Pharmacologic interventions for tinnitus: Challenges in drug development

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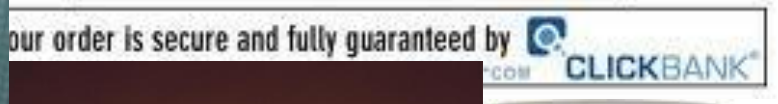
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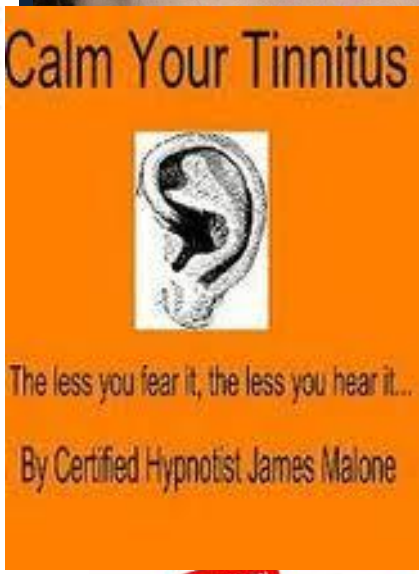
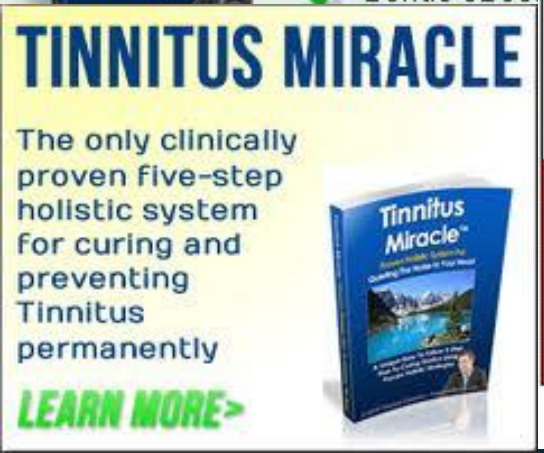

Calm Your Tinnitus
The less you fear it, the less you hear it...
By Certified Hypnotist James Malone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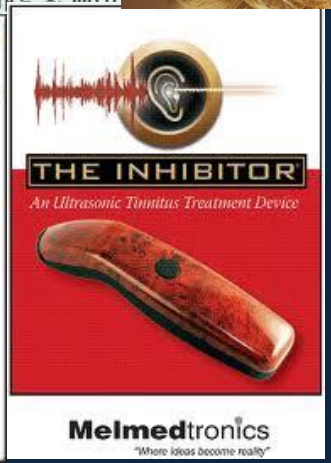
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Overview

Part 1.

History of tinnitus drugs

Challenges of drug development

Part 2.

Animal models, mechanisms and drug trials

Which drugs and which brain regions…..

Part 3.

Translating models to people

Goals of drug treatments for tinnitus

Part 4.

Clinical trial design – pearls and pitfalls

Melatonin

Zinc

SSRI

Prozac (fluoxetine)

Paxil (paroxetine)

Zoloft (sertraline)

ALPRAZOLAM

ACAMPROSATE

LIDOCAINE

Honey Bee Larvae

Cyclobenzaprine

SNRI

Effexor(venlafexine)

Cymbalta(duloxetine)

GINGKO

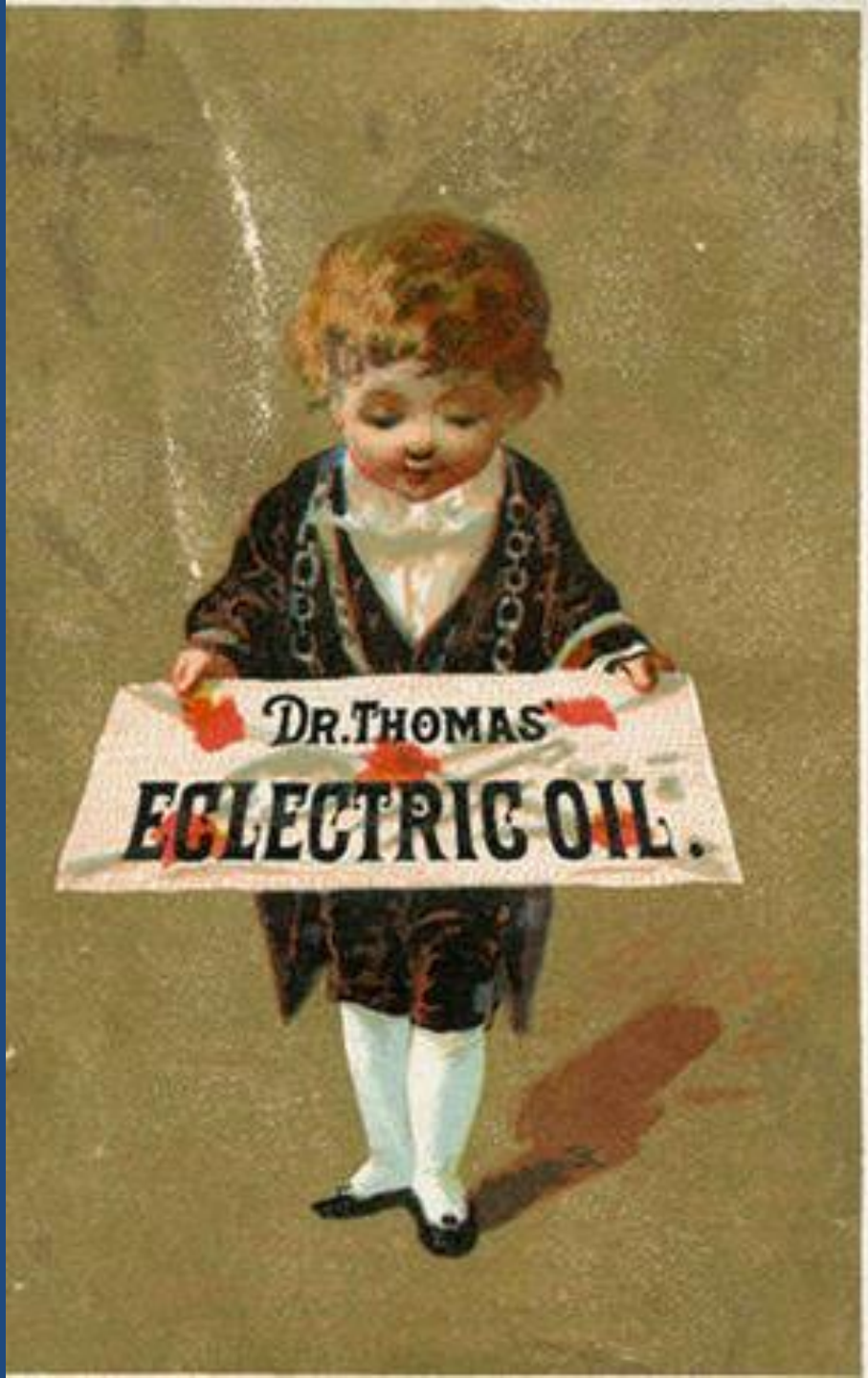
GABAPENTIN

MISOPROSITOL

CLONAZEPAM

TEGRETOL

Hippocrates treating woman, 5th c. B.C.E. relief, Archaeological Museum of Piraeus.



DR. THOMAS' ECLECTRIC OIL.

WHAT IT HAS DONE.

WHAT IT WILL DO.

IT WILL POSITIVELY CURE

Toothache	*in*	*5 Minutes*
Earache	"	*2 "*
Backache	"	*2 Hours*
Lameness	"	*2 Days*
Coughs	"	*20 Minutes*
Hoarseness	"	*1 Hour*
Colds	"	*24 Hours*
Sore Throat	"	*12 "*
Deafness	"	*2 Days*
Pain of Burn	"	*5 Minutes*
" *Scald*	"	*5 "*

Croup it will cease in 5 minutes, and positively cure any case when used at the outset.

Remember that Dr. Thomas' Eclectric Oil is only 50 cents per bottle, and one bottle will go farther than half a dozen of an ordinary medicine.

Presented By
Thompson Barnes
Freemont N H

The “breakthrough” tinnitus treatment

‘Cures’ several pts in a few clinics

Gabapentin significantly improves new onset tinnitus
(Zapp 2001)

Significant improvement in open-label trial of gabapentin and clonazepam in patients with hypoperfusion

(Shulman et al. 2002)

The “breakthrough” tinnitus treatment

When tested …..using standardized measures

-elimination in 10% -
- 30-50% reduction in 30-50% -

-variable outcomes with replication

The “breakthrough” tinnitus treatment

40 percent of placebo subjects report global benefit with reductions in tinnitus loudness and disability

(Dobie 1999)

Pathways of drug development

Serendipitous observation
Lidocaine Minoxidil Sildenafil Gabapentin
Effects are unpredictable, rarely hold up to large-scale trials

Barany 1935
i.v. infusion Procaine

Clinical trials of lidocaine, bupivacaine, oral tocainade

Imaging studies : bivariate activity with lidocaine modulation of tinnitus

Duckert 1984: 40% placebo response

Pathways of drug development

Off-label use of an existing compound
Alprazolam (Johnson 1993) Acamprosate (Azevedo and Figueirido 2005) Tegretol (Levine 2006) Melatonin (Megwalu 2006) Cyclobenzaprine (Coelho et al 2012)
Perhaps useful in specific targeted populations Rare successful placebo controlled, replicated studies

Pathways of drug development

Off-label use of an existing compound
Alprazolam (Johnson 1993) Acamprosate (Azevedo and Figueirido 2005) **Tegretol** (Levine 2006) **Melatonin** (Megwalu 2006)(Hurtuk et al. 2011) **Cyclobenzaprine** (Coelho et al 2012)
Perhaps useful in specific targeted populations Rare successful placebo controlled, replicated studies

Pathways of drug development

Off-label use of an existing compound

Cyclobenzaprine
Coelho et al 2012
Vanneste et al 2012

Perhaps useful in specific targeted populations
Rare successful placebo controlled, replicated studies

Pathways of drug development

Off-label use of an existing compound

Melatonin
Megwalu 2006
Hurtuk et al. 2011

Perhaps useful in specific targeted populations
Rare successful placebo controlled, replicated studies

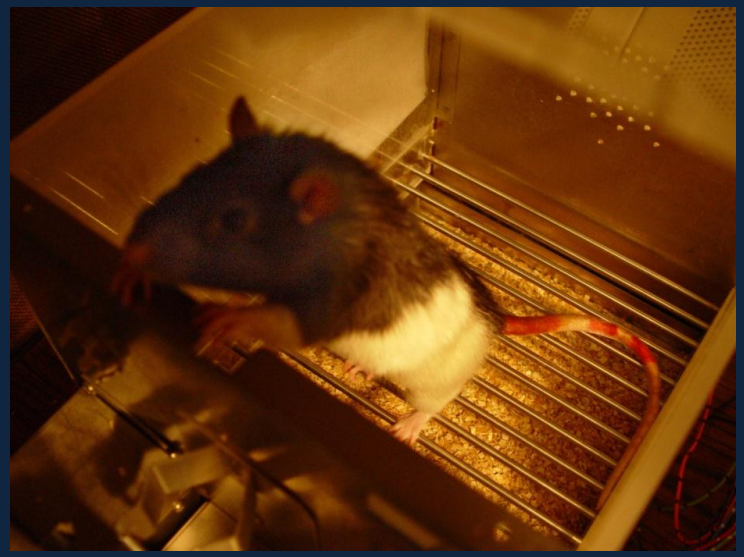
Megwalu : Open label

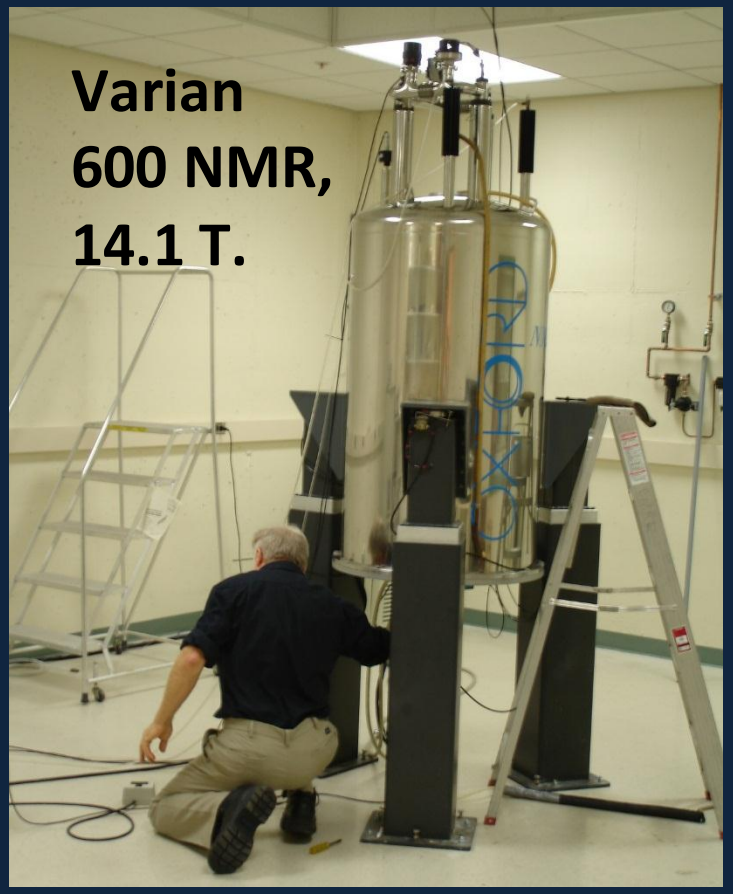
Hurtuk : DBPC; 84 enrolled

Loudness match
Severity index
Self-rated tinnitus

~57% improvement defined as a 'decrease' on at least 2 of 3 parameters

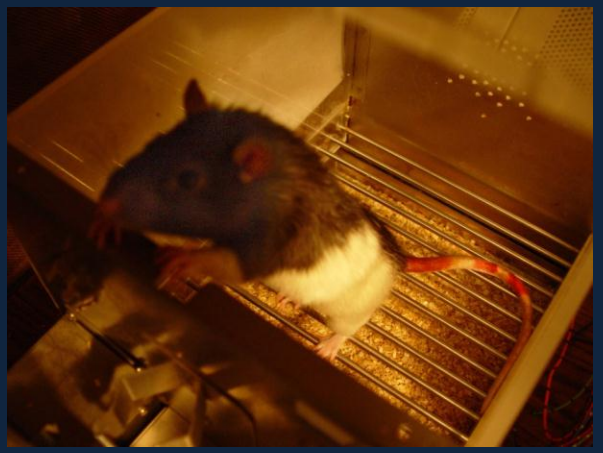
Moving from ‘serendipity’ to salient targets



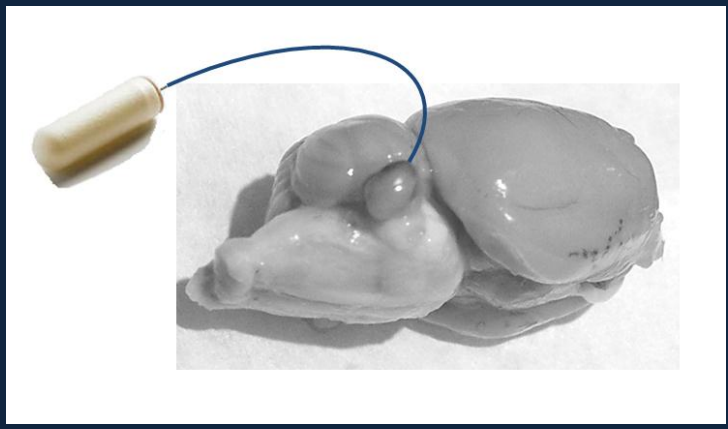


Boris Odintsov, PhD
Beckman Institute
U Illinois Urbana Champaign

Advantages of an animal model



- Uniform population
- Control causal factors
- Eliminate confounding factors
- Utilize invasive measures



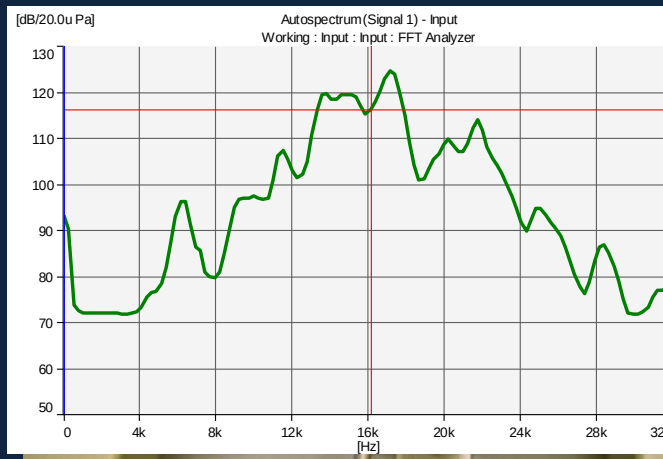
Using an animal model to understand tinnitus

