Translational tinnitus research : from bedside to bench and back again

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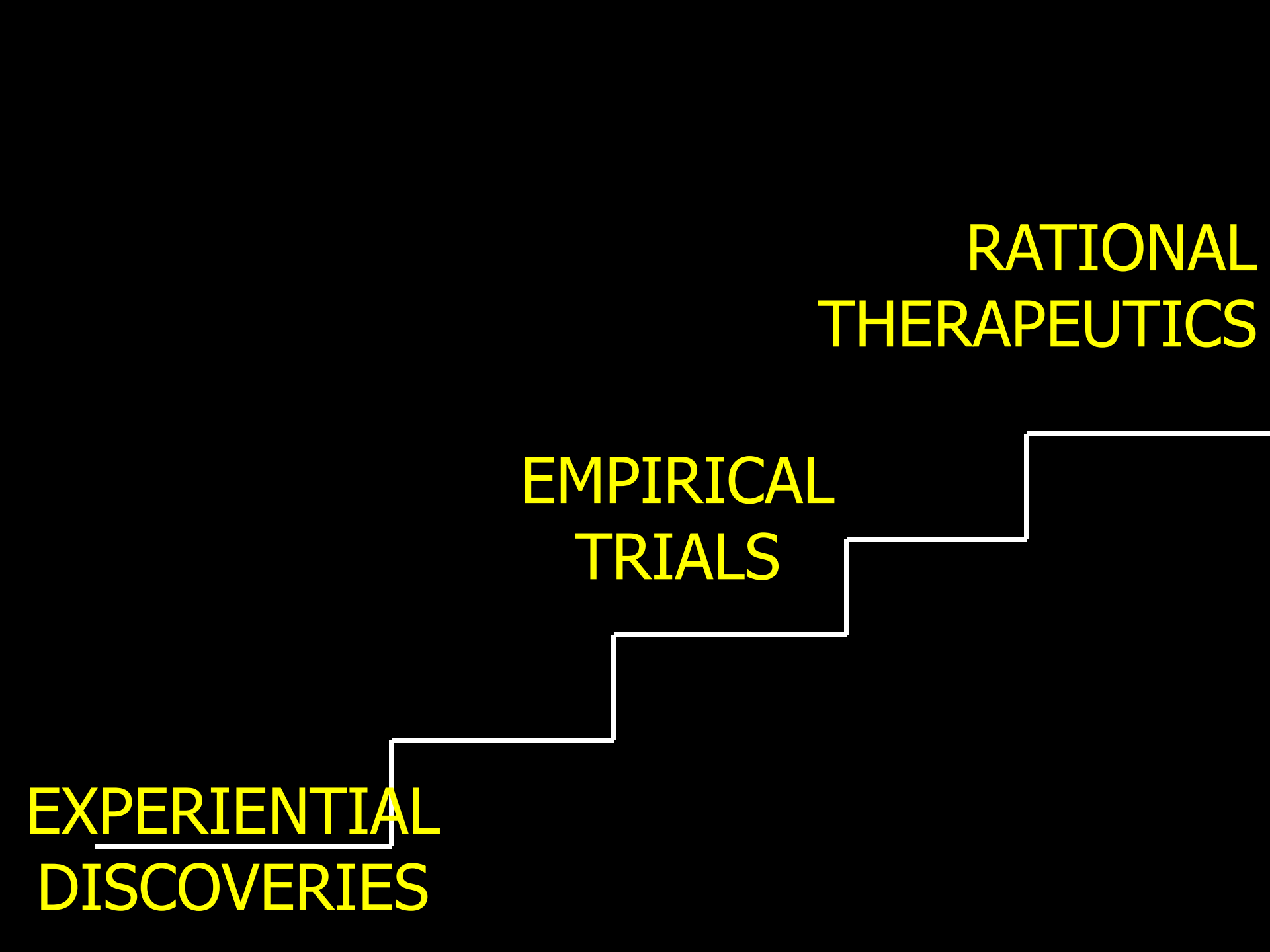
Overview

What is translational research?

Animal models and tinnitus

Examples of translational research

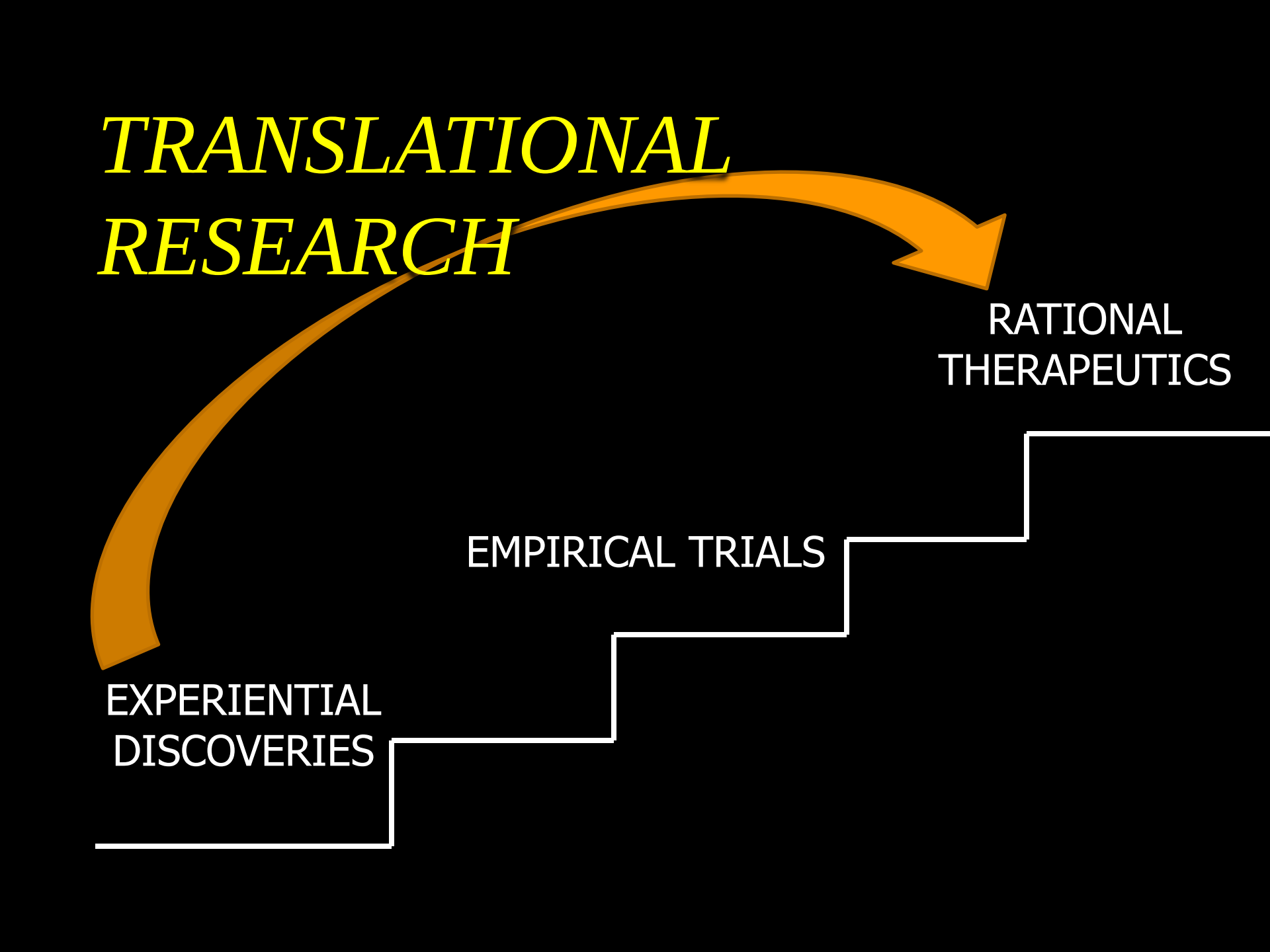
- Somatosensory modulation
- Inhibitory neurotransmitters
- Novel brain areas


RATIONAL
THERAPEUTICS
EMPIRICAL
TRIALS
EXPERIENTIAL
DISCOVERIES

Relevant Drug Classes

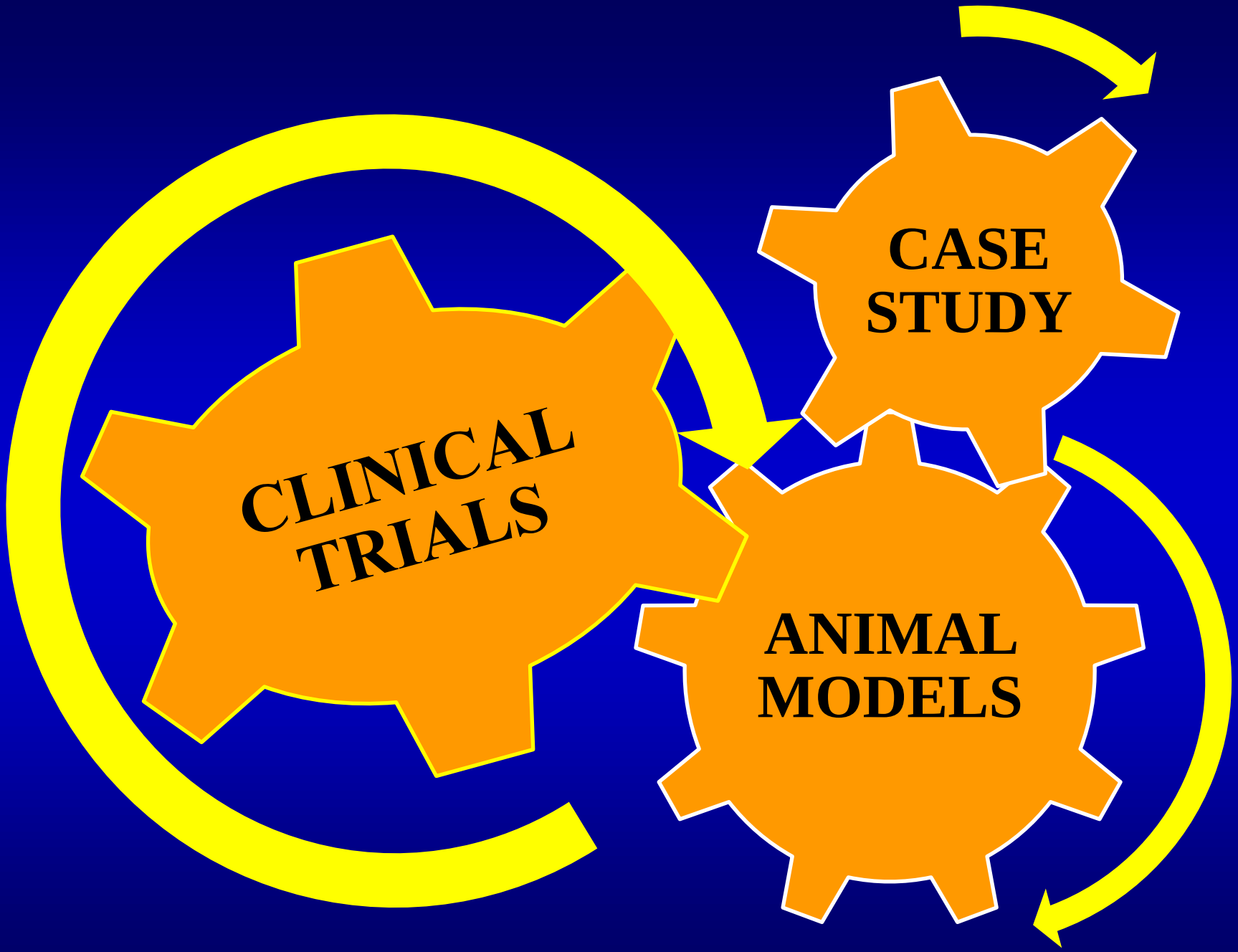
- Neural blockade — LIDOCAINE
- GABA agonists — ALPRAZOLAM
  - Benzodiazepines — CLONAZEPAM
  - Ca channel modulator — GABAPENTIN
  - NMDA Glutamate antag. — ACAMPROSATE
- Anti-convulsants — TEGRETOL
- Antidepressants — (SSRI, SNRI)
- Neural “enhancers” — GINGKO
- Anti-inflammatory — MISOPROSITOL

Tinnitus is the result of central plasticity in response to auditory deprivation


TRANSLATIONAL RESEARCH
RATIONAL THERAPEUTICS
EMPIRICAL TRIALS
EXPERIENTIAL DISCOVERIES

The many flavors of tinnitus research

Observational
Empirical
Controlled trials
"Basic science"


CASE
STUDY
CLINICAL
TRIALS
ANIMAL
MODELS

What is ‘translational research’?

