Functional and Anatomical Neural Networks of Chronic Tinnitus and Hearing Loss

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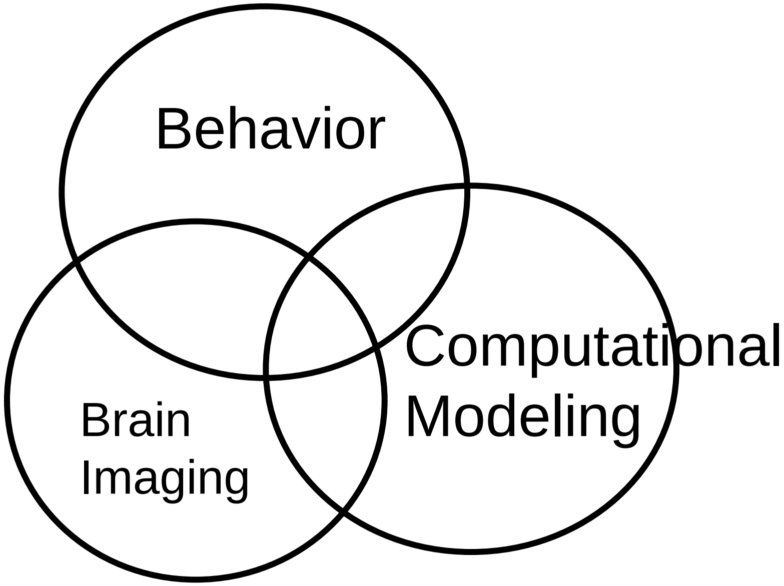
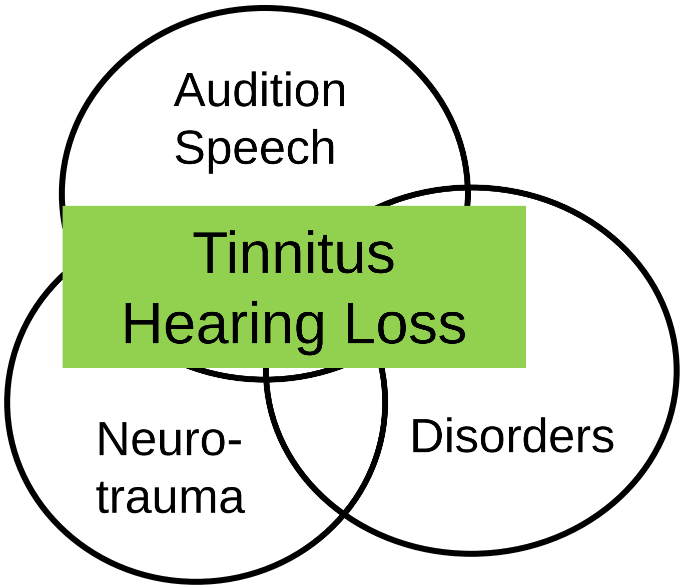
Broad Outline of my talk

TOOLS



QUESTIONS



Tinnitus and/or Hearing loss

- How many service members develop only hearing loss and how many develop hearing loss + tinnitus?
- Which condition is the most annoying and bothersome?
- Is blast-related tinnitus/hearing loss different from non-blast-related tinnitus/hearing loss?

Blast-related tinnitus & hearing loss

- Search keywords “tinnitus” & “blast related” : 7 PubMed articles.
- Numbers improve to 15 if keywords “hearing loss” & “blast related” are used.
- Cave et al.: "Tinnitus can be particularly prevalent for patients who suffer from it secondary to blast injury to their ears, because of the sudden onset of tinnitus in the case of blast injury, instead of the gradual onset of tinnitus developing slowly with progressive hearing loss.”
  - Cave et al., Blast injury of the ear: Clinical update from the global war on terror. *Mil Med.* 2007.
- Fausti et al.: “Auditory system damage resulting from military activity can be caused by blast exposure, noise-induced damage from explosion or weapon firing (acoustic trauma), or ototoxic medications that are used during treatment of injuries and is frequently due to a combination of factors.”
  - Fausti et al., Auditory and vestibular dysfunction associated with blast-related traumatic brain injury , *J. Rehabil. Res. Dev*, 2009.

Blast-related tinnitus & hearing loss

- Noise-Induced Hearing Injury and Comorbidities Among Postdeployment U.S. Army Soldiers: April 2003–June 2009
- Helfer et al., *Am. J. Audiology*, 2011.

Figure 1. Rate comparisons among mild traumatic brain injury (mTBI), posttraumatic stress disorder (PTSD), significant threshold shift (STS), and sensorineural hearing loss (SNHL).

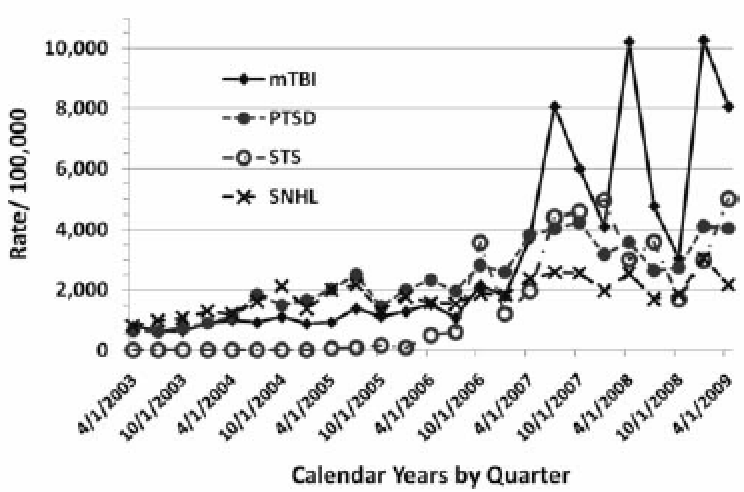


Table 3. Linear regression estimated slope and 95% confidence interval (CI) by diagnostic code group.

