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Allied Health Media AudiologyOnline

Could Tinnitus Be Cured? Bench to Bedside Research

Presenter: Edward Lobarinas, PhD

Moderator: Carolyn Smaka, AuD, Editor in Chief, AudiologyOnline

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Could Tinnitus be cured? Bench to Bedside Research

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School of Behavioral and Brain Sciences

Learner Outcomes

As a result of this Continuing Education Activity, participants will be able to:

1. Describe differences between objective or subjective tinnitus
2. Describe how the current animal research regarding tinnitus relates to human subjects
3. Analyze/evaluate tinnitus research articles based on outcome measures

What is “tinnitus”?

- **Objective Tinnitus-**
  - muscle spasms that cause clicks or crackling around the middle ear
  - pulsatile tinnitus resulting from altered blood flow or turbulence near the ear or as a subjective phenomenon from increased awareness of blood flow in the ear.
- **Subjective Tinnitus-** the perception of sound in the absence of a corresponding external sound

Audiologist Reaction to Tinnitus

Audiology and Tinnitus

- Audiologists assess and provide audiologic treatment for persons with tinnitus using techniques that include, but are not limited to: biofeedback, masking, hearing aids, education, and counseling.
- (American Academy of Audiology Scope of Practice 2004)
  - http://www.audiology.org/resources/documentlibrary/Pages/ScopeofPractice.aspx
- 85% of individuals with tinnitus have hearing loss (Vernon et al., l980)

Tinnitus Prevalence in the General Population

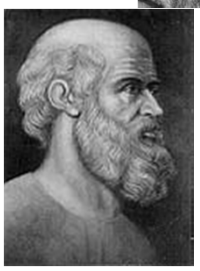
- Tinnitus in adults is estimated to range from 10-15% (Hoffman and Reed 2004)
- European estimates show that 7-14% of the population have talked to their physician about tinnitus and 1-4% suffer from disabling tinnitus (Vesterager, 1997)
- Tinnitus affects 35-50 million people in the US and seriously afflicts 12 million individuals. For 2-3 million , tinnitus is debilitating (American Journal of Medicine 2010)
- 49% of US military personnel exposed to blast trauma experience tinnitus (Kara, et al 2007)

Tinnitus not new

- Ancient Egyptians believed tinnitus was a symptom of a bewitched ear and developed medicinal oils and herbs that were infused into the outer ear canal as a treatment
- Tinnitus may have been described as early as 1650 B.C. or B.C.E.
- The Crocodilopolise (150 B.C.) a medical book contains references to “humming in the ear”

Aristotle and Hippocrates

- Fathers of Masking: In 400 BC realized that a “greater” sound could drive out the lesser sound of tinnitus and suggested it as a potential treatment



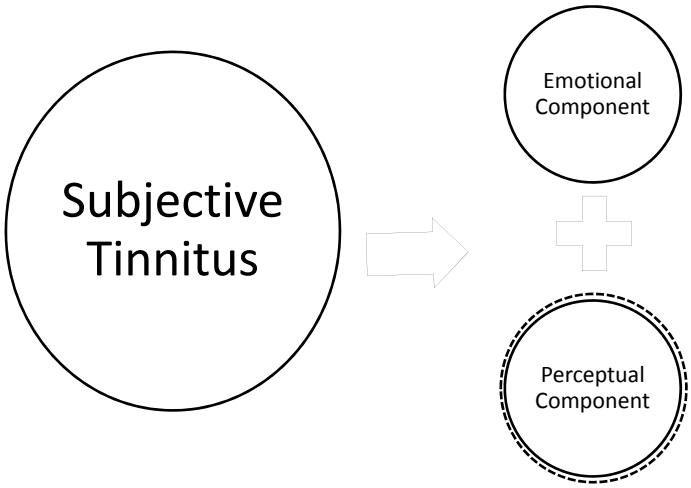
Babylonian Talmud

- Ancient Hebrew Text describes the curse of "Titus" as a buzzing in the brain that responds to sound therapy to aid in habituation

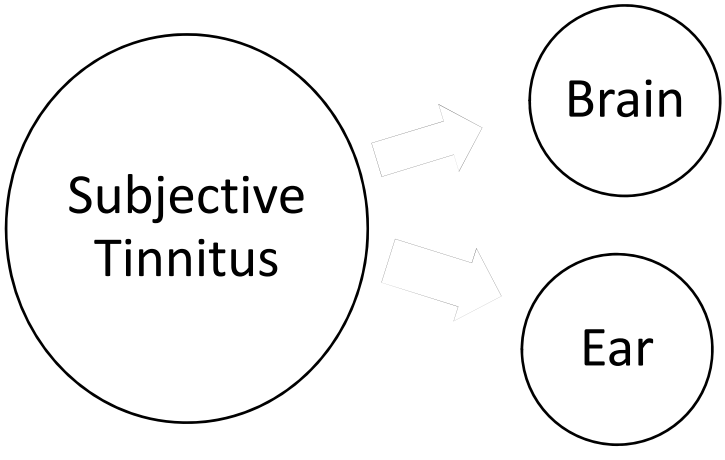
Why does the problem of tinnitus persist?

