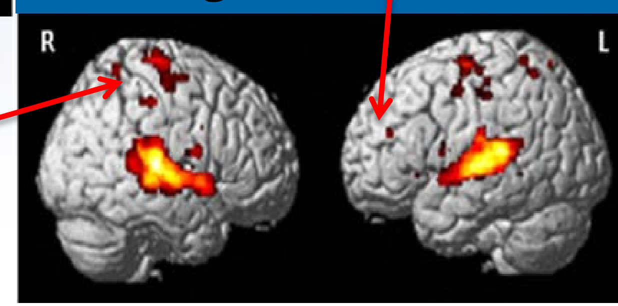


Hearing Loss



Frontal Cortex

Hearing Loss + Tinnitus



Parietal Cortex

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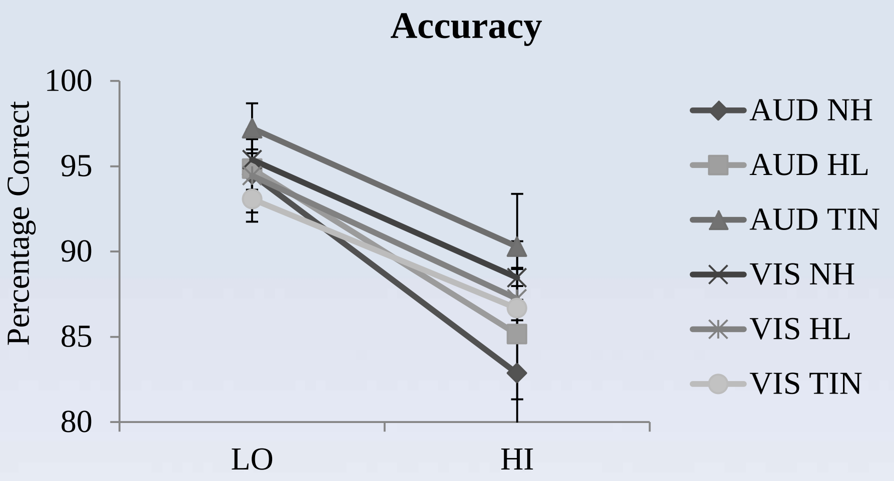
Husain et al., PLoS ONE, 2011

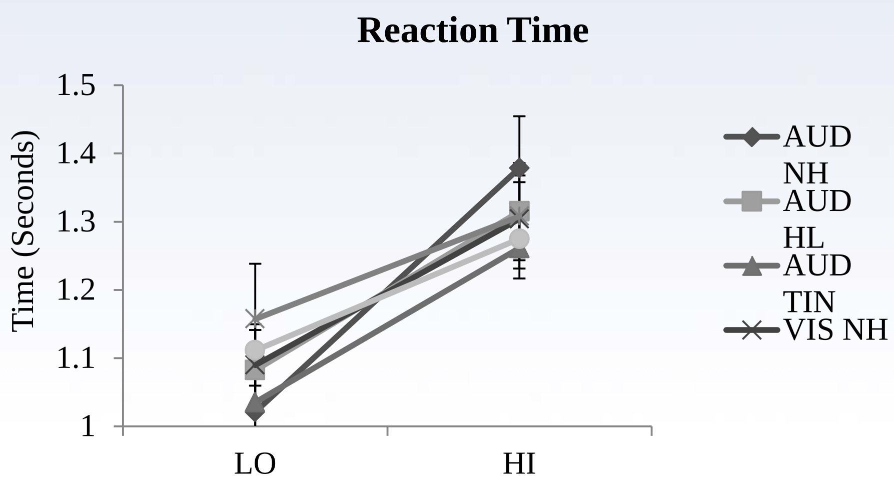
No Behavioral Differences in Auditory or Visual tasks, Varying in Difficulty

(a)



Lo = easy task
Hi = more demanding task

(b)



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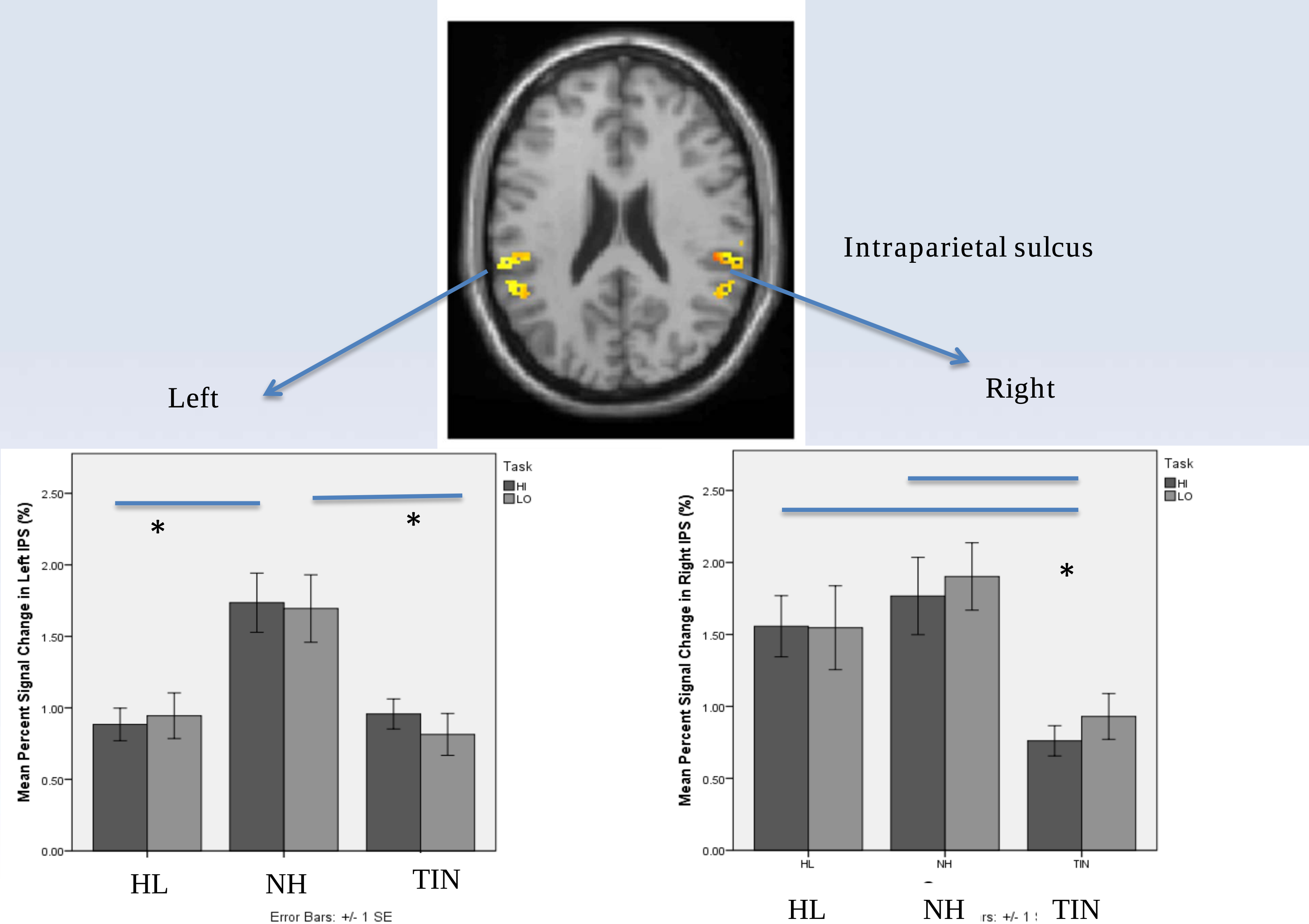
Husain et al., Brain Research, 2015



AUDITORY TASKS: Neural Response

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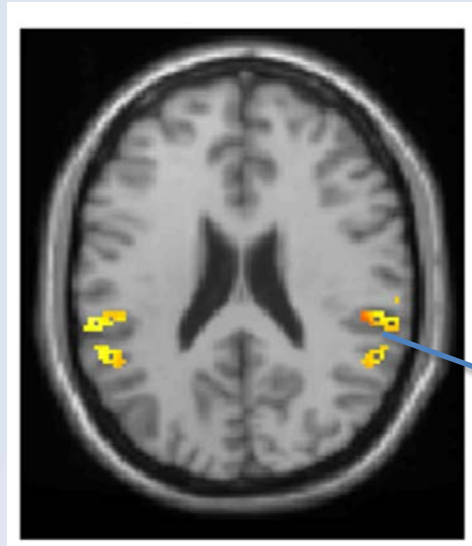
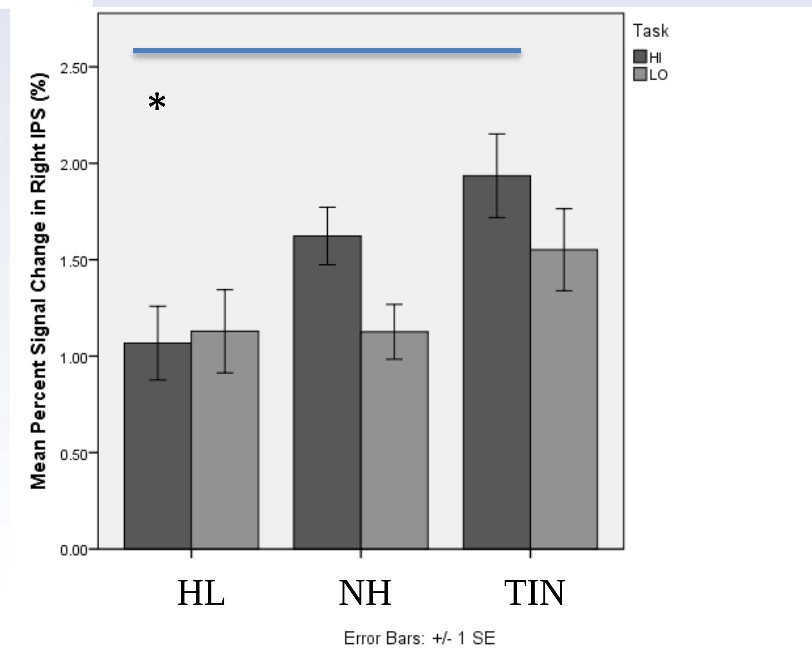