Diagnostic code group	Slope	95% CI
Tinnitus	75.2*	[57.6, 92.7]
Tympanic membrane perforation	8.4*	[4.3, 12.4]
Speech and language disorders	14.7*	[11.2, 18.2]
Dizziness	33.5*	[25.5, 41.6]
SNHL	56.9*	[35.2, 78.5]
NIHL	0.6	[–9.3, 10.5]
PTSD	140*	[110, 171]
STS	206*	[143, 269]
mTBI	329*	[217, 441]

*Significantly increasing slope, $p < .05$.

Rates of incidence of blast-related tinnitus and hearing loss

- TBI before OIF* (non-blast related): 28% hearing loss, 11% tinnitus (ratio: 2.5)
- TBI after OIF
  - Non-blast related: 44% hearing loss, 18% tinnitus (ratio: 2.44)
  - Blast related: 62% hearing loss, 38% tinnitus (ratio: 1.63)
    - Greater incidence of tinnitus with blast-related injuries but hearing loss without tinnitus occurs 1.6 times more often. Are there different neural mechanisms subserving blast-related and non-blast-related tinnitus?

*OIF: Operation Iraqi Freedom

Source: Lew et al., Auditory dysfunction in traumatic brain injury, *J. Rehabil. Res. Dev*. 2007

Research Goals

1. Distinguish neural bases of tinnitus & hearing loss from those of hearing loss alone

2. Develop objective biomarkers of subjective tinnitus

Study I: Differences in functional networks

Dissociate the functional networks of brain regions affected by chronic tinnitus from those affected by hearing loss, using a short-term memory (attentional) task.

Background

Increasing evidence from brain imaging studies suggests large-scale neural networks subserving attention, cognition, and emotion are affected in tinnitus (Cacace, 2003; Giraud et al., 1999; Lockwood et al., 2001; Mirz et al., 2000)

Short-term working memory / Attention network for auditory stimuli has been examined in normal hearing adults, but far less in individuals with hearing loss and tinnitus (brain imaging studies).

Subjects

Three subject populations

- TIN – Tinnitus + Hearing Loss (n = 8)
  - age range = 42-64, <u>mean = 56.13</u>
- HL – Hearing Loss without Tinnitus (n = 7)
  - age range = 31-64, <u>mean = 51.38</u>
- NH – Normal Hearing (n = 11)
  - age range = 32-63, <u>mean = 48.09</u>

All male subjects

TIN subjects had tinnitus for 3-38 years

- Non-pulsatile, subjective, chronic bilateral (not lateralized) tinnitus, various descriptions: buzzing, clear tone, whistle, cicadas
- Well-adjusted to chronic tinnitus; Tinnitus Handicap inventory score in mild range = 10-26
- Excluded: hyperacusis, misophonia, trans-mandibular joint (TMJ) issues
- No changes in hearing or tinnitus status
- According to self-report, TIN group experienced tinnitus during scanning

Tasks

Stimuli: Pure tones, tonal sweeps (up-down, down-up) 500 ms in duration

Low-pass filtered up to 2 kHz, every participant could hear the sounds (verified by pretesting and behavioral responses)

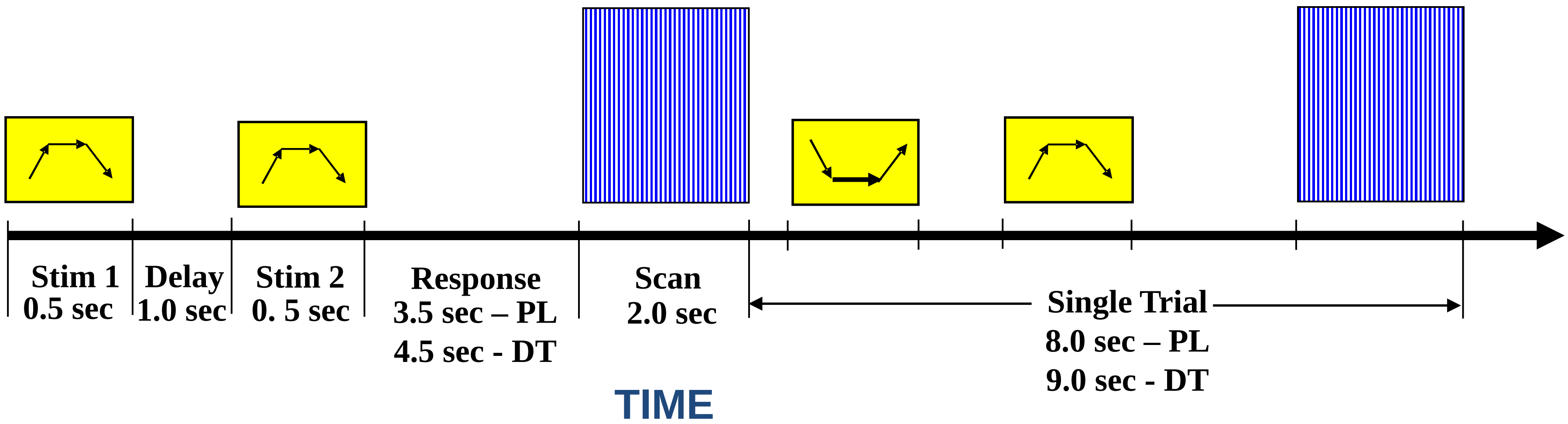
Passive Listening (PL): pairs of stimuli (either tones or sweeps), listen, no response

Discrimination Task (DT): pairs of stimuli (either tones or sweeps), indicate same or different via button presses