- Tinnitus is a symptom with often unknown etiology
- Tinnitus is strongly associated with hearing loss but not all individuals with hearing loss have tinnitus
- Tinnitus definition unclear because of discrepancy between percept and disability
- Two competing viewpoints
  1. The reaction to the sound
  2. The tinnitus sound signal itself

Aspects of Tinnitus



Aspects of Tinnitus



Auditory nerve sectioning

- After surgical removal of acoustic tumours with excision of the auditory nerve in 414 patients, only ***40%*** reported improvement in their tinnitus. Of 68 patients undergoing translabyrinthine eighth nerve section, 60 (80%) had tinnitus preoperatively. Improvement occurred in ***45%***, while 55% reported the condition to be the same or worse.

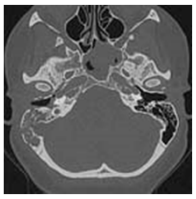
- *Tinnitus: surgical treatment, House JW, Brackmann DE. 1981*

Debilitating Tinnitus: Case 1

- Adult male with normal hearing
- Severely injured when a wheel rim separated
- Family described a sound similar to a cannon
- Result was permanent hearing loss and tinnitus in the exposed ear

Debilitating Tinnitus: Case 2

- Adult male at construction site
- Hit in head with 20,000 pound container
- Skull and temporal bone fracture
- Result: permanent unilateral tinnitus, chronic dizziness, and headaches



Debilitating Tinnitus: Case 3

- Adult male
- Automobile accident front and side airbag deployed
- No serious injury reported other than face going numb at time of accident
- Result: permanent unilateral tinnitus and collapsed sound tolerance

If tinnitus has a biological basis then can animals experience tinnitus?

- Mechanisms underlying tinnitus are likely to be present in other species
- Drug induced tinnitus can be applied to animals
- Animals can be used to study the role of hearing loss on tinnitus
- Therapies can be evaluated in animals to test efficacy and safety

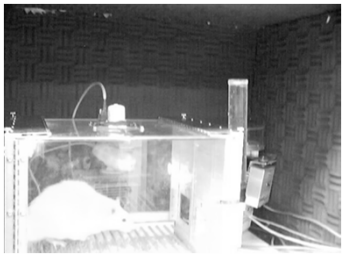
Animal Models of Tinnitus

- Lick Suppression
  - Jastreboff (shock suppression 1988)
- Operant
  - Heffner (Shock Avoidance, Reinforced Licking 2002)
  - Bauer-Brozoski (Suppression, food reinforcement 2003)
  - Ruttiger (Liquid food reinforcement 2003)
  - Guitton (shock avoidance, 2003)
  - Lobarinas-Salvi (2004)
- Startle Reflex
  - Turner (2006)
  - Yang-Lobarinas-Turner (2007)

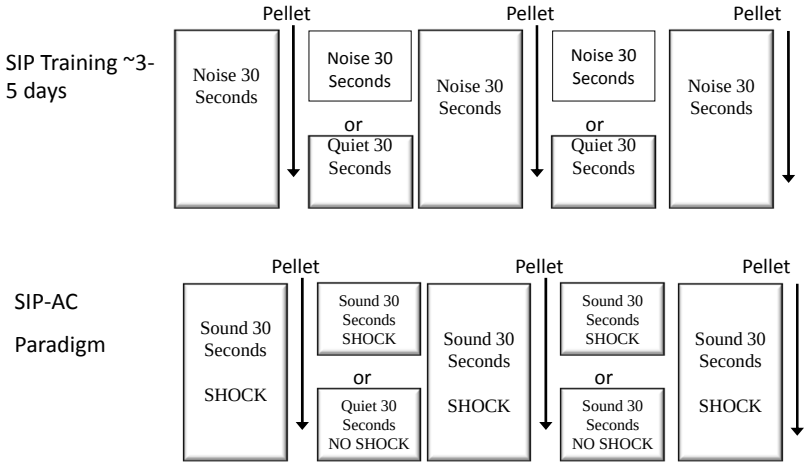
Drug Induced Tinnitus

- Salicylates: the main ingredient of Aspirin (high doses >3,000 mg)
- Quinine: Antimalarial agent also used for restless leg syndrome
- Loop Diuretics: Given for acute renal failure or hypertension
- Chemotherapeutics: Platinum based compounds such as Cisplatin
- Non-Steroidal Anti Inflammatory Drugs: Advil, Naprosyn, Aleve

