THE UNIVERSITY OF WESTERN AUSTRALIA

FACULTY OF SCIENCE

Cochlear involvement in tinnitus

HELMY (WHAM) MULDERS

Tinnitus

Tinnitus affects 5-15% of population.

Can severely affect quality of life

No cure yet

Strong correlation with hearing loss - Prevalence increasing

What is the neural substrate of tinnitus?

Perception-abnormal neuronal activity

(Axelsson and Ringdahl, 1989)

Changes in the brain after hearing loss: Possible mechanisms for tinnitus

1. Changes in tonotopic maps

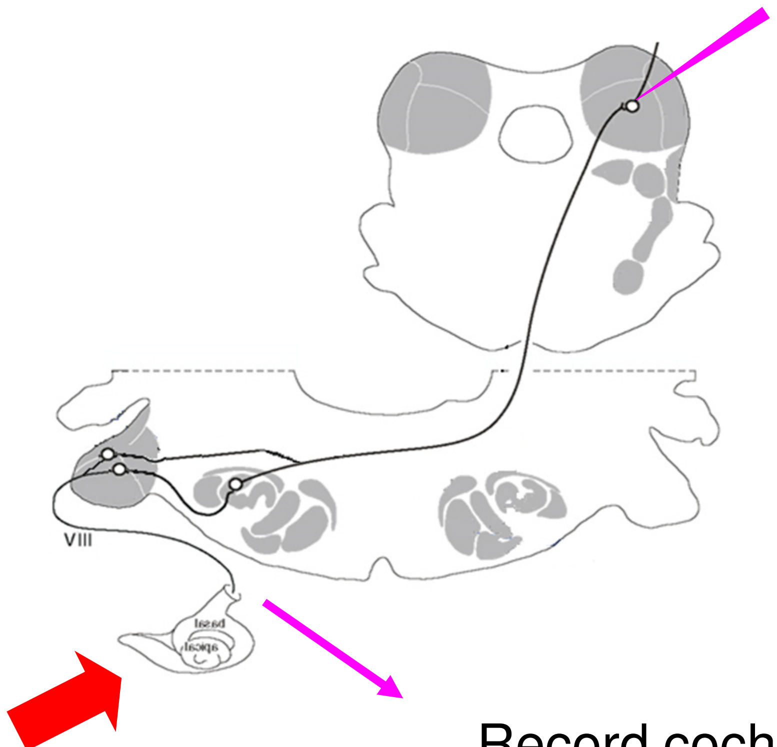
2. Synchronous activity between central structures

3. Increased spontaneous activity (hyperactivity) in central auditory pathway

Note: several theories suggest these changes in the auditory system are accompanied/modulated by changes in non-auditory parts of the brain.

Eggermont and Komiya, 2000; Robertson and Irvine 1989; Norena and Eggermont, 2003

Our guinea pig model to study central hyperactivity and tinnitus



- Recovery 0-12 weeks
- Record single neuron activity in inferior colliculus
- Behavioural tinnitus test

Pure tone acoustic trauma

Record cochlear neural thresholds (CAP) to establish hearing loss

Adapted from Lee Kishnan and Winer

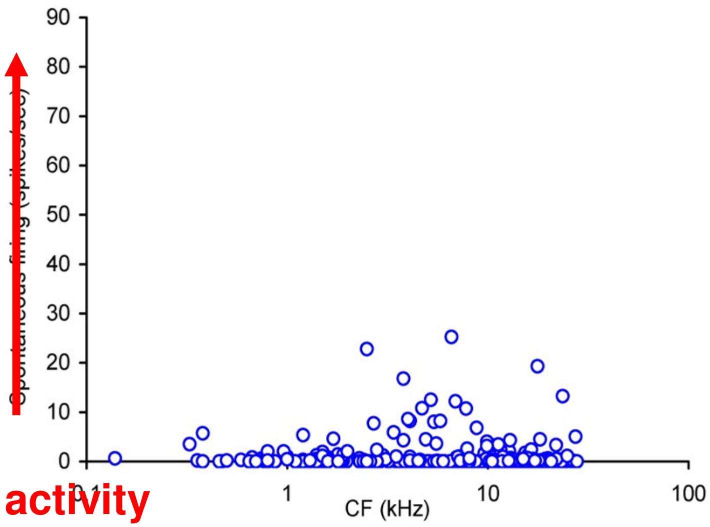
Our animal model to study tinnitus:

Our results:

Increased neural activity in IC without sound present:
HYPERACTIVITY

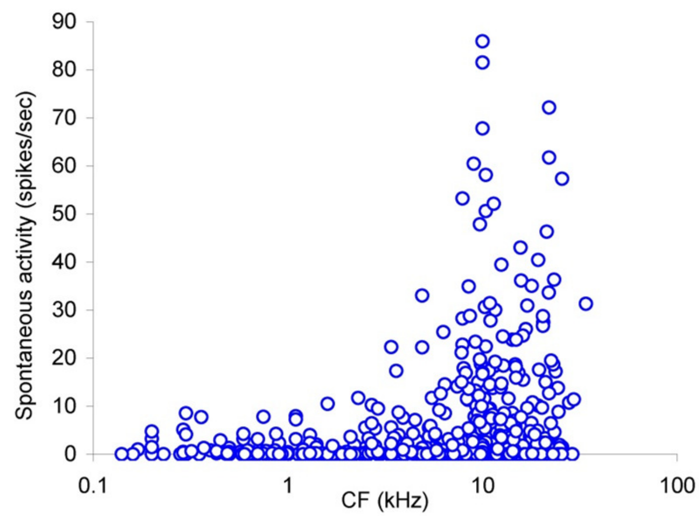
Control data

High activity

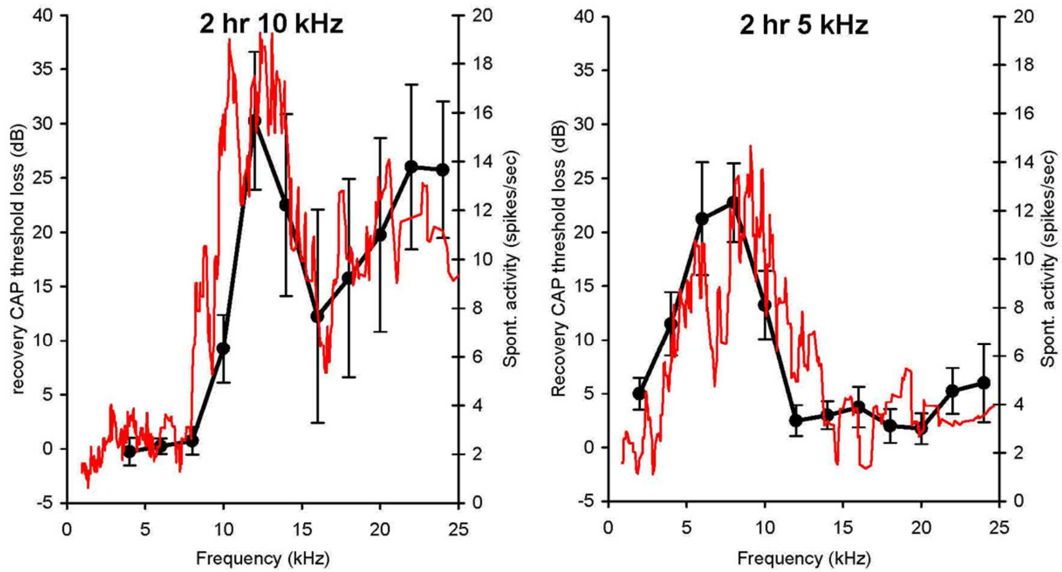


Low activity

Hyperactivity



THE UNIVERSITY OF WESTERN AUSTRALIA



Hyperactivity shows correlation with region of hearing loss

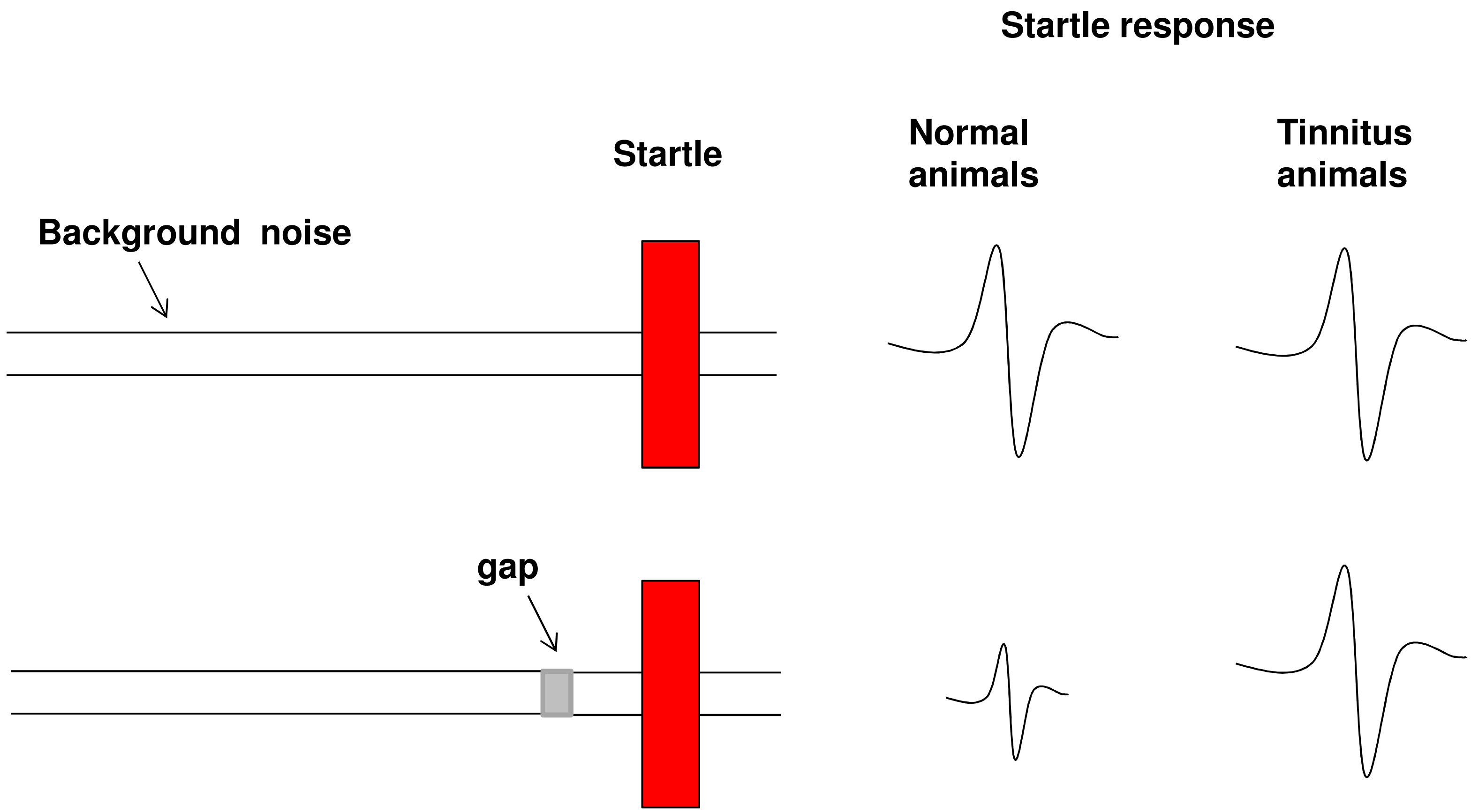
Human studies:

Audiogram vs tinnitus pitch: frequencies of hearing loss closely match pitch of perceived tinnitus

Robertson et al 2013 hearing Res

Measuring tinnitus in animals

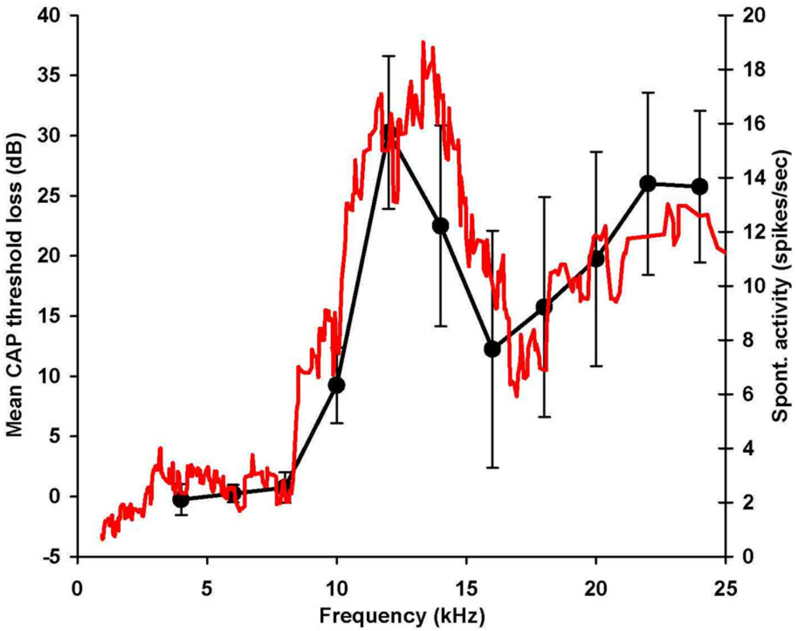
gap prepulse inhibition of the acoustic startle (GPIAS)