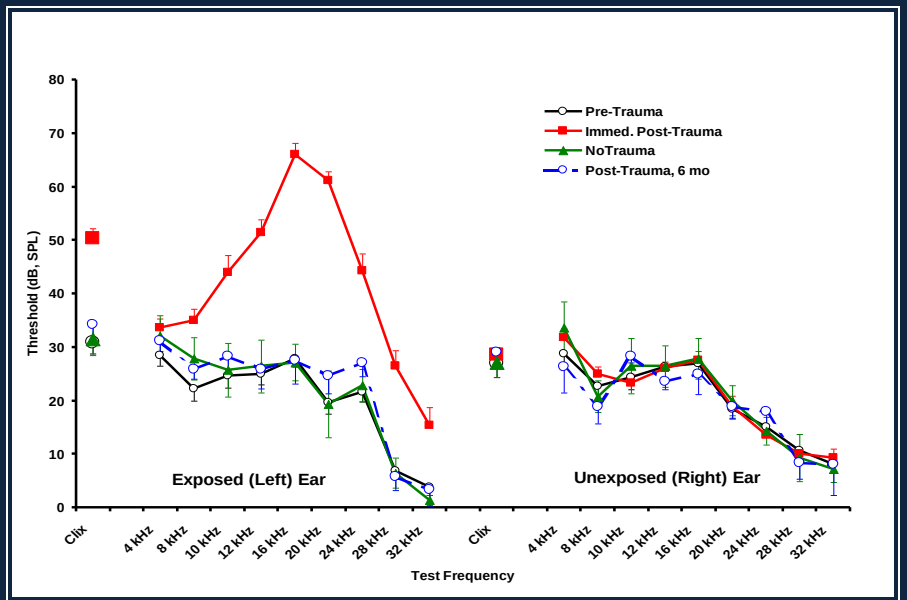
(1) Establish a behavioral task

Psychophysical testing using conditioned suppression to detect tinnitus

(1) Establish a behavioral task

(2) Expose the animal to a tinnitus inducing event



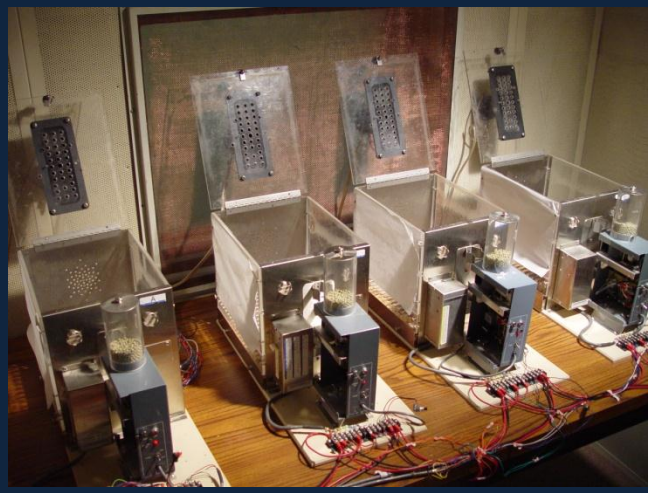


Psychophysical testing using conditioned suppression to detect tinnitus

(1) Establish a behavioral task

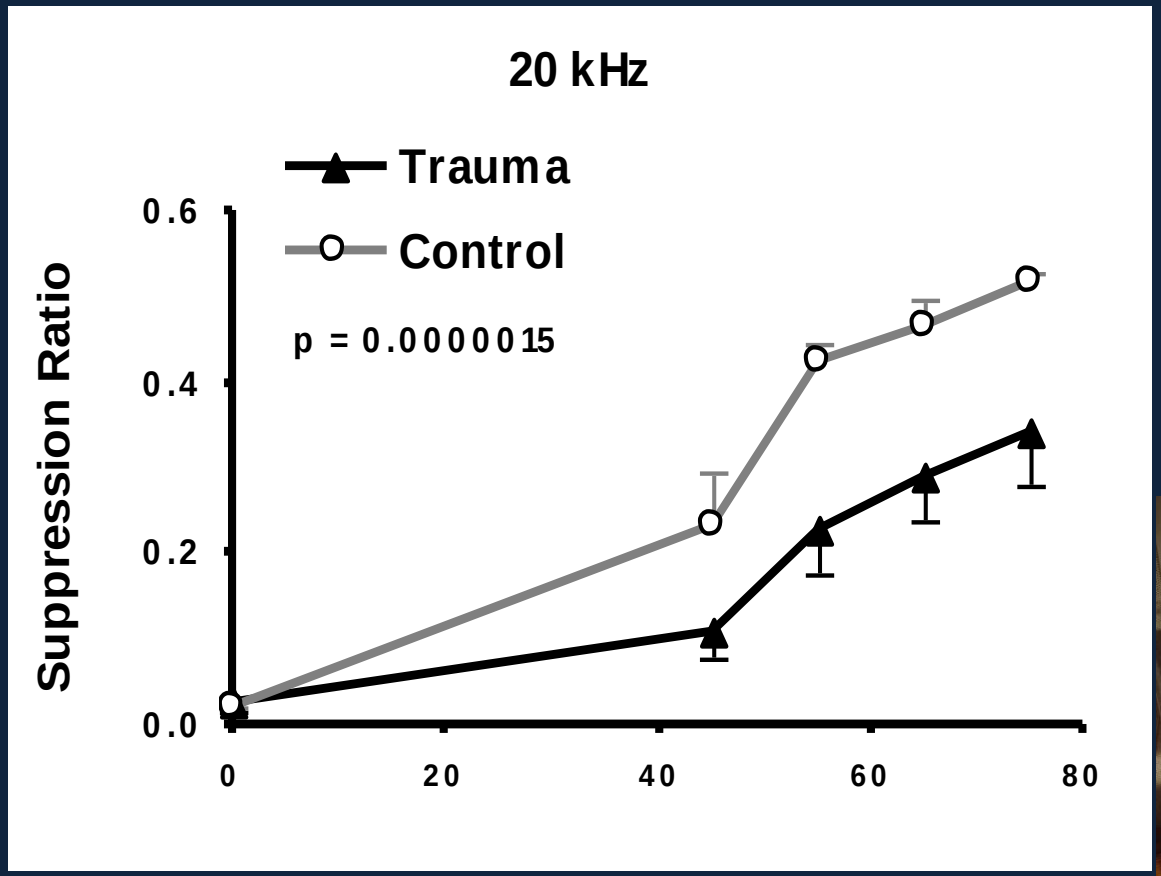
(2) Expose the animal to a tinnitus inducing event

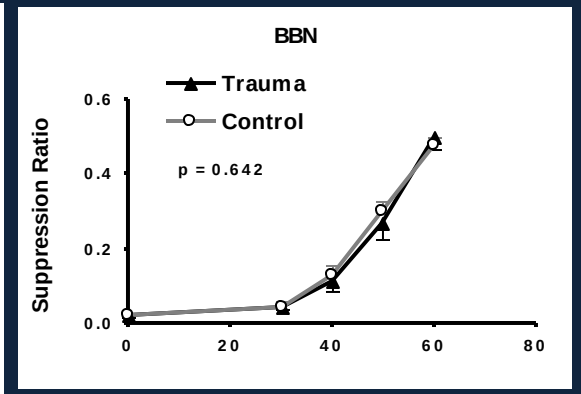
(3) Train animal to listen to auditory cues. Stop lever pressing during "silence".

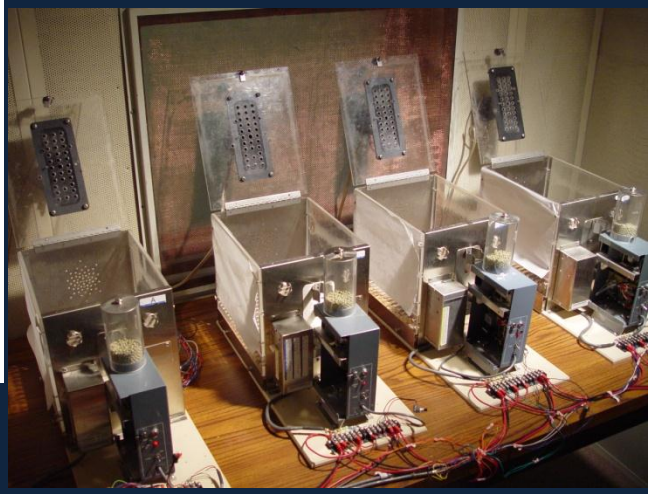


Tinnitus ≠ Silence

Behavioral evidence of noise-induced tinnitus in animals







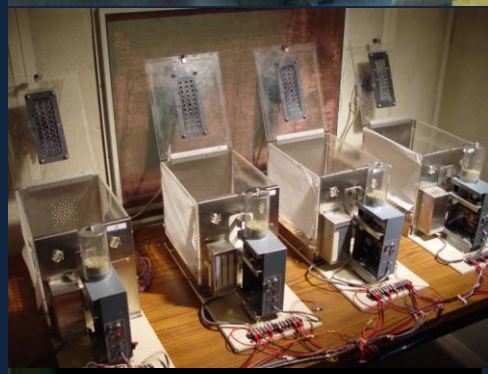
Bauer and Brozoski, JARO 2001

Is there a critical pattern of hair cell damage?

- Behavioral training

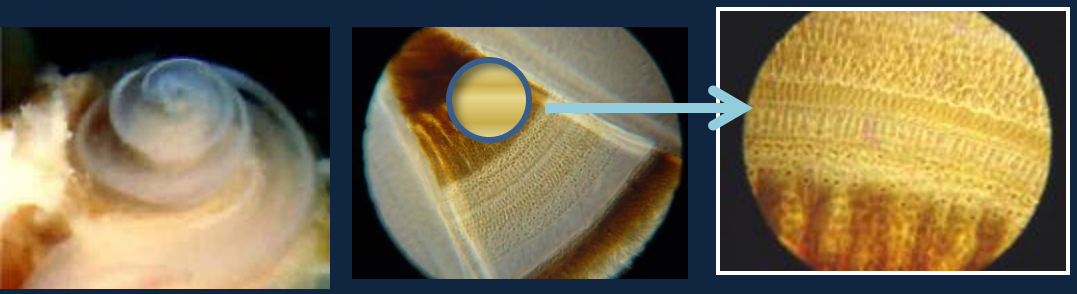
- Control
  Unilateral 4 kHz 1 hour
  RW Cisplatin
  RW Carboplatin

- Cochlear histology

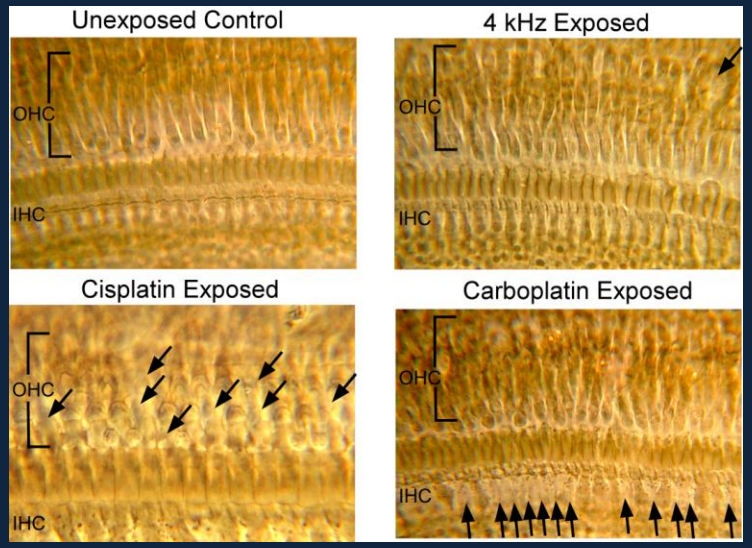


Is there a critical pattern of hair cell damage?

1 kHz tinnitus develops in all subjects with cochlear damage

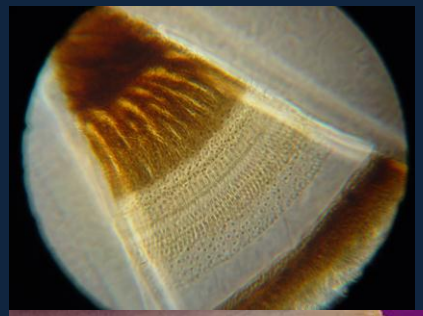


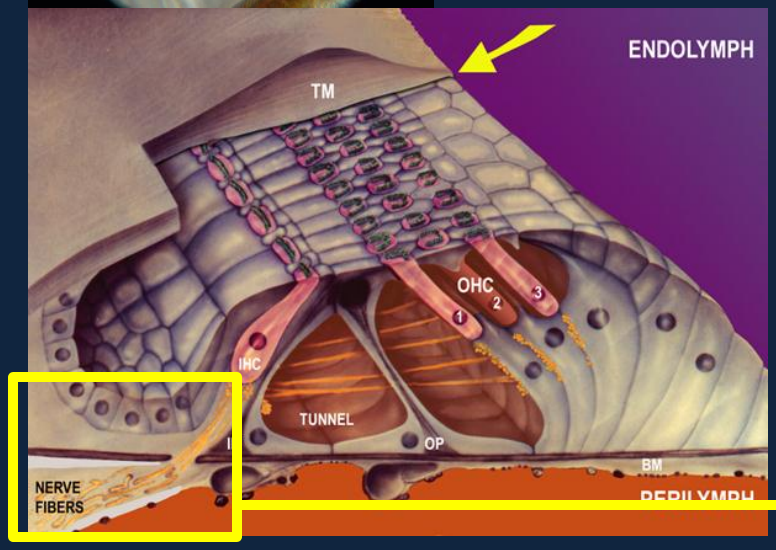
No correlation between tinnitus induced by noise, cisplatin or carboplatin and the pattern of damage



Bauer, Brozoski, Myers *J Neurosci Res* *2007*

Is there a critical pattern of hair cell damage?



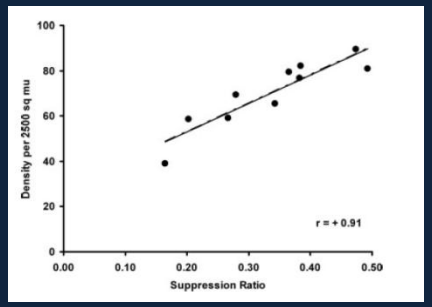


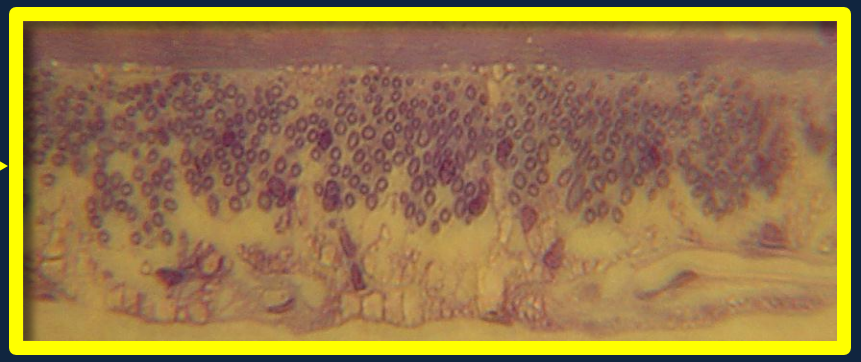
Bauer, Brozoski, Myers

J Neurosci Res 2007

Strong correlation

(r=0.91) between tinnitus and degeneration of high spontaneous rate primary neurons

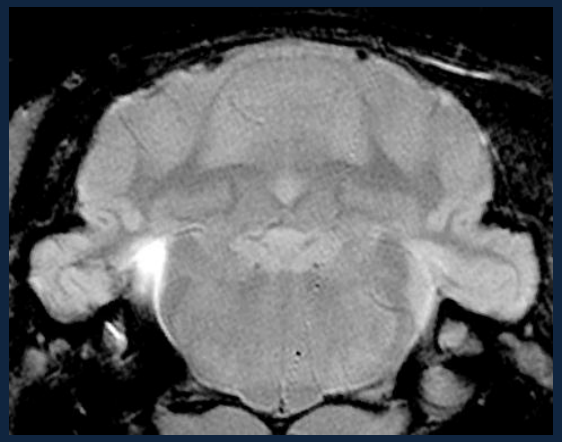


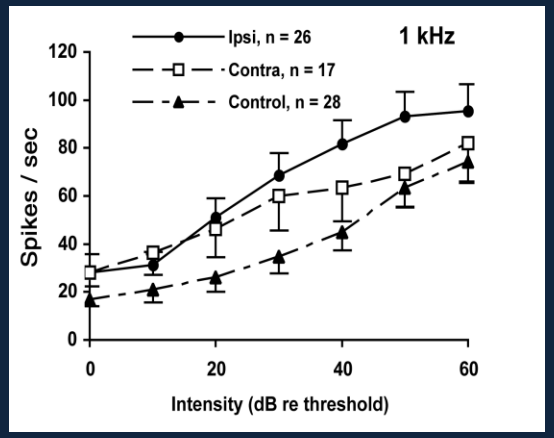


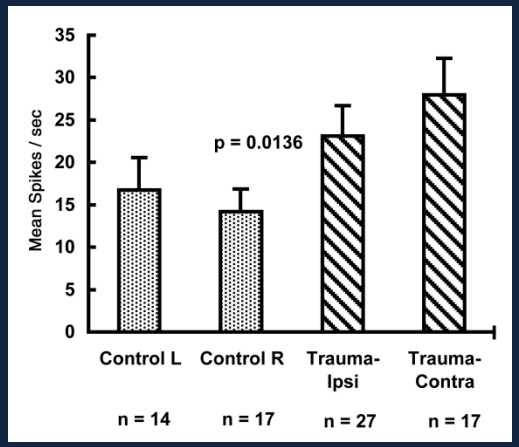
Central changes associated with tinnitus