Research that bridges the gap between basic research and clinical applications that improve clinical practice and health outcomes

Research ‘silos’…Bridging the gap

- Basic research investigating fundamental mechanisms in the lab
- Clinical research investigating treatments in people
- Translational research bridges the gap between basic research and clinical applications that improve clinical practice and health outcomes

Vision without action is a daydream …

Action without mission is a nightmare.

-*Japanese proverb*

The typical story of the "breakthrough" tinnitus treatment

Works in one patient (case report)
Works in several pts in a few clinics (case series)
(Works in an animal model)
Standardized measurement of tinnitus improvement shows elimination of tinnitus in 10% and a 30-50% reduction in 30-50% of pts

When tested against placebo, no difference

What happened?

Different doses
Different patient groups
No subject stratification for severity, hearing loss, etiology, modulators, co-morbidities

What happened?

Unknowns :

Natural history of tinnitus

Predictors of suffering

Features of at risk populations

Genetics

The two faces of tinnitus

AFFECTIVE

Depression

Anxiety

Sleep

Cognitive

PSYCHOPHYSICAL

Loudness

Tonality

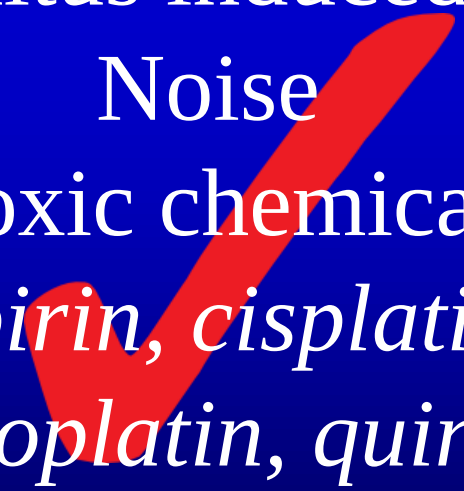
Fluctuation

Sound sensitivity

Utility of an Animal Model

Study a single cause of tinnitus in a homogeneous population

Tinnitus induced by
Noise
Ototoxic chemicals :
aspirin, cisplatin, carboplatin, quinine



Current Limitations

Age-related tinnitus
Co-morbidities and tinnitus
Genetic influence on tinnitus

Current Limitations

Co-morbidities of tinnitus :

Cognitive impairment

Social interactions

Sleep Disturbance

Distress

Depression

Anxiety

Animal Models of Tinnitus

- Jastreboff et al. (1988): shock avoidance
- Bauer / Brozoski (1999): conditioned suppression
- Heffner / Harrington (2002): forced choice
- Guitton et al. (2003) : conditioned avoidance
- Lobarinas et al. (2004): conditioned avoidance
- Turner et al. (2006) : gap detection

Basics of Behavioral Testing

First- teach the animal to talk

Identify a “natural” behavior – drinking, eating – or an operant behavior – eg. lever press– should be ….

reasonable ….. “natural”…..

repeatable over many trials…..easily measured

Basics of Behavioral Testing

Second- teach the animal to listen

Pair SOUND

with access to food pellets/water spout

Pair “SILENCE” with exposure to a foot shock

Basics of Behavioral Testing

Third – expose the animal to a tinnitus inducing event and ask what it hears.

If the rat has associated "sound" with food/water/safety -

and has associated silence with foot shock –

The rat will display different behavior under different auditory conditions (sound, silence).

Design parameters in an animal model of chronic tinnitus

Behavior: conditioned suppression of lever pressing

Tinnitus induction: unilateral acoustic trauma

Training Method:

Train to discriminate between sound and “silence”

Stop lever pressing during “silence”

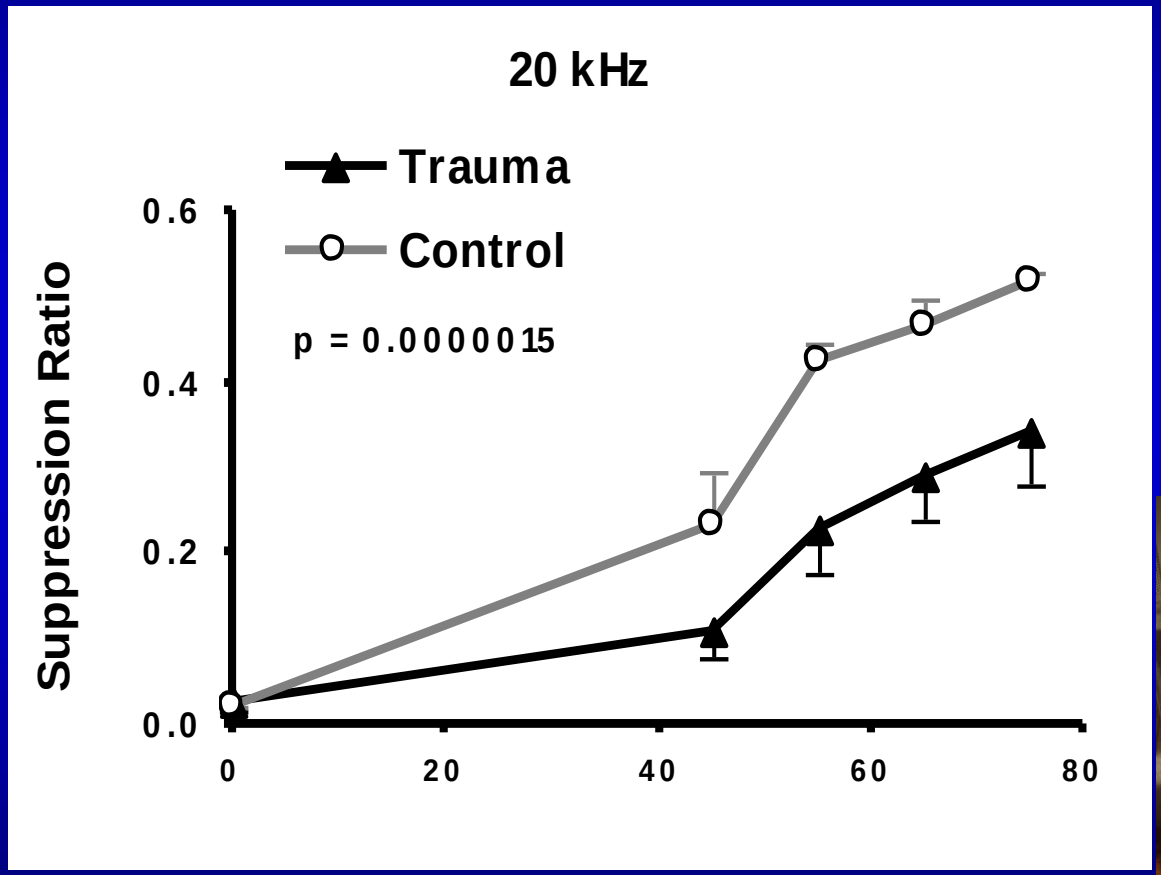
Testing method:

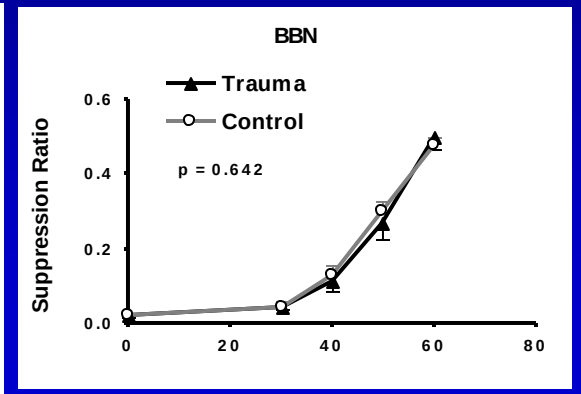
Measure lever pressing during sound and silent trials

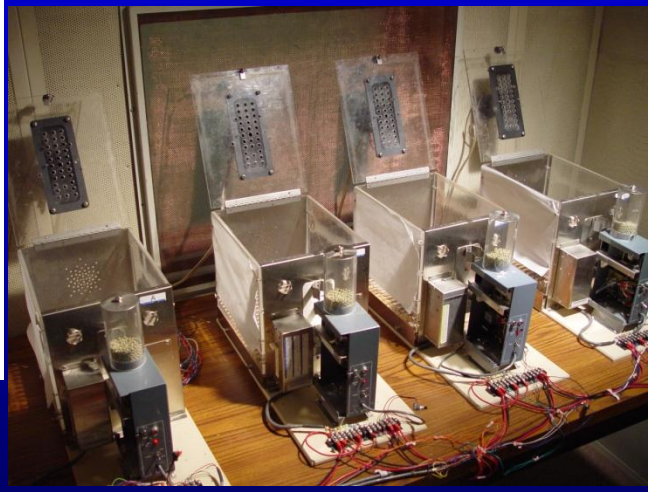
Sample segment of a data record.

TRIAL	RESPONSE	REINFMNT	R	STIMULUS
9	53	3	0.546	Noise
10	52	2	0.495	Noise
11	**48**	**4**	**0.480**	**10 kHz**
12	49	3	0.505	Noise
13	37	3	0.430	Noise
14	36	5	0.493	Noise
15	31	3	0.463	Noise
16	**2**	**2**	**0.061**	**Silence**
17	39	4	0.951	Noise

Behavioral evidence of noise-induced tinnitus in an animal model







Bauer and Brozoski, JARO 2001

3 EXAMPLES OF TRANSLATIONAL TINNITUS RESEARCH

- Tinnitus modulation by touch, movement, muscle tension

Clinical Observation

Bench studies

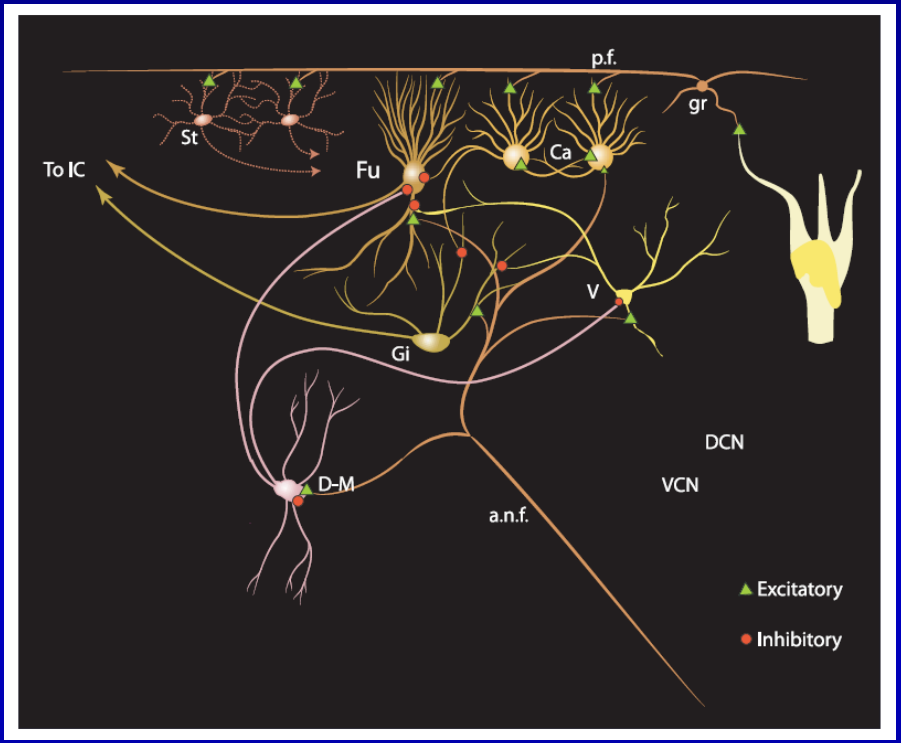
- Connection between auditory and trigeminal pathways

- **?**

Refine concept in clinic

Functional activity in frontal cortex, limbic system and cerebellum:

Lockwood et al. 1998
Giraud et al. 1999
Lickwood et al . 2001



S.E. Shore, European Journal of Neuroscience, 2005. DCN schematic adapted from Young (1998).