Brief pre-training of 5-10 mins prior to scanning

Similar behavior across all three groups – above 90% accuracy. No significant difference in reaction times

fMRI: clustered acquisition

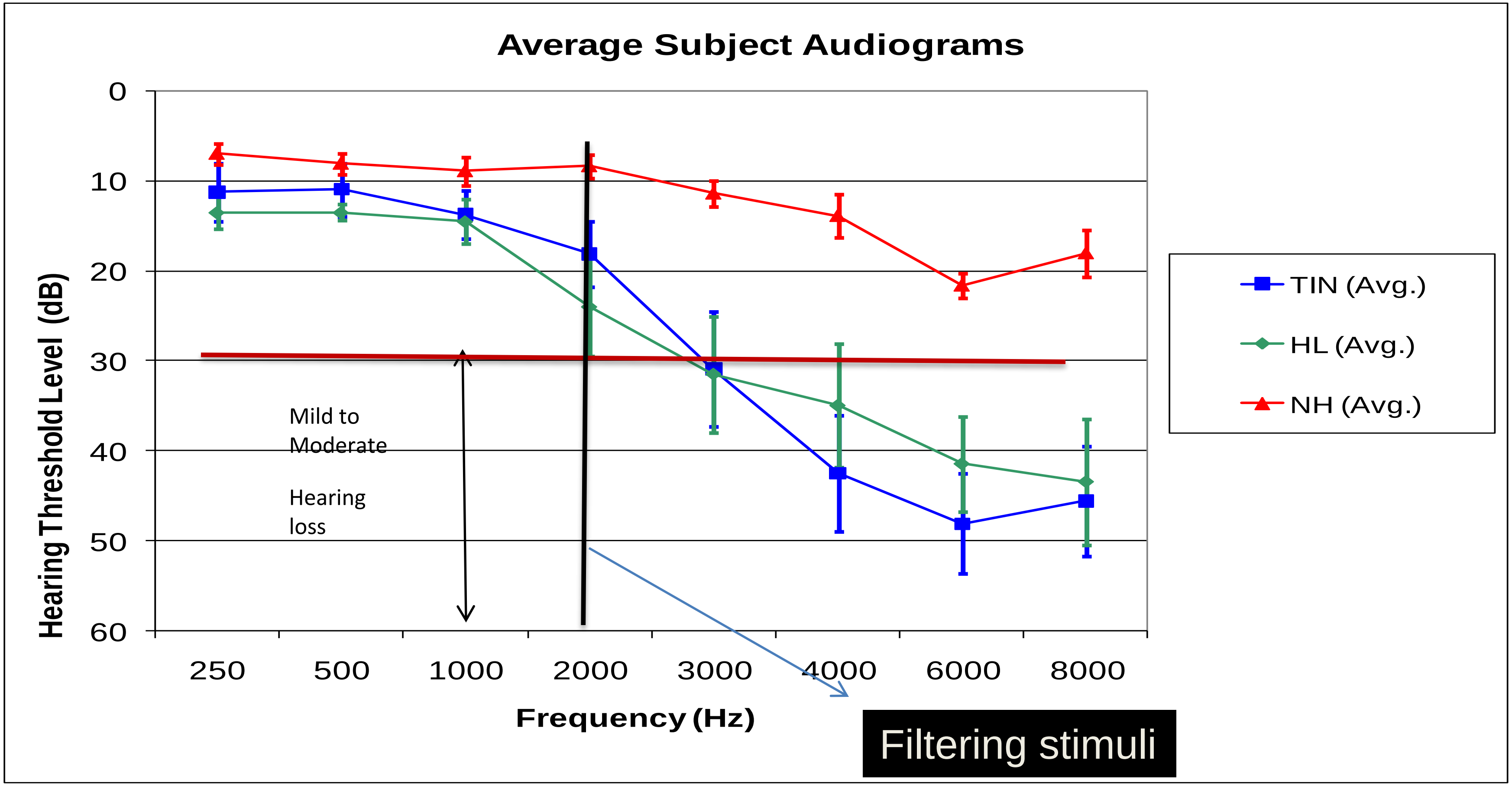


Reduced noise during sound presentation. Radio frequency gradients (major source of MRI noise) turned on only during image acquisition (scan). Relative silence during sound presentation.

3T GE scanner, 32 interleaved slices, whole-brain image acquisition.

Data analysis using SPM5 software: realignment, normalization, smoothing, fixed effects analysis

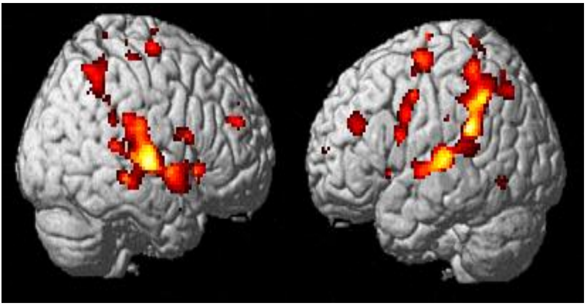
Subject Groups & Hearing Profiles



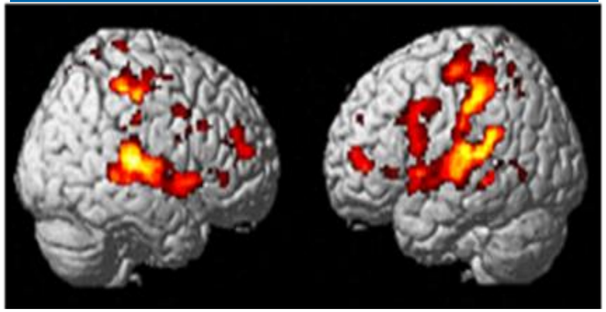
All groups : Discrimination task > rest

No difference in behavior, but difference in fMRI patterns.