Dorsal cochlear nucleus

Brozoski, Bauer & Caspary *J Neuro Res 2002*

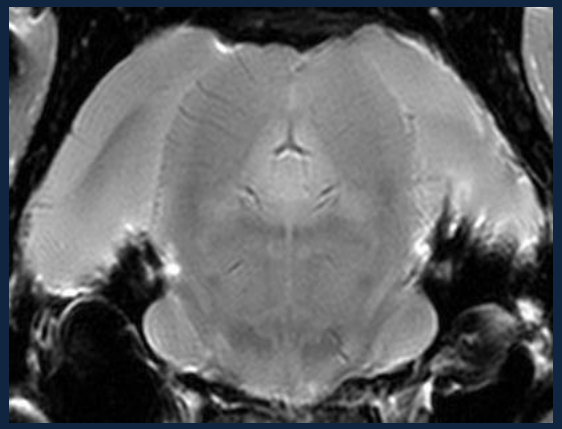


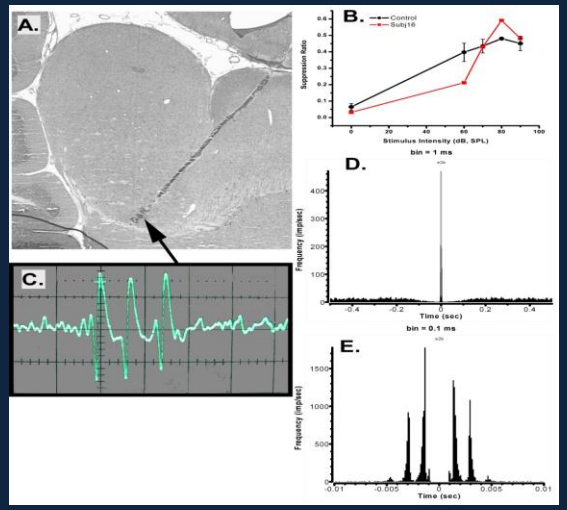




Inferior colliculus

Bauer et al. *Neuro Res 2008*

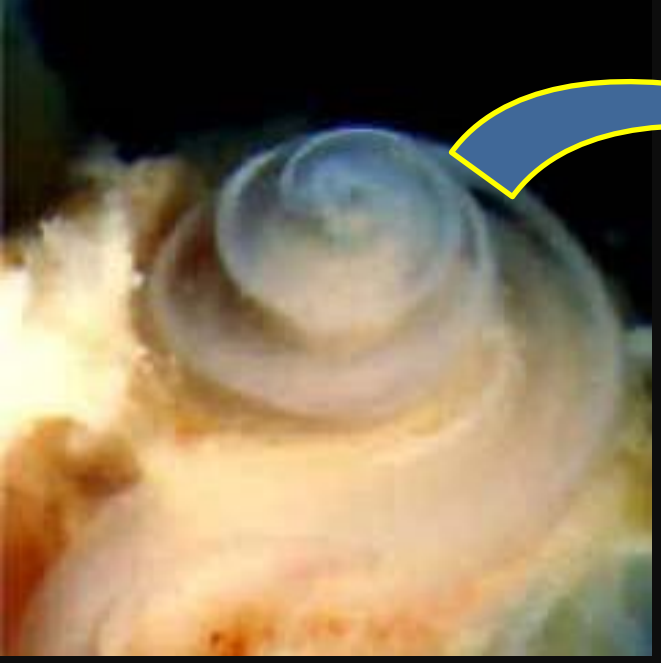




-increased bursting

-increased regularity of bursting

-peak frequency within burst matching tinnitus frequency



Loss of primary afferent activity leads to *compensatory changes* within the central auditory pathway

Functional representation of Increased gain

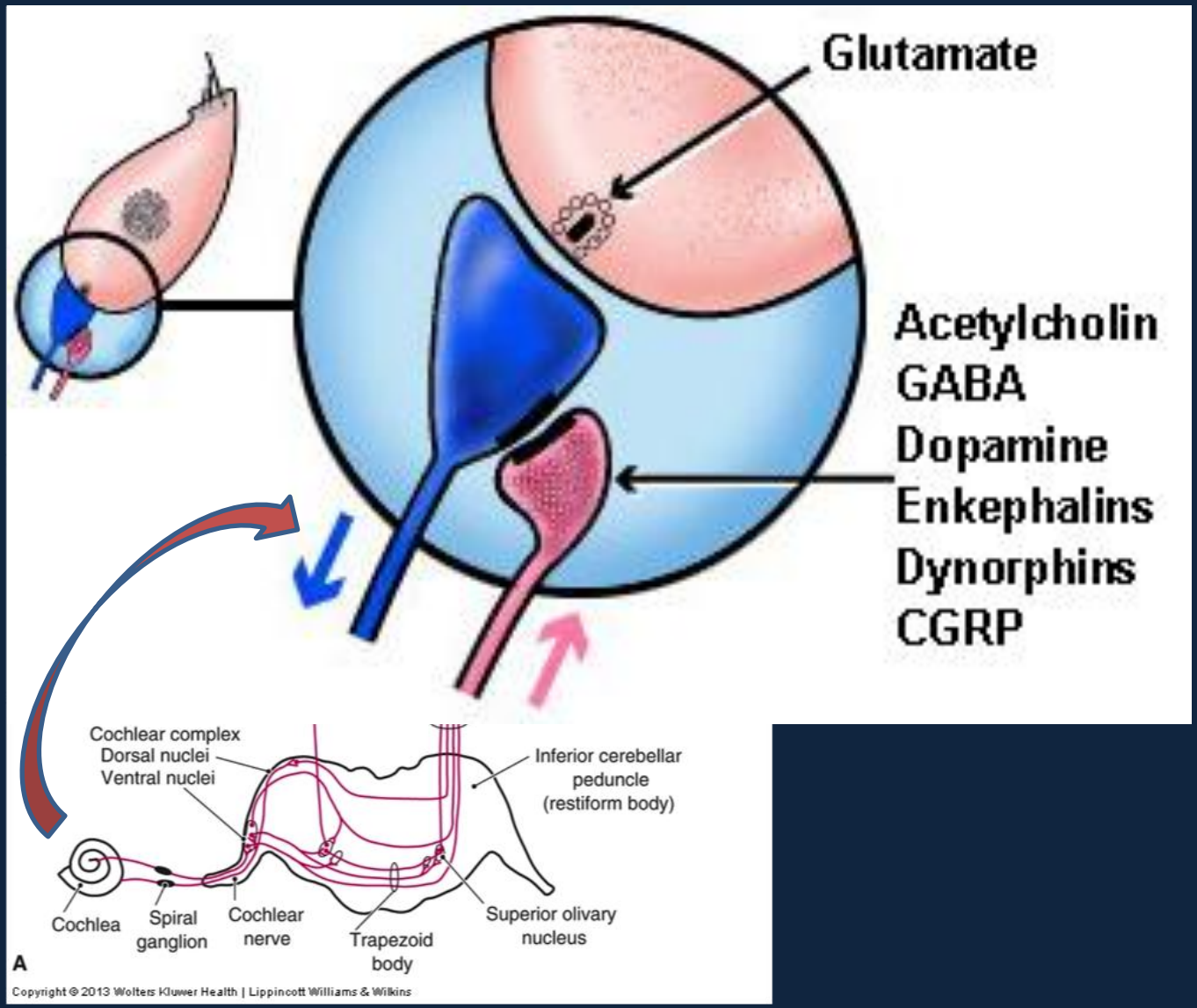
Increased spontaneous neural activity
Increased synchronous activity
Increased regularity of action potentials
Over-representation of “lost” frequency bands

Potential mechanism (s)….

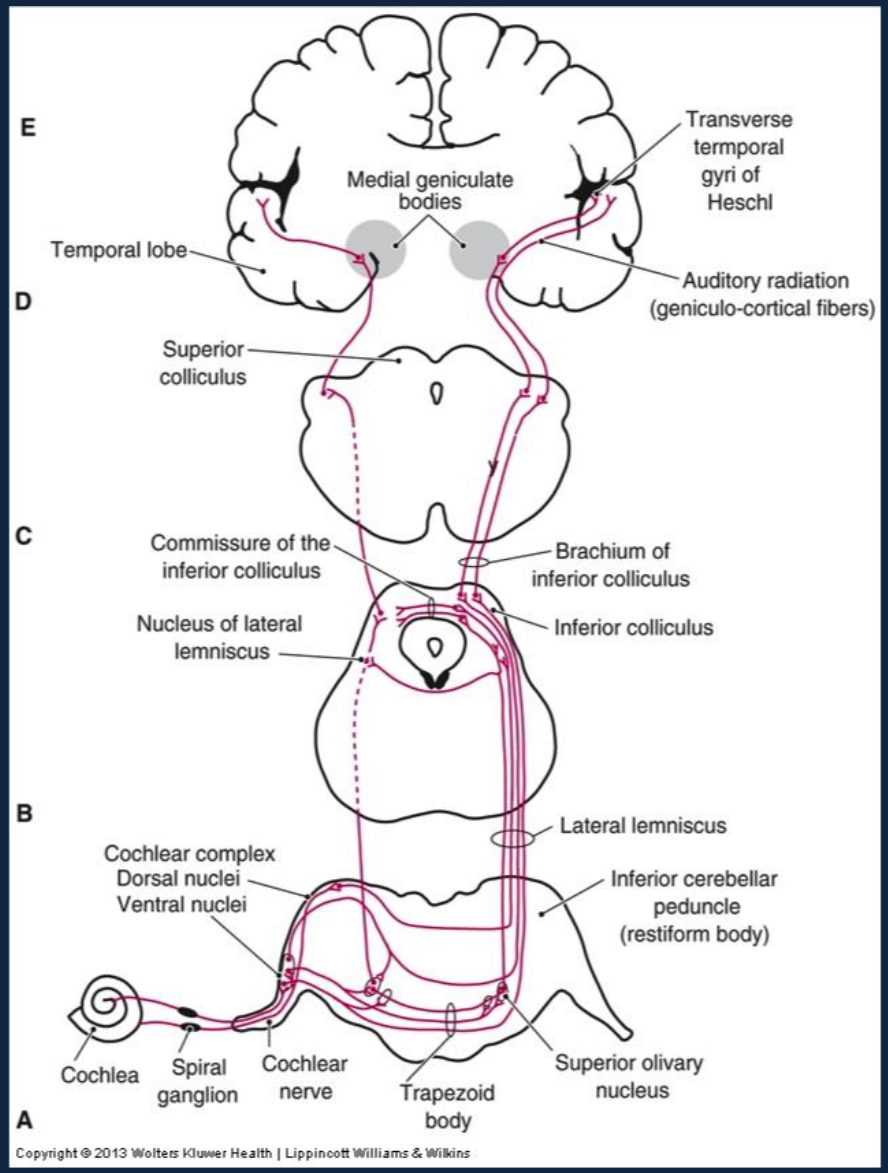
Down-regulation of inhibitory neurotransmitters, such as γ-amino butyric acid (GABA)and glycine

Up regulation of excitatory neurotransmitters, eg. glutamate (Glu).

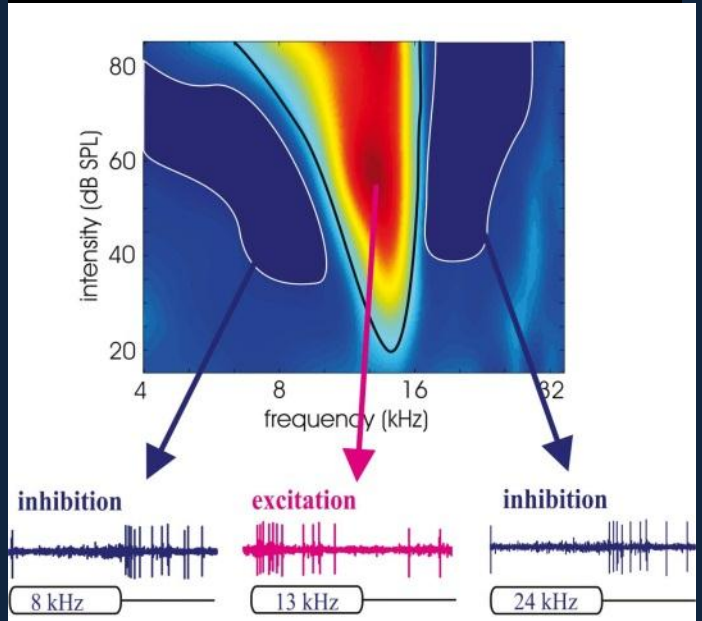
Auditory neurotransmitters



Auditory neurotransmitters



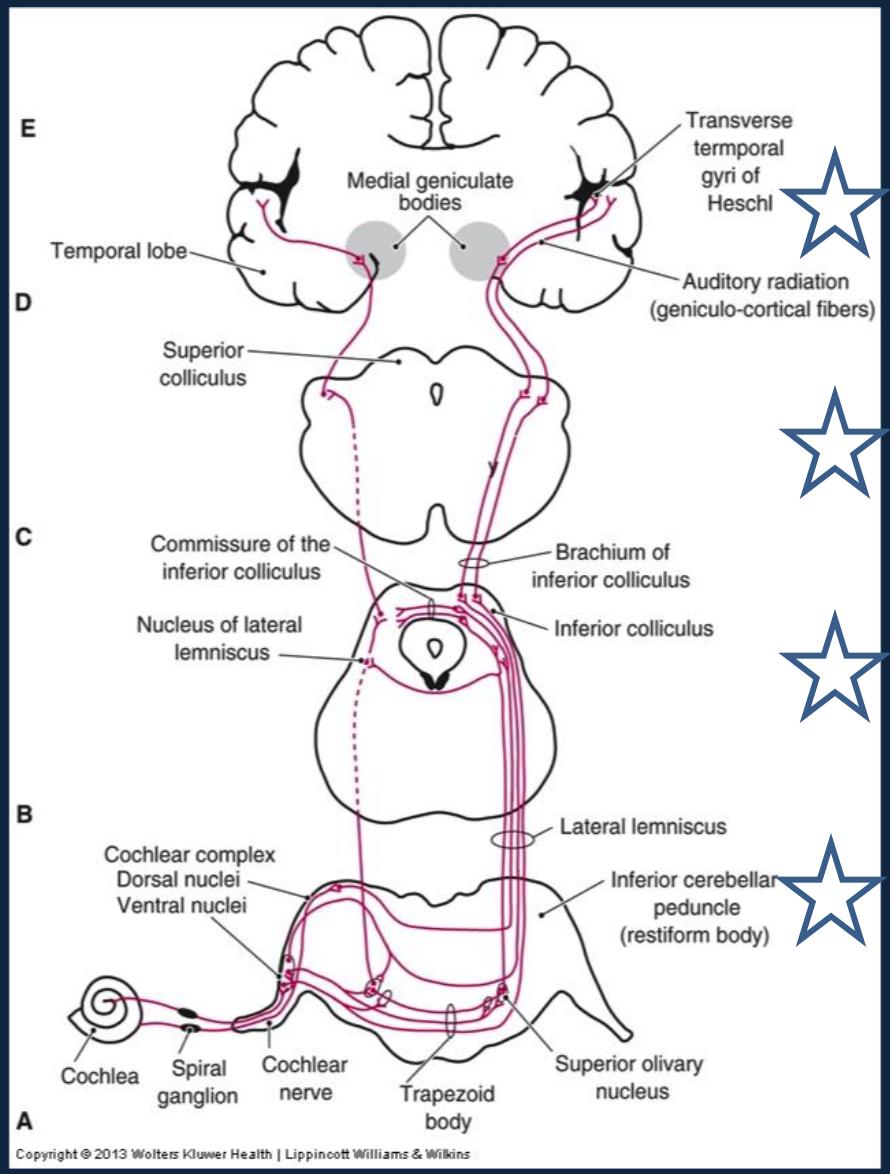
Glutamate



Glycine

GABA

Auditory neurotransmitters



Glutamate

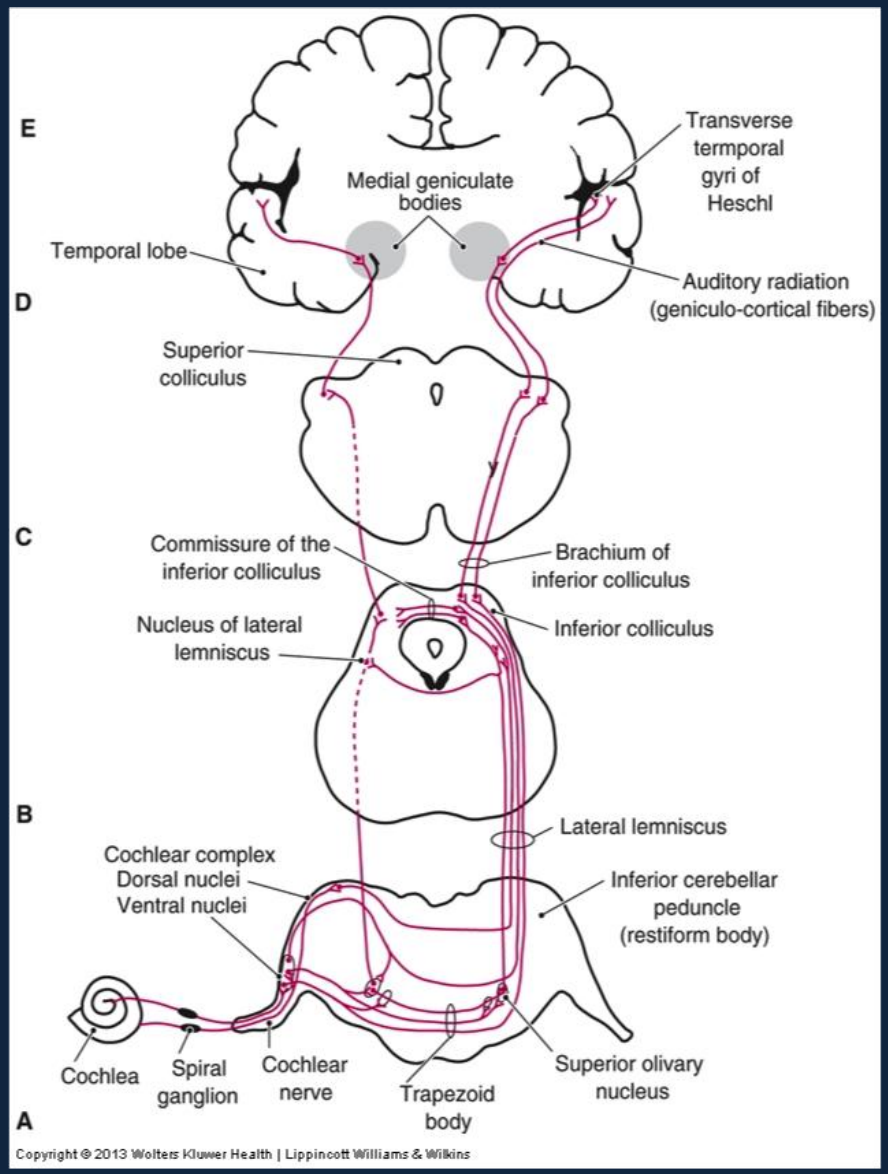
Serotonin

Salience
Significance

Glycine

GABA

Auditory neurotransmitters



Glutamate

Attention
Learning
Memory

Dopamine

Glycine

GABA

Pathways of drug development

Off-label use of an existing compound
Alprazolam (Johnson 1993) Acamprosate (Azevedo and Figueirido 2005) Tegretol (Levine 2006) Melatonin (Megwalu 2006) Cyclobenzaprine (Coelho et al 2012)
Perhaps useful in specific targeted populations Rare successful placebo controlled, replicated studies