Stidham et al. 2006 Evaluation of botulinum toxin A in treatment of tinnitus

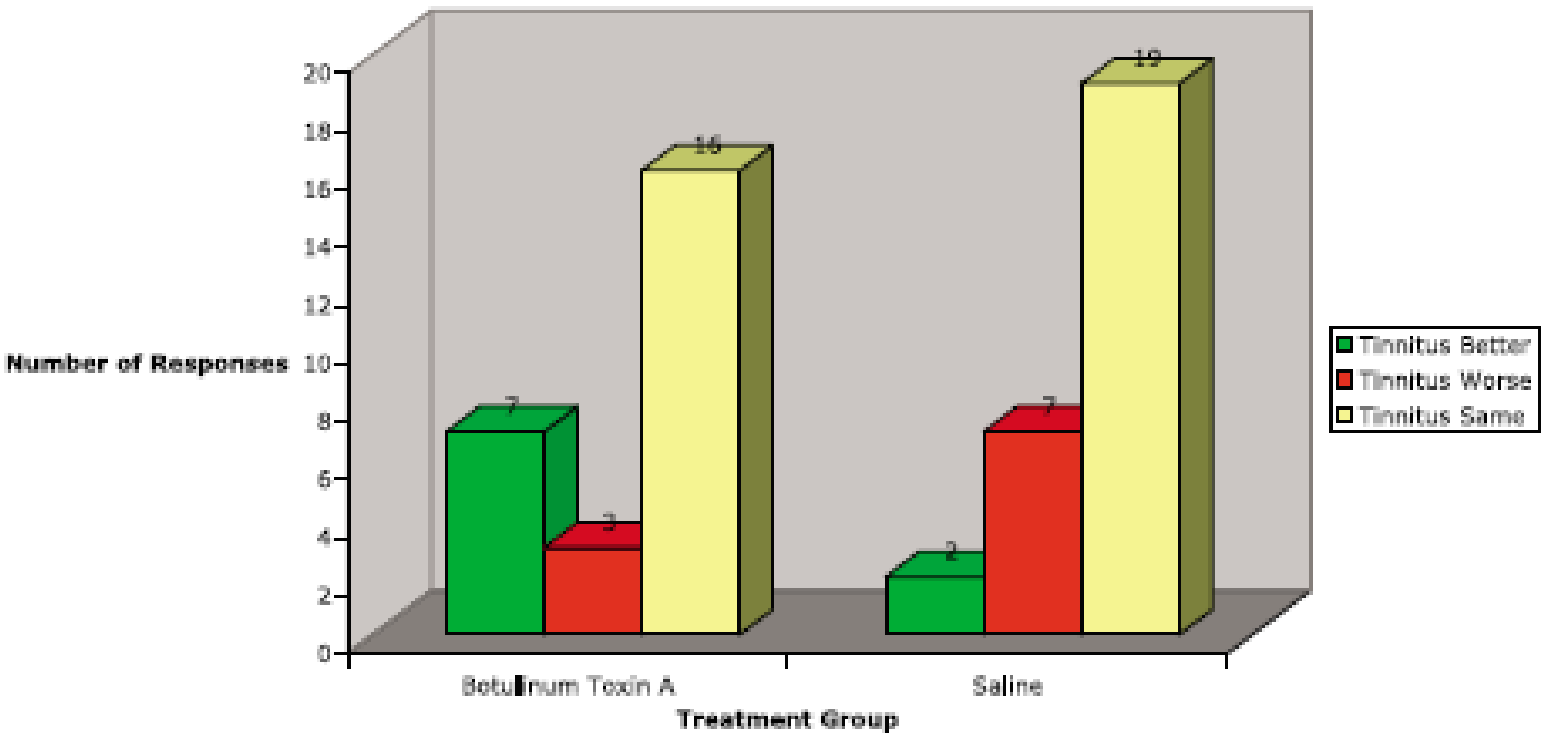
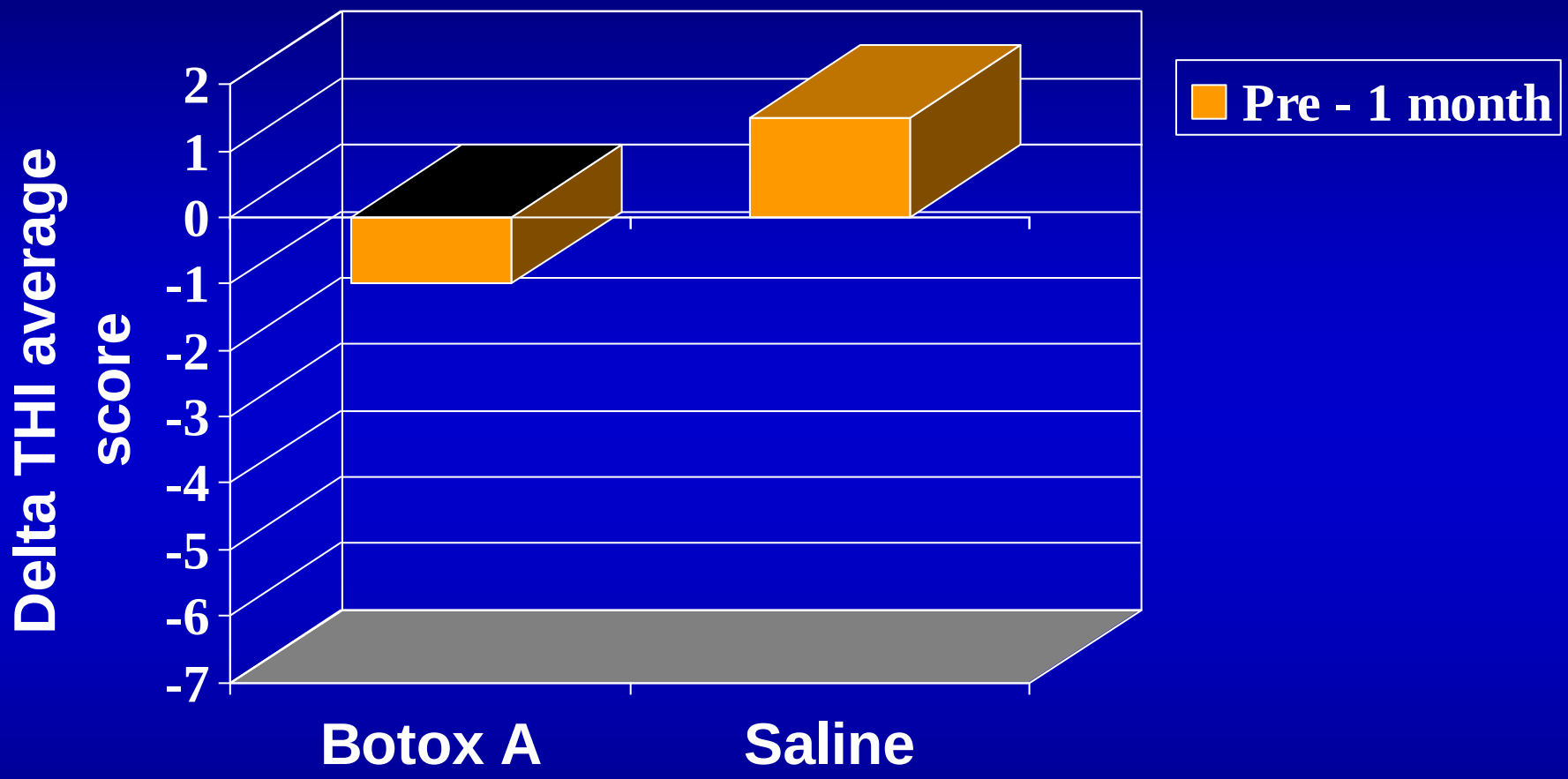
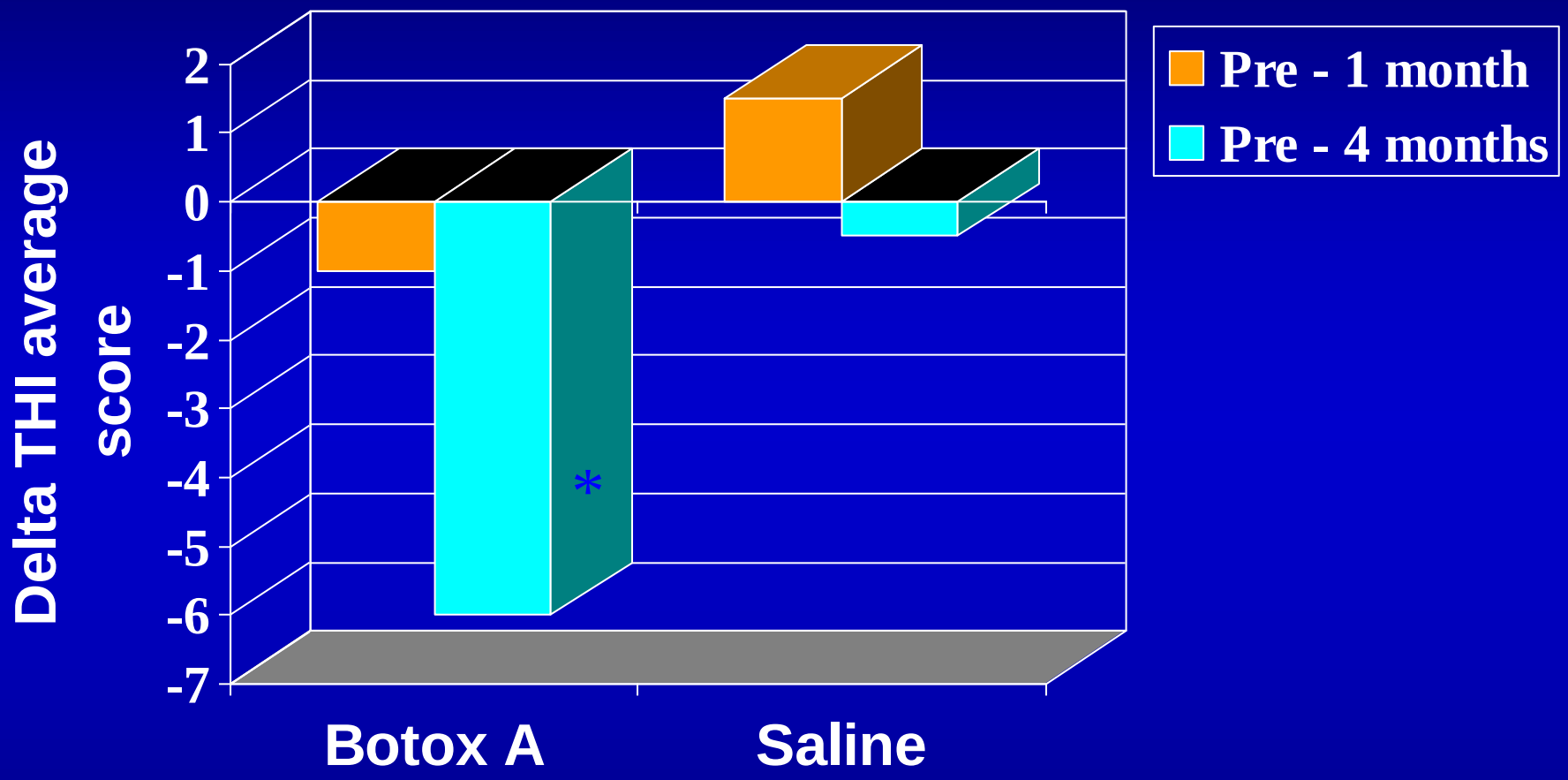


Fig 1. Subjective patient response to botulinum toxin A and placebo.