Intraparietal sulcus

Right

Left

No significant difference



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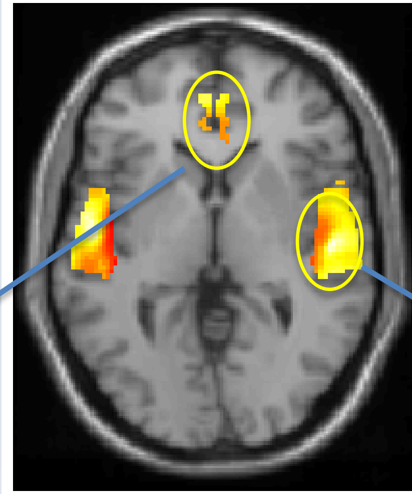
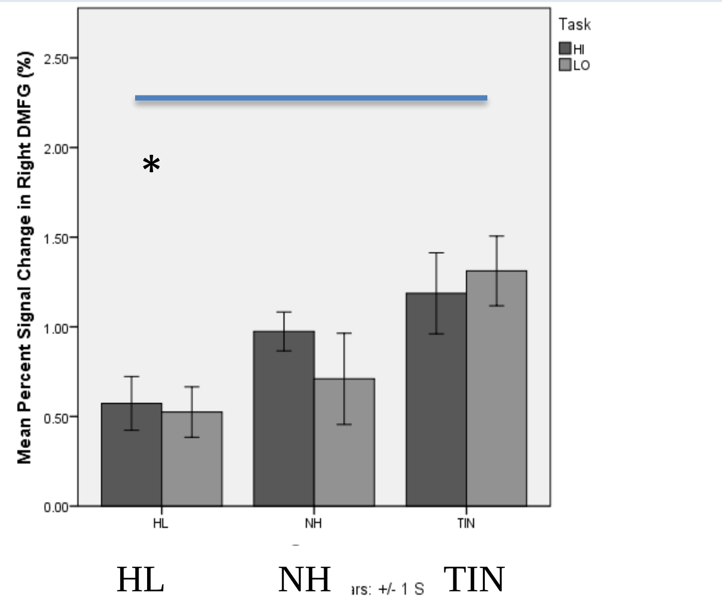
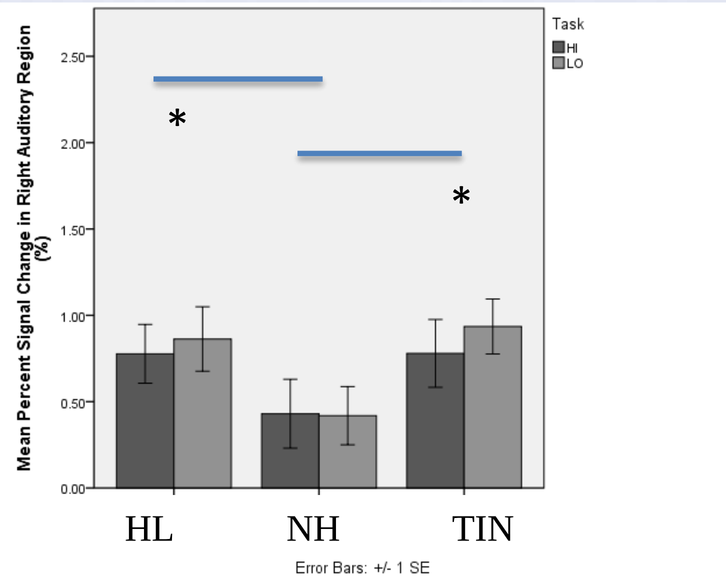
VISUAL TASKS: Neural Response



Dorsomedial Frontal gyrus



Right Auditory Cortex



VISUAL TASKS: Neural Response

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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*

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EMOTION

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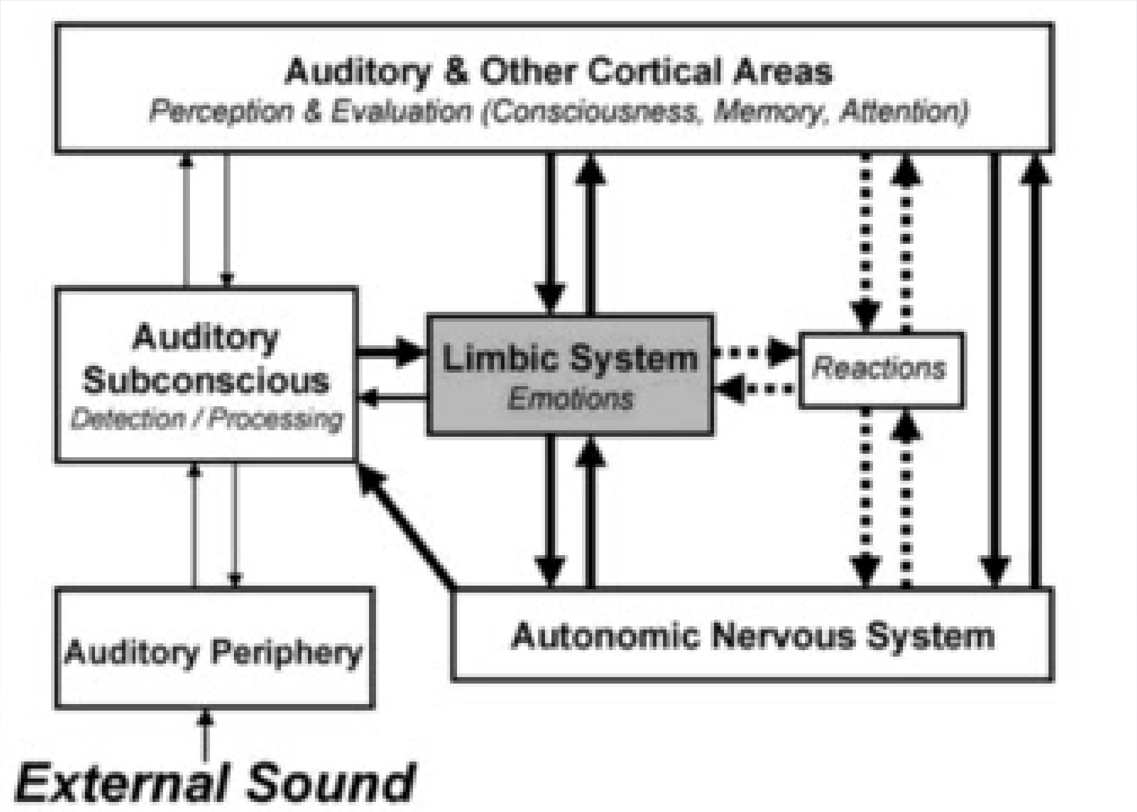
Where does emotion processing happen?

- Periphery and central auditory pathways
- Limbic system
- Frontal cortex

Tinnitus and emotion processing...



Jastreboff, 1990

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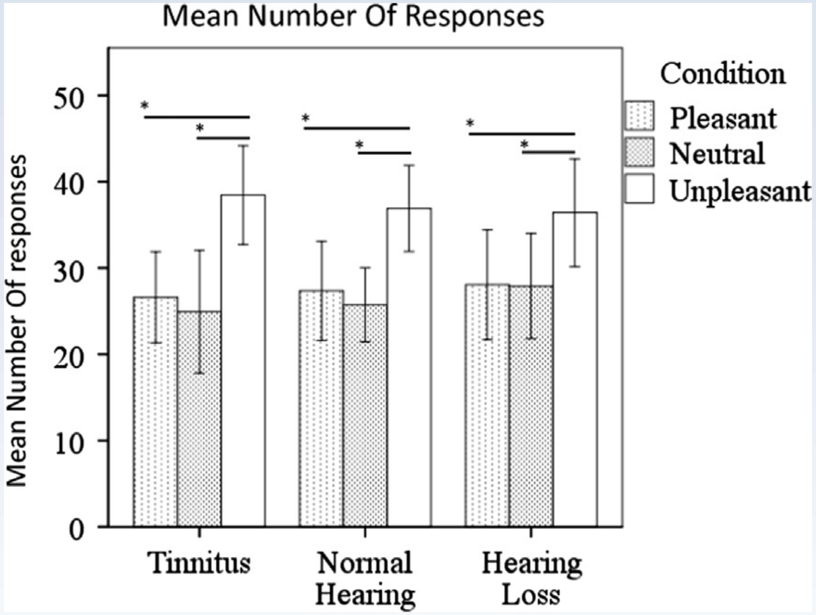
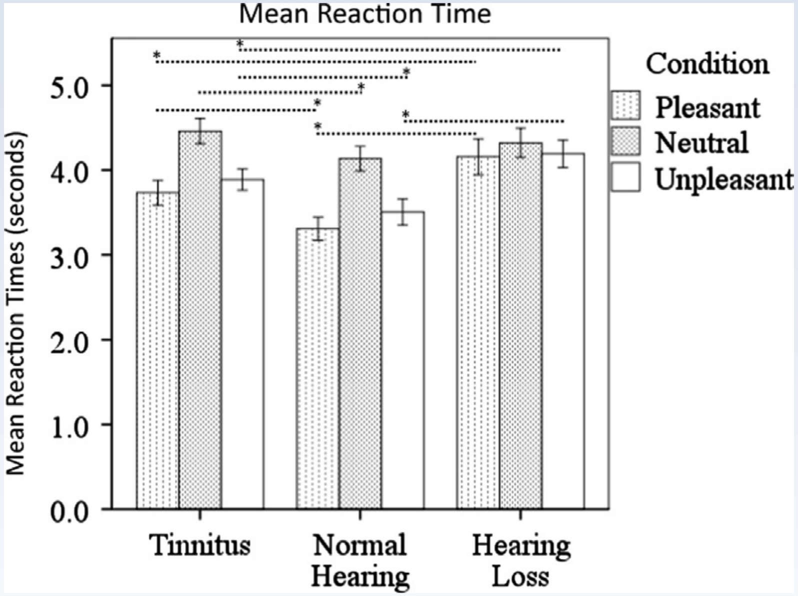
Neural correlates of emotion processing

- 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**

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Carpenter-Thompson et al., Brain Research, 2014