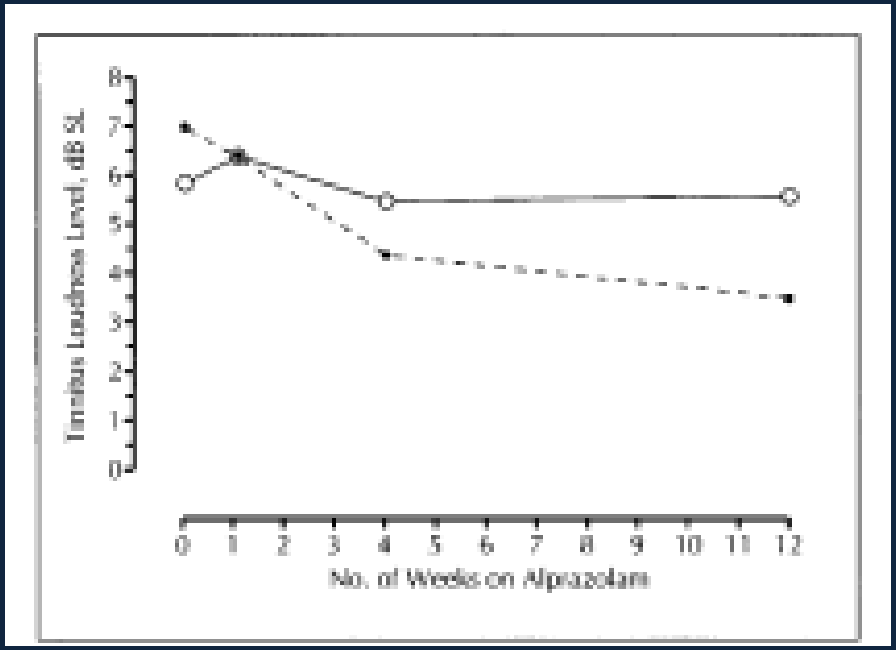
Alprazolam

Modulate GABA receptors (agonist)
: anxiolytic, hypnotic, anticonvulsant properties

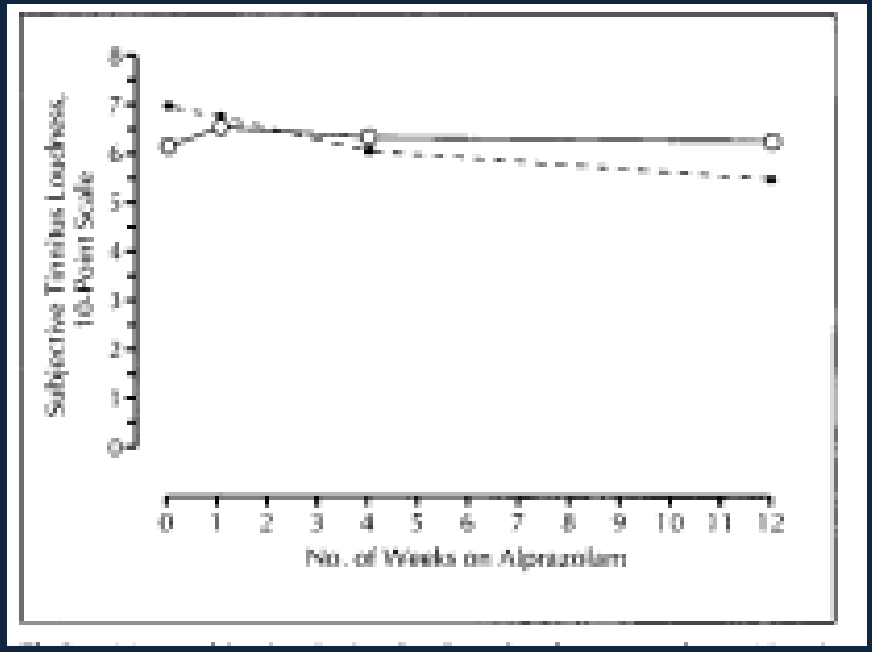
Johnson et al. 1993

- Double-blind, placebo controlled (n=40)
- Chronic tinnitus, unspecified severity
- No depression or anxiety
- Loudness (dB and VAS)

Alprazolam (Johnson et al. 1993)



Objective loudness (dB)



Subjective loudness (VAS)

Decreased loudness match
Deceased subjective loudness (clinically significant?)
No change in MML

Alprazolam

Jalali et al. 2009

- Randomized, triple-blind, crossover, placebo-controlled
- Chronic tinnitus, no depression/anxiety
- Outcomes : THI, VAS severity, loudness (dB)

Alprazolam (Jalali et al. 2009)

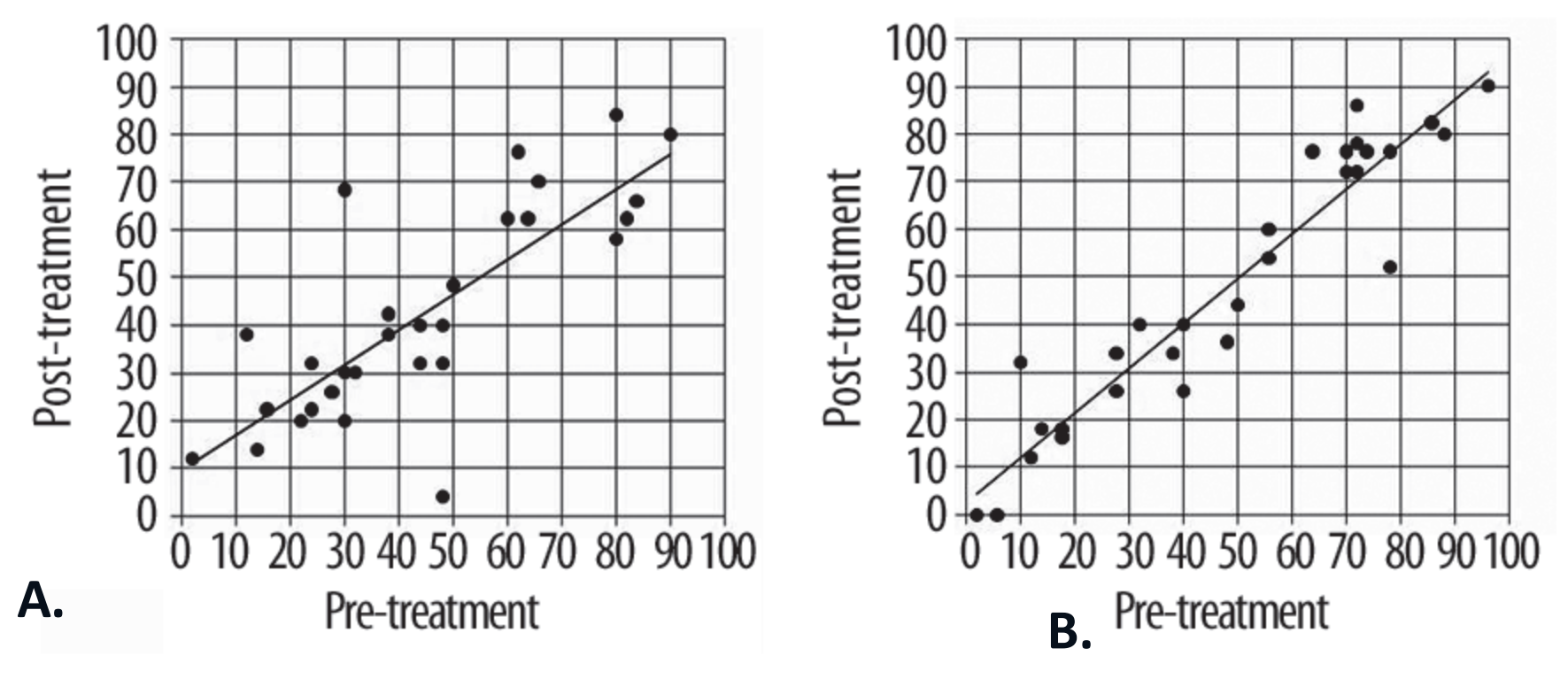


Figure 3. THI pre- and post-treatment scores
A Alprazolam; **B** Placebo

The use of benzodiazepines for tinnitus : a systematic review

NE Jufas, R Wood *J of Laryngology and Otology 2015*

Results : Six clinical trials were included. Clonazepam was found to be effective in three studies, but these studies had limitations regarding adequate blinding. The effectiveness of alprazolam was equivocal.

Conclusion : Benzodiazepine use for subjective tinnitus does not have a robust evidence base. Clonazepam has the most evidence to support its use and is relatively less likely to lead to abust because of its longer half-life, but caution is still needed given the other serious side effects.

Pathways of drug development

Off-label use of an existing compound

Acamprosate
Azevedo&Figueirido 2005
Sharma et al 2012

Off-label but a rational application

Dual mechanism of action
- glutamate antagonist
- GABA agonist

DBPC *
50% improvement in 50% of subjects vs 11% on placebo

DBPC, crossover
~50% improvement

Pathways of drug development

Off-label use of an existing compound

Acamprosate
Azevedo&Figueirido 2005
Sharma et al 2012

Off-label but a rational application

Dual mechanism of action
- glutamate antagonist
- GABA agonist

DBPC *
Pre 6.75 Post 2.87
Pre 5.72 Post 5.17

DBPC, crossover
VAS Pre 7.1 Post 4.05
QOL Pre 66 Post 36
TLM Pre 50 Post 43 (dB)

Multisite DBPC trial
Data unpublished

Pathways of drug development

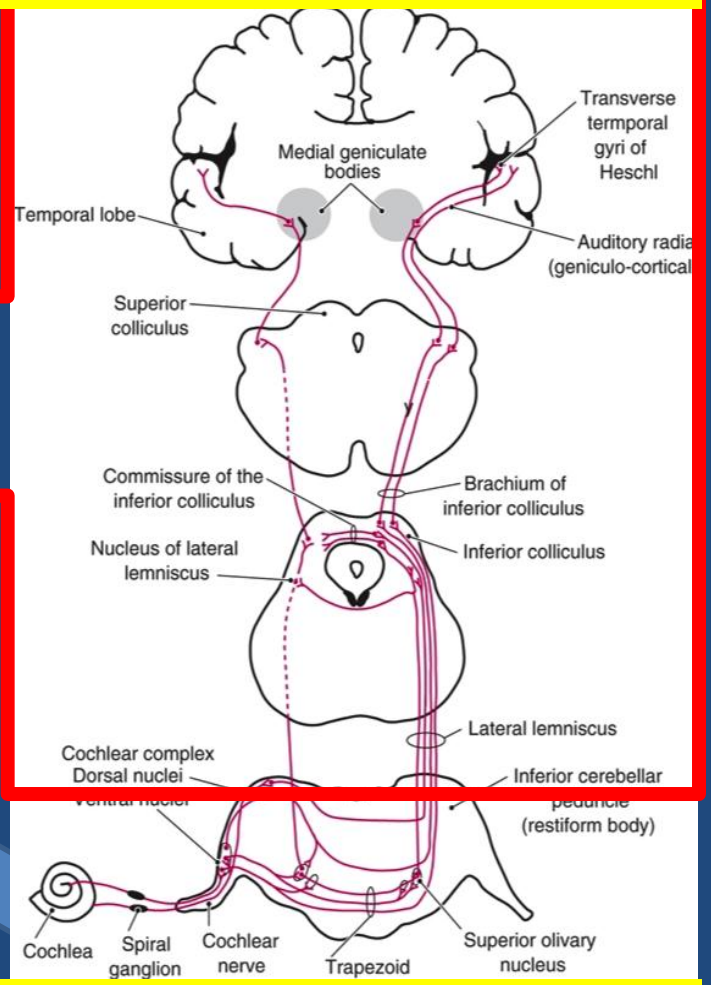
Novel drug development

Autifony 0063 (2011)

AM101 (2003)

$$$$$$

Antagonist of voltage-gated K channels



S-Ketamine cochlear infusion

Pathways of drug development

Novel drug development

Autifony 0063 (2011)

AM101 (2003)

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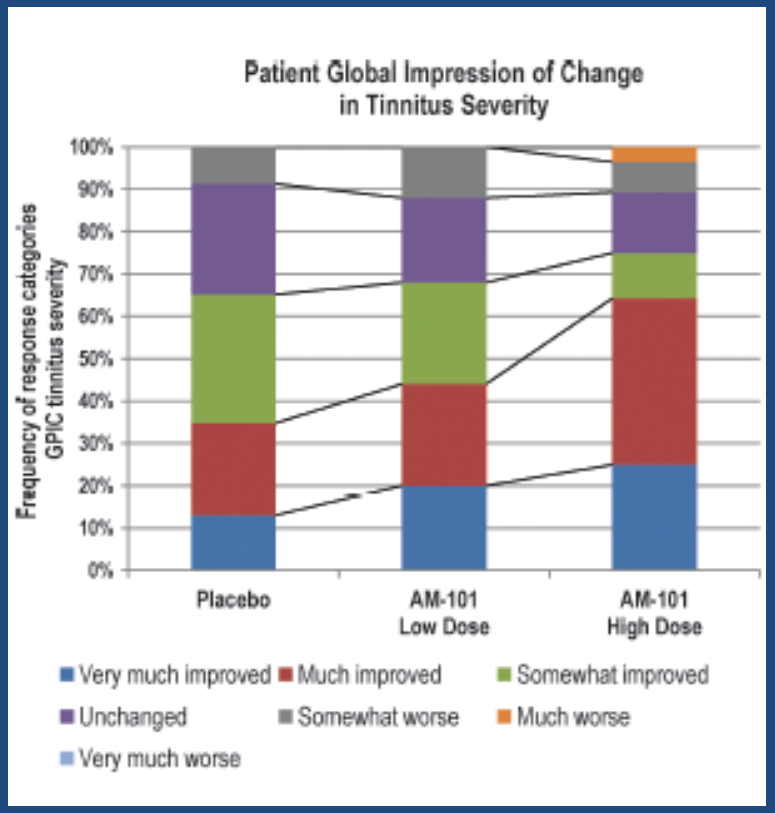
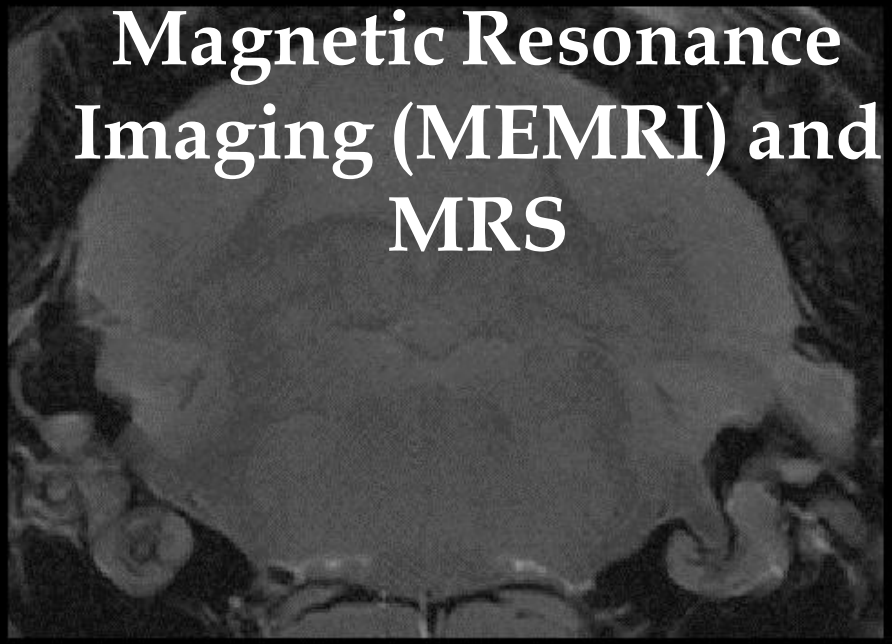
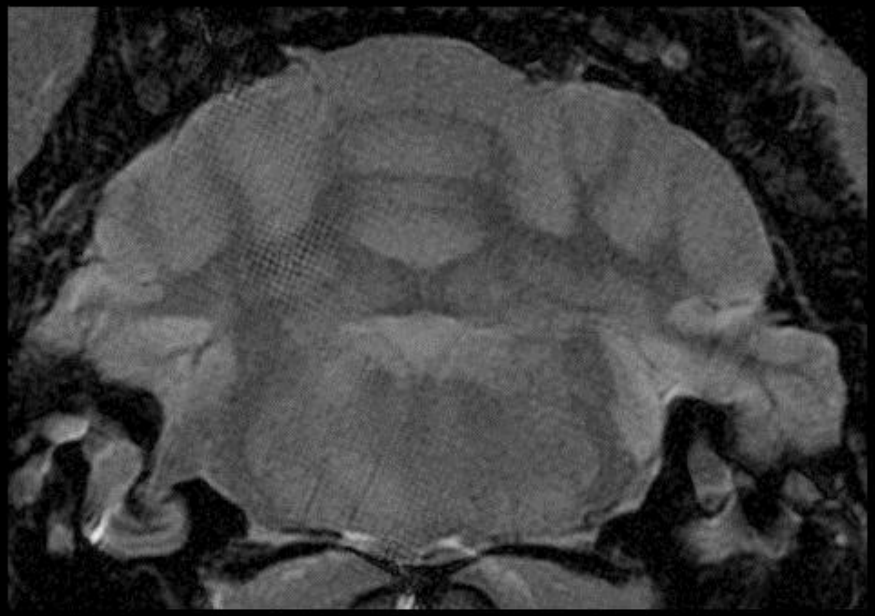