Delta THI average score
2
1
0
-1
-2
-3
-4
-5
-6
-7
Botox A
Saline
Pre - 1 month


Delta THI average score
2
1
0
-1
-2
-3
-4
-5
-6
-7
*
Botox A
Saline
Pre - 1 month
Pre - 4 months

* p=0.042

Vanneste et al. Experimental Brain Research 2010

Examined effect of transcutaneous electrical nerve stimulation (TENS) on tinnitus

- constant current with pulse 1-200 Hz
- intensity range 0-100 mA

Applied to L and R C2 dermatomes

240 patients : no tinnitus subtypes
all had somatosensory modulation

Vanneste et al. Experimental Brain Research 2010

240 patients : no tinnitus subtypes categorized
all had somatosensory modulation

Overall : VAS loudness (1-10)*

Pre 6.16 Post 5.56

Only 18% of subjects responded to TENS : but had a mean improvement of 43% and 6 had 100% reduction of tinnitus loudness.

Herraiz et al. Progress in Brain Research 2007

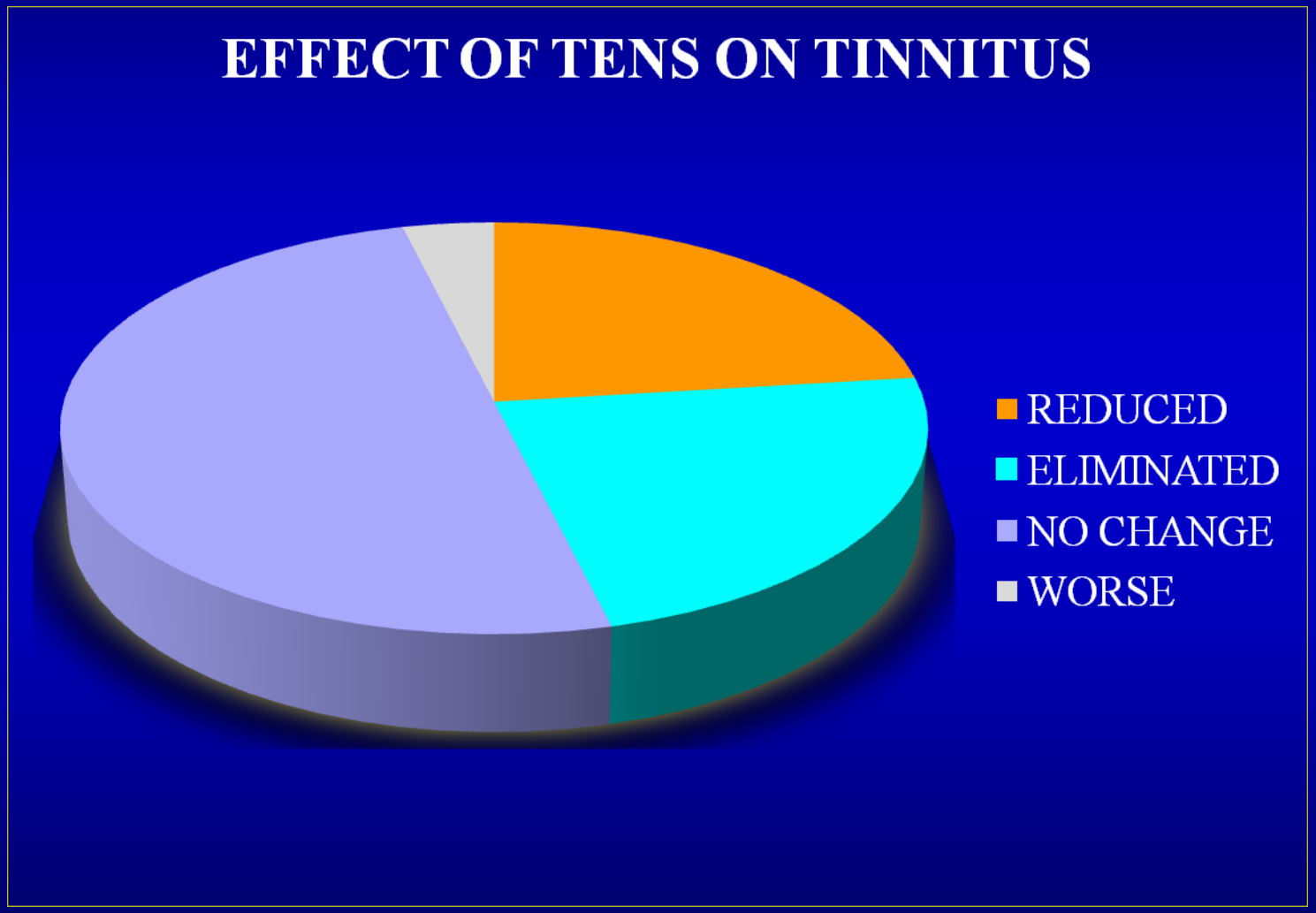
Examined effect of transcutaneous electrical nerve stimulation (TENS) on tinnitus

- constant current with pulse 150 pps
- intensity range 0-60 mA
- stimulated 2 hours/d x 2 weeks

Herraiz et al. Progress in Brain Research 2007

Typewriter tinnitus modified by jaw motion	31%
Tinnitus secondary to cervical spasm	15%
Tinnitus related to TMJ dysfunction	7%
Tinnitus onset after molar extraction	7%
Tinnitus from otologic cause, with somatic modulation	31%

Herraiz et al. Progress in Brain Research 2007



Herraiz et al. Progress in Brain Research 2007

	IMPROVED
Typewriter tinnitus modified by jaw motion	**88%**
Tinnitus secondary to cervical spasm	**59%**
Tinnitus related to TMJ dysfunction	
Tinnitus onset after molar extraction	
Tinnitus from otologic cause, with somatic modulation	**14%**

- Tinnitus modulation by touch, movement, muscle tension

Clinical Observation

Bench studies

- Connection between auditory and trigeminal pathways

- Specific drugs?
- Biomarkers ?

Refine concept in clinic

- *Lidocaine eliminates tinnitus*

Clinical Observation

Bench studies

- Loss of inhibition causes hyperactivity

- **?**

Refine concept in clinic

Loss of neural inhibition within the central auditory pathway

Gamma-aminobutyric acid (GABA)

Dysfunctional auditory processing

- temporal integration
- speech discrimination
- *TINNITUS*

- Bledsoe
- Kaltenbach
- Moller
- Salvi
- Caspary
- Eggermont
- Suneja

GABA release

GAD expression

GABA immunolabeling

COCHLEAR ABLATION

ACOUSTIC TRAUMA

PRESBYCUSIS

OSSICULAR DISRUPTION

Loss of Inhibition

Clinical observations

Lidocaine injection and elimination of tinnitus Barany 1935

"Ear-clicking tinnitus responding to carbamazepine" Mardini 1987

"Typewriter tinnitus" Levine 2006

Reduction of new-onset tinnitus with gabapentin Zapp 1995

Gabapentin (Neurontin®)

- Structural analog of GABA
- Mechanism of action : GABAergic, calcium channel modulator
- FDA approved as anti-epileptic
- Extensive off-label use with efficacy reported for migraine, neuropathic pain

Clinical and experimental observations

Subjective improvement in new onset tinnitus using low-dose gabapentin.

Zapp. Gabapentin for the treatment of tinnitus: a case report.

ENTJournal 2001; 80:114-6

Open-label trial of gabapentin and clonazepam in patients with hypoperfusion.

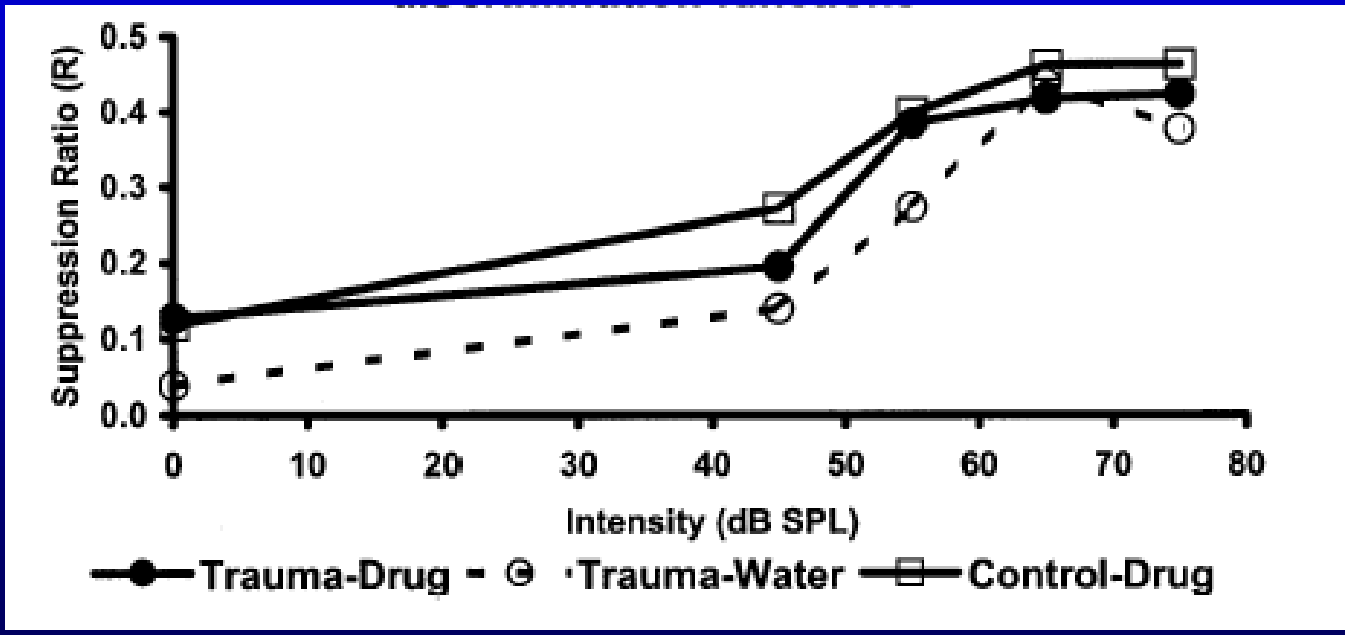
Shulman, et al. Receptor-targeted therapy for tinnitus control.