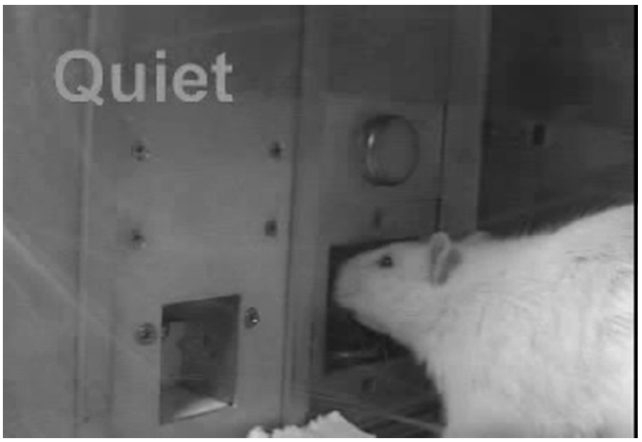
Salicylate Induced Tinnitus using Schedule Induced Polydipsia Avoidance Conditioning (SIP-AC)


SIP-AC

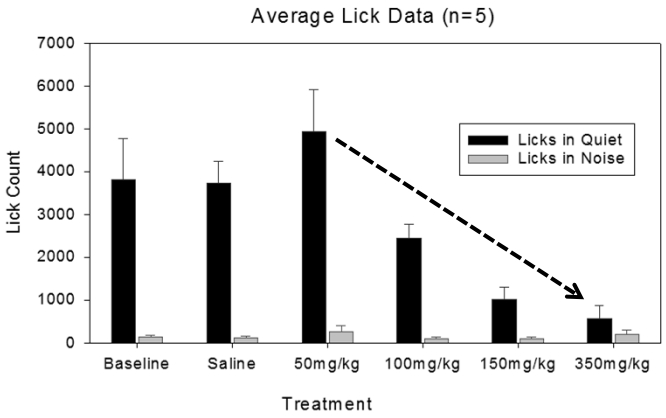


SIP-AC Animal Model of Tinnitus



Lobarinas, et al 2004

Effects of Sodium Salicylate

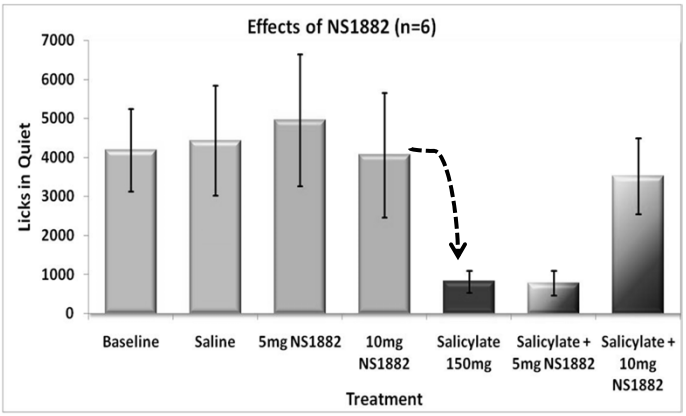


Lobarinas et al 2004

Tinnitus Treatment

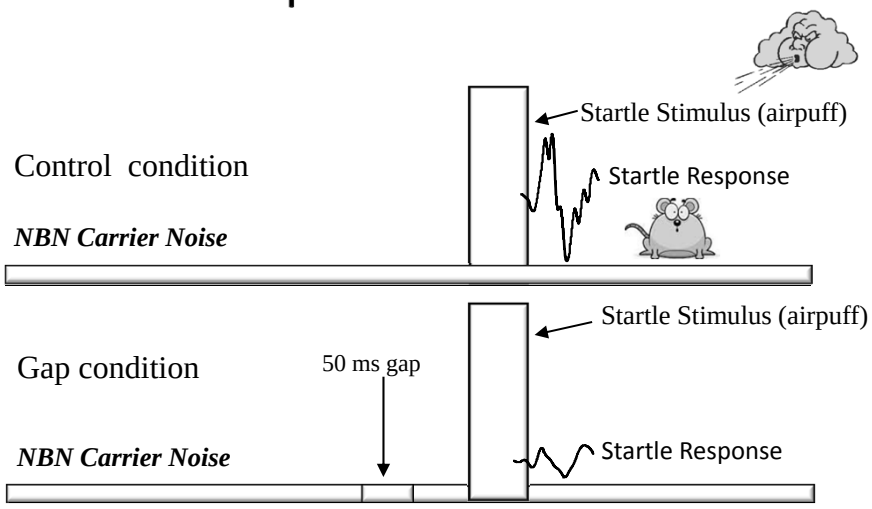
- Maxipost **(NS1882)**
  - Mechanism- KCNQ4/5 and BK potassium channel activator and KCNQ1 inhibitor
  - Uses- potential therapy for hyperactive disorders such as epilepsy