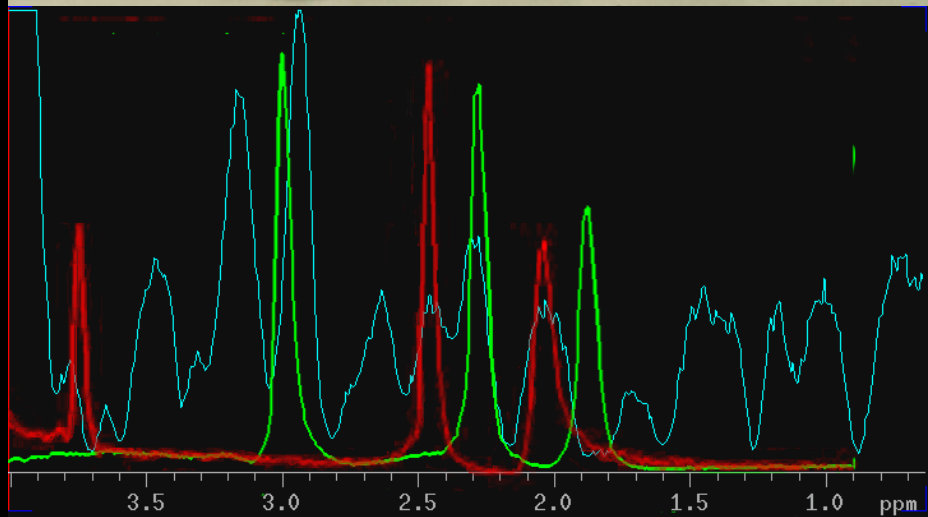
S-Ketamine cochlear infusion

Locate and investigate critical brain areas associated with tinnitus

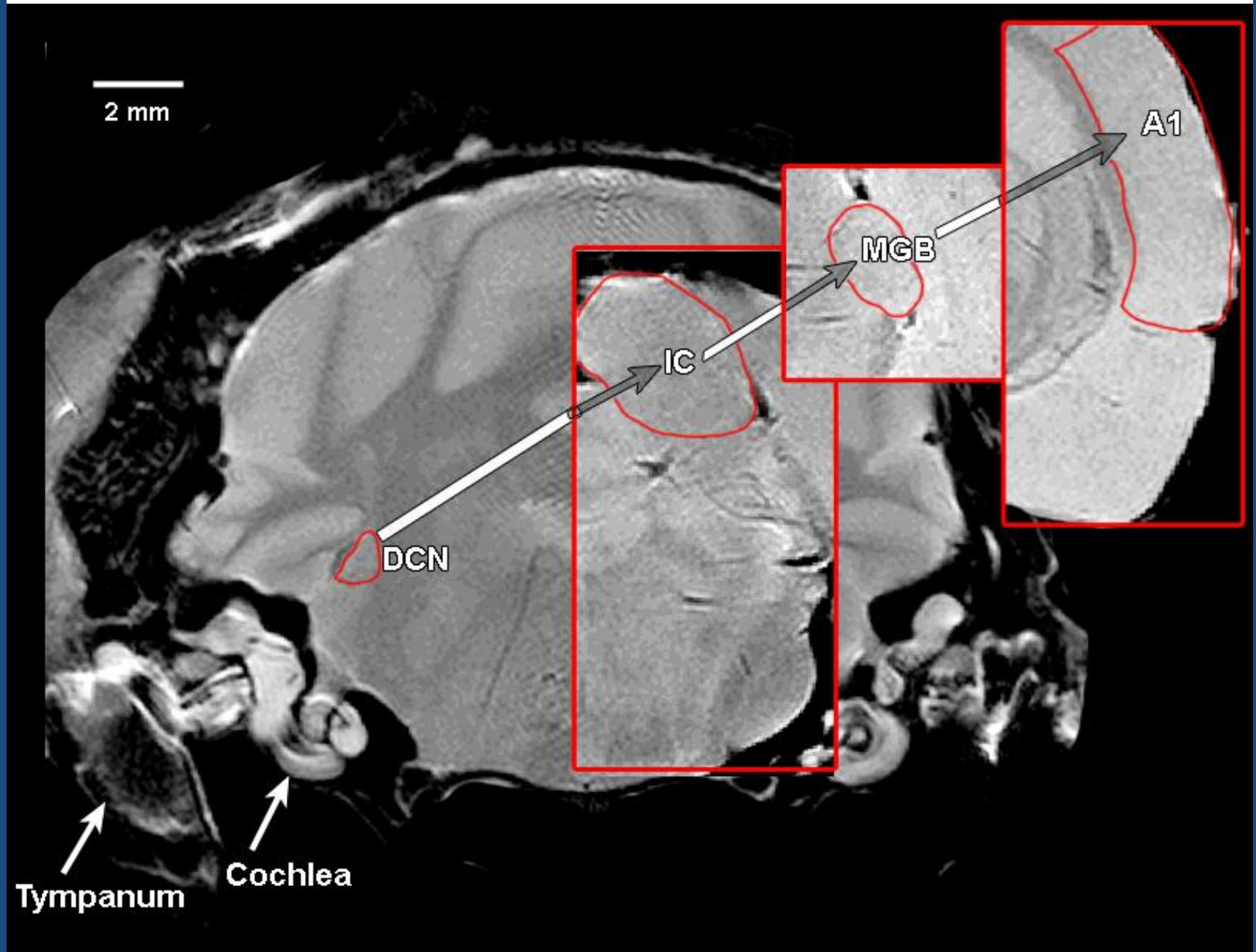
Manganese-enhanced Magnetic Resonance Imaging (MEMRI) and MRS

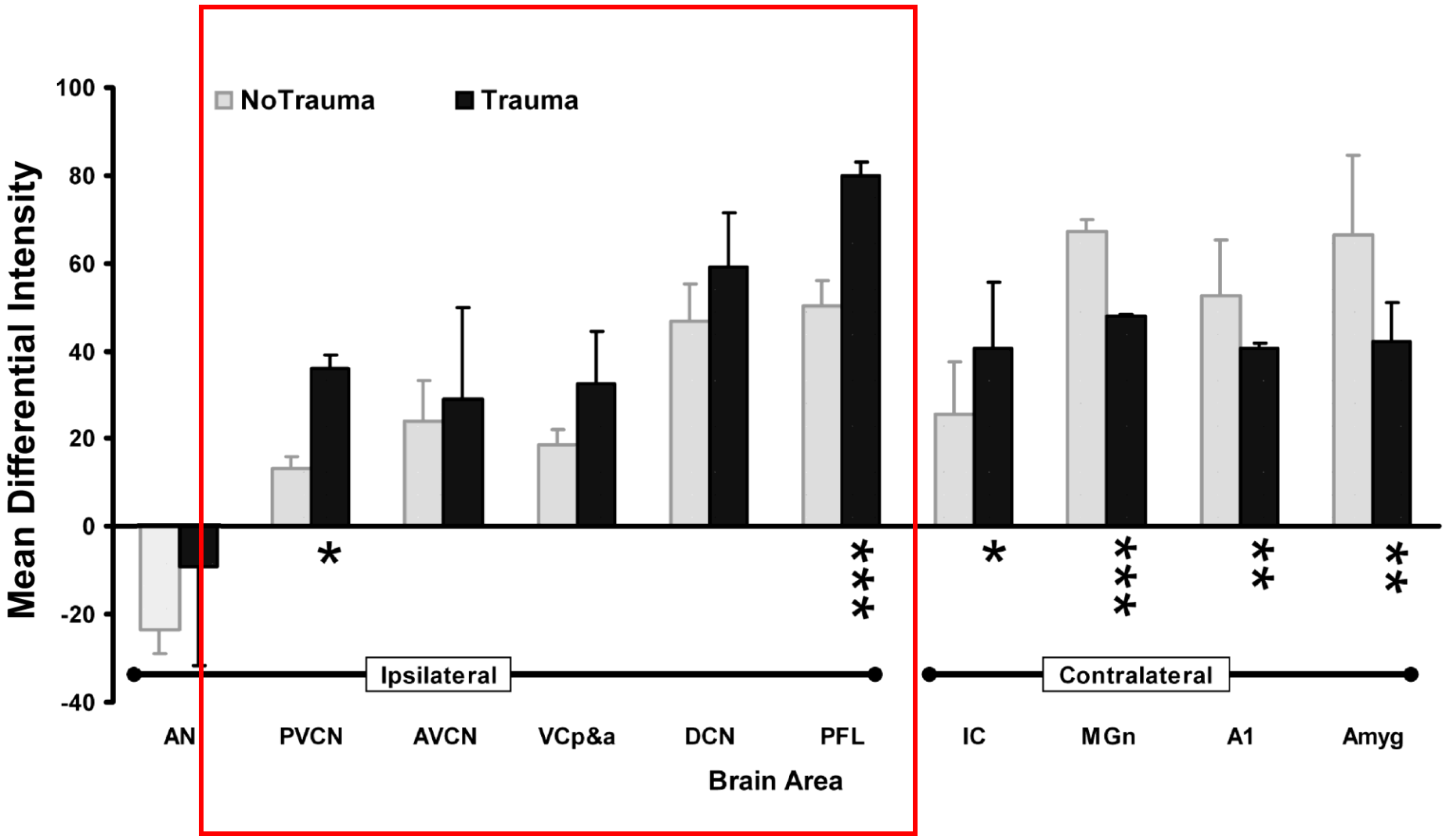




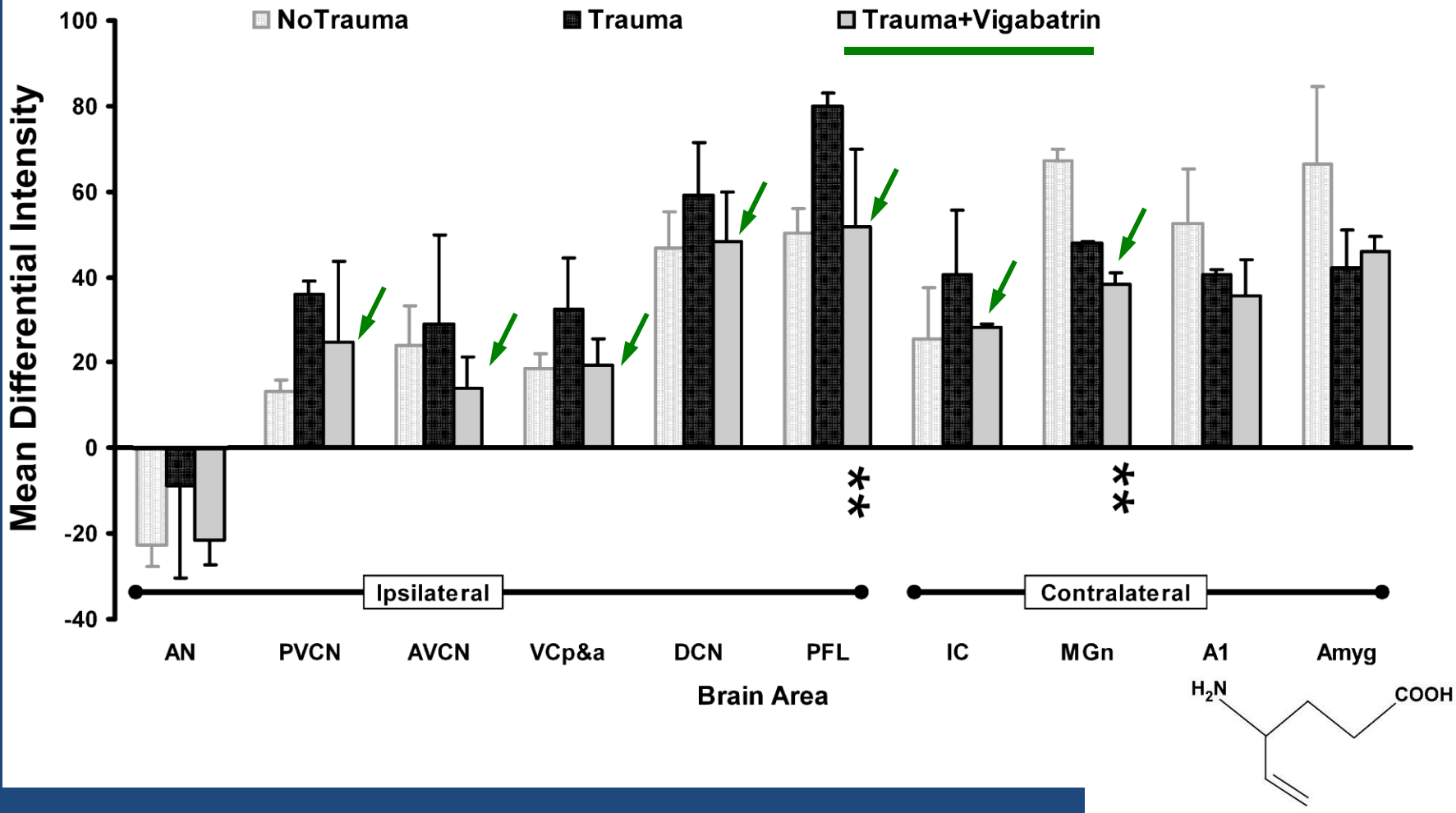


Slice thickness: 300 μ Planar resolution: 26 μ




NoTrauma
Trauma
Mean Differential Intensity
100
80
60
40
20
0
-20
-40
*
*
***
*
***
**
**
Ipsilateral
Contralateral
AN
PVCN
AVCN
VCp&a
DCN
PFL
IC
MGn
A1
Amyg
Brain Area

Vigabatrin effect on Mn+ uptake

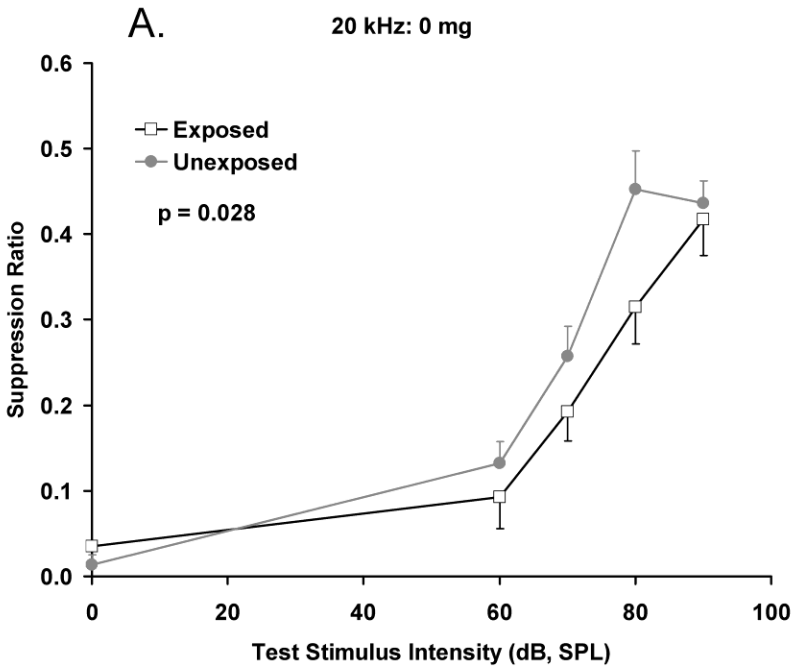


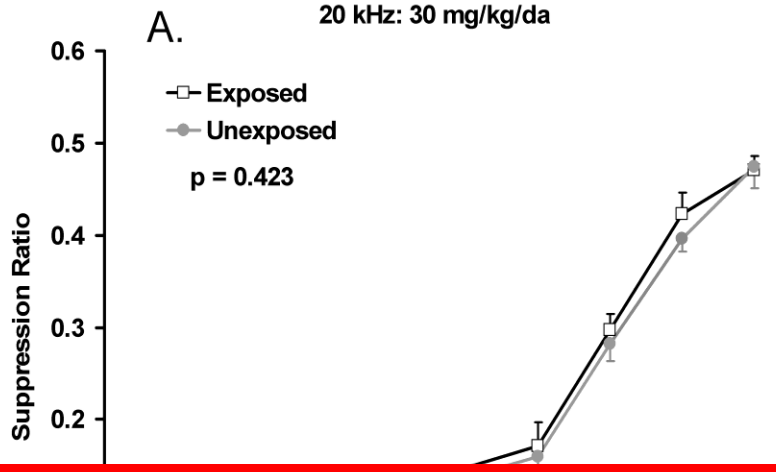
Vigabatrin (4-aminohex-5 enoic acid)