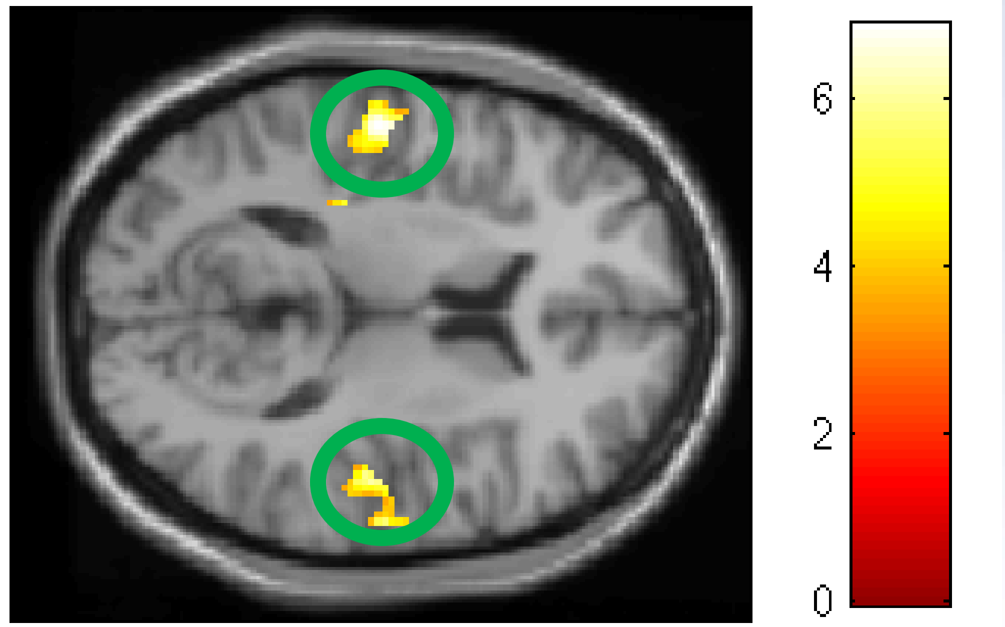
Behavior in Mild & Severe tinnitus

The only behavioral difference was that the Mild group responded significantly faster to Pleasant sounds compared to the Severe group

Carpenter-Thompson et al., PLoS ONE, 2015

Processing Emotional Sounds: Auditory cortex

Mild>Severe Tinnitus



Greater response
In mild tinnitus

Carpenter-Thompson et al., 2016

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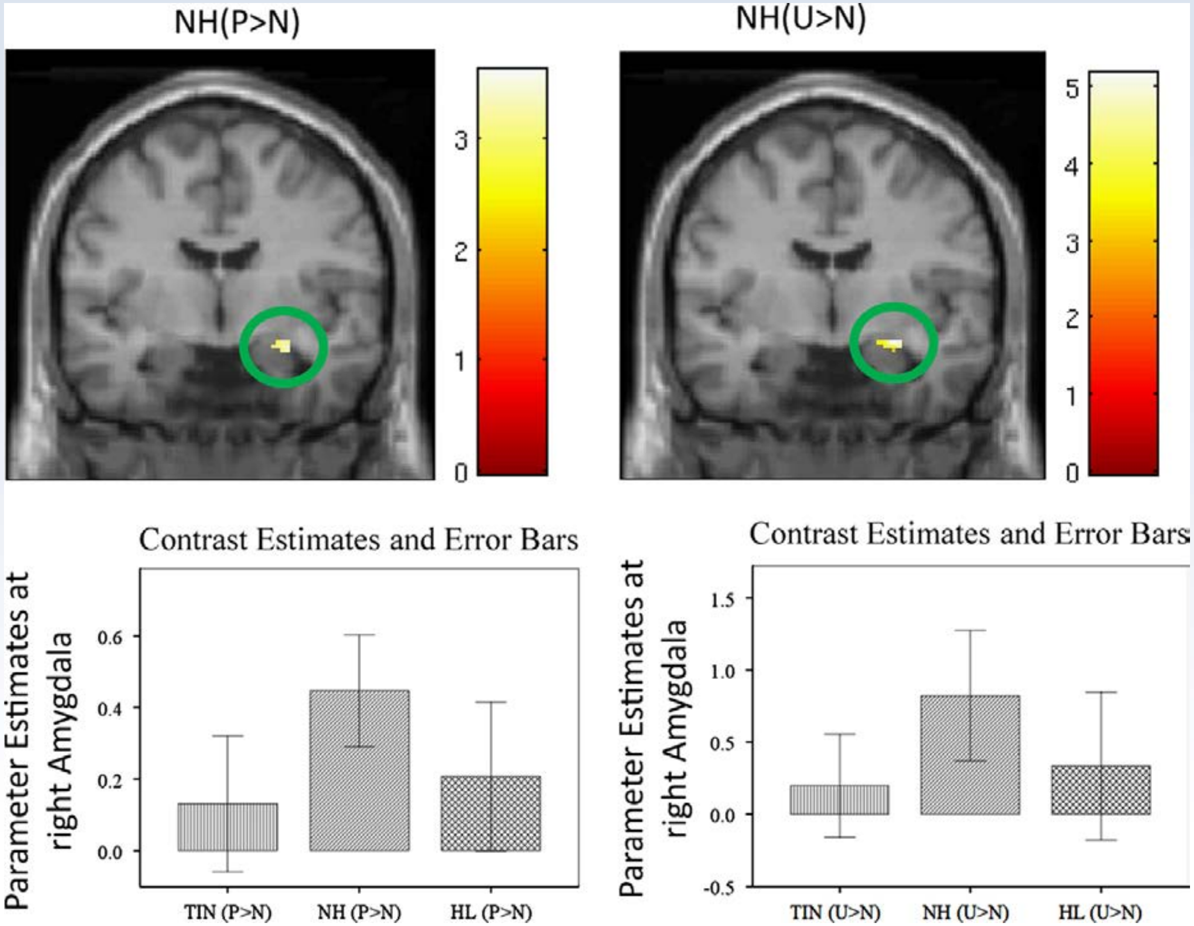
Mild Tinnitus, Processing emotional sounds: Right Amygdala



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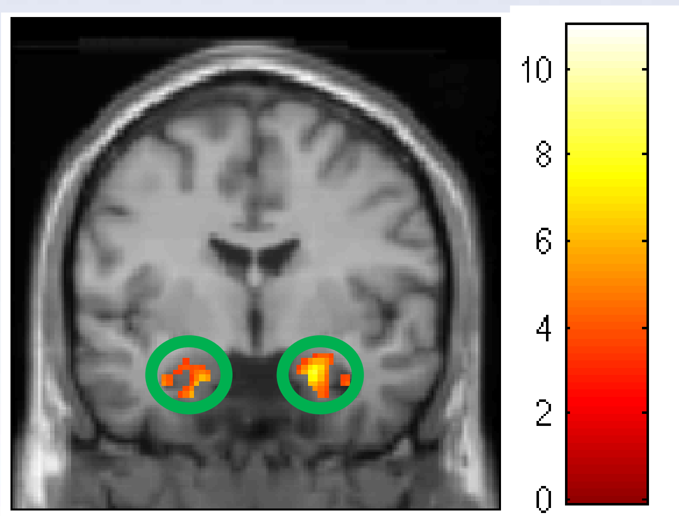
Carpenter-Thompson et al., Brain Research, 2014

Response to emotional Sounds – Varies with Tinnitus Severity

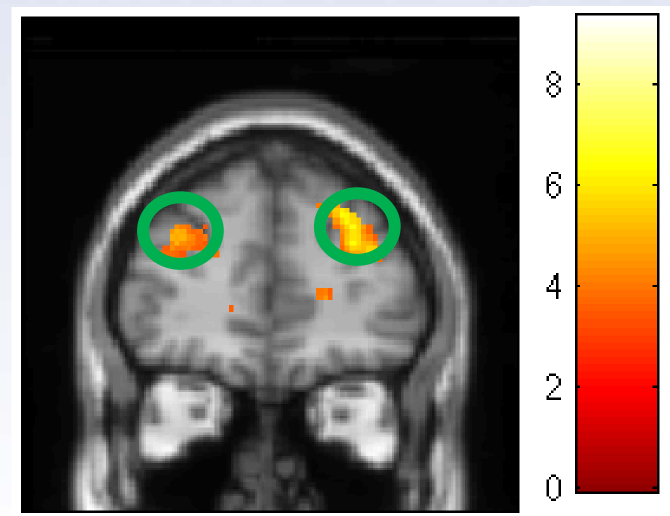
Hyper-response of the amygdala in those with severe tinnitus and more engagement of the frontal cortex in those with mild tinnitus

Severe > Mild tinnitus



Bilateral Amygdala

Mild > Severe tinnitus



Bilateral Frontal Gyri

Carpenter-Thompson et al., Brain Research, 2014
Carpenter-Thompson et al., PLoS ONE, 2015

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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

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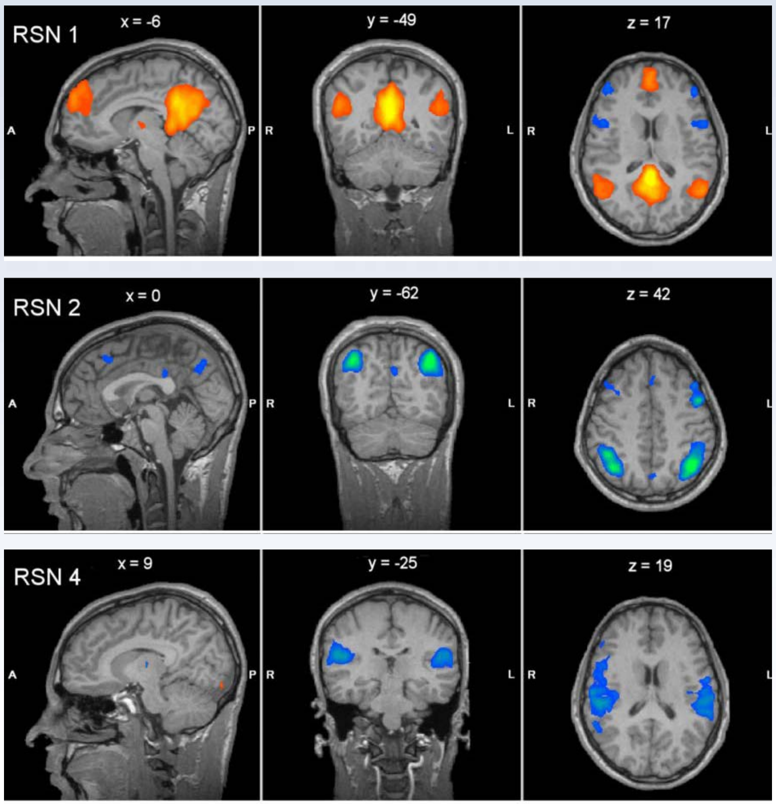
Resting State Functional Connectivity (RS-FC)