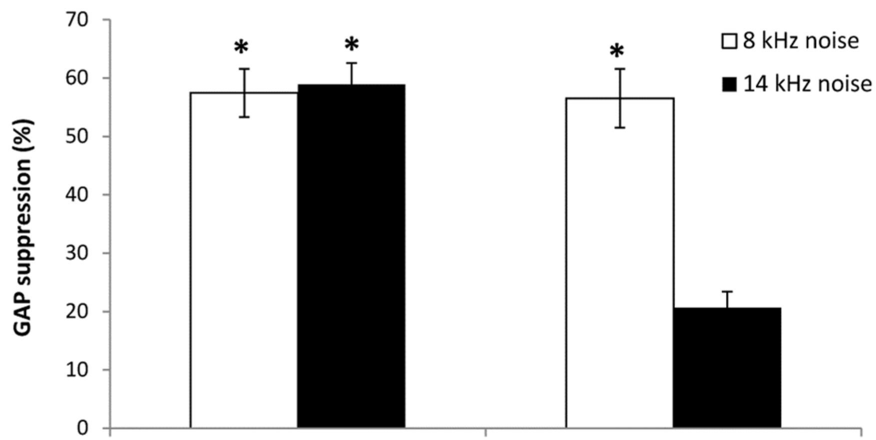
Turner et al. 2006

Our guinea pig model: central hyperactivity and tinnitus

Correlation hearing loss and hyperactivity



Tinnitus: GPIAS



Before acoustic trauma

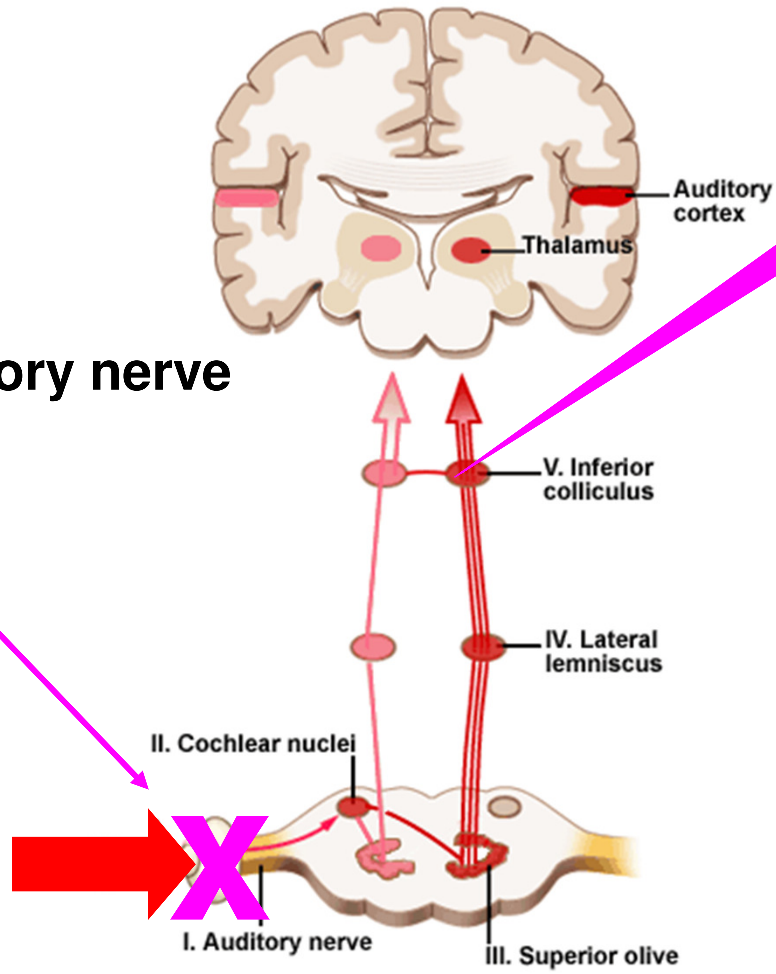
After acoustic trauma

Can we modulate the central hyperactivity?

Measure single neuron activity Hyperactivity

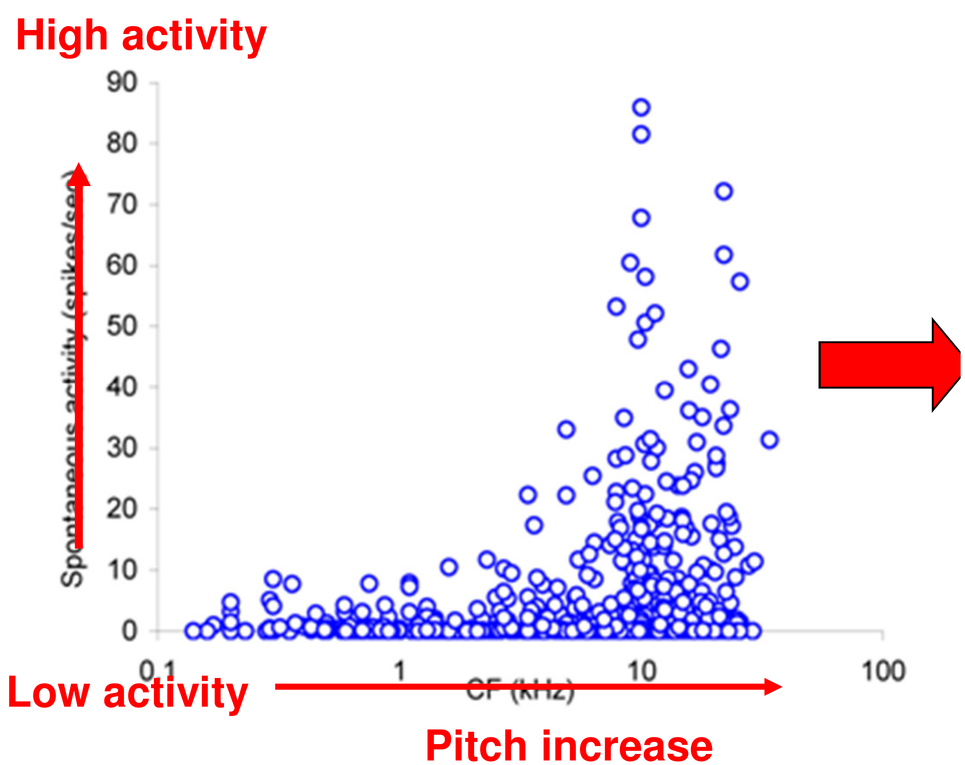
Stop activity auditory nerve

Acoustic trauma



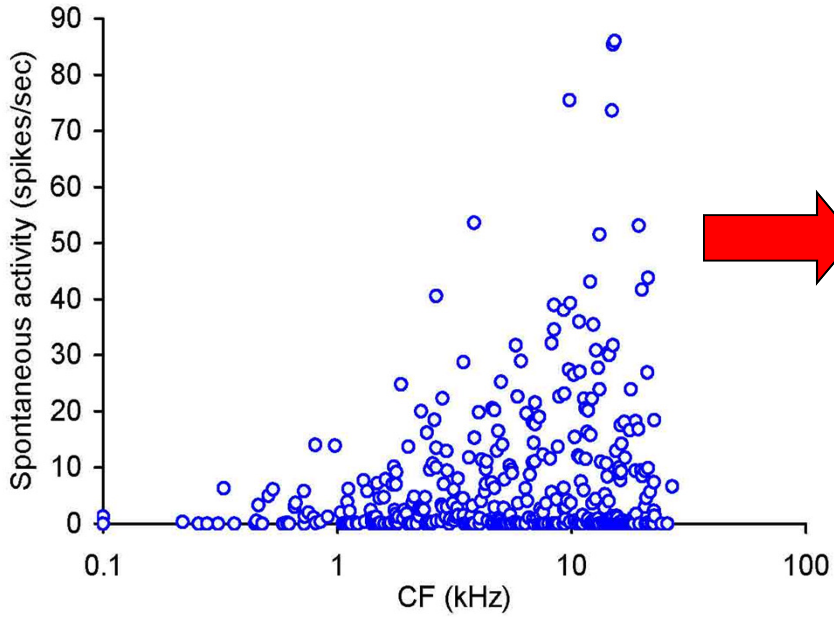
1-6 weeks recovery: <u>Acute</u> destruction of auditory nerve after recovery period eliminates hyperactivity