VIGABATRIN : GABA-transaminase inhibitor

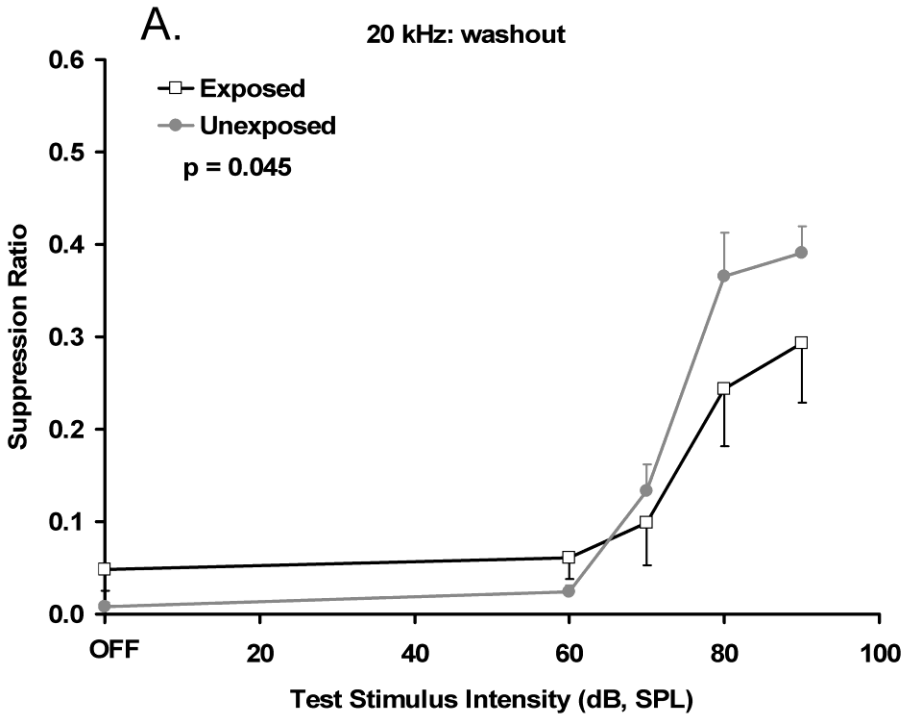
Pre-Drug

Vigabatrin, Low Dose





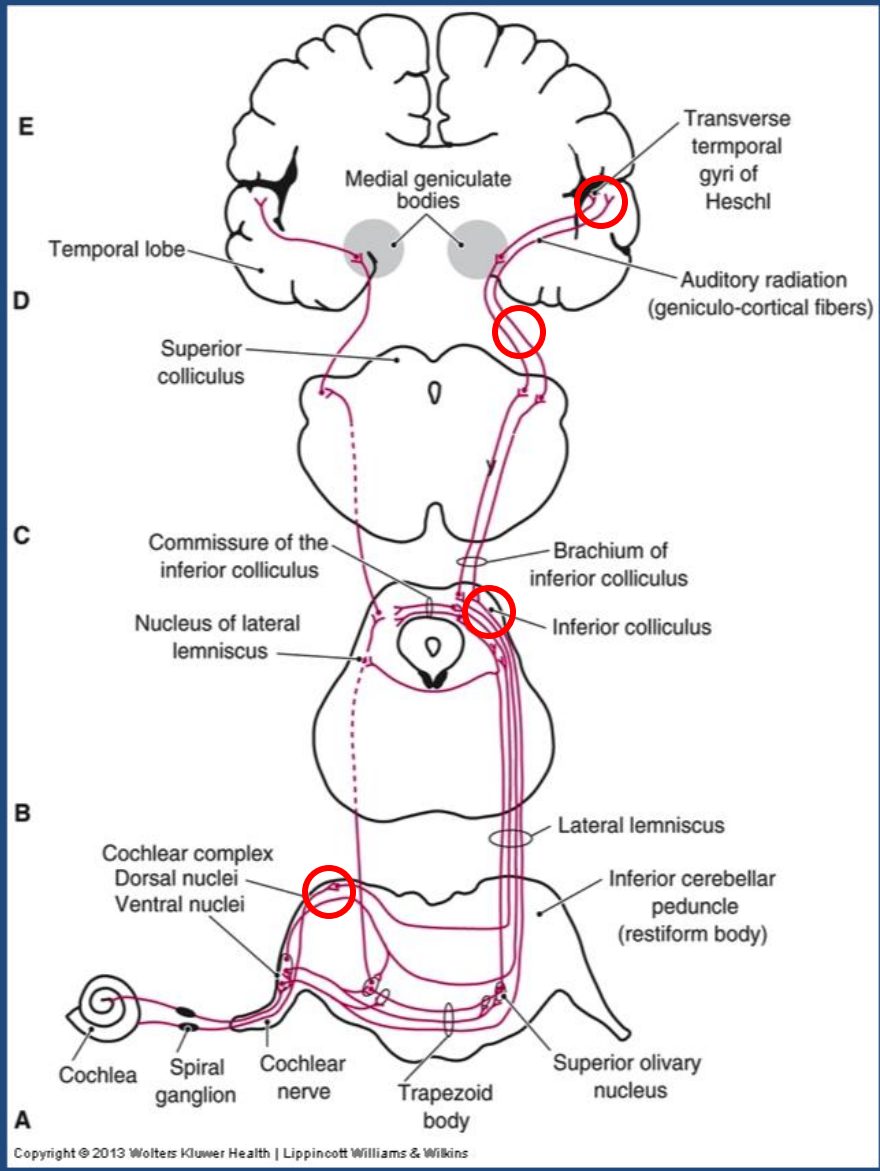
Tinnitus Returns After 7-week Washout



Brozoski TJ, Spires TJ, Bauer CA, (2007). J Assoc Res Otolaryngol, 8,105-18.

Neurotransmitter levels and tinnitus?

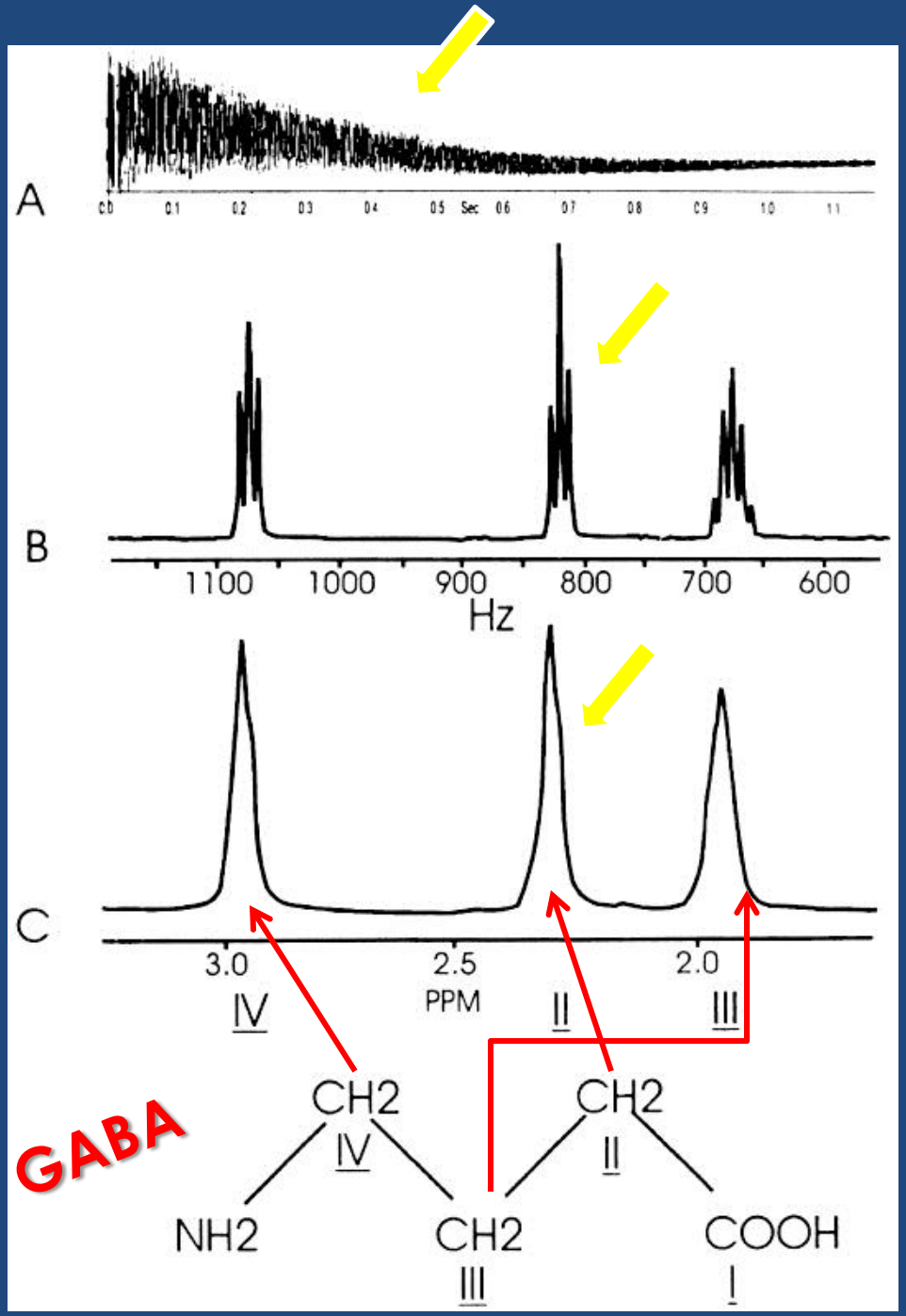
Measure endogenous GABA, glutamate, and choline levels using volume-localized proton magnetic resonance spectroscopy (^{1}H-MRS).



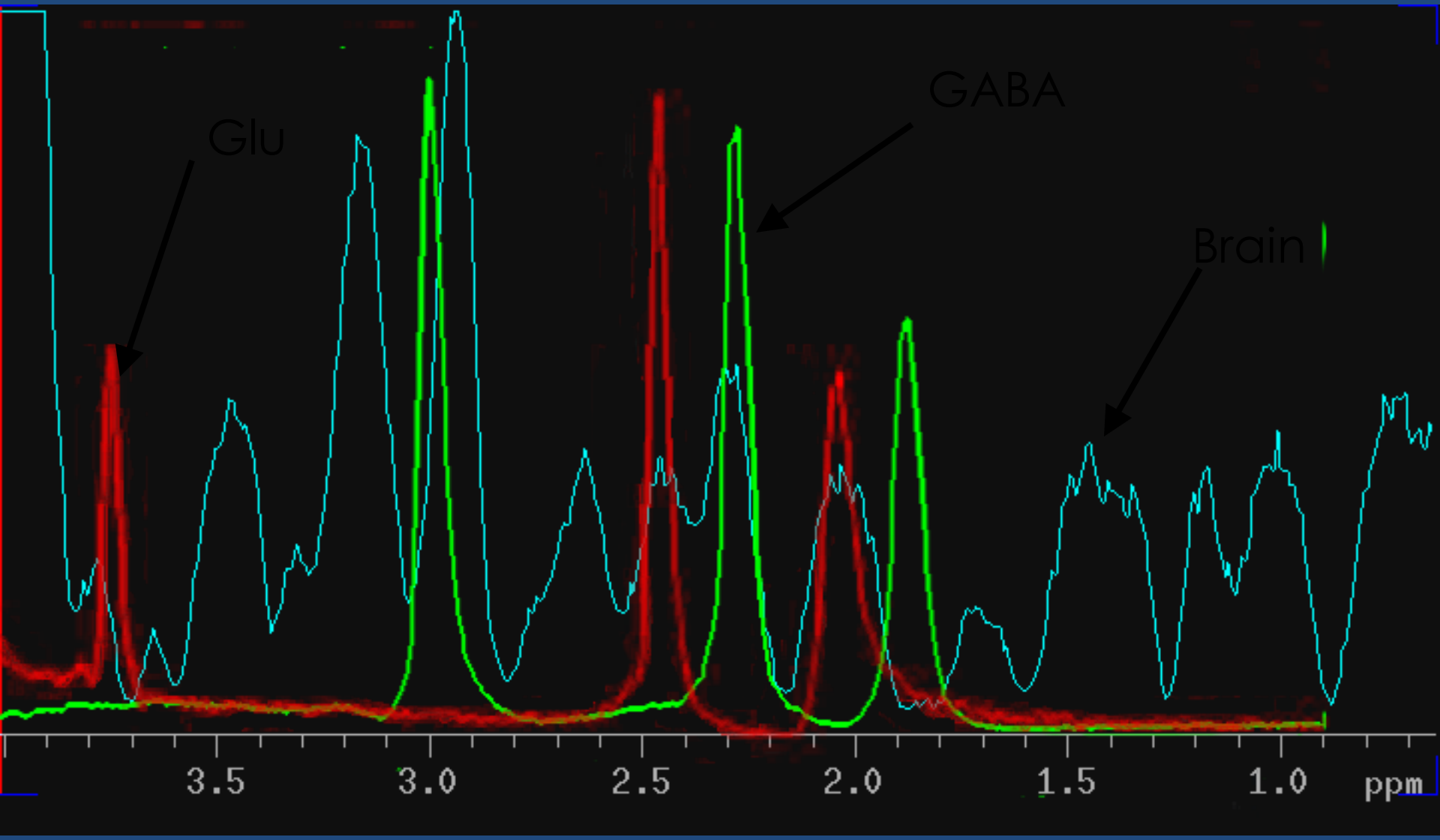
A. Free induction decay (FID) of molecular resonance induced by a tuned RF pulse. Average of 128 FIDs.

B. Fourier transform of the FID with 1-Hz line broadening. The x axis is the frequency difference in Hz between the reference and the resonant frequencies of the three pairs of methylene protons of GABA.

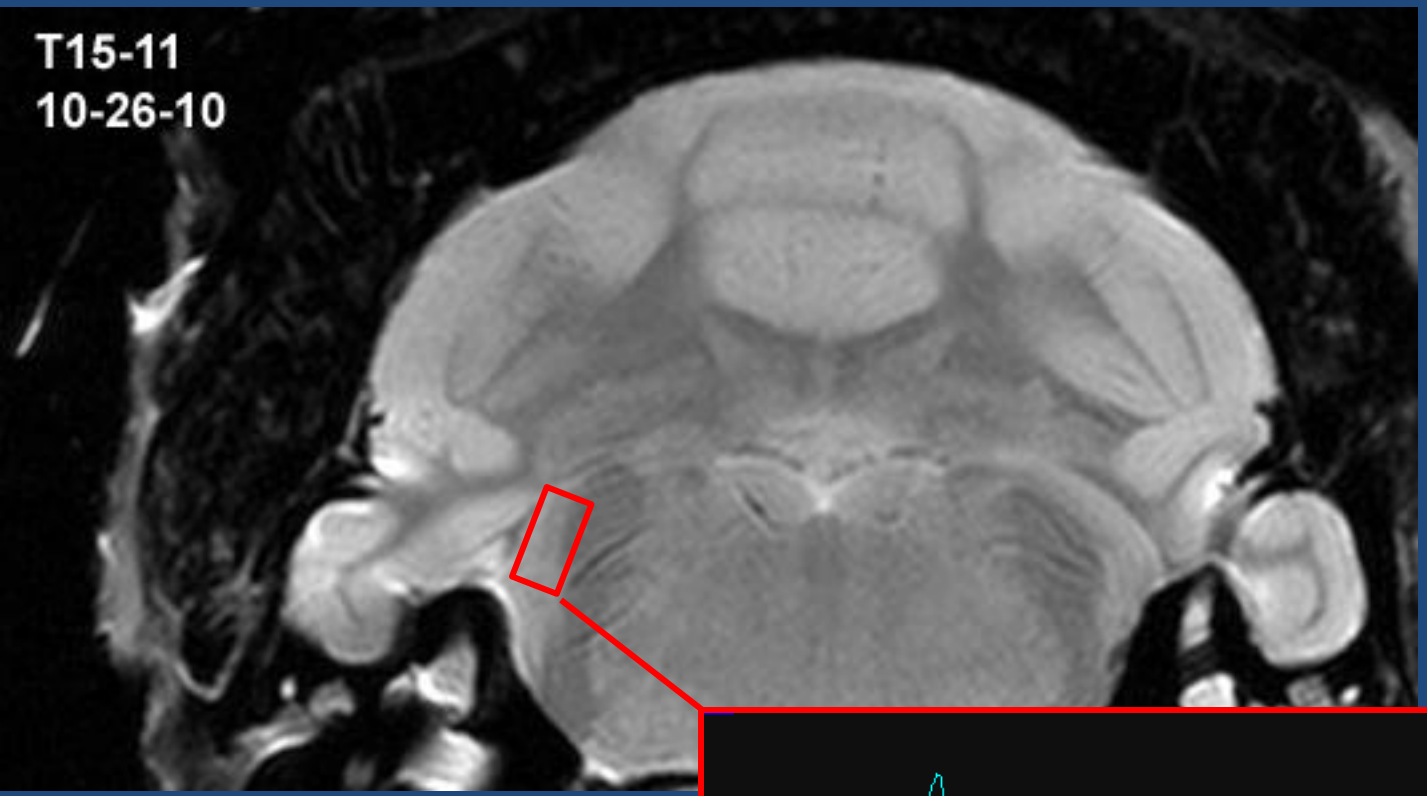
C. A relative proton spectrum: The Fourier transform of the FID has line widths broadened to 7-Hz (widths expected of the GABA protons in vivo). ***The scale of the x-axis is in parts/megahertz (ppm), which is a relative scale of molecular resonance, independent of the field strength of the magnet***. The index numbers under each peak correspond to the methylene proton groupings shown below in the GABA structure.



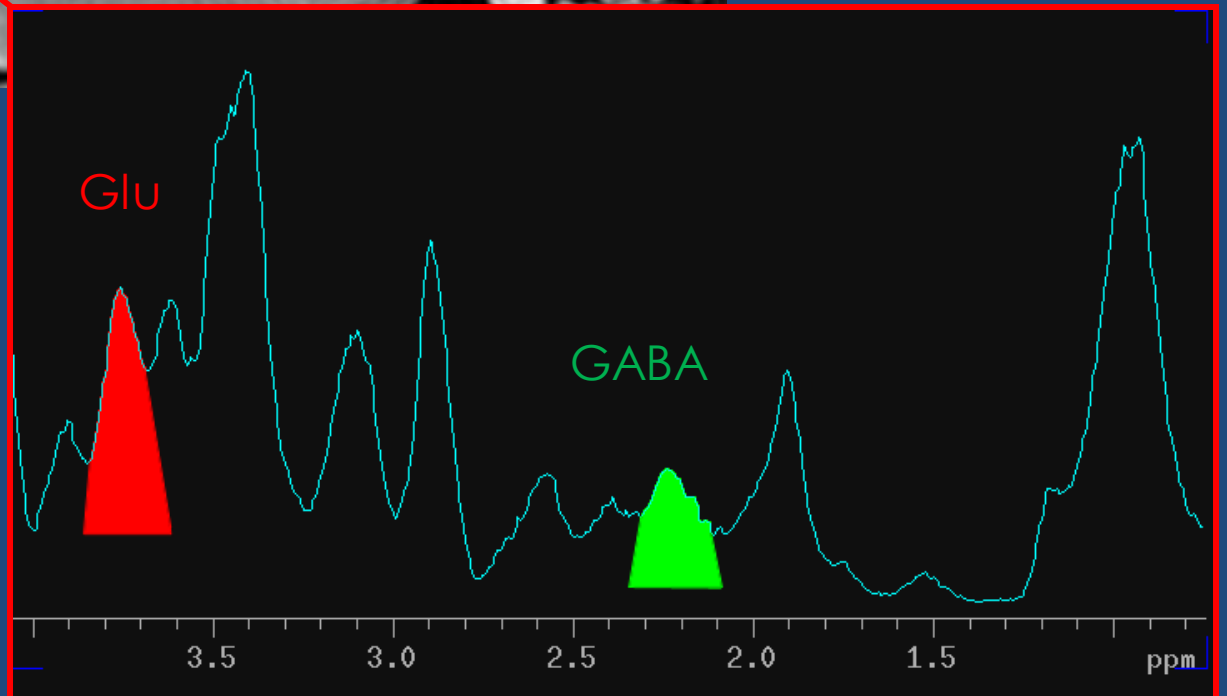
Quantifying Spectra: *Use a peak <u>not</u> confounded by other compounds.*