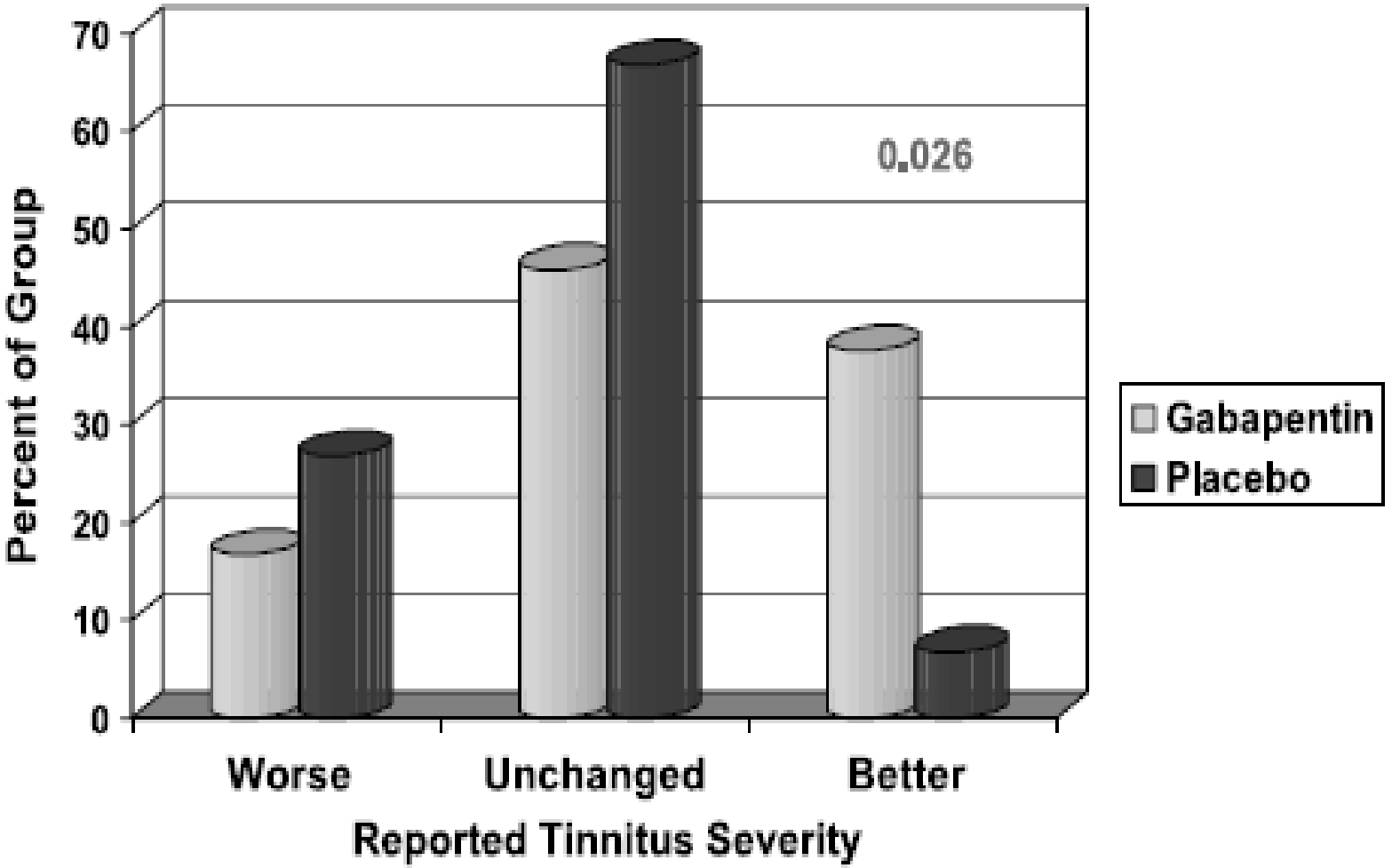
Int Tinnitus J 2002; 8:30-6

Clinical and experimental observations

Gabapentin attenuated the psychophysical evidence of chronic trauma-induced tinnitus in rats.

Bauer and Brozoski (2001)





Witsell et al. 2006

Effect of Gabapentin on the sensation and impact of tinnitus

Bauer and Brozoski. 2006

Blinded, within subject control design with repeated measures.

Subjects categorized into tinnitus attributed to noise exposure and tinnitus not related to noise exposure

Methods

Placebo 1:	0 mg/day	14 days
DOSE 1:	800 mg/day	21 days
DOSE 2:	1800 mg/day	35 days
DOSE 3:	2400 mg/day	21 days
DOSE 4:	900 mg/day	28 days
Placebo 2:	0 mg/day	21 days

Methods:

Assessment measures :

entry, placebo 1, all drug doses, placebo 2

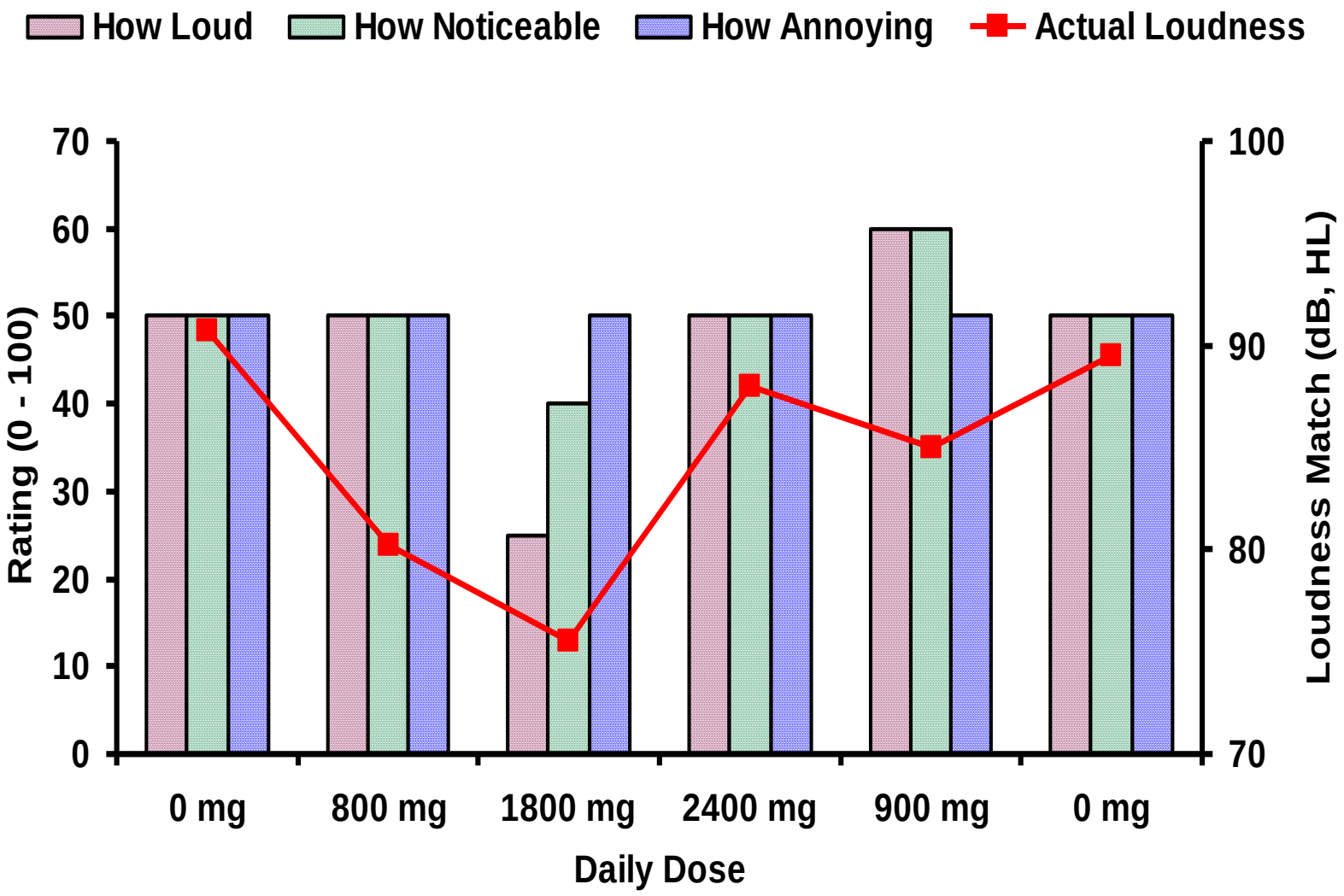
Health Survey Questionnaire (SF-36)

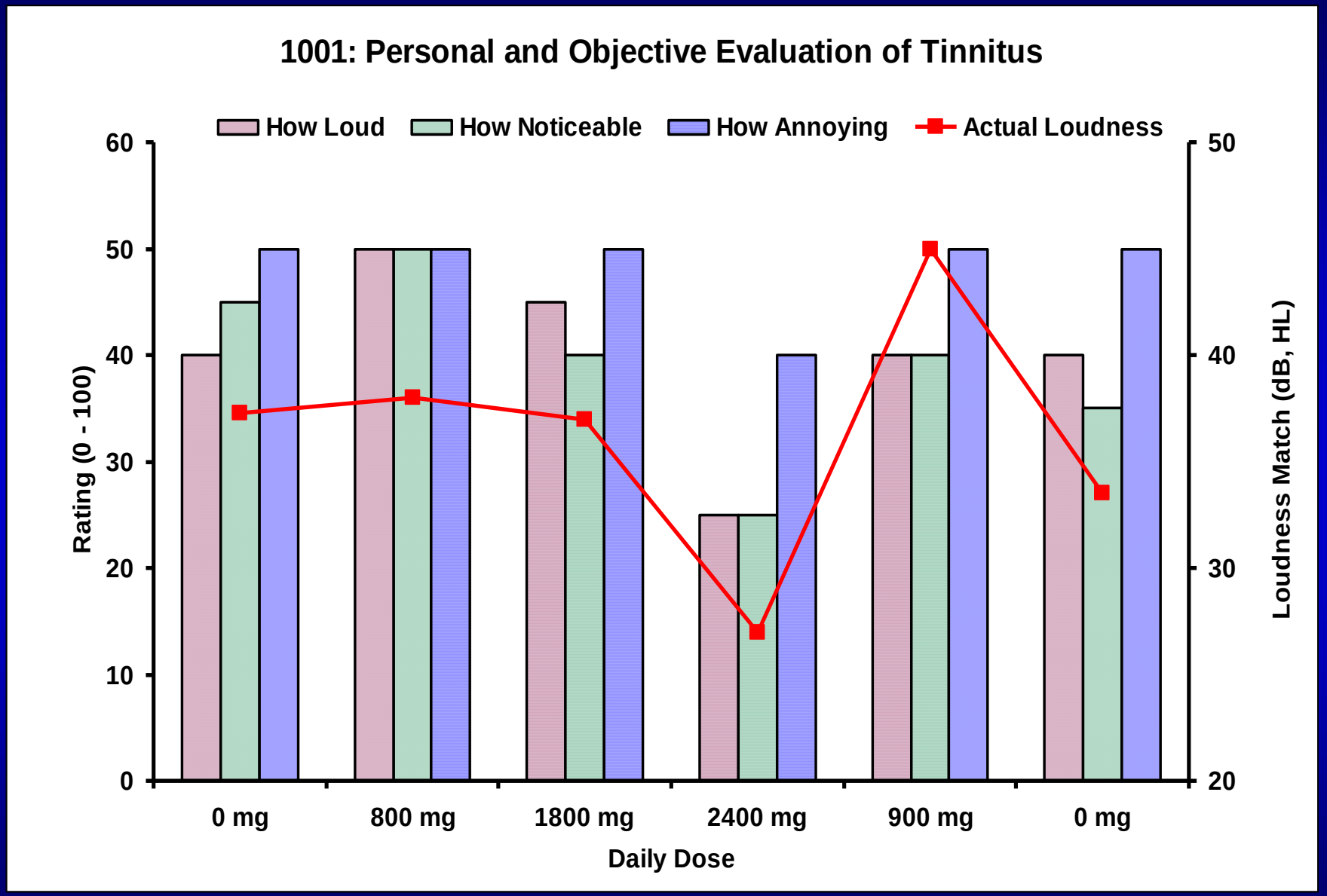
Tinnitus Handicap Questionnaire

Tinnitus Experience Questionnaire

Hearing thresholds

Tinnitus loudness match

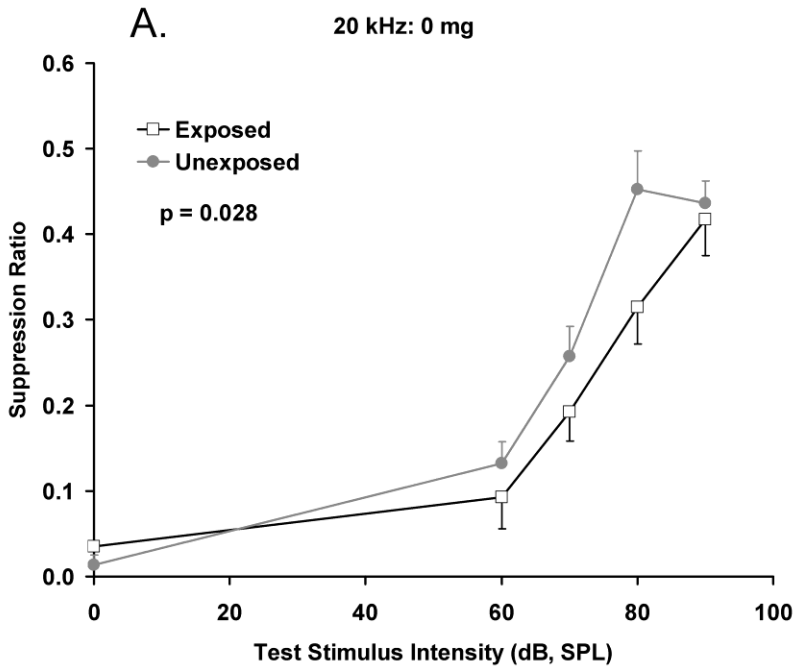

How Loud
How Noticeable
How Annoying
Actual Loudness
Rating (0 - 100)
Loudness Match (dB, HL)
70
60
50
40
30
20
10
0
100
90
80
70
0 mg
800 mg
1800 mg
2400 mg
900 mg
0 mg
Daily Dose