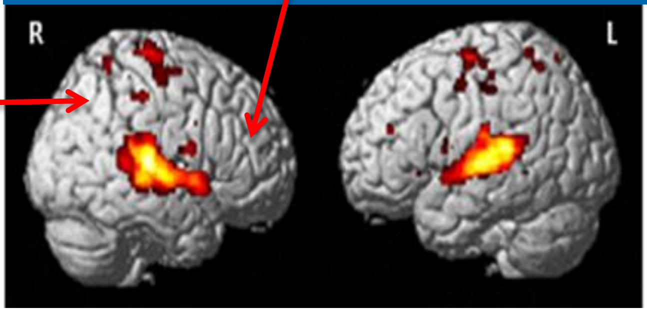
Normal Hearing



Hearing Loss

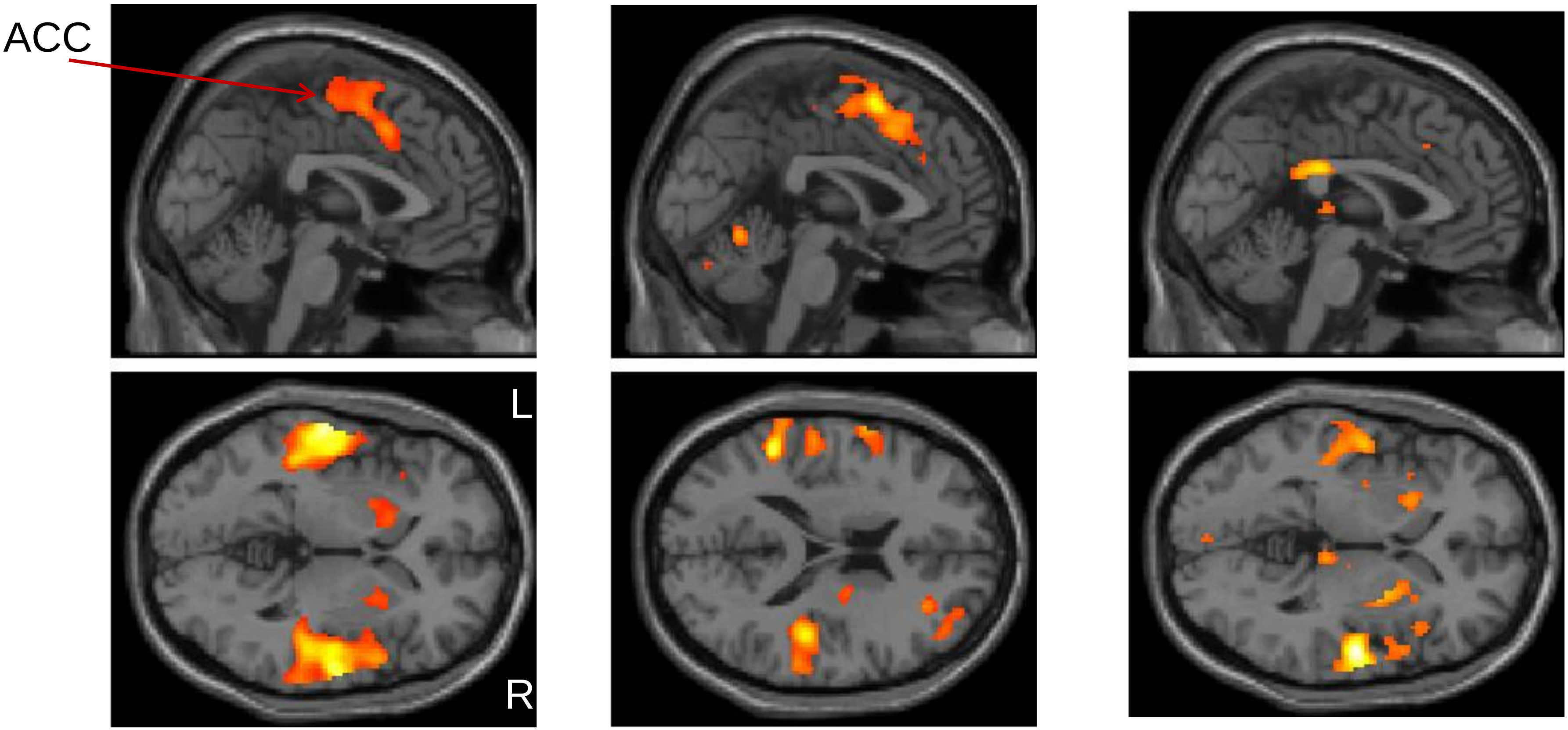


Hearing Loss + Tinnitus



Husain et al., PLoS ONE, *in press*

HL+ Tinnitus | Hearing Loss (HL) | Normal Hearing



ACC= ant. Cingular cortex

Husain et al., PLoS ONE, *in press*

Discussion – Study I

High frequency hearing loss affects perception and discrimination of low frequency sounds.

Differential response of working memory / attentional network:

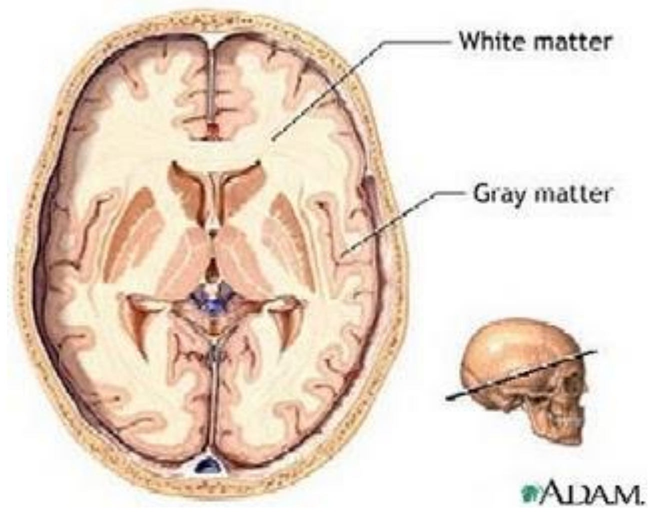
> *Hearing Loss: Maximize attentional resources to compensate for hearing impairment*
>
> *Tinnitus + Hearing Loss: Modulate attentional resources, ignore distracter (tinnitus sound) while attending to external stimulus*
>
> *Neural plasticity changes in those with tinnitus + hearing loss differ from those with hearing impairment alone*

Explicitly testing these predictions in our current fMRI studies

Study II: Differences in anatomical networks

1. Gray Matter: Changes in volume of neuronal cell bodies using voxel-based morphometry

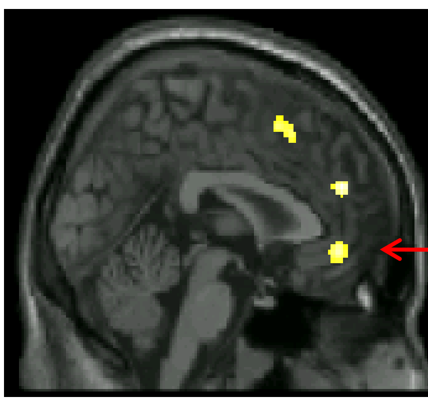
2. White Matter: Changes in orientation of neuronal tracts using diffusion tensor imaging