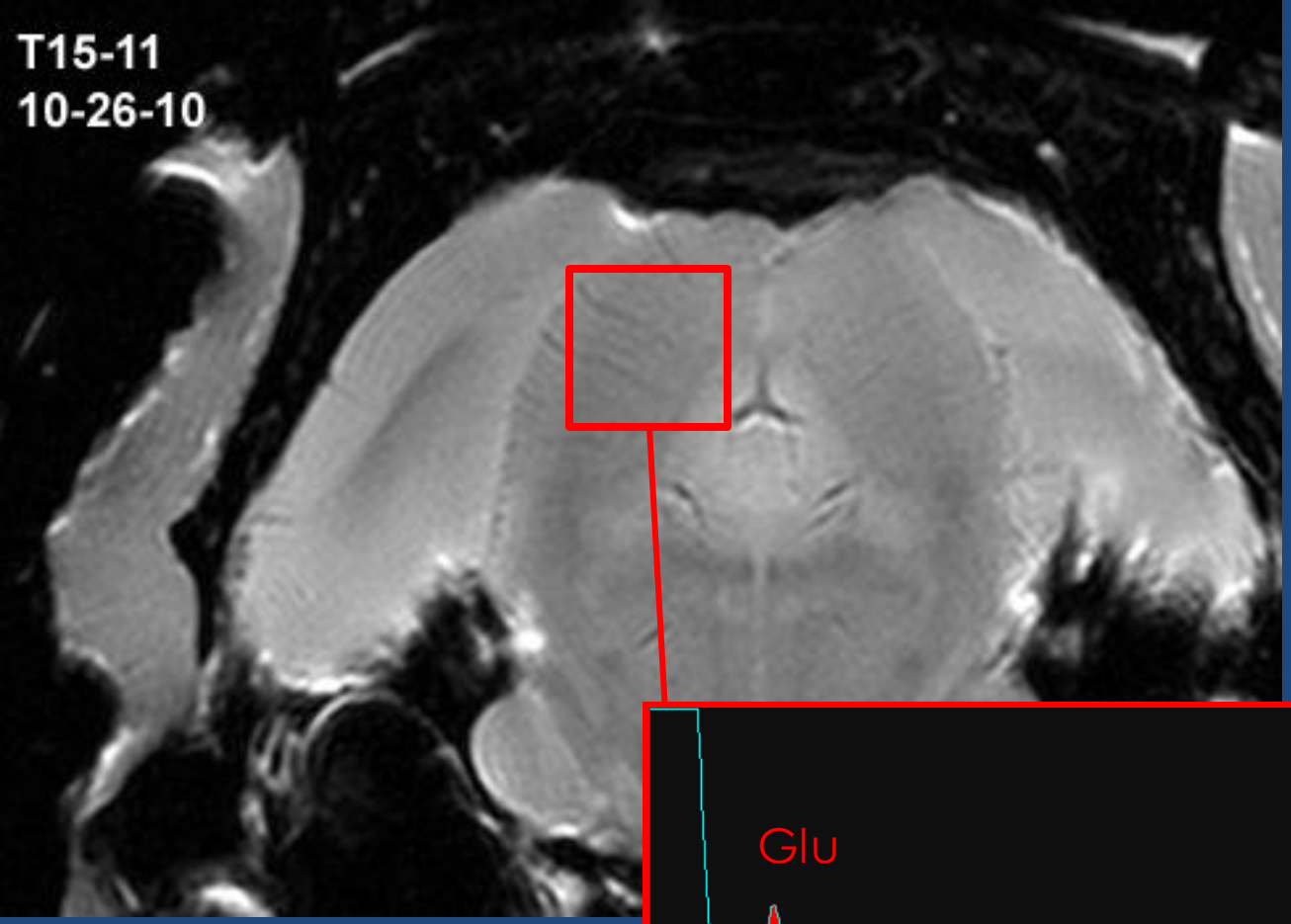


Blue: Representative spectrum (MGB,right)
Green: GABA phantom, 10 mM; Red: Glu phantom, 10 mM

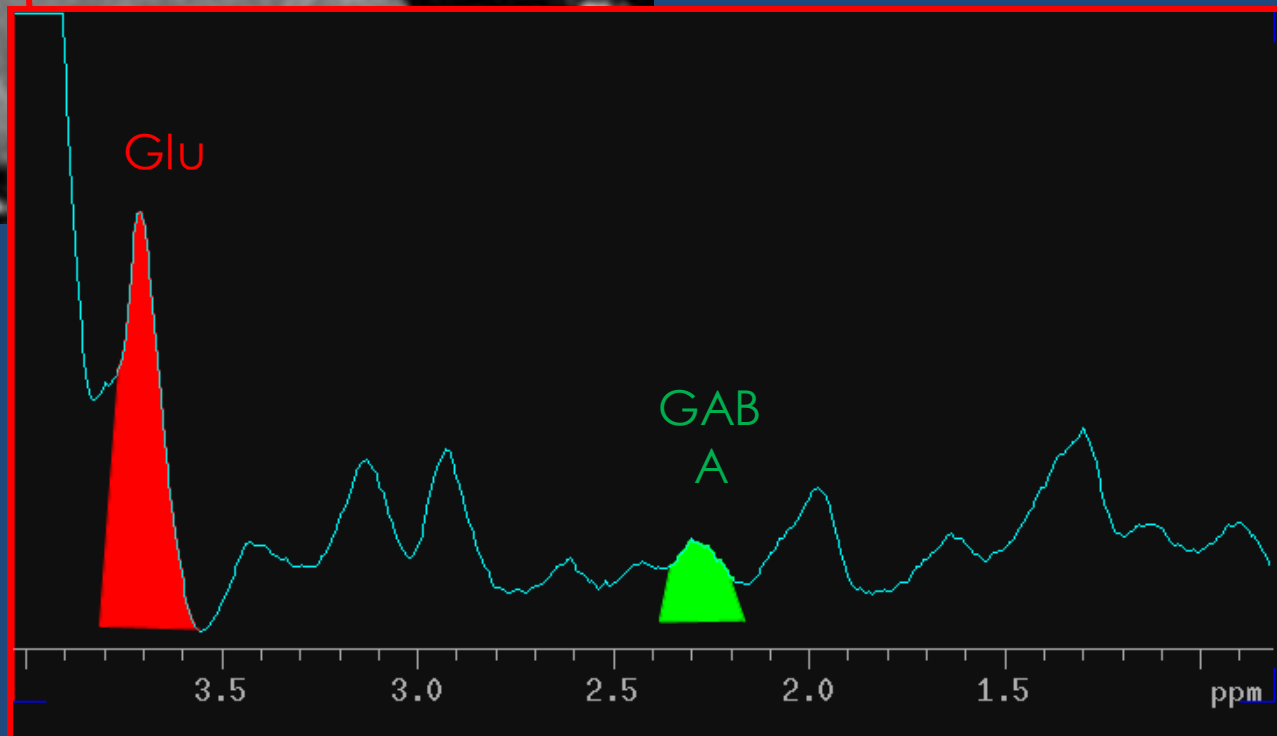


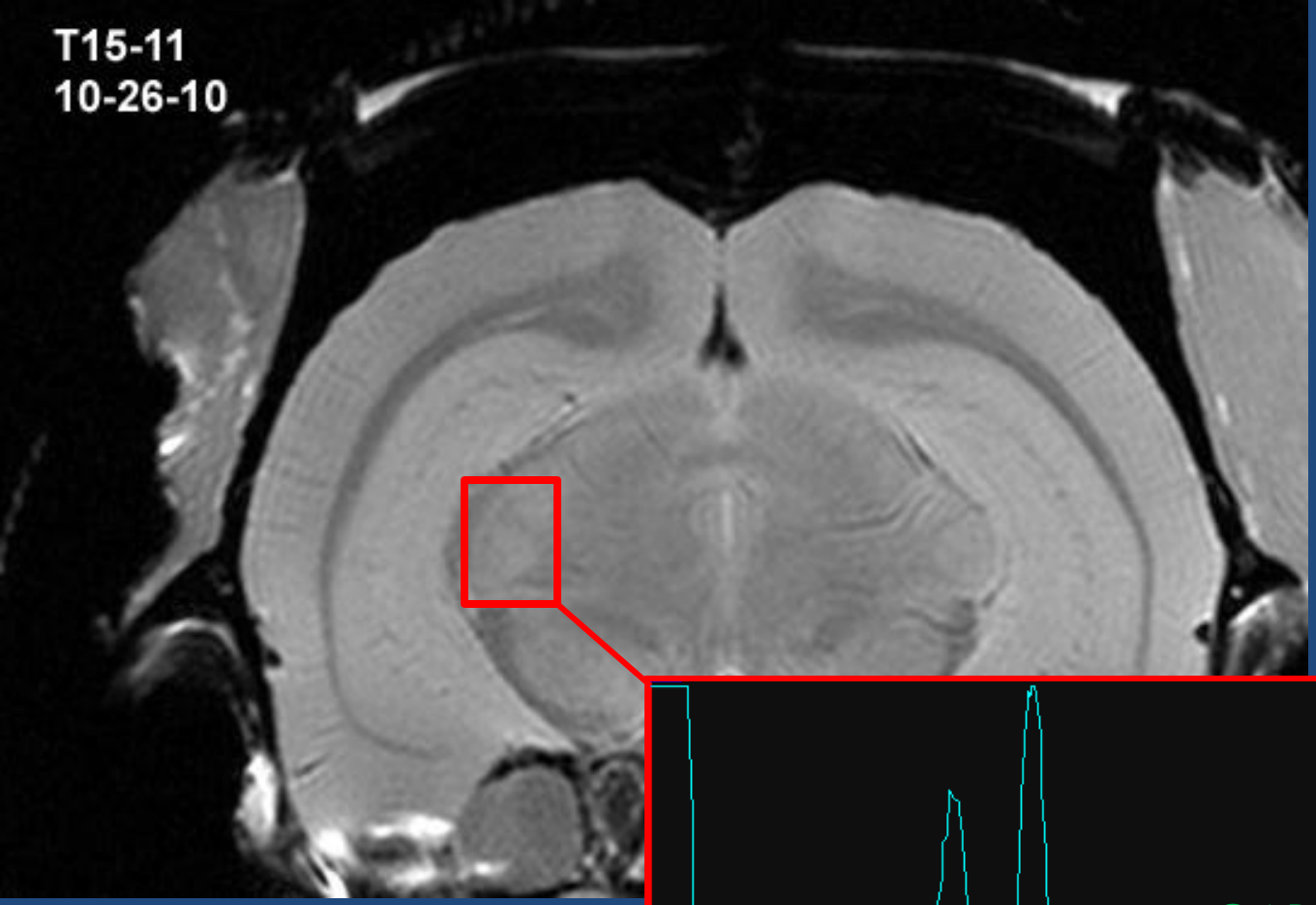
Dorsal cochlear nucleus (DCN)



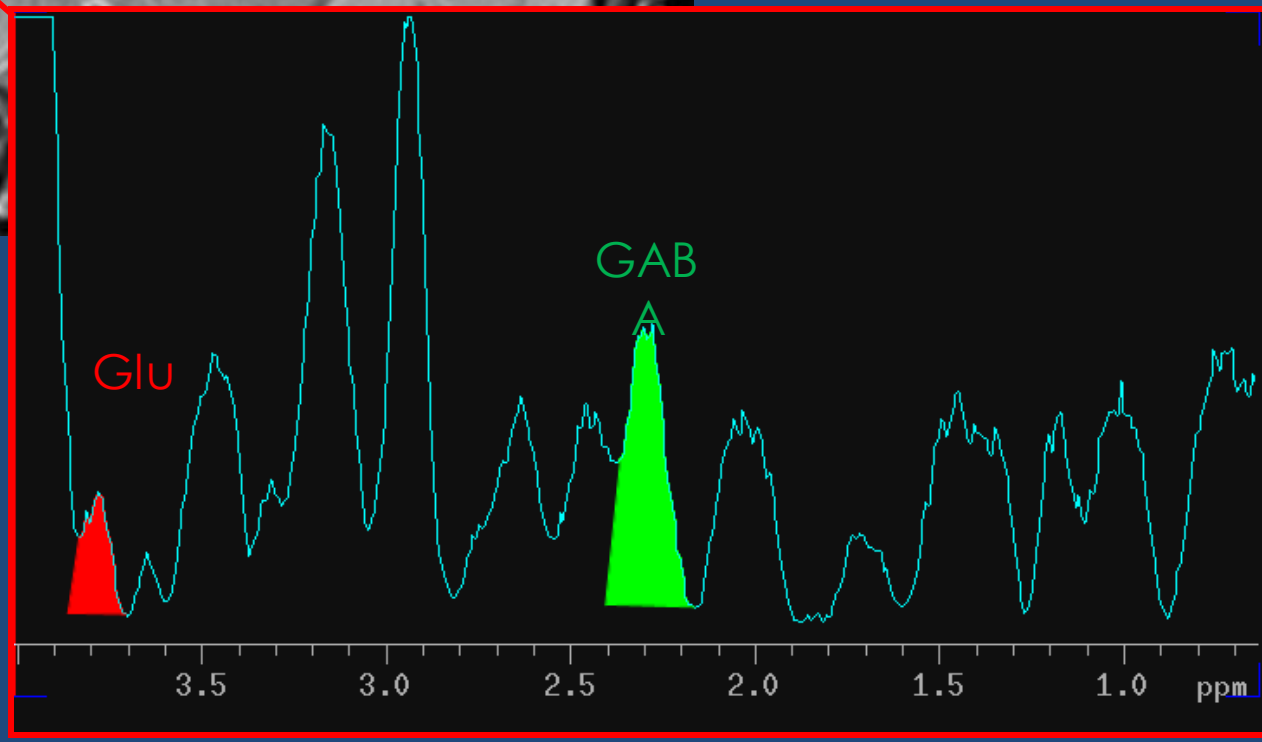


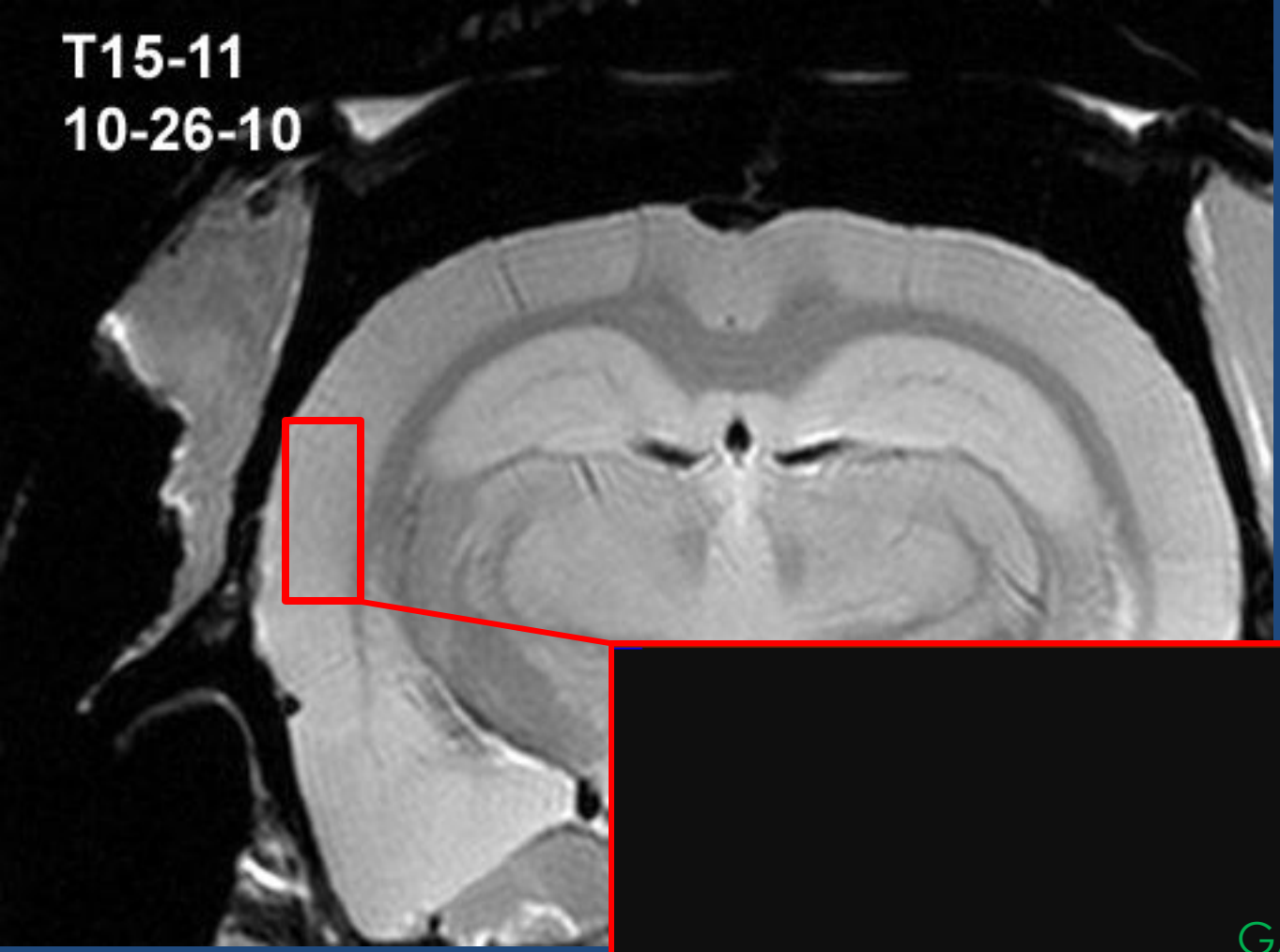
Inferior Colliculus (IC)