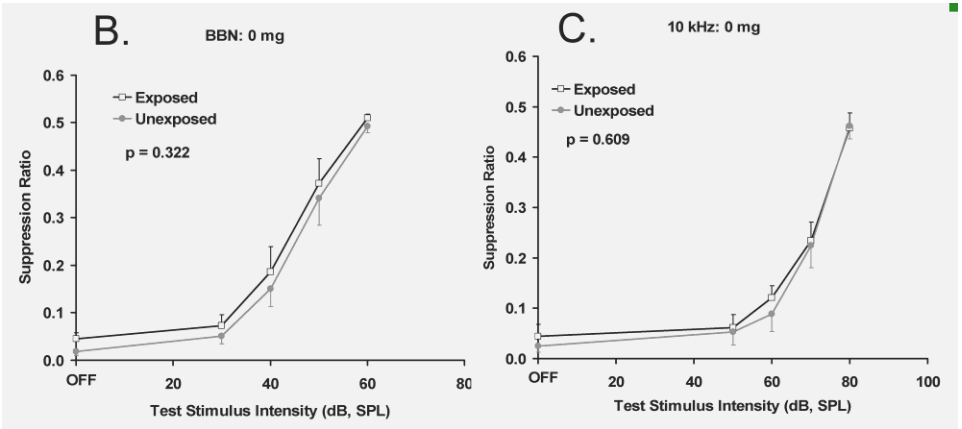

1001: Personal and Objective Evaluation of Tinnitus
How Loud
How Noticeable
How Annoying
Actual Loudness
Rating (0 - 100)
Loudness Match (dB, HL)
60
50
40
30
20
10
0
50
40
30
20
0 mg
800 mg
1800 mg
2400 mg
900 mg
0 mg
Daily Dose

Group results

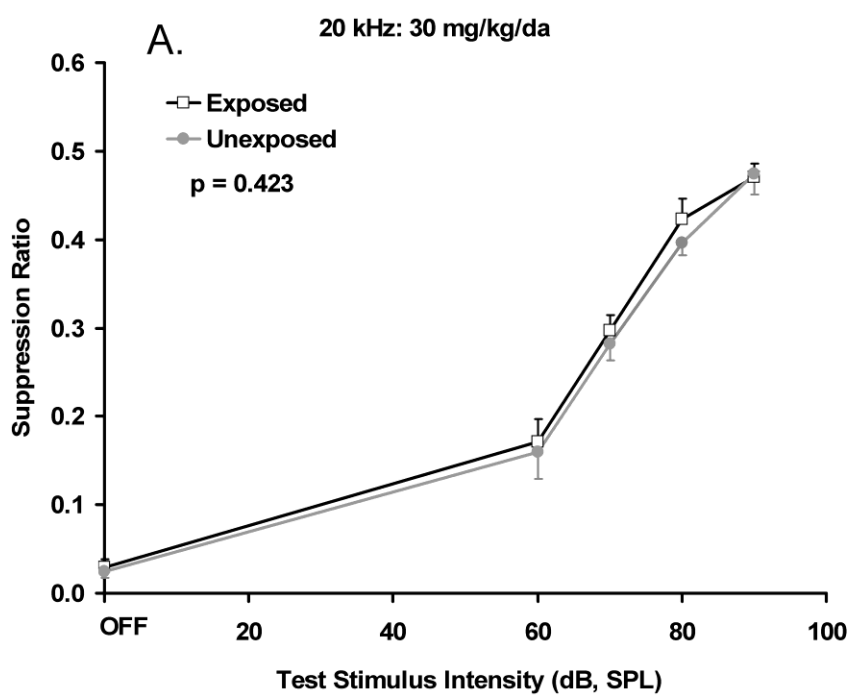
- Gabapentin decreases the objective loudness of chronic tinnitus in some subjects.
- ***Four of 19*** Non-trauma subjects experienced a mean improvement of 33%
- ***Six of 20*** Trauma subjects experienced a mean improvement of 30%