Gray matter - Results

- No changes in volume for TIN when compared to NH group
- Declines in gray matter volume in HL group when compared to both NH & TIN groups

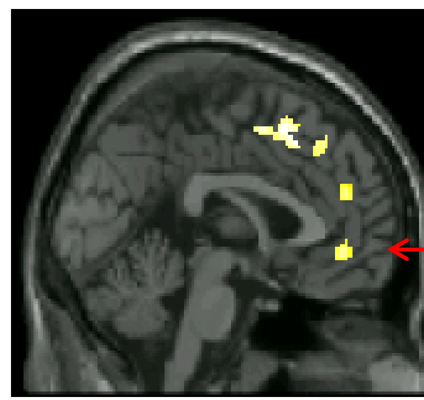
HL<NH



ACC

x= 2

HL<TIN



ACC

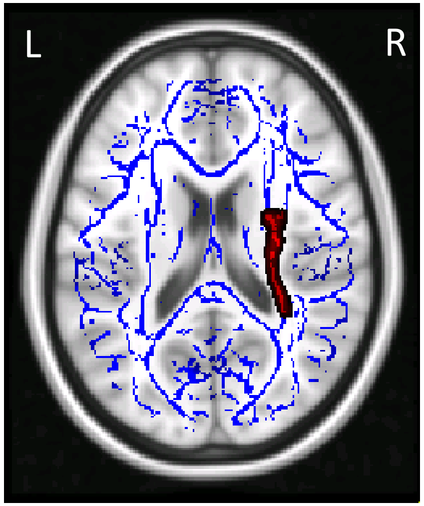
x= 0

Husain, et al., *Brain Research,* 2011

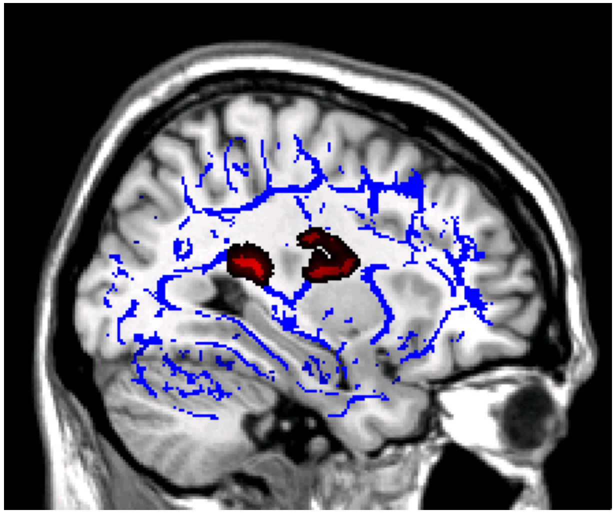
White matter- Results

- No statistical significant differences in HL compared to TIN or TIN and NH.

- Changes in orientation values (Fractional Anisotropy, FA) of white matter tracts (indicative of poor microstructure integrity) for HL compared to NH.