Effects of Maxipost (NS1882) a BK channel activator on Salicylate induced tinnitus



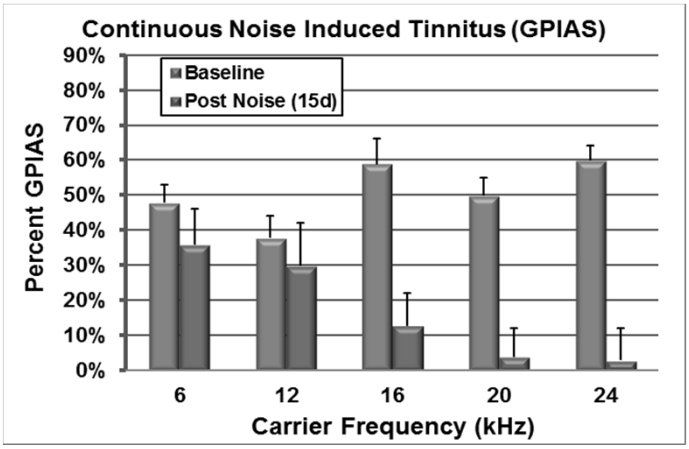
Gap Prepulse Inhibition of the Acoustic Startle (GPIAS)

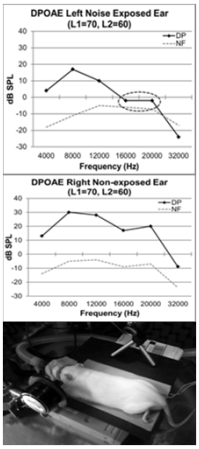
Prepulse inhibition



GPIAS

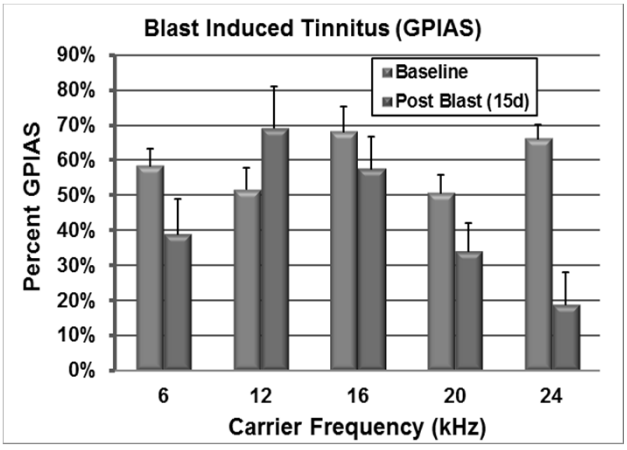
Chronic Unilateral Tinnitus from 126 dB NBN centered at 16 kHz

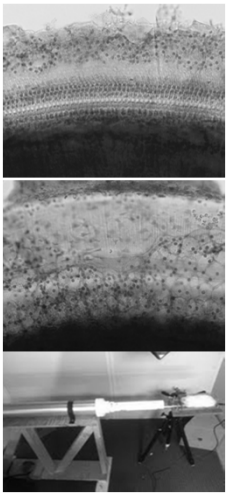




Lobarinas, Blair et al 2011 presented at the Department of Defense International State-of-the-Science Meeting on Blast-Related Tinnitus