Default mode network

Dorsal attention network

Auditory network

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

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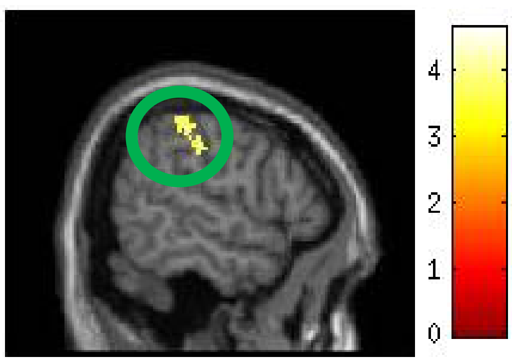
Images from Mantini et al, 2007

Attention

- Decreased connectivity between seeds in Dorsal Attention and Default mode networks and attention-related regions in mild tinnitus

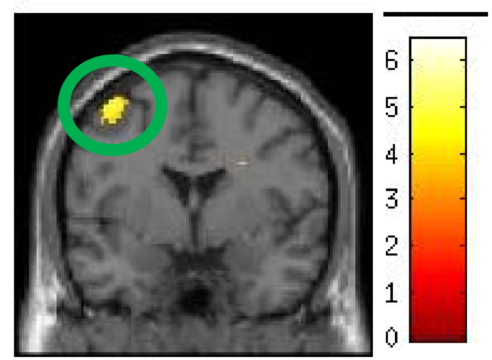
Dorsal Attention



HL>TIN

Right supramarginal gyrus (ips seeds)

Default Mode



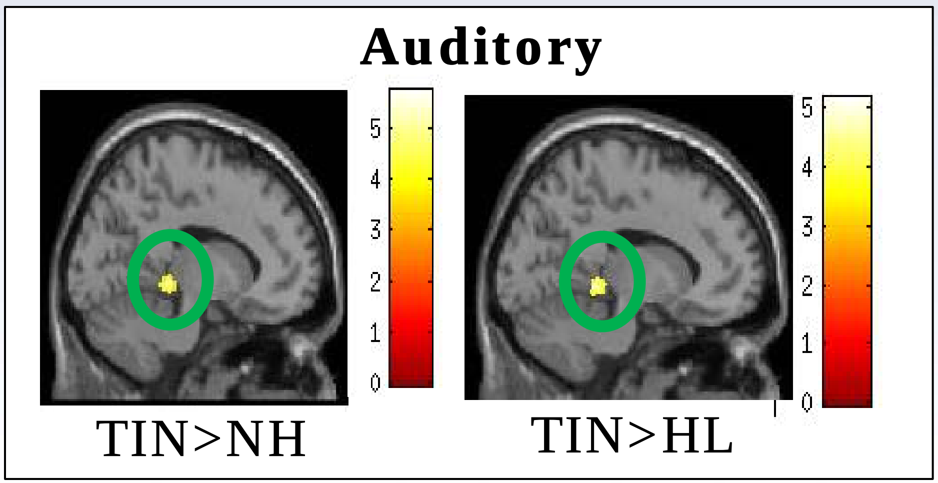
HL>TIN

Left precentral gyrus

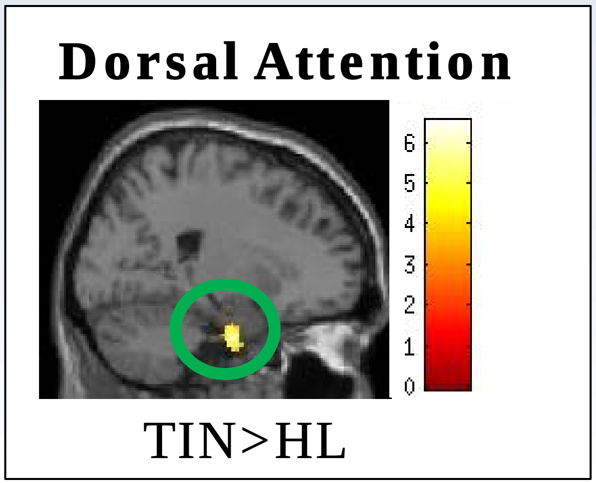
Images from Schmidt et al., PLoS One, 2013

Interaction with Emotion

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



Left parahippocampus
(only a trend vs HL)



Right parahippocampus
(fef seeds)

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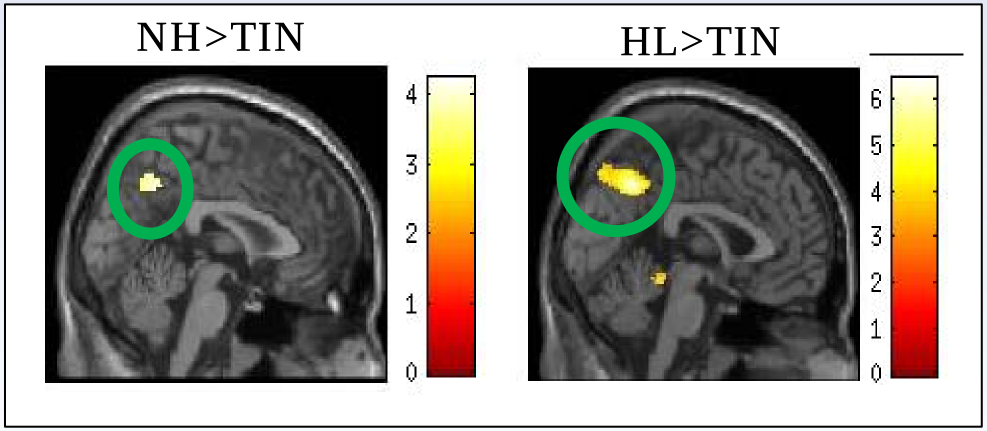
Images from Schmidt et al., PLoS One, 2013

Default Mode Network

- The default mode network is disrupted in tinnitus



Precuneus

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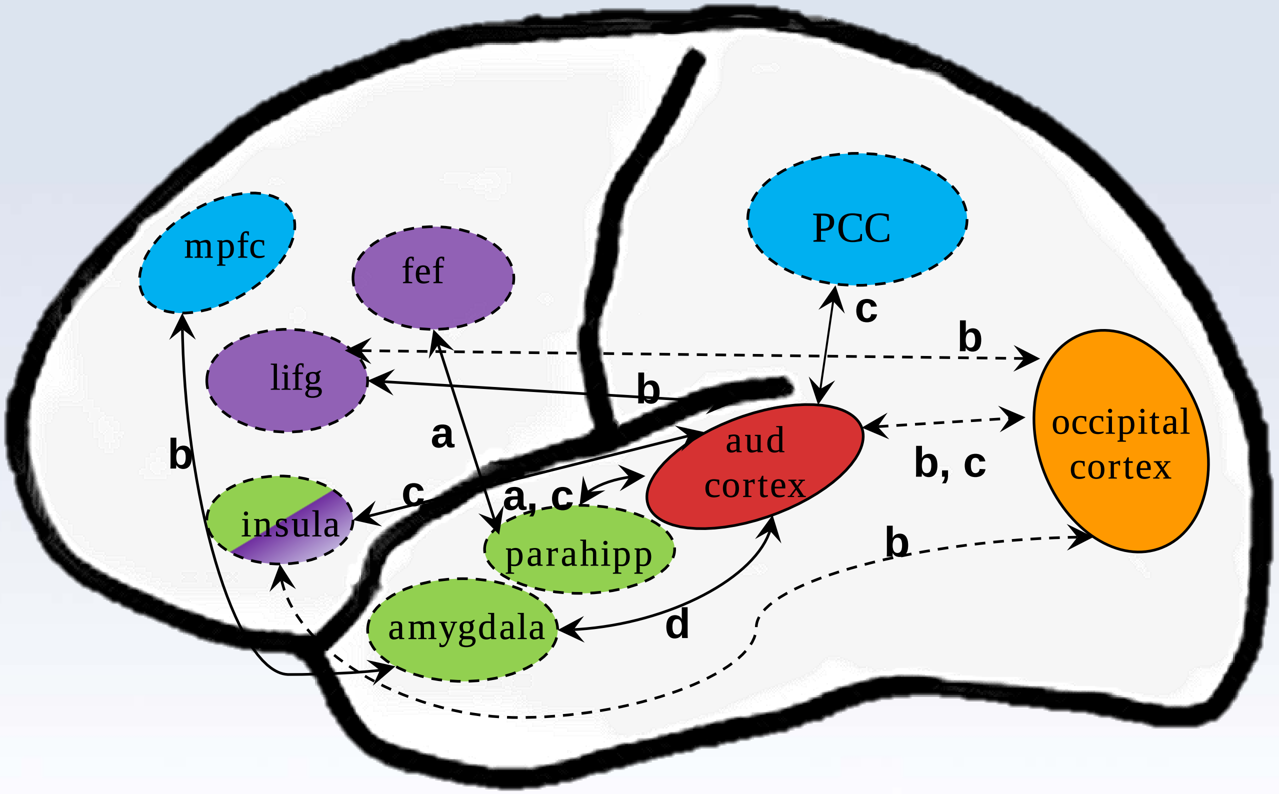
Images from Schmidt et al., PLoS One, 2013