z= 15

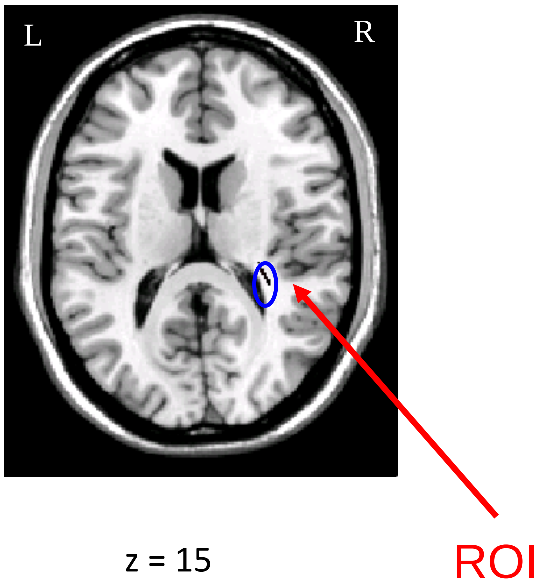


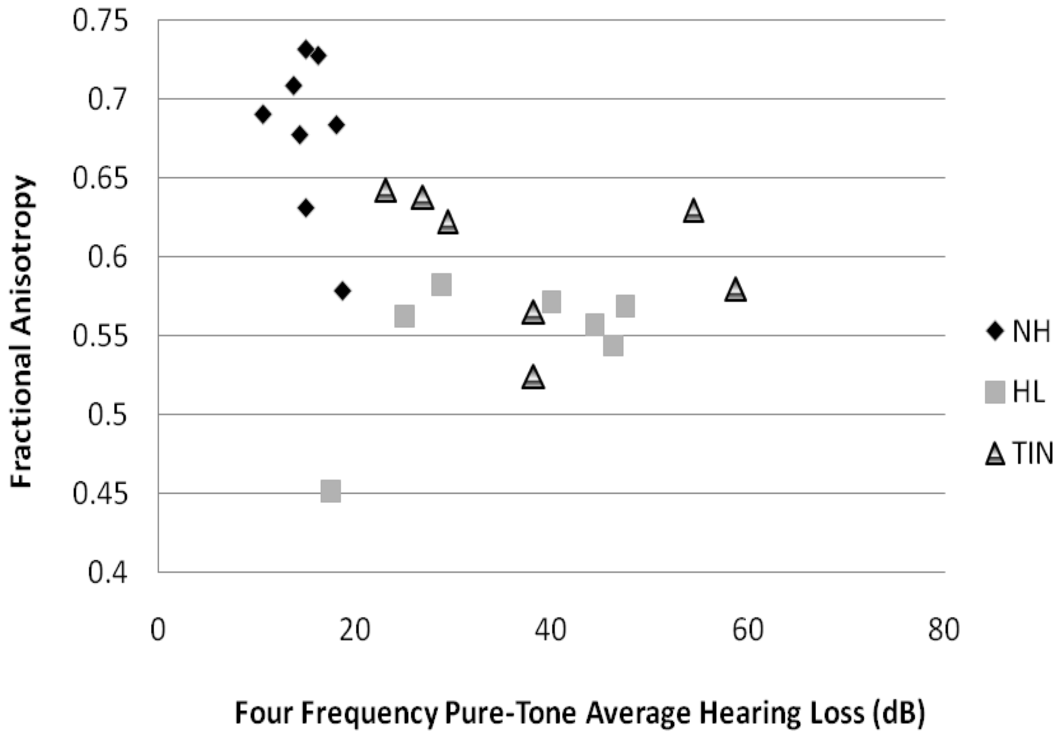
x = 31

HL < NH

Husain, et al., *Brain Research*, 2011

Imaging biomarkers of tinnitus and hearing loss





FA from a defined ROI vs. Hearing loss for the groups.
FA values decreased with increasing hearing loss → poorer organization of pathways as hearing loss worsens.

Discussion – Study II

- More profound changes in HL compared to TIN or NH groups, whether in gray matter or in white matter.
- For the groups considered, tinnitus appears to have a ‘neuro-protective’ effect on hearing loss-related plasticity
- Caveat: Effect of normal aging on white and gray matter changes not taken into account.
- More studies with larger cohorts needed to verify results.

Implications for TBI or blast-related hearing loss and tinnitus

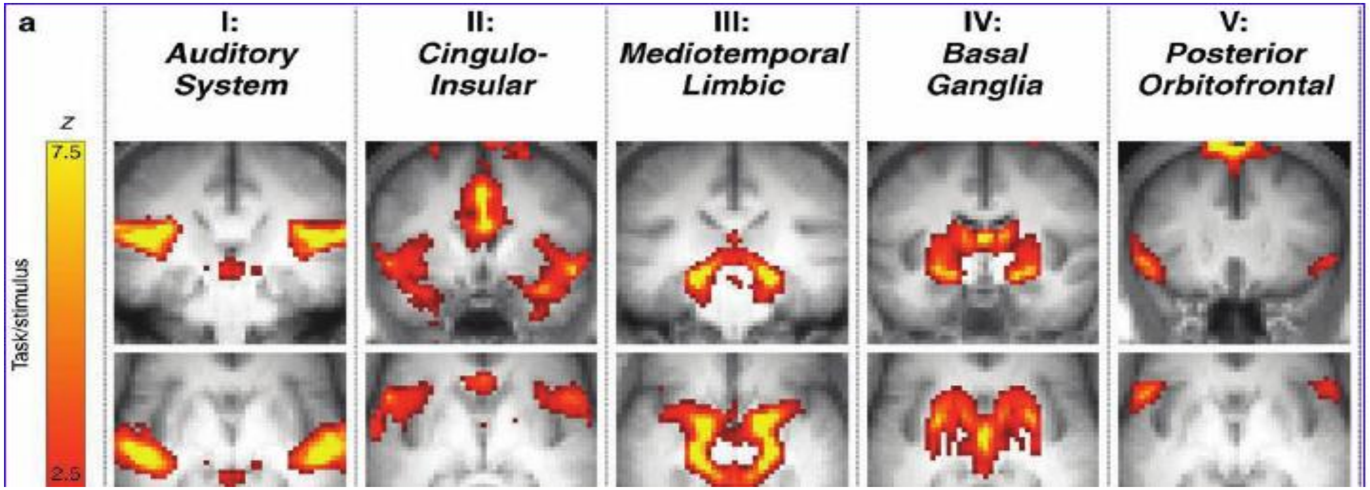
1. Assessments: evaluate TBI aspects, evaluate attentional, emotional networks, evaluate changes in structure using MRI (especially, diffusion tensor imaging) and fMRI. Relate imaging biomarkers with extent of injury and severity of tinnitus.

2. Therapies: use brain imaging to evaluate effects of different therapies, e.g. progressive tinnitus management.

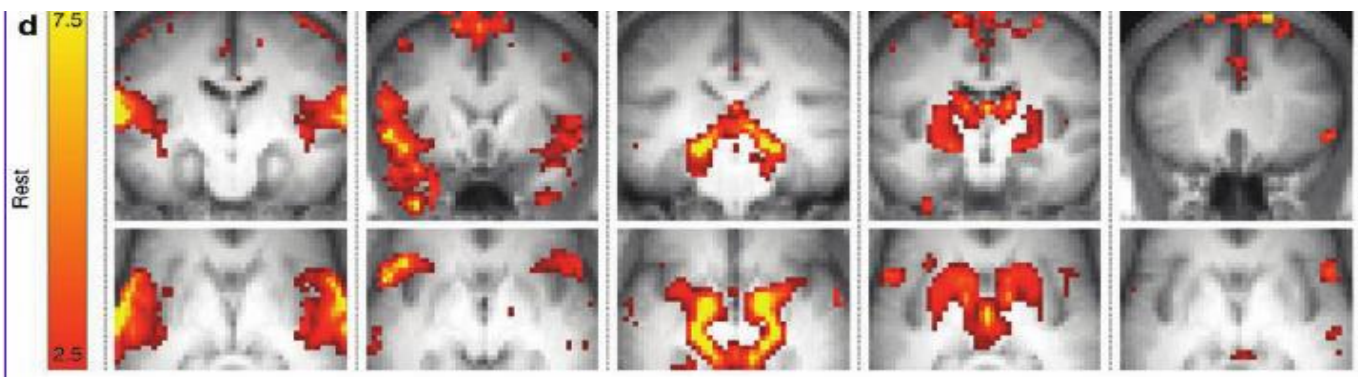
Future Directions of research (based on work in our lab)

1. Anatomical connectivity studies of blast-related tinnitus: relating tinnitus severity to white matter injury or gray matter declines due to blast
2. Functional Connectivity Studies of blast-related tinnitus: estimations of functional links between brain regions during a task or at rest based on correlations of the fMRI data of these regions.
3. Computational Models of blast-related tinnitus: integrating human brain imaging and animal physiology data with mechanical/physical data on effect of blasts on the brain.