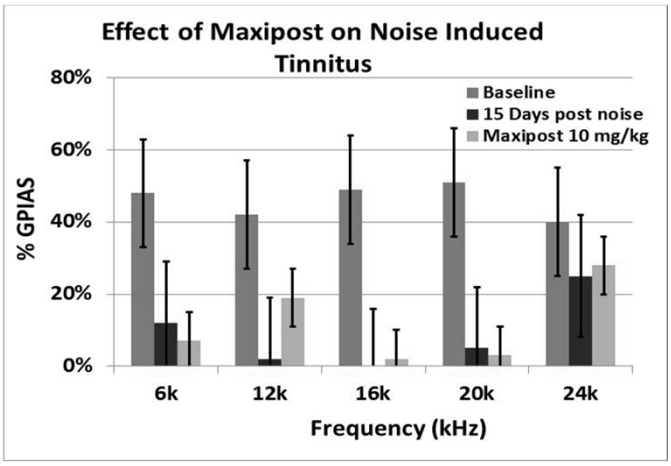
Tinnitus and Blast Trauma





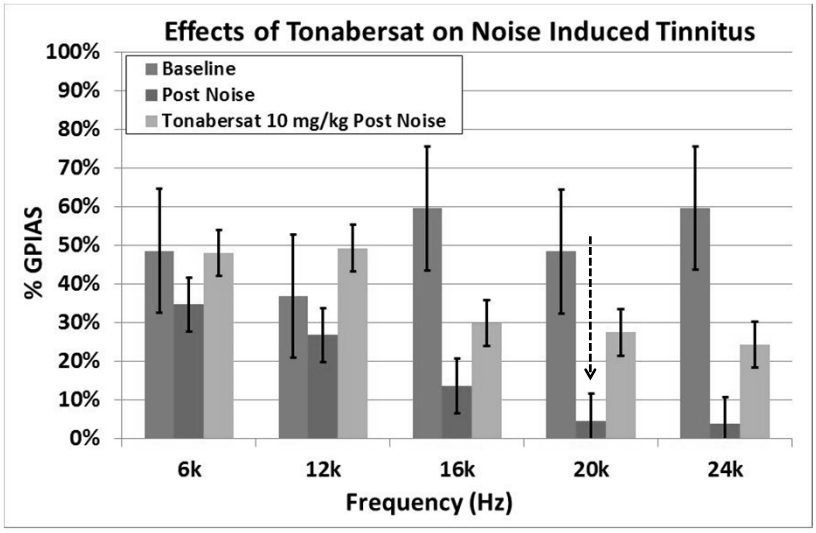
Lobarinas, Blair et al 2011 presented at the Department of Defense International State-of-the-Science Meeting on Blast-Related Tinnitus

GPIAS- Effects of Maxipost on Noise Induced Tinnitus



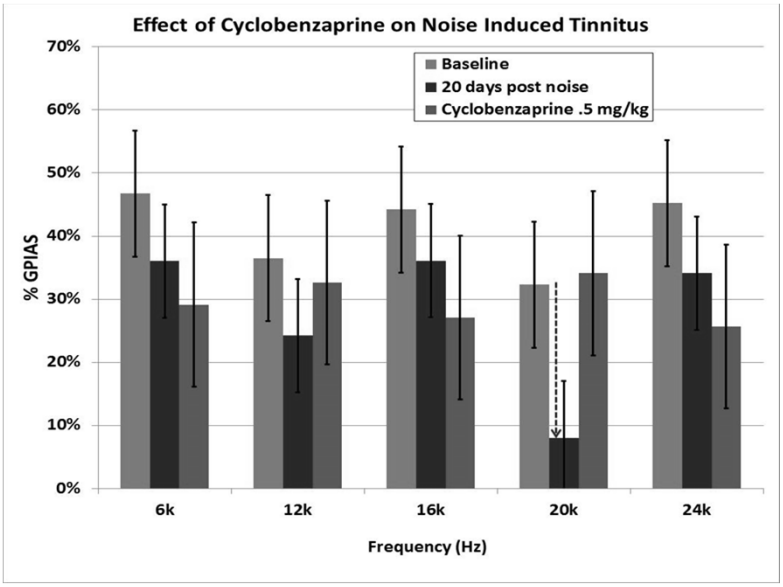
Tinnitus Treatment 2

- Tonabersat
  - Mechanism- gap junction blocker (connexin 26)
  - Uses- migraines with auras (clinical trials)



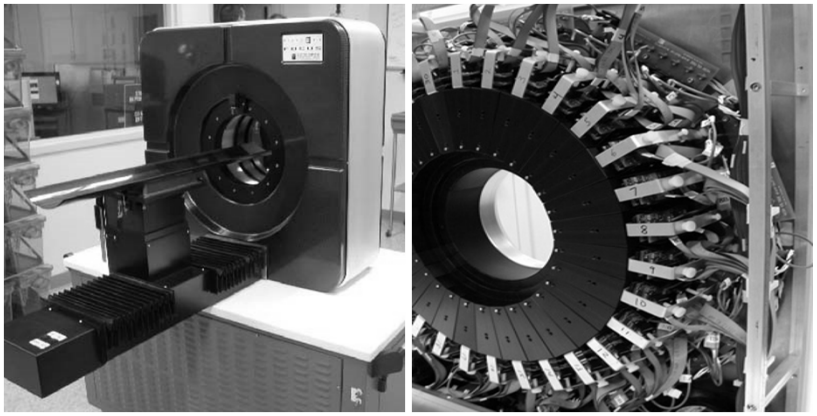
Tinnitus Treatment 3

- Cyclobenzaprine
  - Mechanism- structured like tricyclic antidepressant, shown in rats to activate the Locus Coeruleus in the brainstem (stress and panic)
  - Uses- muscle relaxant sleep aid and treatment for fibromyalgia