RS-FC findings in tinnitus



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

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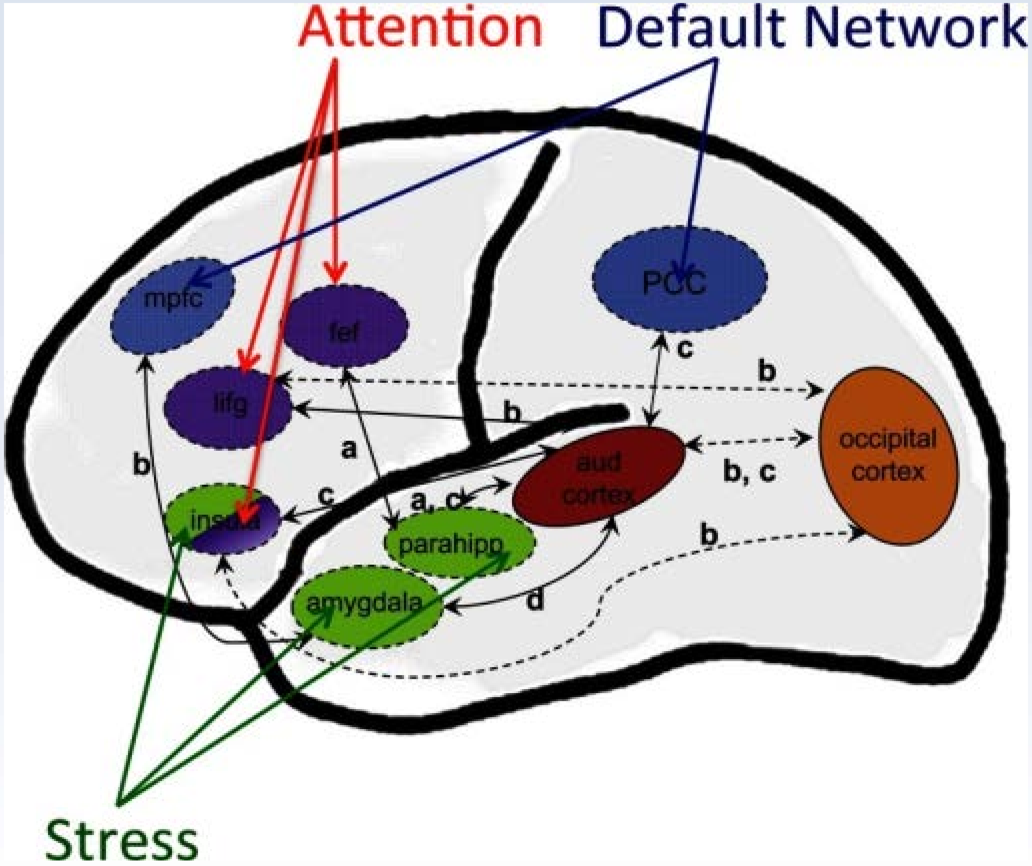
From Husain and Schmidt, 2014



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

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RS-FC in tinnitus across studies

Kim et al, 2012	Group ICA to extract auditory network, ROIs within auditory component
Burton et al, 2012	Seed-based analysis (seed-to-seed, seed-to-voxel)
Wineland et al, 2012	Seed-based analysis (seed-to-seed, seed-to-voxel)
Maudoux et al, 2012a, 2012b	Connectivity graph analysis of auditory component from group ICA
Schmidt et al, 2013	Seed-based analysis (seed-to-voxel)
Ueyama et al, 2013	Regional mean functional connectivity strength (with and without effect autocorrelation coefficient)
Davies et al, 2014	Group ICA to extract auditory network, ROIs within auditory component
Chen et al, 2014	amplitude of low frequency fluctuations (spontaneous neural activity)
Chen et al, 2015a	voxel-mirrored homotopic connectivity (interhemispheric functional connectivity)
Chen et al, 2015b	Regional homogeneity, region of interest (connectivity)
Zhang et al, 2015	Seed-based analysis (in left and right thalamus)

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RS-FC in tinnitus across studies

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

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

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

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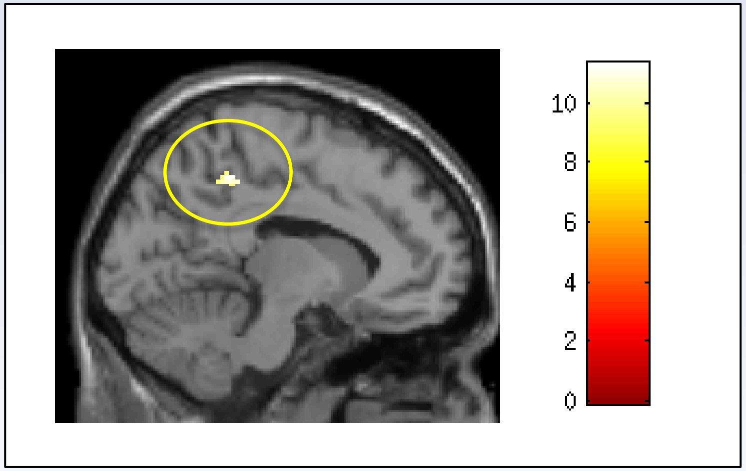
ANOVA results

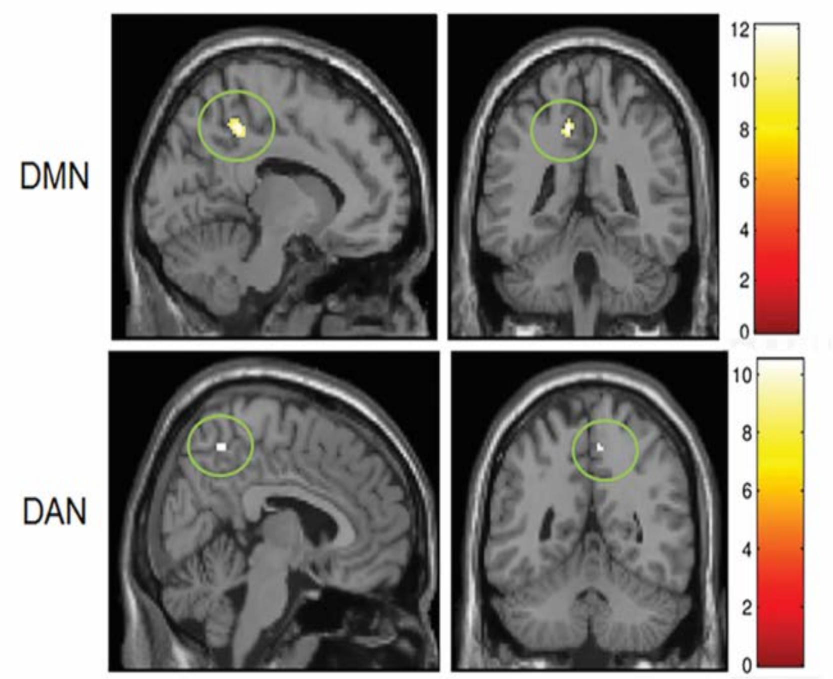


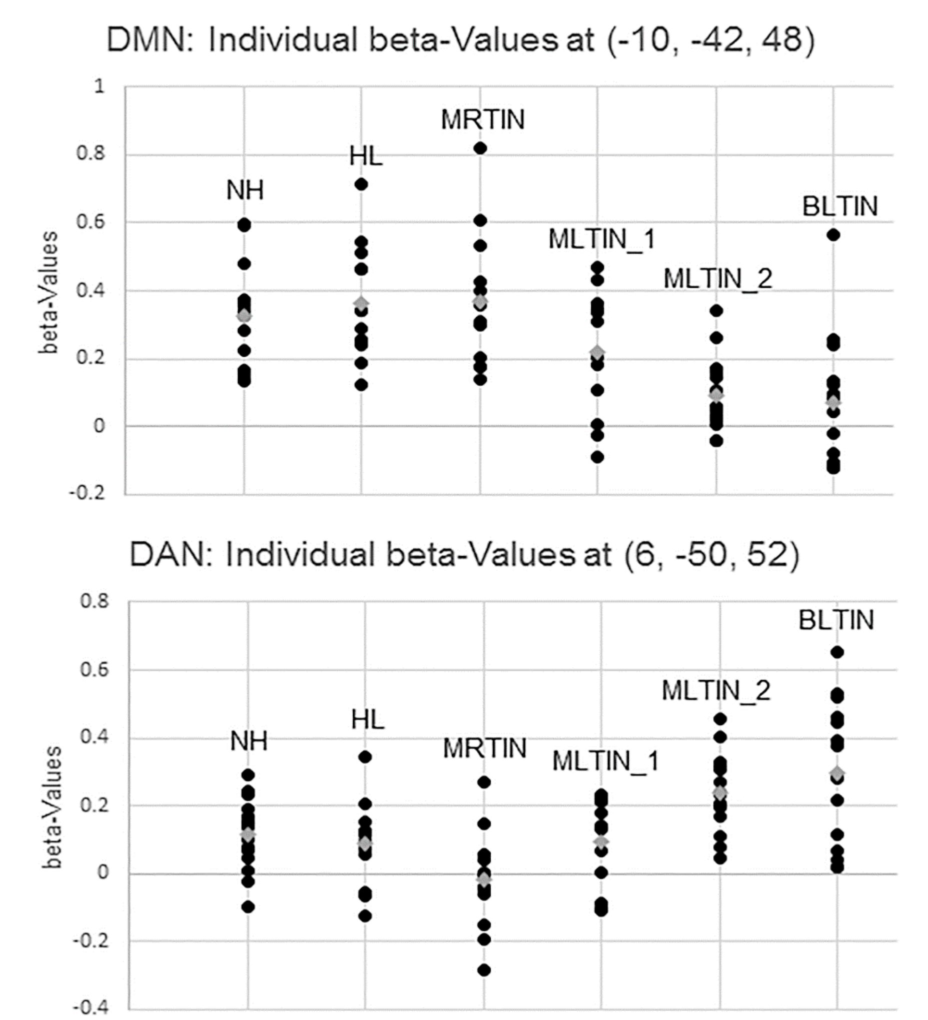
One area of significance at $p < 0.05$ FWE corrected: the precuneus.