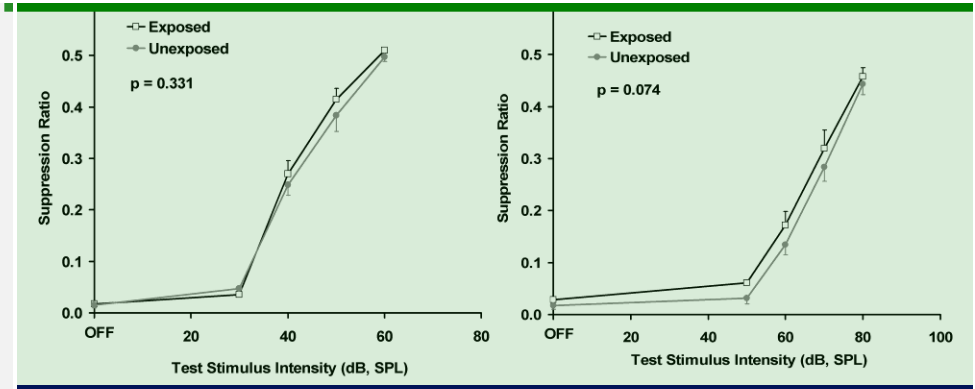
Pre-Drug





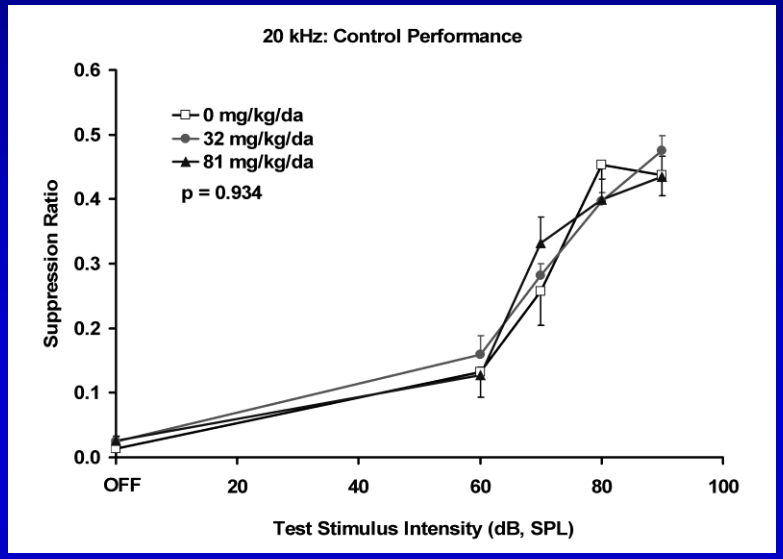
Vigabatrin, Low Dose

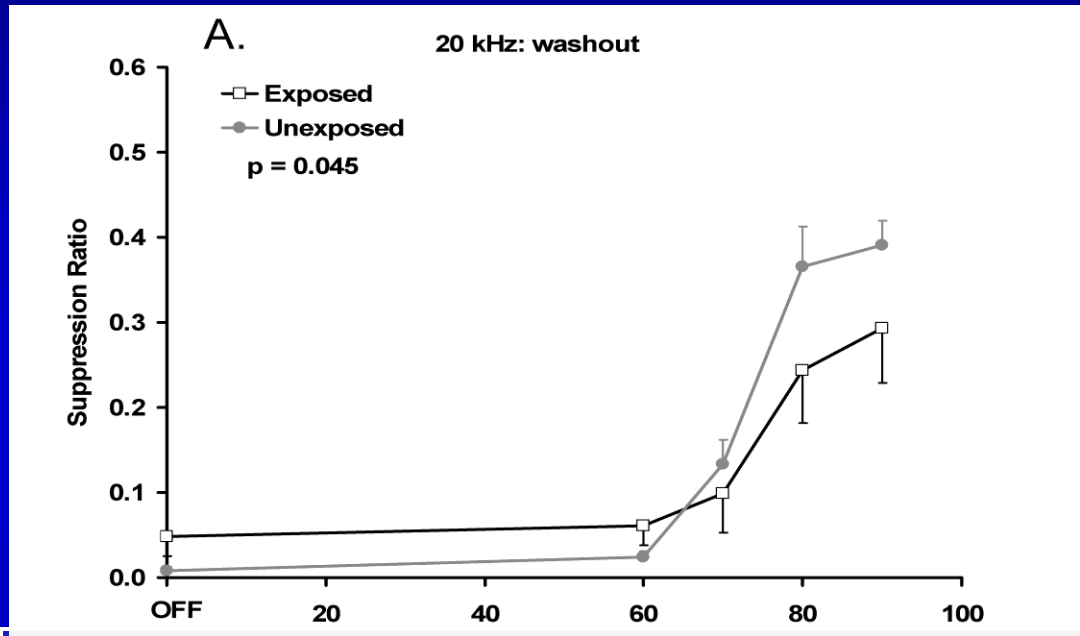




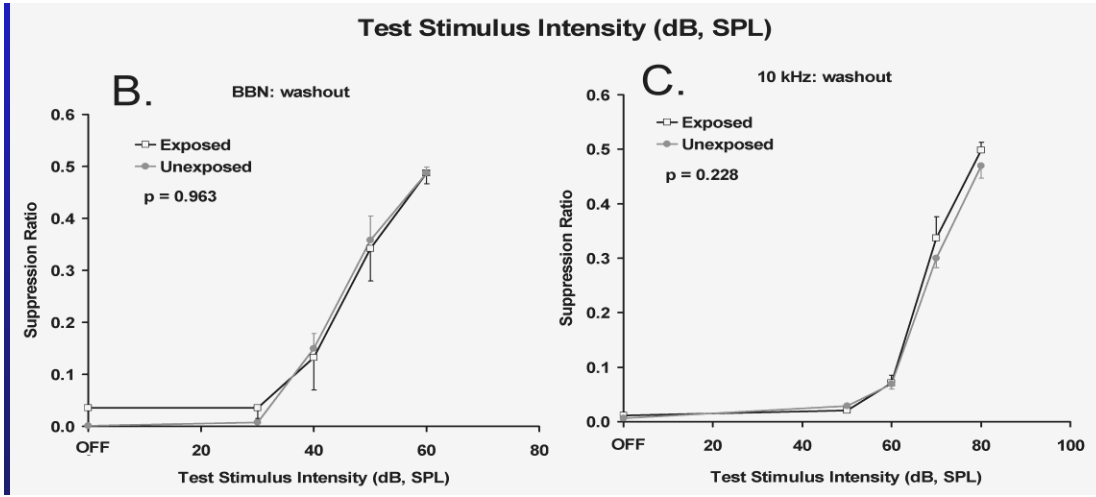
Tinnitus Returns

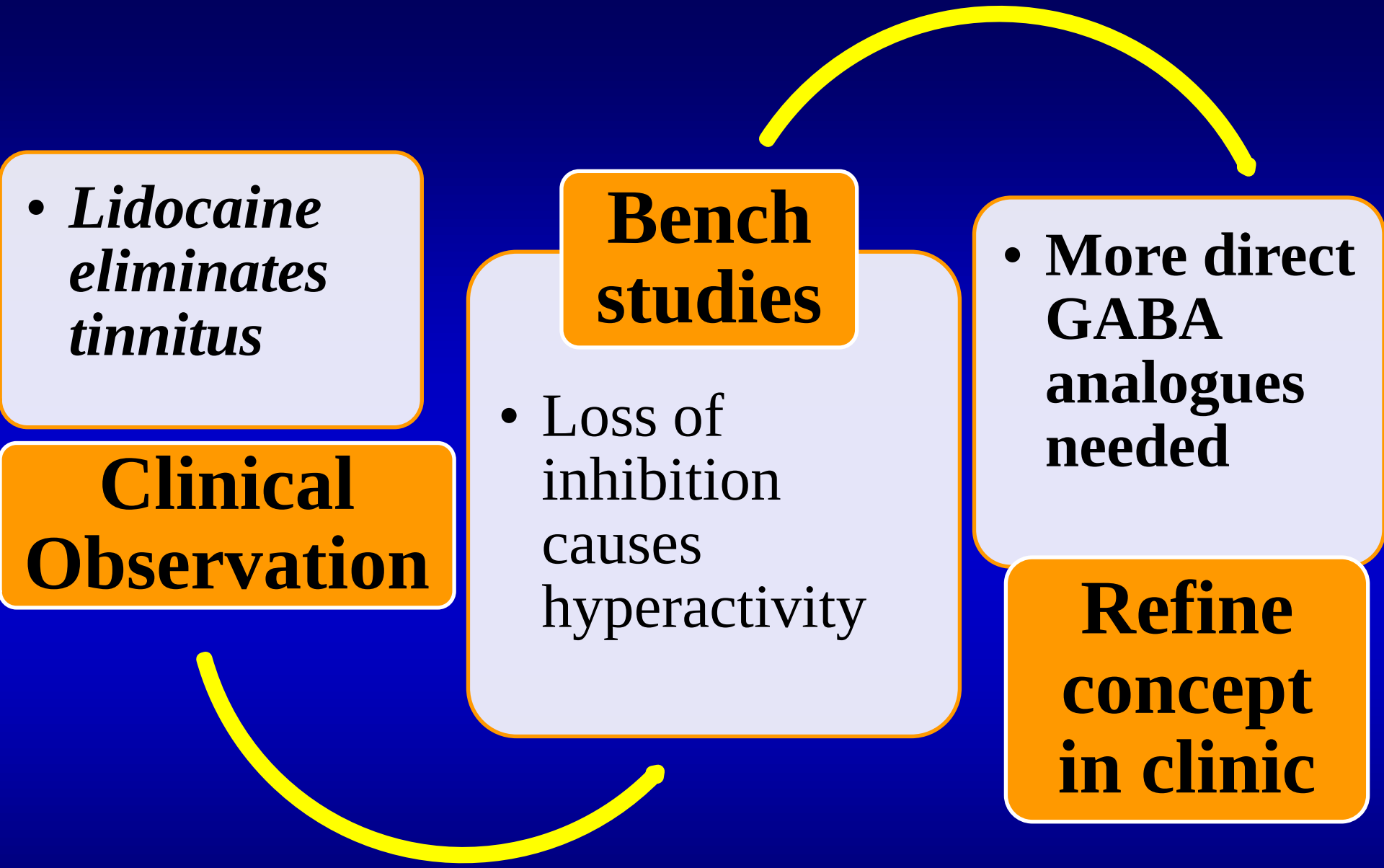
After 7-week Washout





No Drug Effect on Controls




• *Lidocaine eliminates tinnitus*
Clinical Observation
Bench studies
• Loss of inhibition causes hyperactivity
• More direct GABA analogues needed
Refine concept in clinic

- Cochlear implants eliminate tinnitus

Clinical Observation

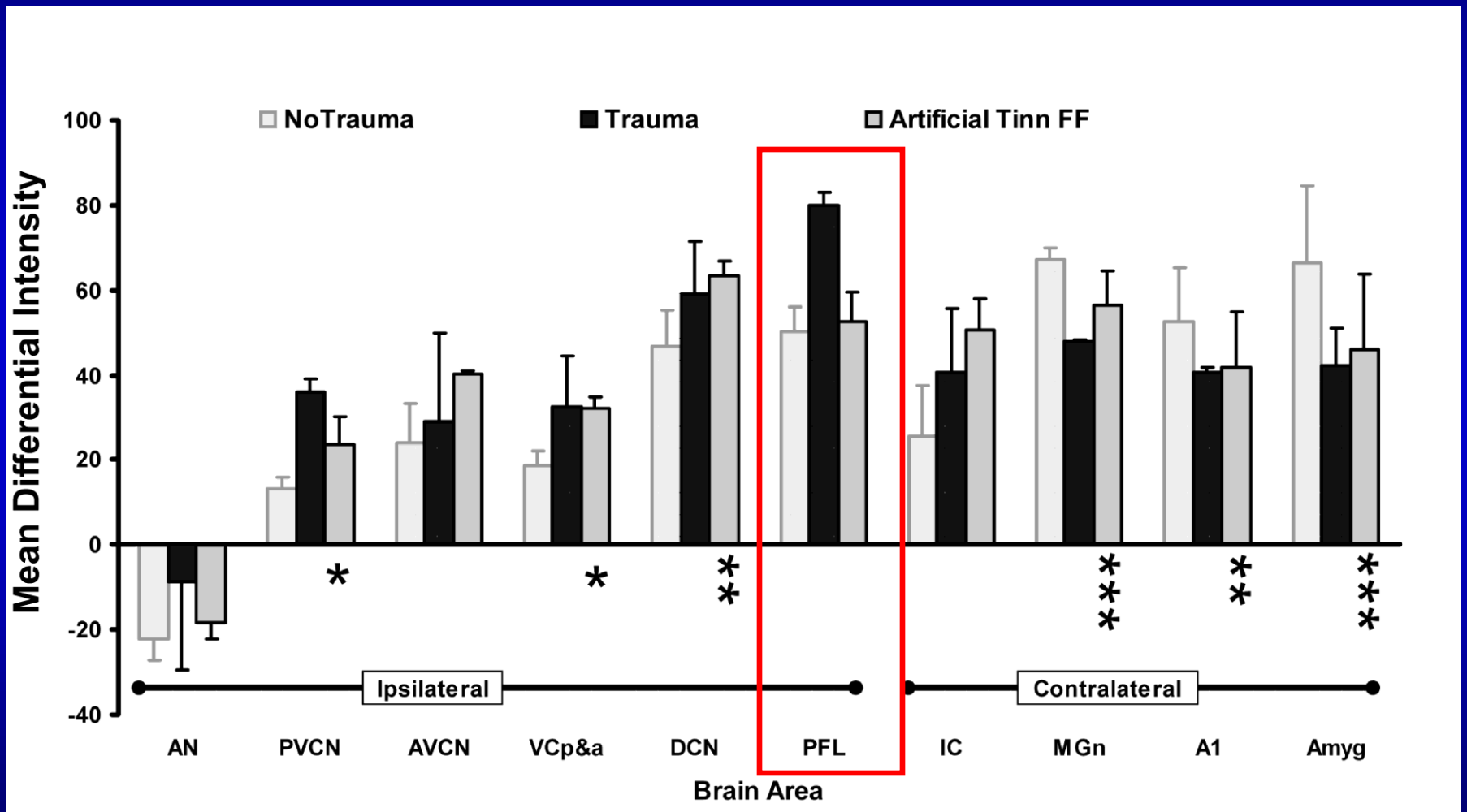
Bench studies

- Is the cerebellum a modulator of chronic tinnitus?

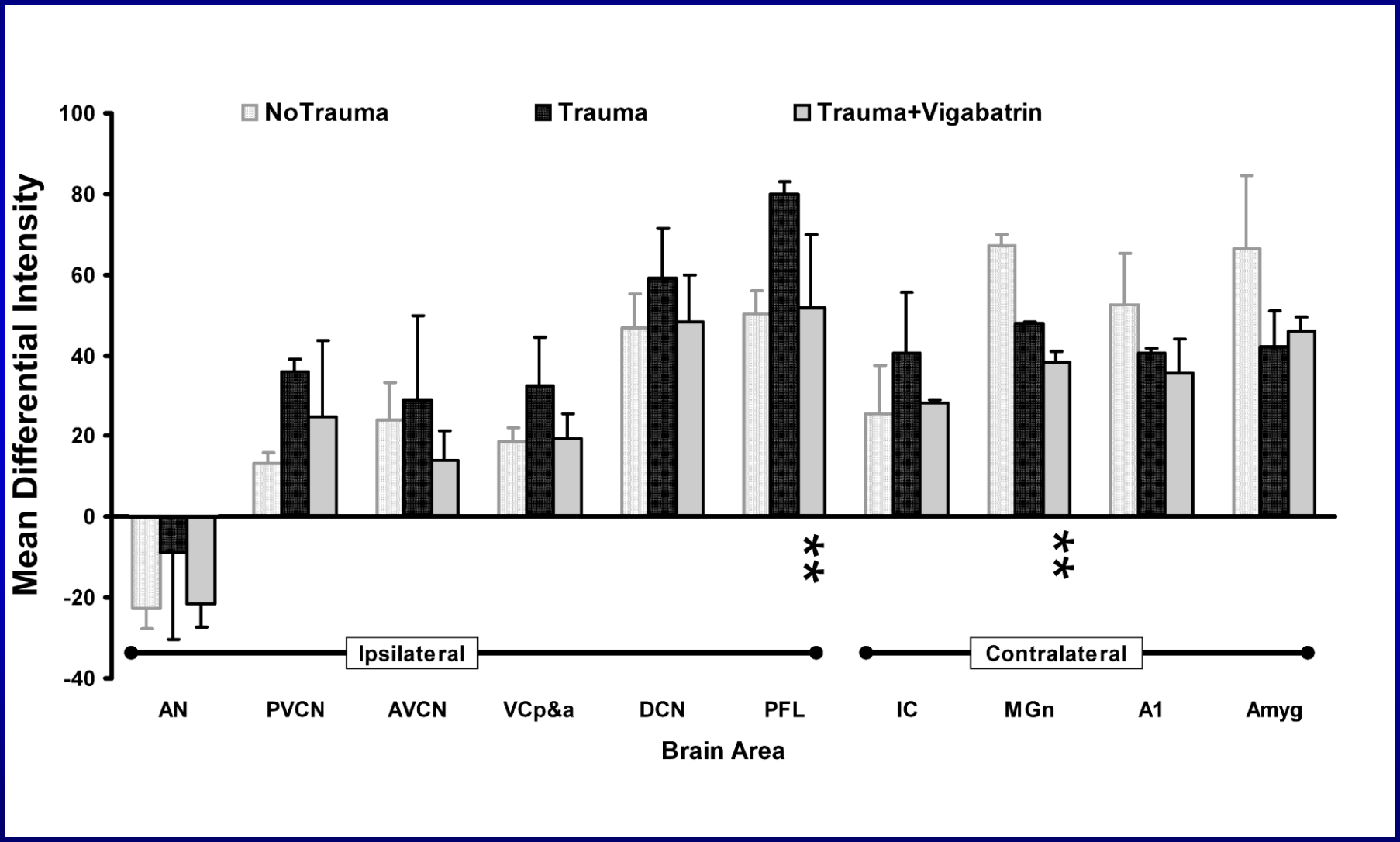
- ?