Post recovery-pre-ablation

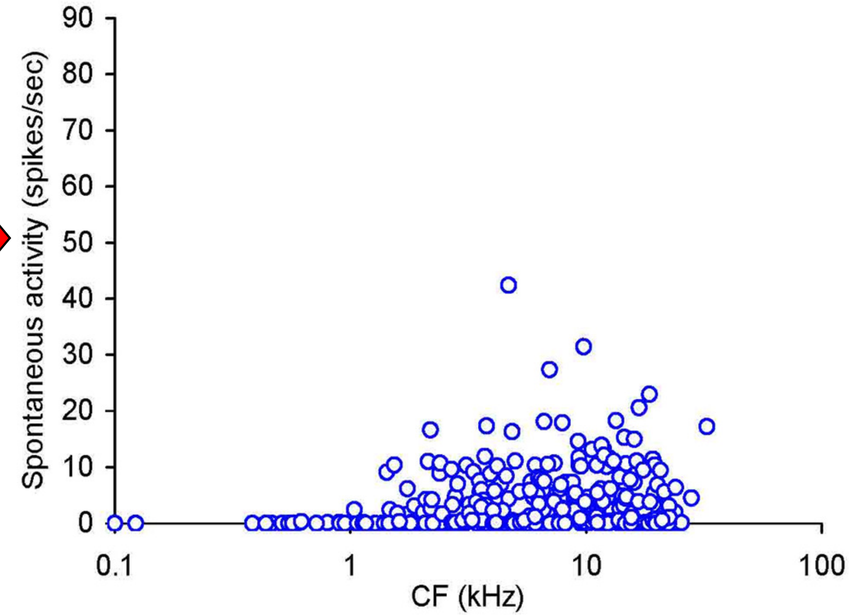


8-12 weeks recovery: Acute destruction of auditory nerve does **NOT** completely eliminate hyperactivity