Functional Connectivity: engagement of nonauditory networks during sound processing



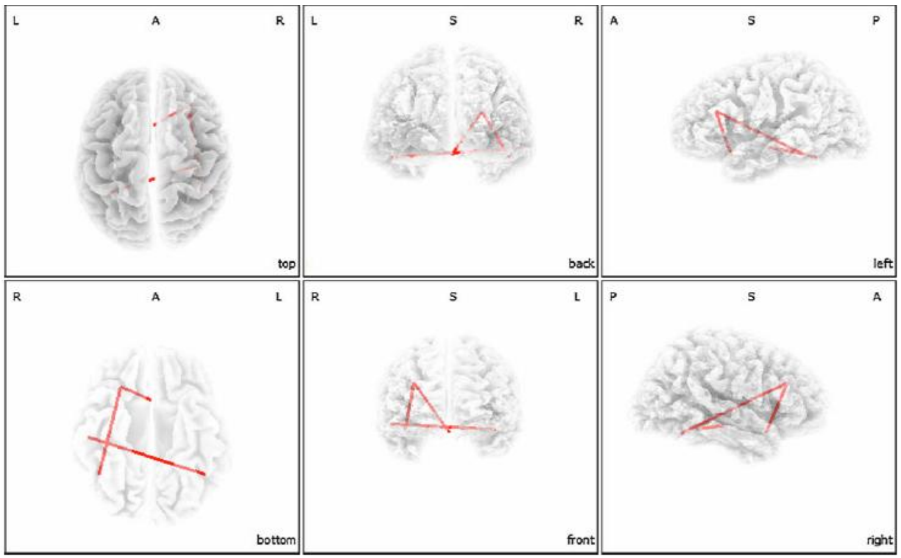
Task-based



Rest:
non-task-based,
Similar to task-based

Study: Langers and Melcher, *Brain Connectivity*, 2011.
Caveat: Study did not use whole-brain imaging, is missing frontal & occipital lobes. Cannot describe activity and connectivity related to attention, vision, introspection. No tinnitus group, only normal hearing without tinnitus.

Functional Connectivity: differences between responders and non-responders of tDCS treatment

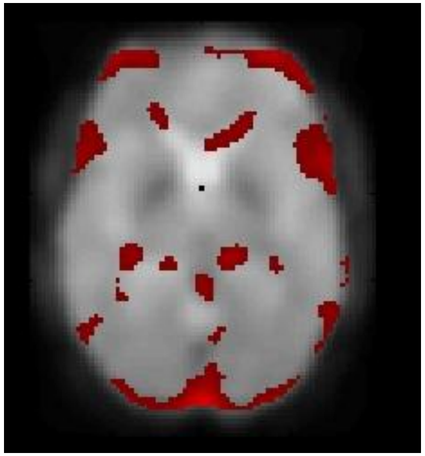


Connectivity contrasts between responders and non-responders for bifrontal transcranial direct current stimulation (tDCS). Coherence & phase synchronization between time series of different spatial locations is indirect measure of functional connectivity.

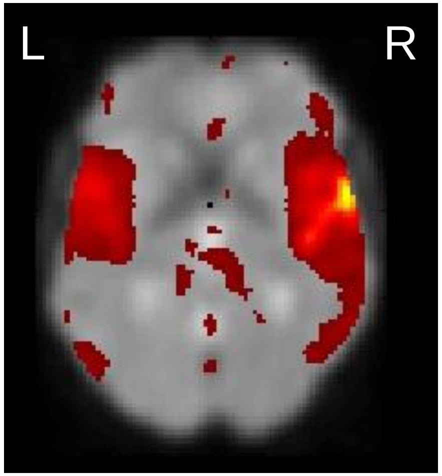
Study: Vanneste et al., *Exp. Brain Research*, 2011.
Caveat: Study used EEG, not fMRI. Spatial resolution is poor and source localization, coherence estimation may be challenging.

Functional Connectivity: differences in resting state functional connectivity in individuals with and without tinnitus (preliminary data from our lab).

Control group, normal hearing (n=4)
Highest correlation with auditory cortex

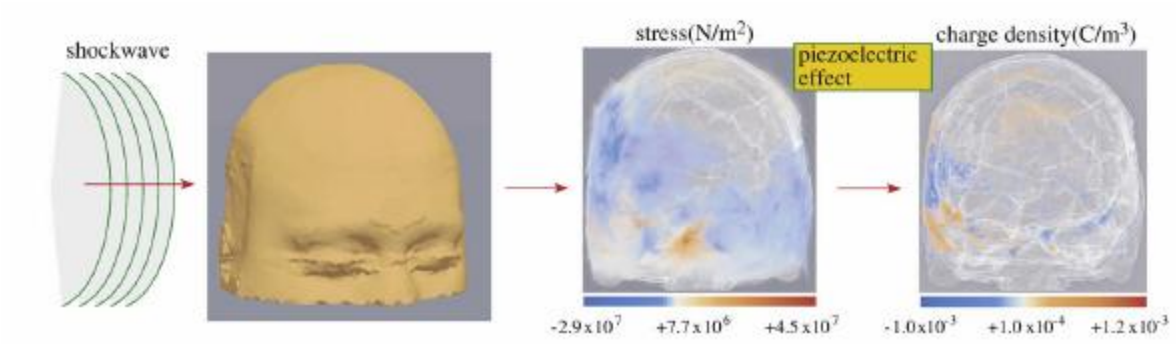


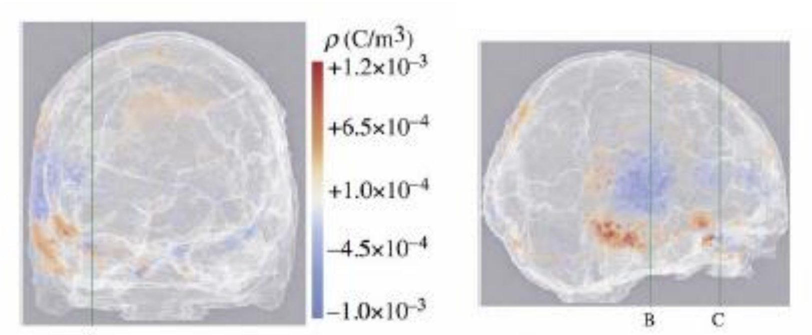
Tinnitus group (n=4)
Highest correlation with auditory cortex



Caveat: Preliminary data. Ongoing study. Results may change.