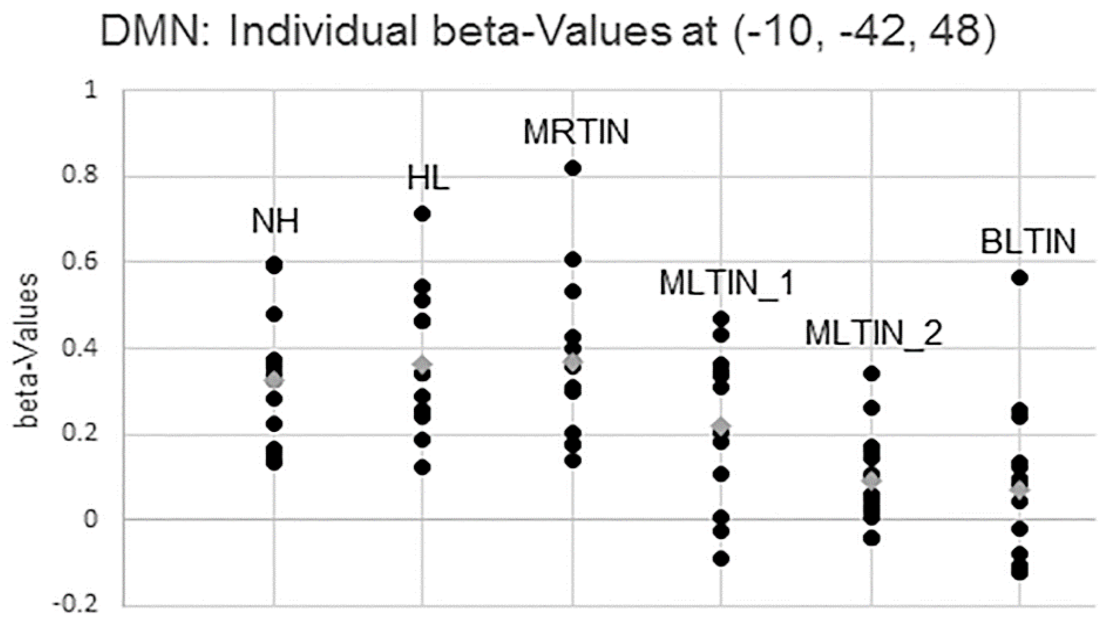
episodic memory, consciousness, visuospatial memory, reflections on self

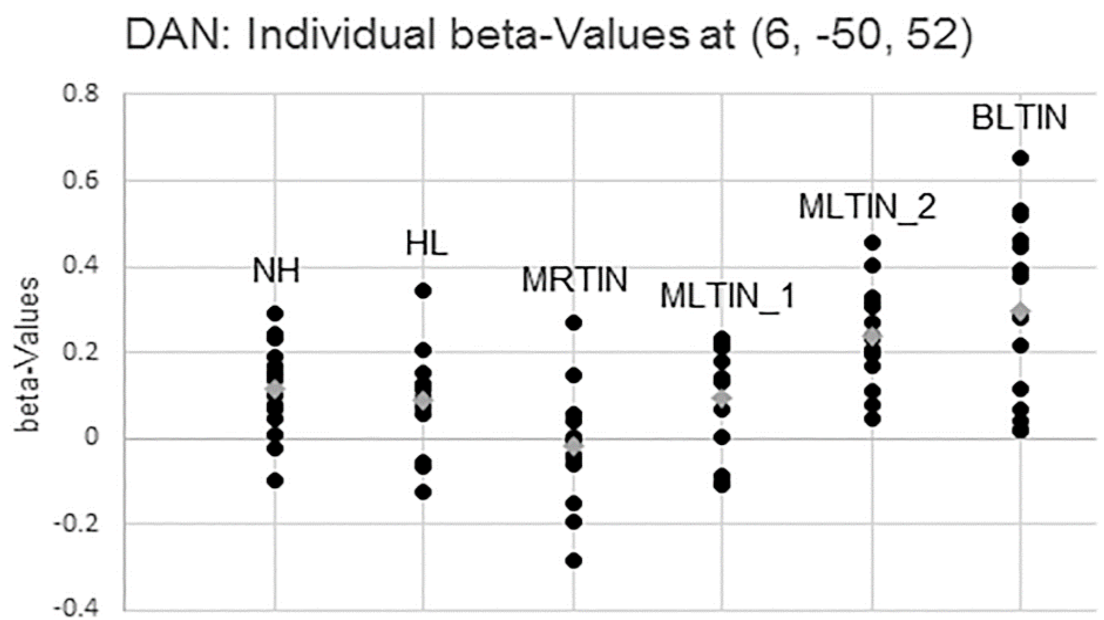
RS-FC connectivity across subgroups

ANOVA
Results









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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?

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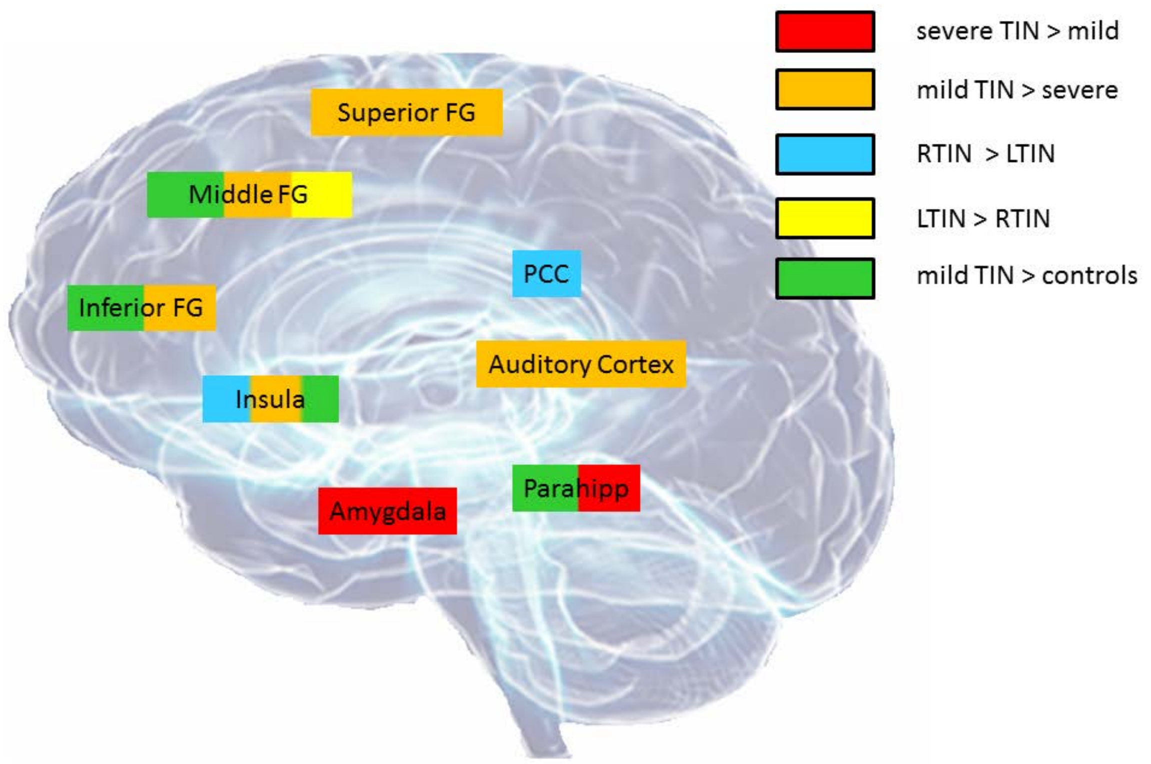
Model of Severity & Habituation: Neural Response

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



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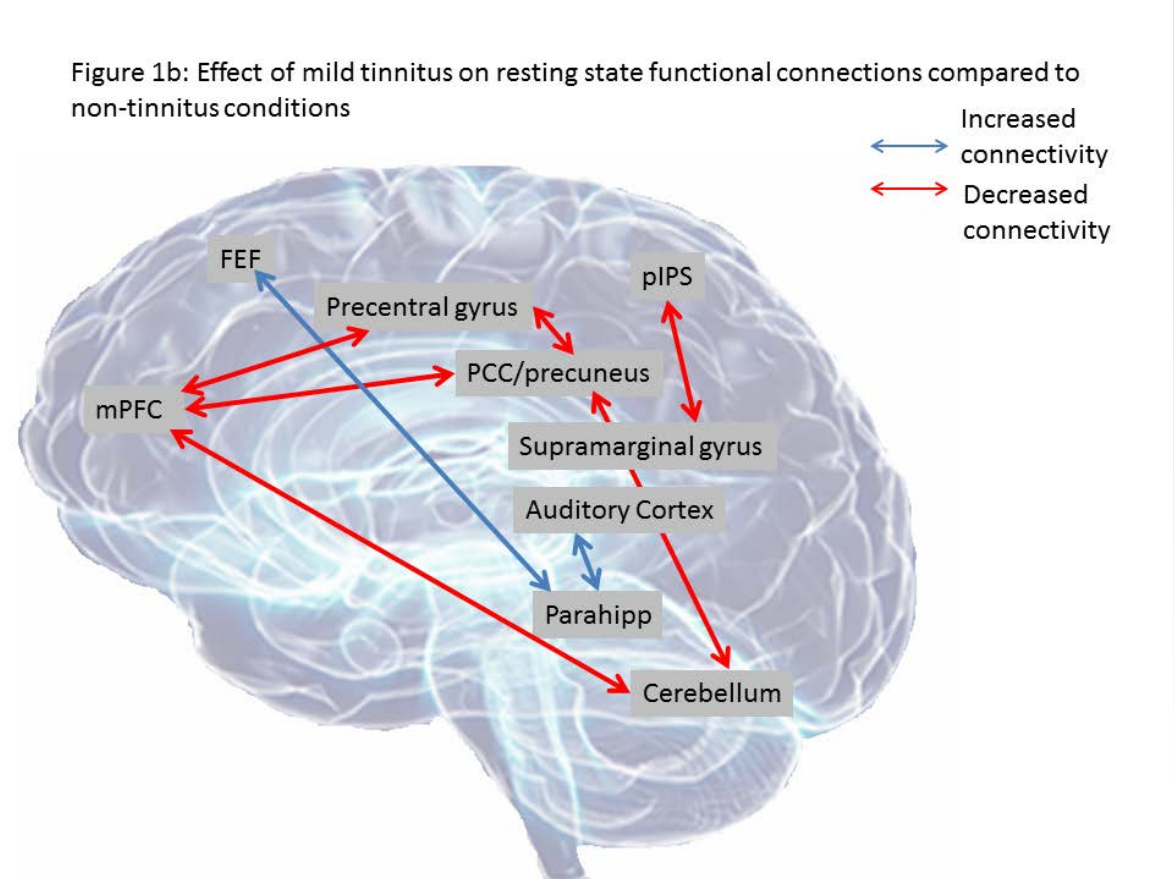
Husain, Hearing Research, 2016

Model of Severity & Habituation: Functional Connectivity



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Husain, Hearing Research, 2016