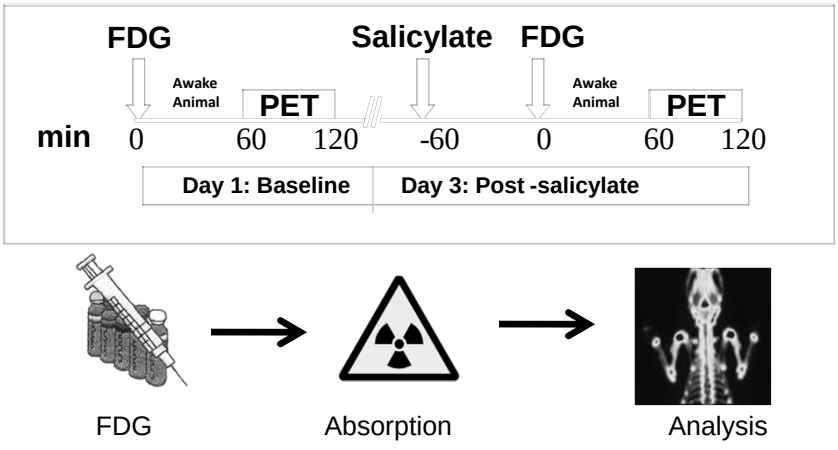


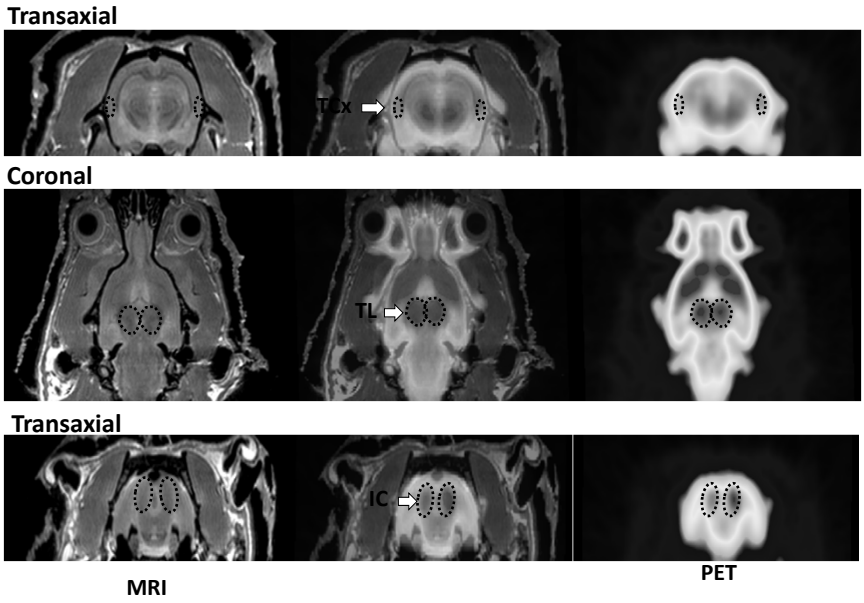
If tinnitus results from increased activity in the brain can we see it with functional imaging?

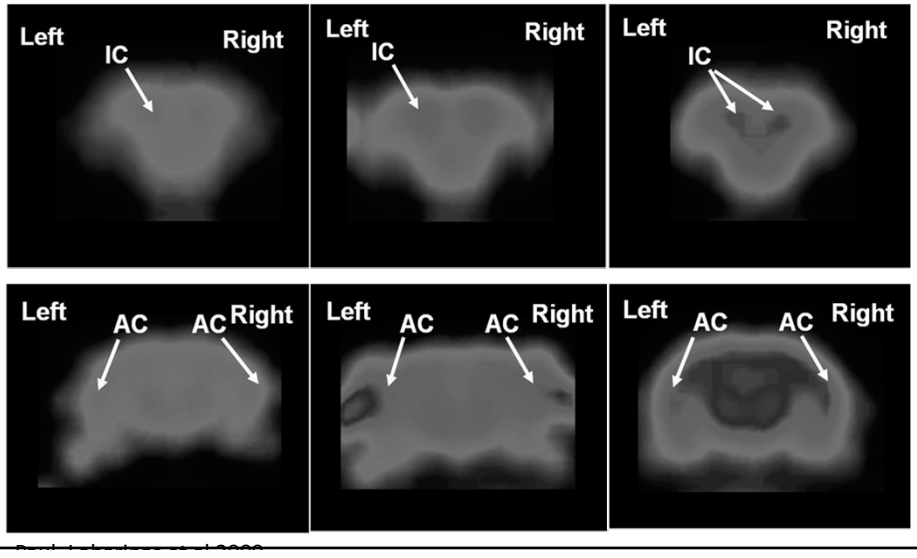
Positron Emission Tomography using MicroPET