Models: integrating human, animal data





(a) Volume charge density from the front

(c) Volume charge density from the side

Blast-induced electromagnetic fields in the brain from bone piezoelectricity: Bone polarizes electrically in response to mechanical stress and produces electric fields that may have an effect similar to repetitive transcranial magnetic stimulation (rTMS). Different effects of front and side blasts.

Study: Lee et al., *NeuroImage*, 2011.

Caveat: No direct observation of electric fields generated by shocked cranial bone.

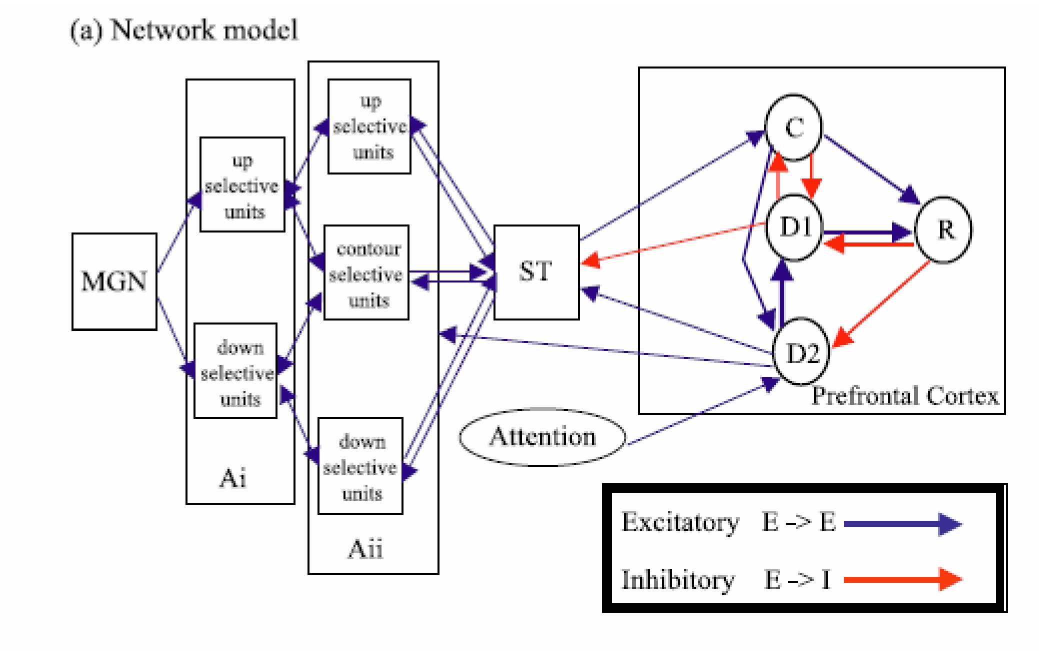
Models: integrating human, animal data

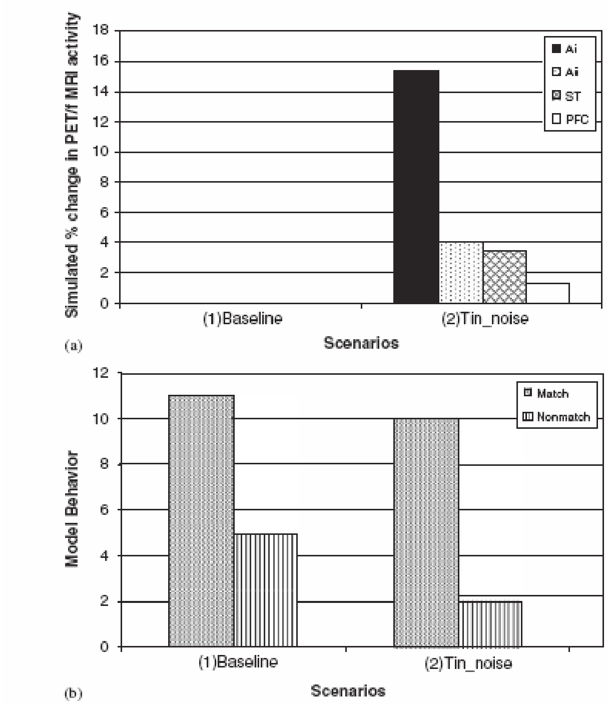
Animal studies of blast-related tinnitus:

1. Hamernik RP et al., *Hearing Research*, 1984: Exposure to blast waves at 160 dB peak SPL caused separation of 5-7 mm strip of sensory epithelia consisting of outer hair cell, Deiter cells and Hensen cells but not inner hair cells. Similar studies conducted between 1984-1997. Is the ratio of inner to outer hair cells altered, leading to tinnitus? Caveat: No mention of tinnitus, only hearing loss.

2. Mao J, et al., *J. Neurotrauma, 2011*: Animal exposed to 194 dB SPL. Diffusion tensor magnetic resonance imaging results demonstrated significant damage and compensatory plastic changes to certain auditory brain regions, with the majority of changes occurring in the inferior colliculus and medial geniculate body. Caveat: Animals, unlike humans, recovered fairly quickly from blast-related tinnitus.

Models: integrating human, animal data





Models allows experimentation not possible in animals. Models make it possible to evaluate contribution of different neural mechanisms, treatments in a principled manner. Can combine, animal, human (fMRI, rTMS, behavior) data. Possible to simulate blast-related effects by simulating rTMS.

Studies: Husain et al., *NeuroImage*, 2004; Husain et al. *JOCN*, 2005, Husain, *Progress in Brain Research, vol. 166*, 2007 & Husain et al., *NeuroImage*, 2002.

Caveat: Model of tinnitus is in prototype stage.

Acknowledgments

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