Cognitive Control of Emotion: Model of Severity & Habituation

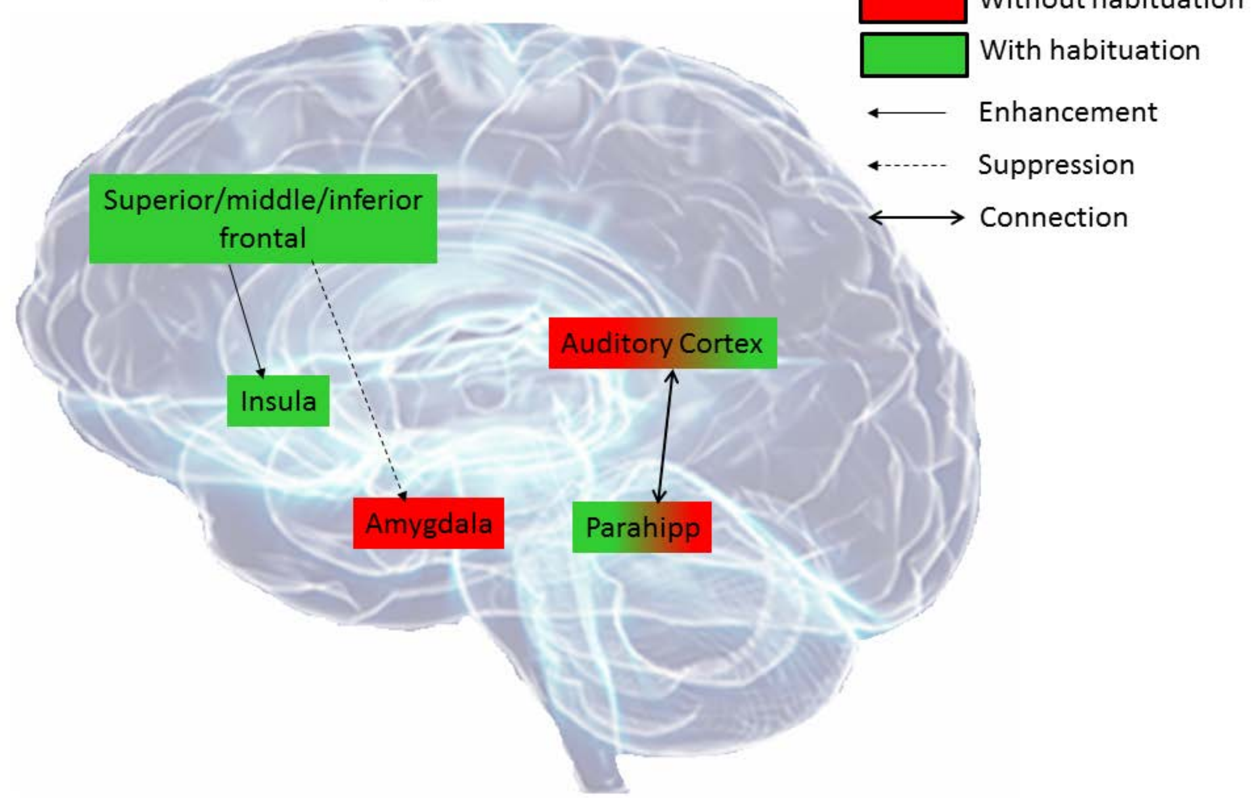

Figure 1c: Proposed model of emotional processing in habituated and non-habituated tinnitus and proposed connections

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Husain, Hearing Research, 2016

Cognitive Control of Emotion

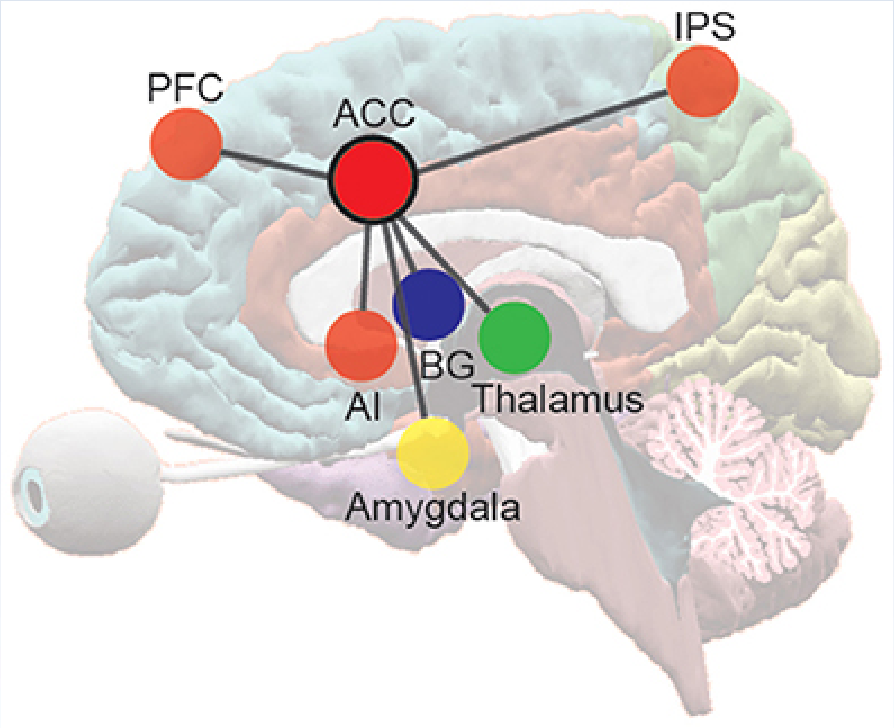

Image from “An information theory account of cognitive control”, Fan, 2016

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

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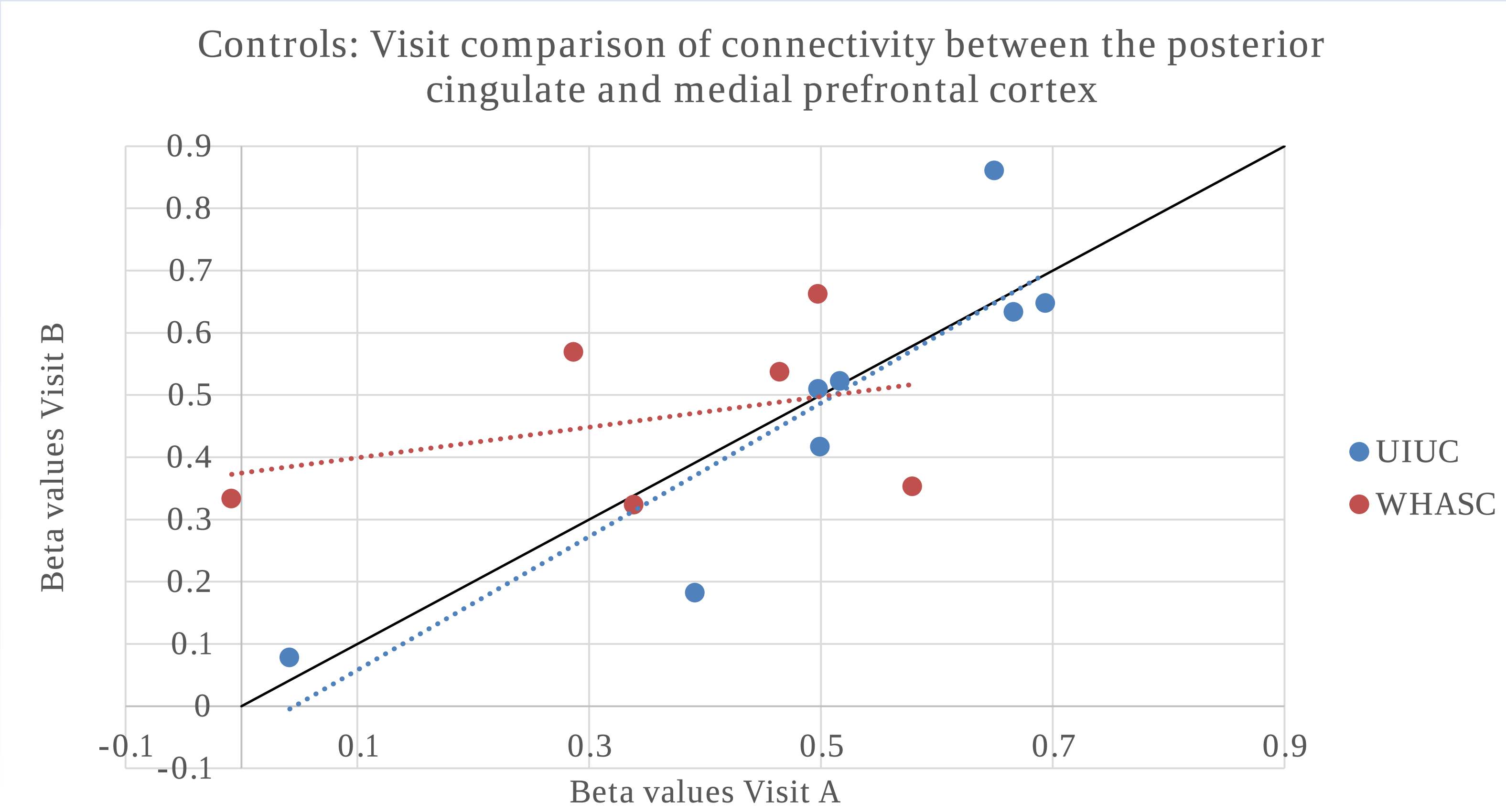
Replication of Default Mode Network Connectivity: Controls