Refine concept in clinic

Artificial Tinnitus

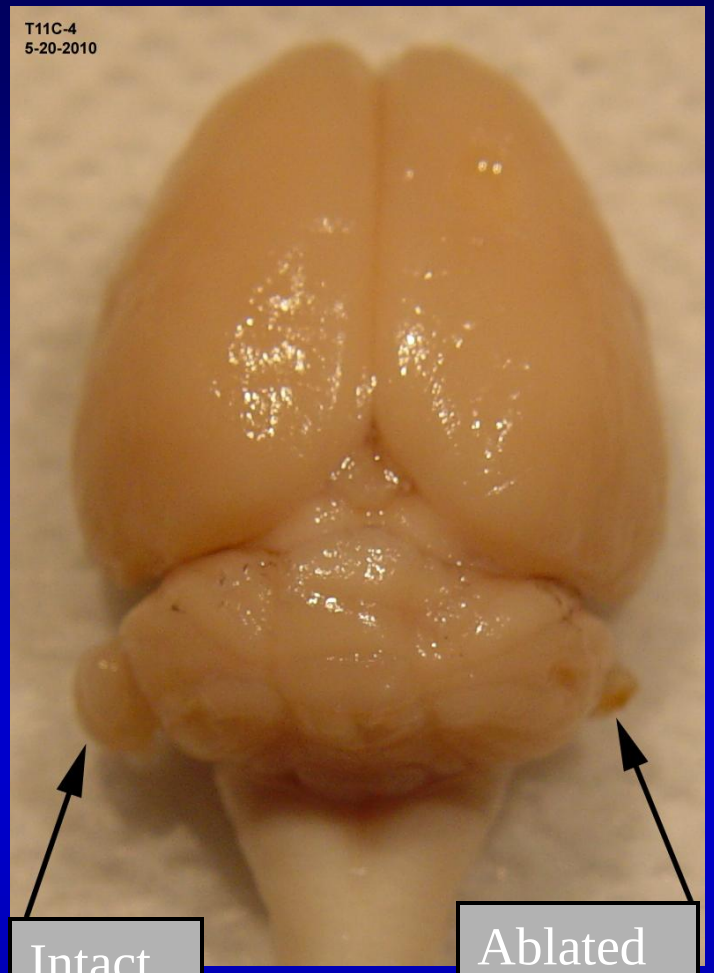


Vigabatrin Treatment

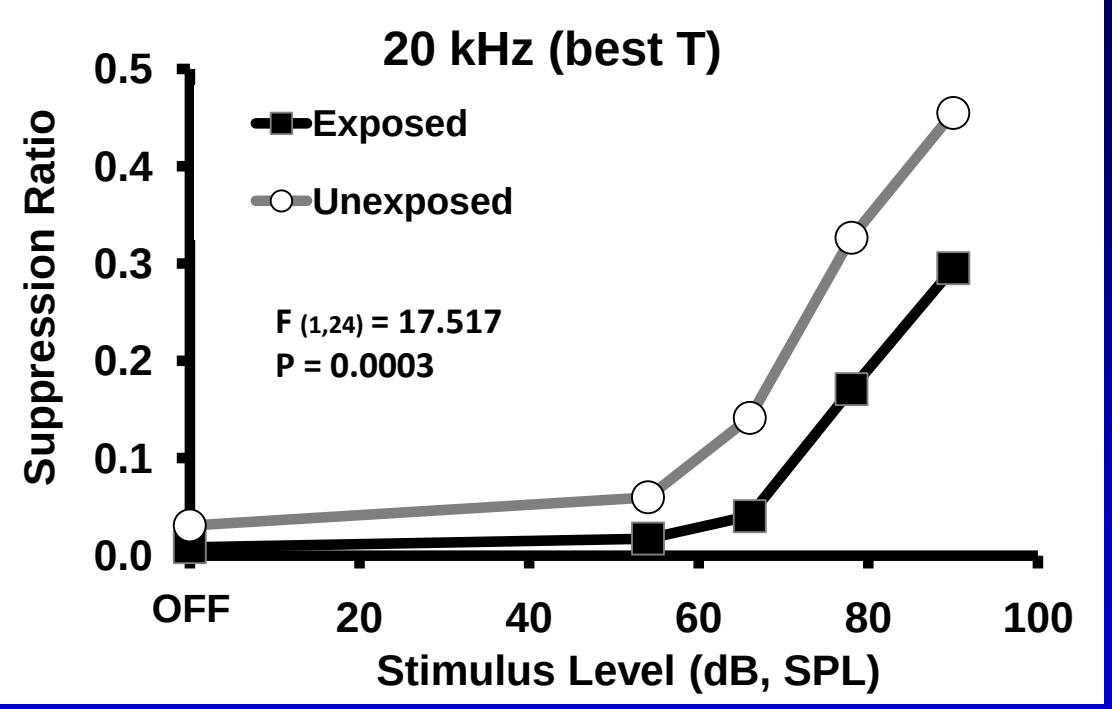


The Potential Role of the Cerebellum in Chronic Tinnitus: An Animal Model Experiment.

Representative Ipsilateral Ablation.

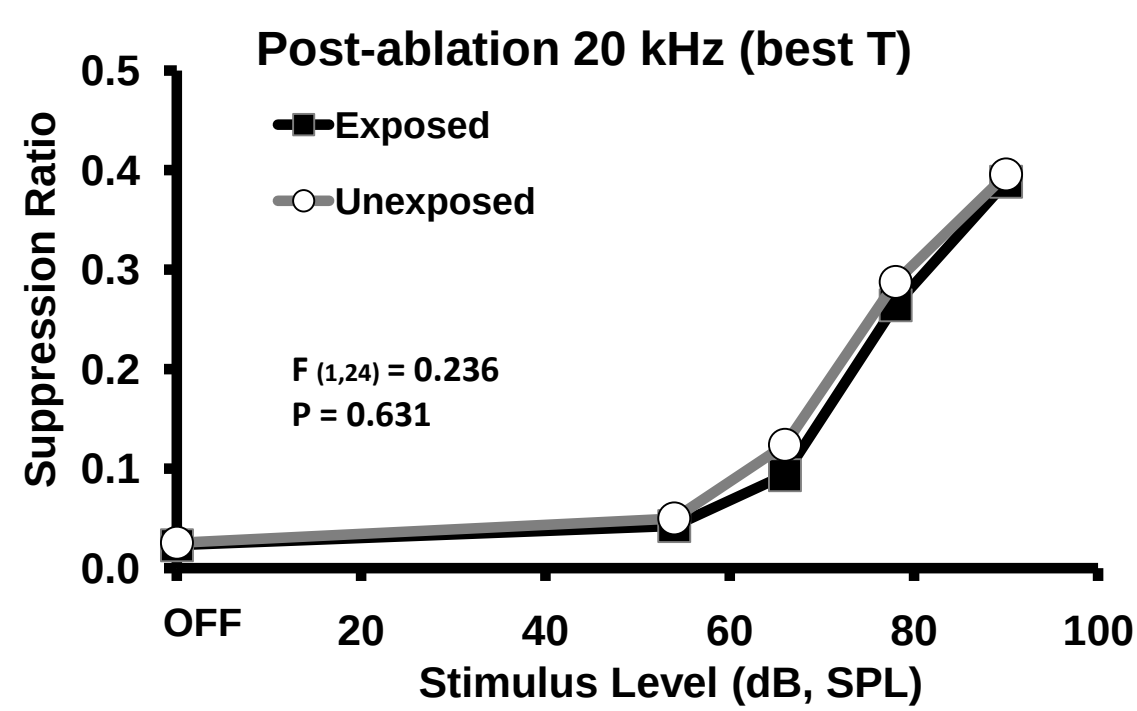


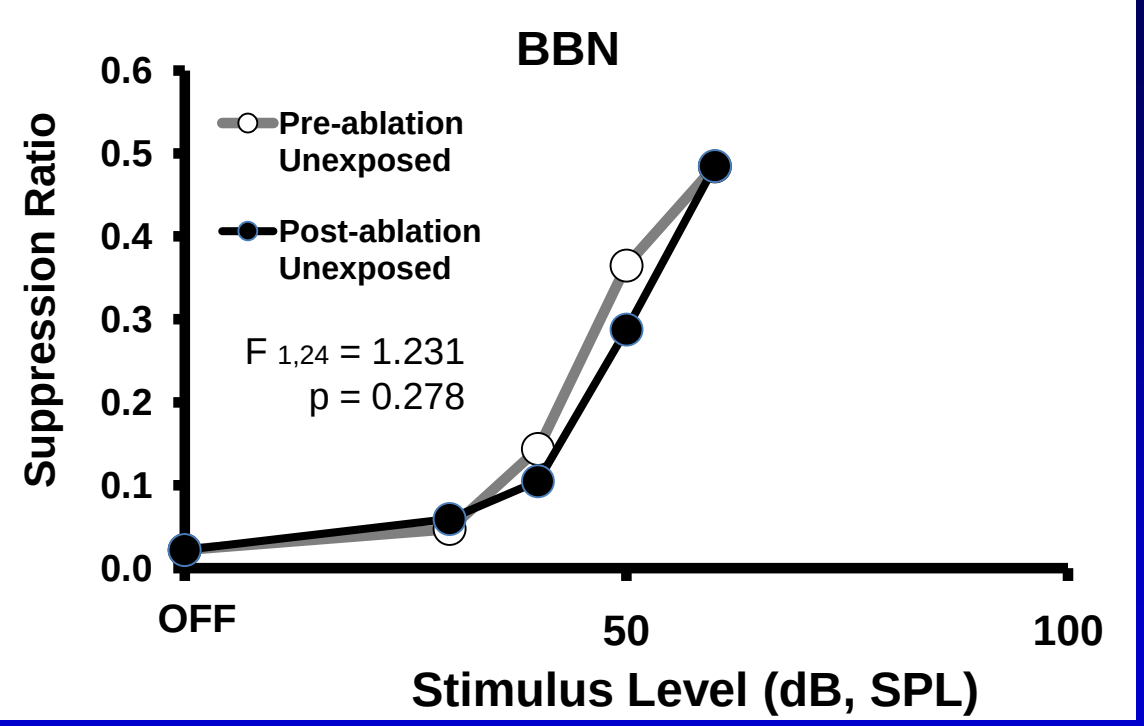
Exposed vs Unexposed Group Comparisons



Pre-ablation

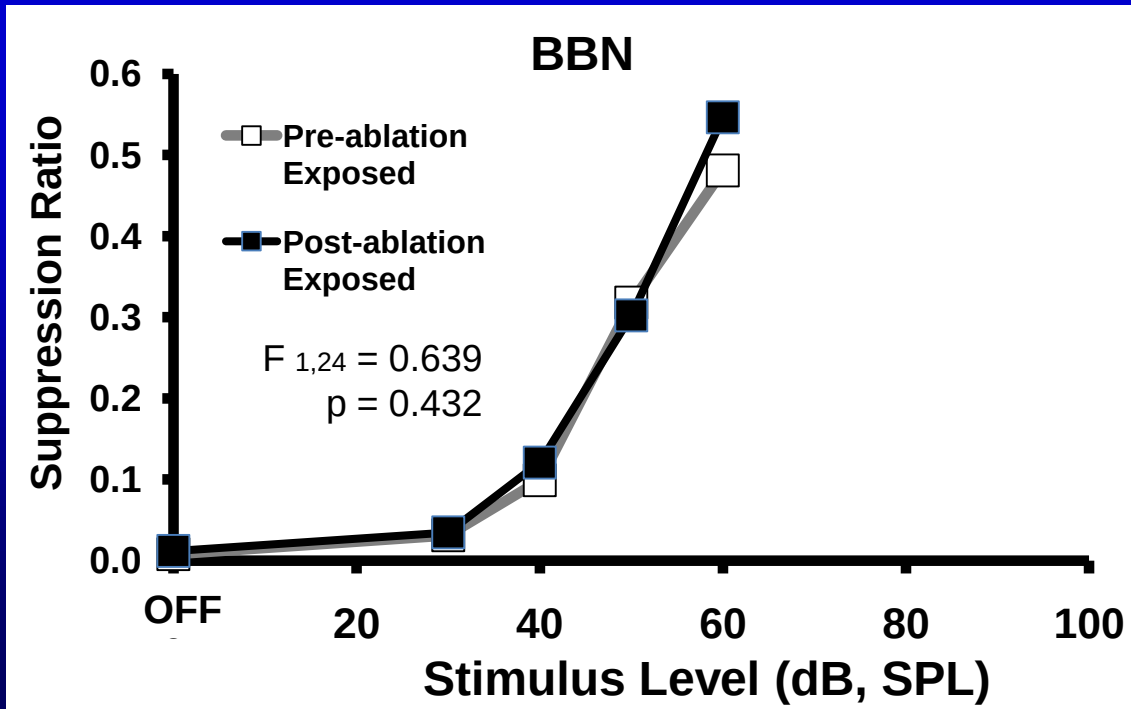
Post-ablation





Unexposed Control

Exposed



- Cochlear implants eliminate tinnitus

Clinical Observation

Bench studies

- Is the cerebellum a modulator of chronic tinnitus?

- Targeted drugs?
- Targeted implants?

Refine concept in clinic