PET Imaging Protocol




Transaxial
TCx
Coronal
TL
Transaxial
IC
MRI
PET
Fused MRI-PET


MicroPET inferior Colliculus and Auditory Cortex
Left
IC
Right
Left
IC
Right
Left
IC
Right
Left
AC
AC
Right
Left
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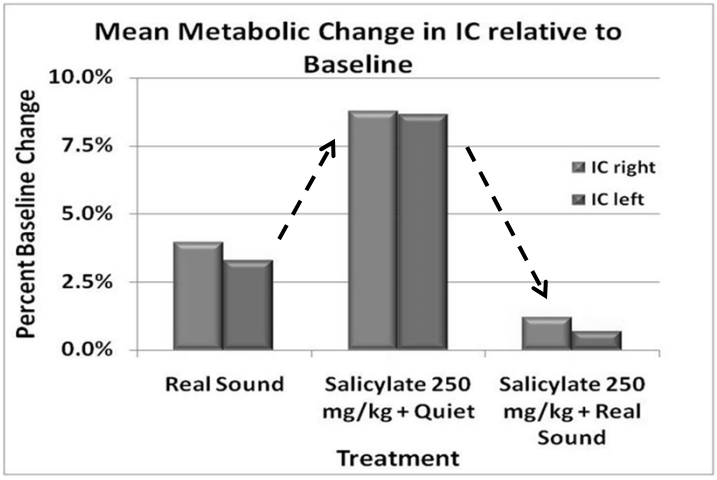
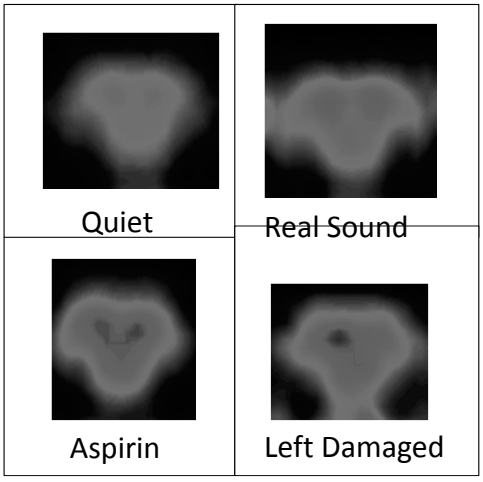
Right
Left
AC
AC
Right

Quantification



Sound and Brain Activity



MicroPet Studies

- **Salicylate increased activity in the IC and AC under quiet conditions to levels similar to those under real sound**
- **Under Salicylate no behavioral or DPOAE evidence of hearing loss was found**
- **Unilateral noise trauma alone caused a decrease of activity under sound contralateral to the hearing loss**
- **More studies are needed to look at tinnitus after unilateral noise exposure whereas salicylate reliably induced tinnitus**

Clinical Study

- Participants: Subjects recruited from the University at Buffalo, Tinnitus Support Group (n=20)
- Objective: Determine the relationship between the Tinnitus Handicap Questionnaire, and the measurable properties of tinnitus
- Methods:
- Establish puretone audiometry
- Determine loudness discomfort levels
- Determine tinnitus pitch and intensity match
- Determine if tinnitus could be masked
- Determine THQ

Study Data

Characteristic	
Demographics (n=20)	
Age (mean)	63.7±7.9
Gender (% male)	17(85%)
Race (% white)	20(100%)
Audiometric Characteristics (n=20)	
Hearing loss (% HL .25-8 kHz)	19 (95%)
Hearing loss (% HL .25-16 kHz)	20 (100%)
Mean threshold (.25-8 kHz)	33.8±18.9
Mean threshold (.25-16 kHz)	60.0±17.2
Loudness discomfort level (% abnormal)	2 (10%)
Mean loudness discomfort level (40 ears)	96.2±8.8
Tinnitus Location (n=20)	
Bilateral	17(85%)
Right ear	2(10%)
Left ear	1(5%)
Description of Tinnitus	
Hiss	7(35%)
Ring	6(30%)
Whistle	5(25%)
Other	2(10%)
Tinnitus Severity	
Mean THQ total	29.87±12.9
Mean THQ 1 (social-emotional)	23.4±13.7
Mean THQ 2 (tinnitus and hearing)	29.8±21.0
Mean THQ 3 (outlook on tinnitus)	54.4±20.9