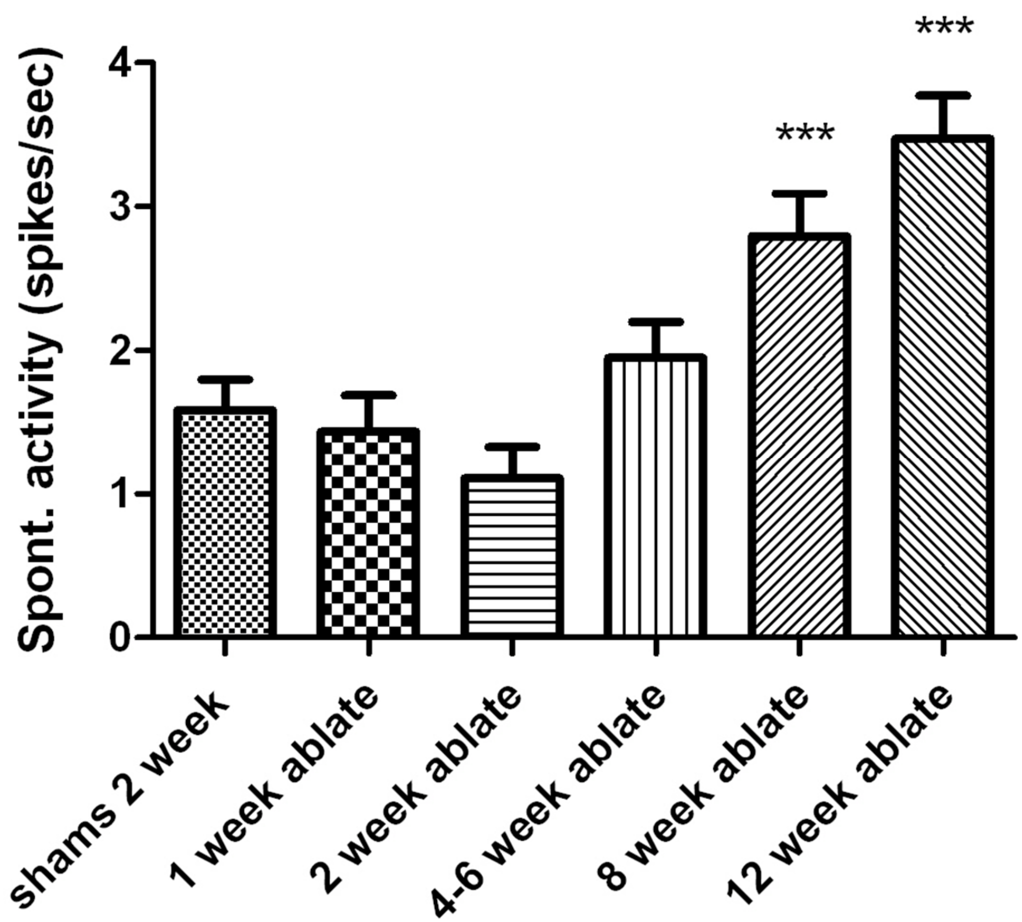
Post-recovery-pre-ablation



After acute cochlear ablation

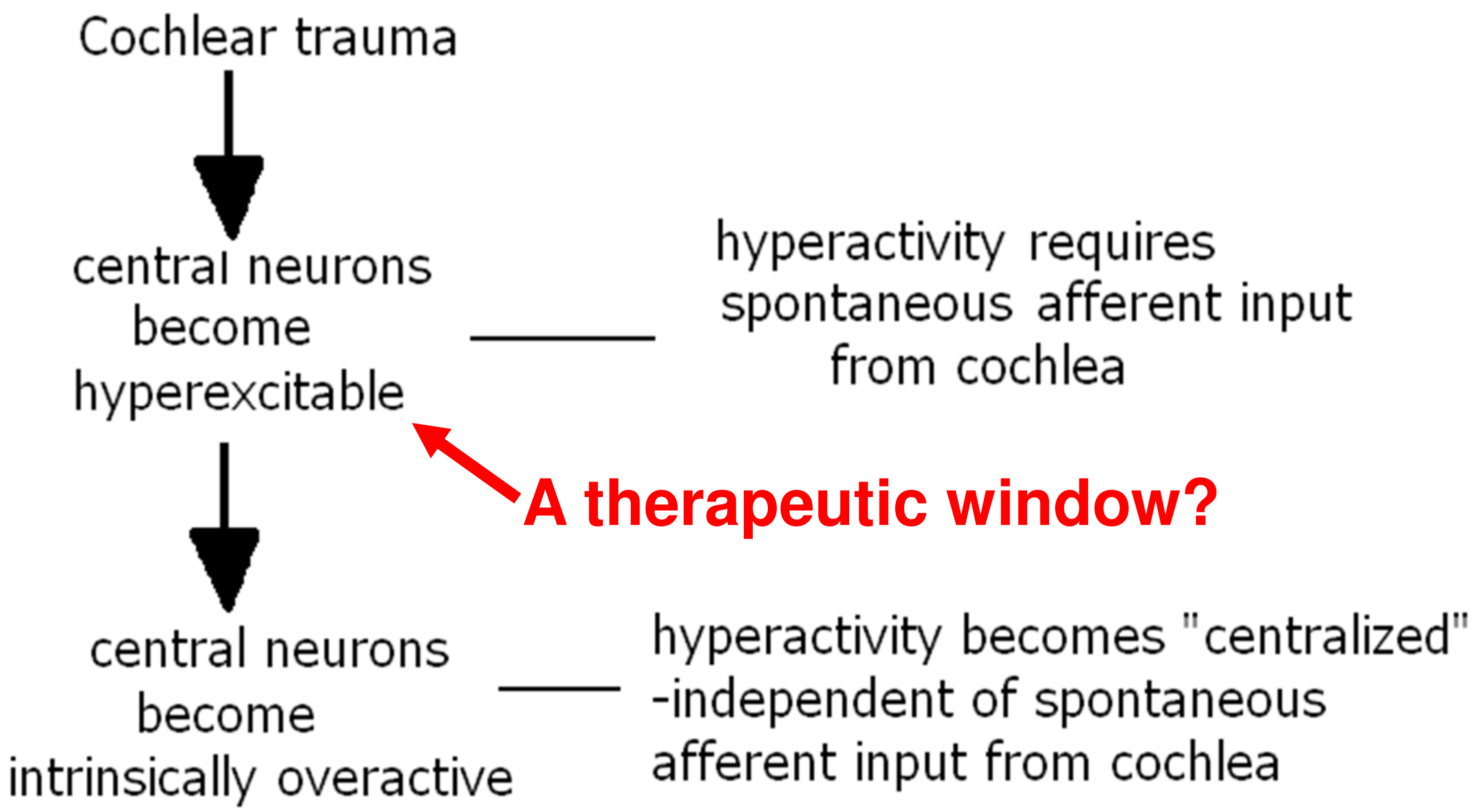


Mulders and Robertson 2011 Neurosci



Mulders and Robertson 2011 Neurosci

Central Hyperactivity-a two stage process?



The Big Question

In stage 1:

Reduction spontaneous activity in auditory nerve: hyperactivity ↓

In stage 1:

Reduction spontaneous activity in auditory nerve: tinnitus ↓ ???

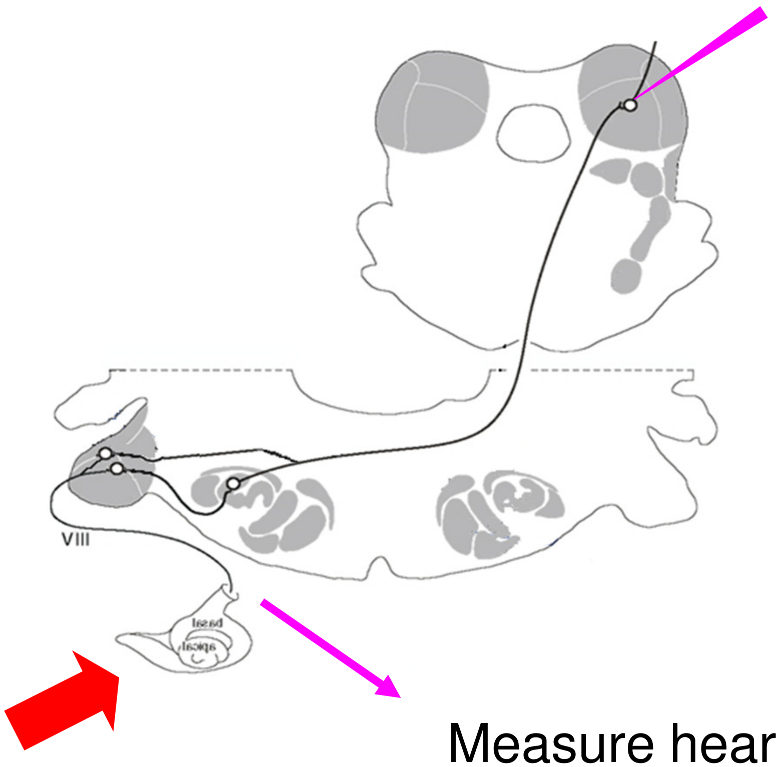
How can we suppress spontaneous activity of the auditory nerve fibres?