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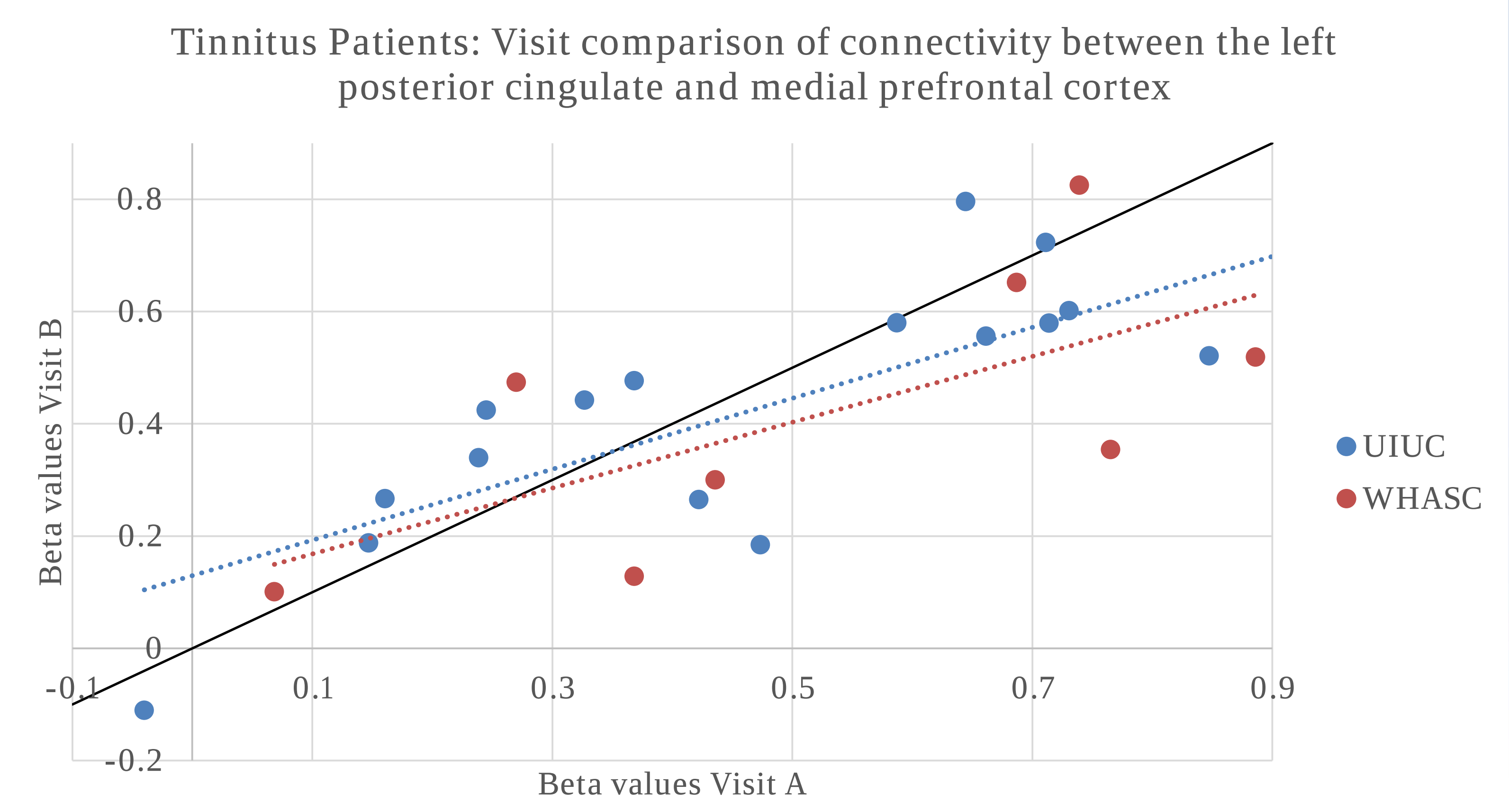
Replication of Default Mode Network Connectivity: Tinnitus



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Schmidt et al., in prep

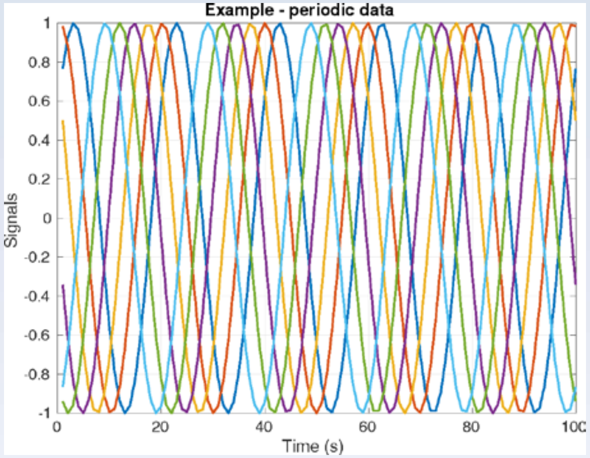
Summary

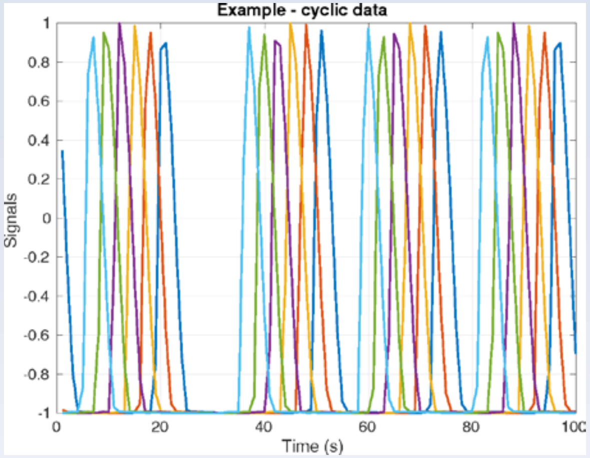
- Resting state functional connectivity appears to be replicable for both controls and participants reporting tinnitus
- Reliable and useful tool to objectively measure impact of tinnitus in the brain
- Over multiple studies and now multiple sites, we are beginning to understand the functional connections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

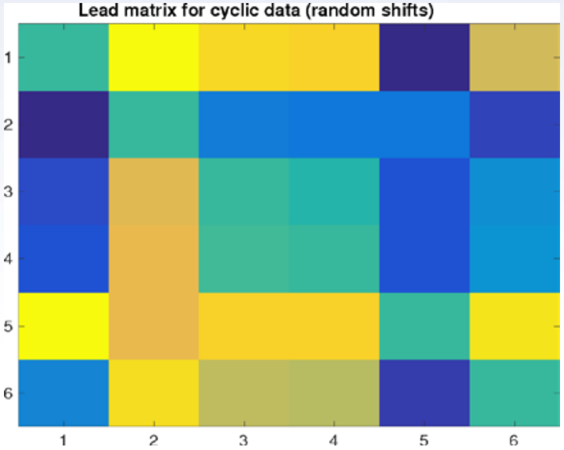
Objective diagnostic biomarkers of tinnitus

DIFFERENTIATING PATIENTS VS. CONTROLS

Cyclicity of fMRI data







- From the cyclicity analysis , it is possible to generate a matrix the defines 'leader-follower' relationships between two signals.
- A different way to look at "functional connectivity"

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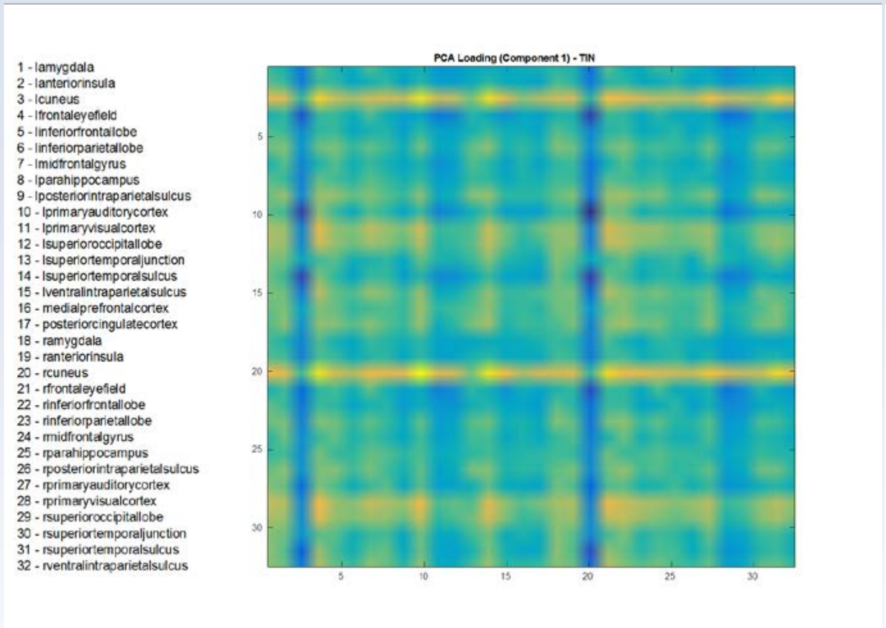
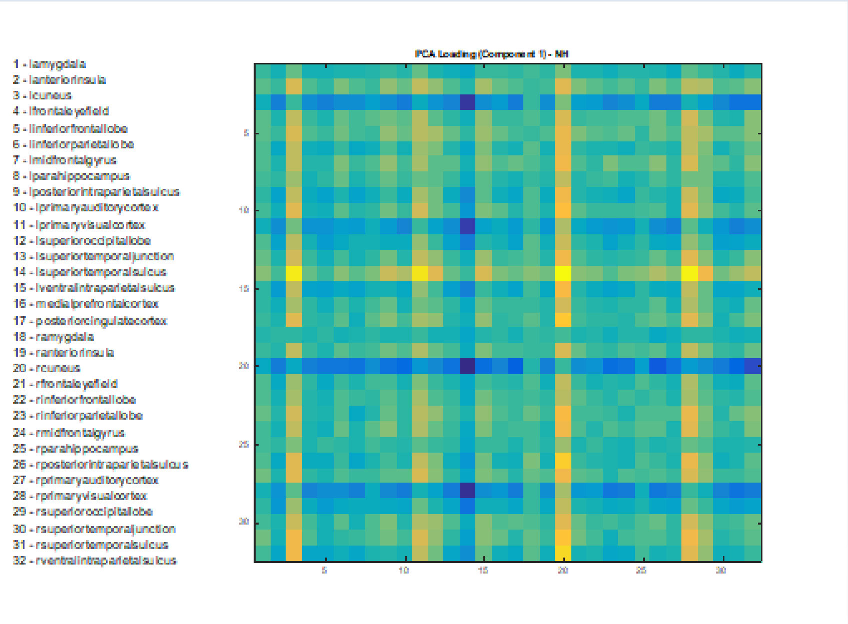
Group lead matrices

Controls



Tinnitus



Certain ROIs have consistently strong leader-follower relationships, but did not differ between groups. Different patterns for patients and controls.

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Classification

Partial Least Squares Discriminant Analysis

Method: PLS-DA (20 components) **Accuracy: 78 %** **Unclassified: 135**		Predicted Group	
		Normal Hearing	Tinnitus
True Group	Normal Hearing	73.0%	27.0%
	Tinnitus	17.4%	82.6%

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

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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

$\Rightarrow$Evaluate interventions

$\Rightarrow$Develop new interventions

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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!

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