Normative THQ Data

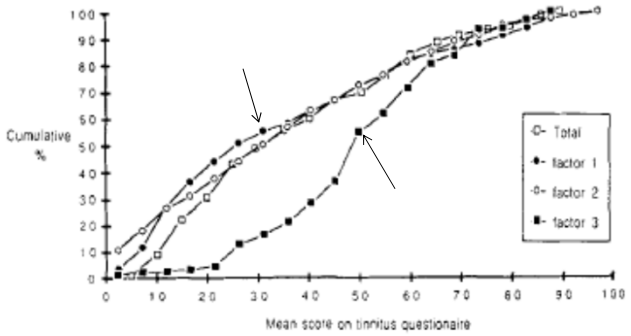
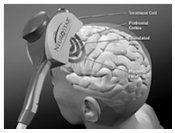


Figure 2. Cumulative percent-mean score functions for total and subscale mean scores ($N = 275$).

Results and Conclusions

- Tinnitus was rated as high on a 10 point scale (6-10). However, there was no relationship between actual frequency and rating
- Loudness rating was directly correlated with actual tinnitus intensity in dB HL but not dB SL
- In all patients masking was effective with BBN and NBN. NBN intensity was directly related to tinnitus intensity while BBN was not.
- There was *no relationship* among THQ and tinnitus loudness, masking level, or tinnitus pitch

Current Therapies


- Therapies are varied but none have been conclusively shown to be effective across a wide range of patients

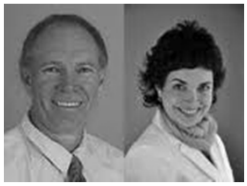
Drug Therapies

- Extensive review showed that no drug reliably reduced tinnitus in the majority of patients and no drug exceeded placebo control (Dobie 1999)
  - Tocainide (lidocaine analog, Na channel blocker) and related drugs
  - Carbamazepine (anticonvulsant, Na channel inactivator, potentiates GABA receptors)
  - Benzodiazepines (enhance GABA-A)
  - Tricyclic antidepressants (serotonin-norepinephrine reuptake inhibitors)
  - Caroverine (AMPA receptor antagonist)
  - Zinc (antioxidant)
  - Melatonin (sleep aid)
  - Baclofen (GABA-B agonist)
  - Flunarizine (Calcium channel blocker, reduces migraines)
  - Betahistine (Histamine mixed agonist/antagonist, may increase serotonin)

Treatments That Have Shown Limited Efficacy

- Sound therapy: Hearing aids, Tinnitus Maskers, Neuromonics
- Cognitive Behavioral Therapy: Biofeedback, Tinnitus Retraining Therapy (TRT)
- Combined Therapy: TRT, counseling and sound generators
- Repeated Transcranial Magnetic Stimulation, Neurostimulation
- Drug Therapy: Tegretol (Carbamazepine) for typewriter tinnitus, Neuroleptics for Musical Hallucinosis

Cyclobenzaprine



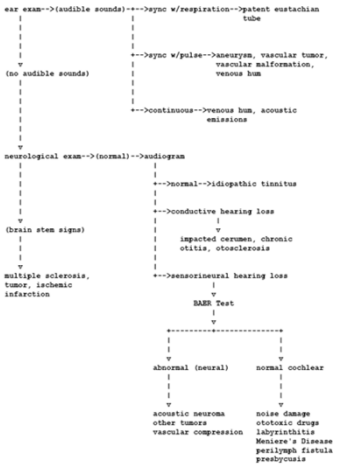
- Muscle Relaxant with tri-cyclic antidepressant action
- On-going open label trial
- High-dose cyclobenzaprine (30 mg) resulted in a significant reduction in the Tinnitus Handicap Inventory (THI) score between baseline and week 12
- A 2nd study by Vanneste, Fiqueiredo, and De Ridder shows
  - In 24% of the tinnitus patients a reduction of 53% on tinnitus intensity
  - In 25% a clear response to cyclobenzaprine with a reduction of 55% on tinnitus distress
  - Particular subgroups, namely pure tone tinnitus patients and unilateral tinnitus patients, responded better to cyclobenzaprine

Conclusions

- Animal models are an important part of finding the underlying mechanisms for tinnitus and evaluating new therapies
- The psychoacoustic characteristics can help in identifying potential underlying conditions that contribute to tinnitus
- Although we do not have a “cure” yet, there are a number of effective means of managing tinnitus for many patients

Tinnitus cheat sheet

The following flowchart from the *Cecil Textbook of Medicine*, 1992 (19th ed.), W.B. Saunders, shows the logic for diagnosing the common causes of tinnitus (note that this chart omits some causes, such as TMJ disorders).



Questions