Possibility: **Furosemide**

- Loop diuretic (affecting membrane transport).
- Known to affect kidney and inner ear
- Decreases spontaneous firing rate auditory nerve fibres (Sewell 1984)
- Can suppress tinnitus in human subjects (Risey et al 1995; Caesarani et al. 2002)

THE UNIVERSITY OF WESTERN AUSTRALIA

Can we modulate hyperactivity and tinnitus in our animal model using furosemide?



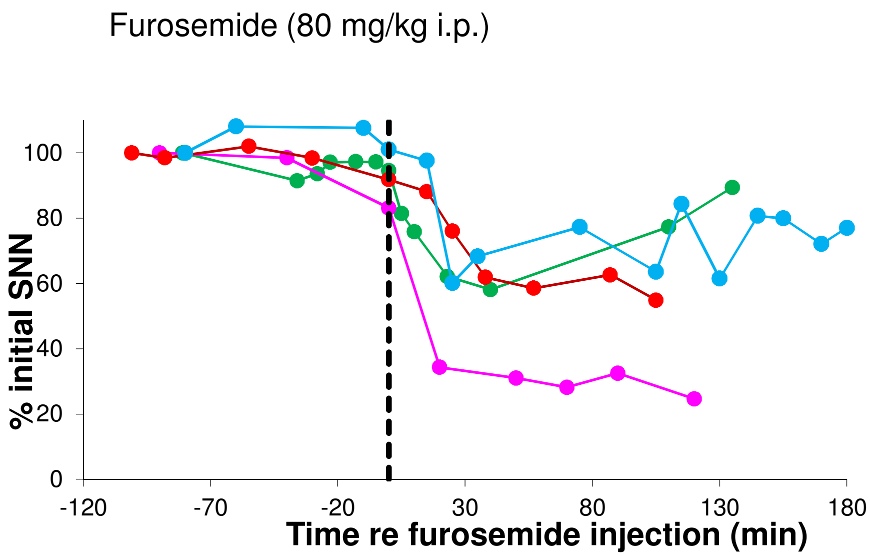
- Recovery 0-12 weeks
- Measure brain activity: effect of furosemide
- Behavioural tinnitus test: effect of furosemide