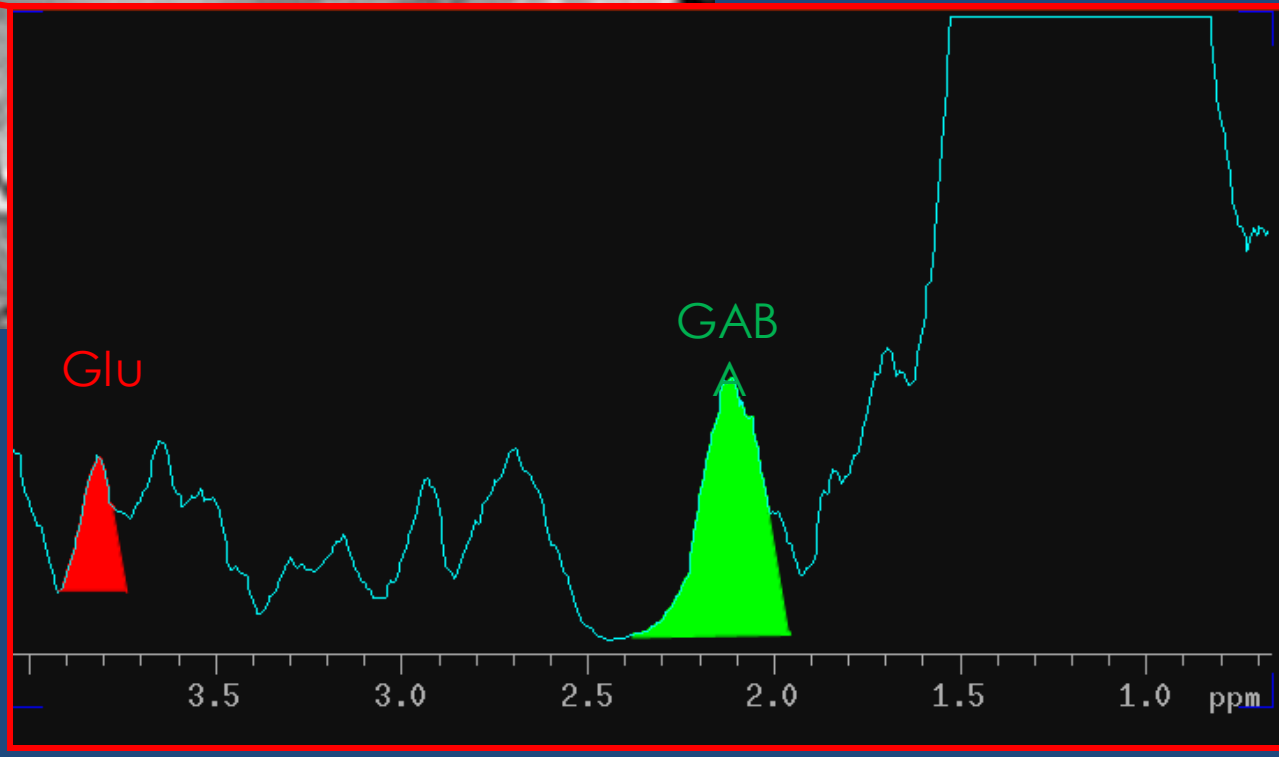


Medial Geniculate Body of the Thalamus (MGB)





Primary Auditory Cortex (A1)

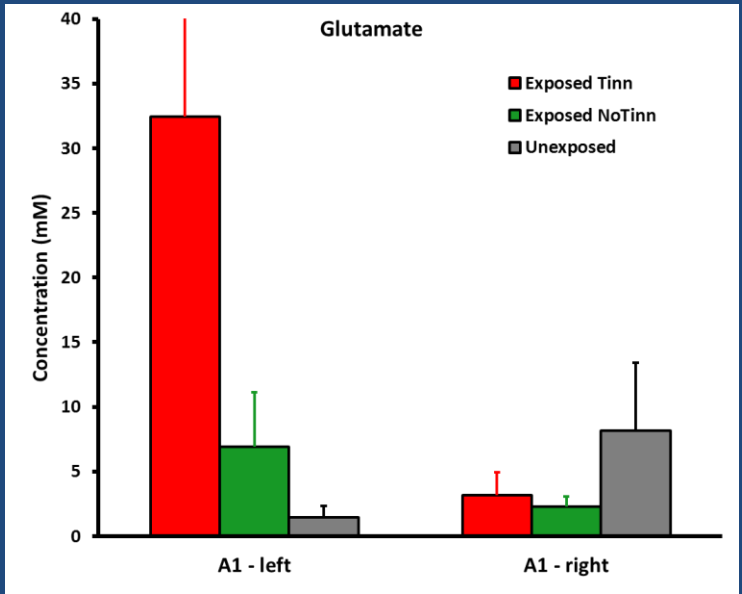


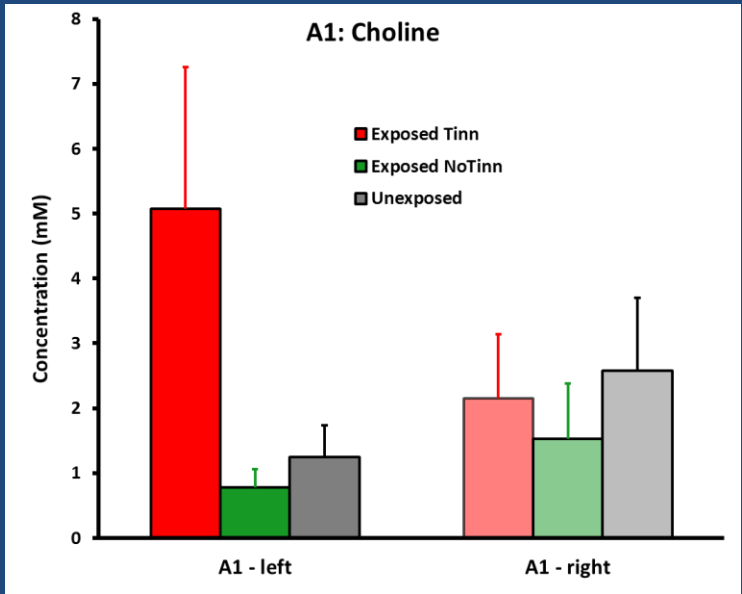
RESULTS

Dramatic GABA level decreases were NOT seen in tinnitus

Small GABA increases were seen in the contralateral (re exposure) DCN and A1.

Glu increases in the ipsi DCN and contra A1 with tinnitus





MRS profile (in the rat):

-mixed GABA alterations

-selective Glu increases

and a potential cholinergic component

present a picture of interactive neurotransmission in the "tinnitus" brain.

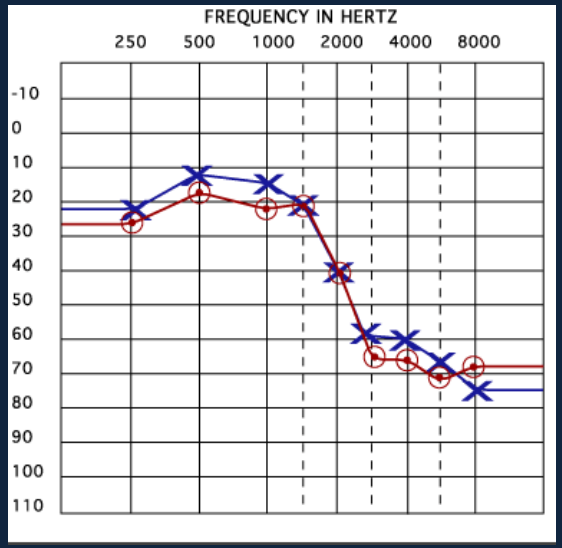
Can animal models facilitate drug development?

from The Better Hearing Institute : Self-Reported Efficacy of Treatments, Kochkin et al. 2011

I can't remember how long I have had ringing in my ears. It may have started 5 or 10 years ago. It has always been very soft. **I am worried now that it is louder and it is making it very hard to hear.** Everyone has to repeat what they say to me because I don't understand them and if we are in a store or with family it is even worse.

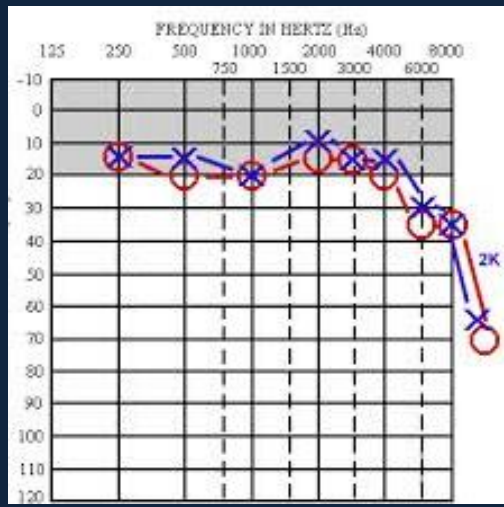
It doesn't bother me at night – it's like having summer crickets outside all year round. I can knit and read books without it bothering me.

The biggest problem is the crickets blocking my ability to hear.



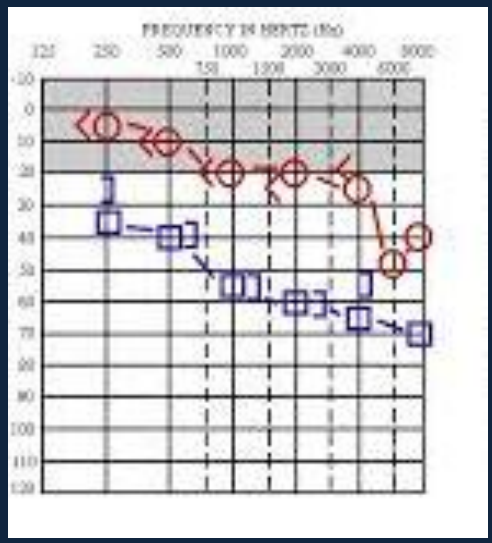
It just happened one night last year to be honest. For the first 10 days, it was constant. I felt extremely depressed and lost 11 pounds from not eating. I wasn't taking it seriously as I still smoked marijuana the first few days and once a week for 3 weeks until I resented pot because it just made the sound louder . Drinking alcohol also made my whole head ring.

Anyways, after the first ten days it has been on and off (or not noticeable). I have often thought *finally, this is going away and I can do things normally again*. It would usually come back though. Now I constantly test myself to hear if it is there or not.



I got tinnitus 12 weeks ago. I went to a concert and the 'music' was very, very loud. I realized part way through that I had been standing next to one of the speakers for 2 hours. The next morning I woke up with ringing in my left ear. I thought it would go away but it didn't. By the following week I knew I was in trouble.

Since then its been three months of hell. I cant think about anything else and am kicking myself for not moving away from that speaker. I feel terrified that I will have this all my life and am so worried about the effect of it on my job (self-employed computer programmer). I can't focus on my work because of the constant distracting sound.



HEARING LOSS

EMOTION REACTION

SENSATION

ATTENTION COGNITION

HEARING LOSS

Reverse hearing loss, prevent hearing loss, prevent onset of tinnitus

EMOTION

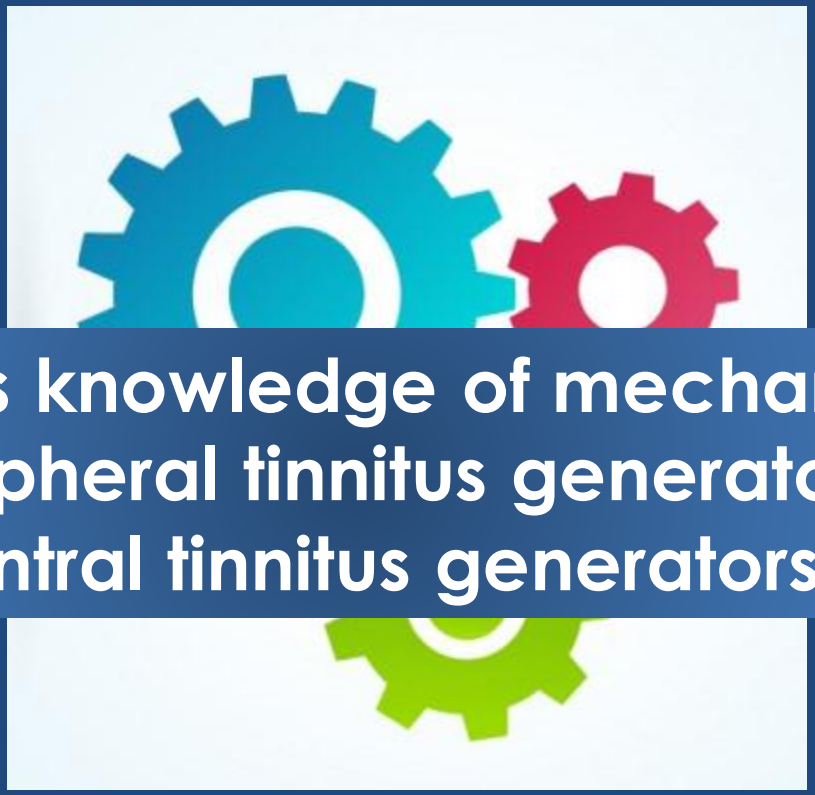
Magnesium
AM 101

SENSATION

ATTENTION

HEARING LOSS

Eliminate the percept
Reduce the loudness



EMOTION

Requires knowledge of mechanisms
-peripheral tinnitus generator-
-central tinnitus generators-

SENSATION

ATTENTION

HEARING LOSS

Depression
Anxiety

EMOTION

SENSATION

Address the co-morbid reactions to tinnitus

ATTENTION

Clinical trials : antidepressants for tinnitus
(*from* S.Robinson, PBR 2007)

Sullivan et al. (1993) NORTRIPTYLINE	Robinson et al. (2005) Paroxetine	Zoger et al. (2006) Sertraline	Mihail et al. (1988) Trimipramine
Severe tinnitus > 6 months	Unspecified severity > 6 months	Severe tinnitus No specified duration	No selection criteria for severity or
All subjects depression			ed
No change i Significant improvemer HRSD 6 dB decrea loudness			on 7 pt erity scale se in

Robinson et al. 2009

-participants with more severe tinnitus show greater response to treatment particularly with co-morbid depression and anxiety

Clinical trials : antidepressants for tinnitus

Clinical Practice Guideline (AAOHNS 2014) : 7 RCTs and 1 Cochrane review fail to demonstrate preponderance of benefit over harm, not recommended

AHRQ (2013) : reviewed RCTs of antidepressants, etc; 6 studies with benefit in tinnitus specific QoL and 5 for subjective loudness… no recommendation based on low/insufficient strength of evidence

Cochrane review (Baldo 2012) : low quality evidence, no significant benefit, not recommended

HEARING LOSS

Cognition : selective attention, memory, information processing

EMOTION

SENSATION

Address the co-morbid reactions to tinnitus

ATTENTION

A.K.T.A.R.I.
Arizona Ketamine Treatment *and* Research Institute

Changing lives, and creating hope through a new, effective and meaningful approach to your care.

For appointments call (480) 626-2727

Ketamine Therapy Provides Hope for Tinnitus Sufferers

Tinnitus (Chronic "Ringing in the Ears")

To the millions of Americans who suffer from Tinnitus, a constant low or high-pitched ringing in the ears, it is more than an annoyance. Tinnitus is a psychological and emotional assault on the senses that taxes and exhausts those with this disorder. It can affect sleep and concentration, and can inhibit the ability and desire to interact socially.

Until now, Tinnitus treatments have focused on helping sufferers cope with the condition. Cognitive behavioral training is used to learn how to tune out the sound, and physical therapies help individuals learn to manipulate the pitch and tone of the ringing by clenching the muscles around the neck and ear. Standard medication therapies, in general, are minimally effective for Tinnitus sufferers.

> "It seems the more severe the tinnitus, the better it works, because many of the same problems—pain and phantom noises—can predispose to depression and PTSD."

Dr. David E. Potter, Chairman of Pharmaceutical Sciences, Texas A&M University's Rangel College of Pharmacy

Important points for *developing* – *testing* – *using drugs* for tinnitus

Important points for *developing – testing – using drugs* for tinnitus

Clearly identify the target to be treated

-the perception (quality, loudness)

-the reaction/emotion

-the attention/vigilance directed towards tinnitus

Important points for *developing* – *testing* – *using drugs* for tinnitus

Measure what you are modulating

Clearly define the target population :

- -acute vs chronic
- -associated hyperacusis
- -stratified for severity, other factors

Must have a placebo arm

Account for stability of subjective ratings and changes with study enrollment

Important points for *developing* – *testing* – *using drugs* for tinnitus

KAS 10: Medical therapy

STATEMENT 10. MEDICAL THERAPY: Clinicians should not routinely recommend antidepressants, anticonvulsants, anxiolytics, or intratympanic medications for a primary indication of treating persistent, bothersome tinnitus. *Recommendation against based on systematic reviews and randomized controlled trials with methodological concerns, with a preponderance of benefit over harm.*

THIS DOES NOT MEAN THAT DEPRESSION, ANXIETY, AND SEIZURE DISORDERS SHOULD NOT BE TREATED WITH MEDICATIONS

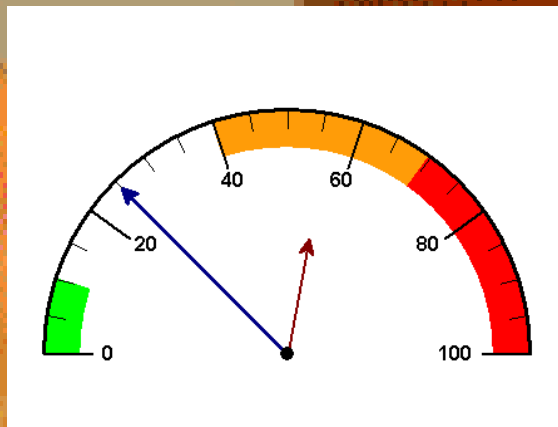
THESE MEDICATIONS HAVE NOT BEEN SHOWN TO IMPROVE TINNITUS SPECIFIC MEASURES

Developing a drug for tinnitus

What is the treatment goal?

Measure what you intend to modulate

Define your patient population



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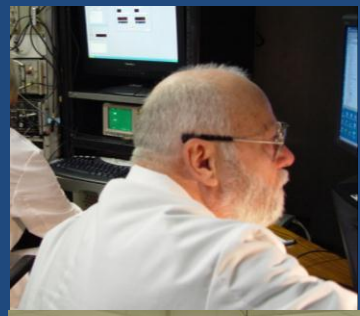
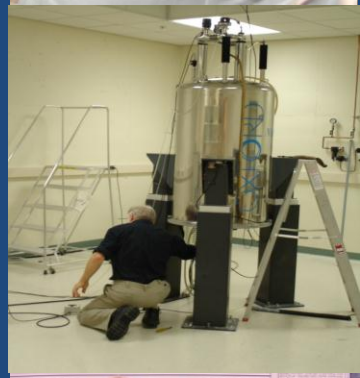
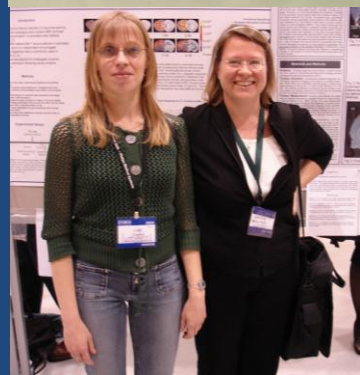
Tinnitus Research Consortium
American Tinnitus Association

BIC







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