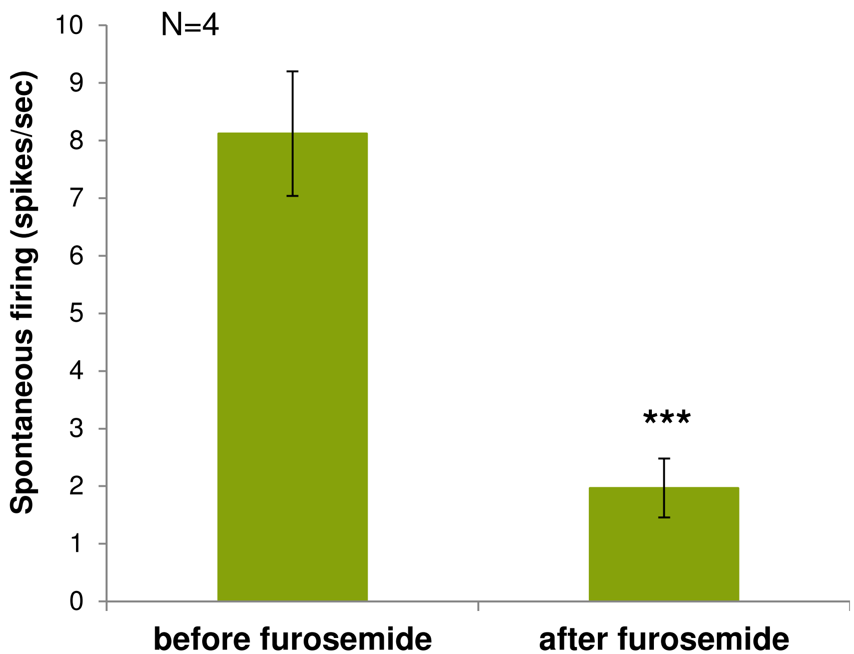
Partial deafness

Measure hearing loss

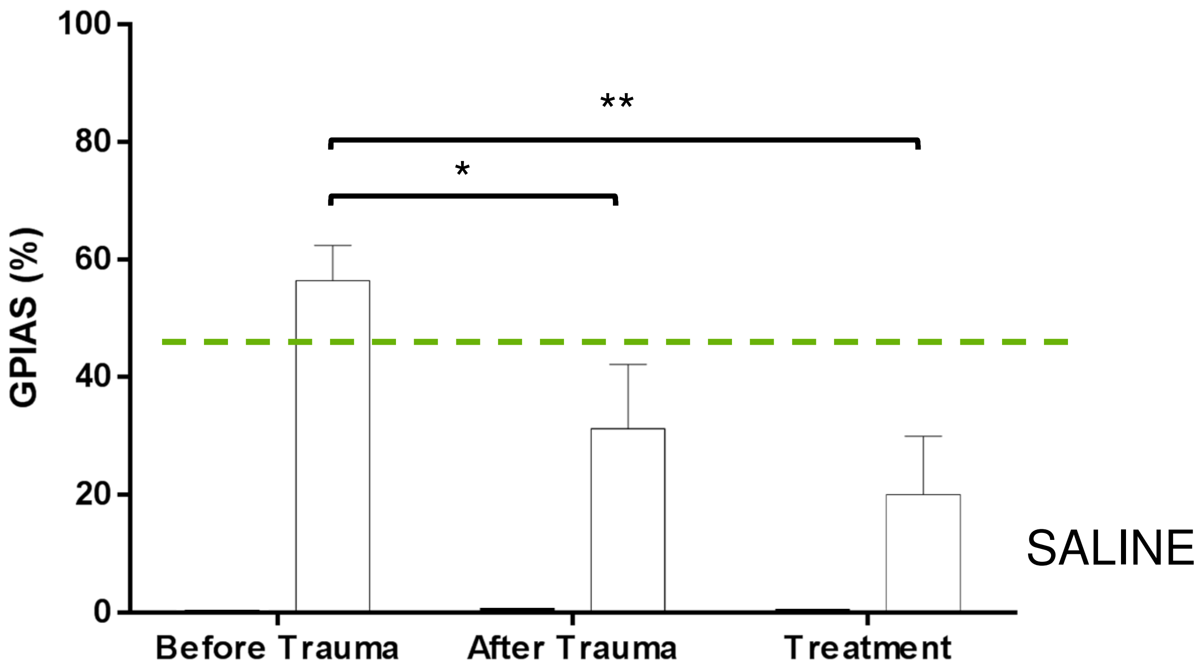
Adapted from Lee Kishnan and Winer

Furosemide acutely decreases spontaneous firing auditory afferent nerve fibres (SNN) and central hyperactivity

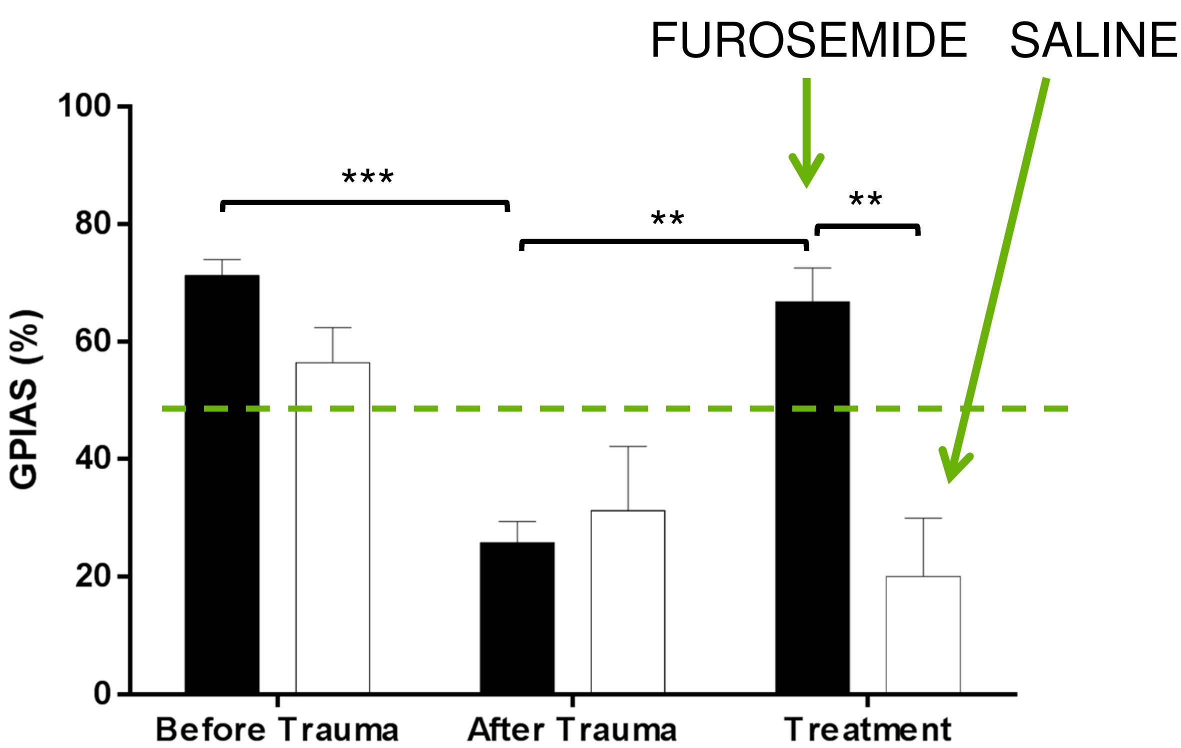




Saline i.p. has no effect on behavioural signs of tinnitus



Furosemide i.p. eliminates behavioural signs of tinnitus



Mulders, Barry and Robertson 2014 Plos One

In conclusion

- **Our data suggest that furosemide can suppress the behavioural signs of tinnitus in our animal model.**
- **Our data strengthens the argument that hyperactivity is involved in the generation of tinnitus.**
- **Our data supports the notion that there may be a therapeutic window for some time after acoustic trauma.**

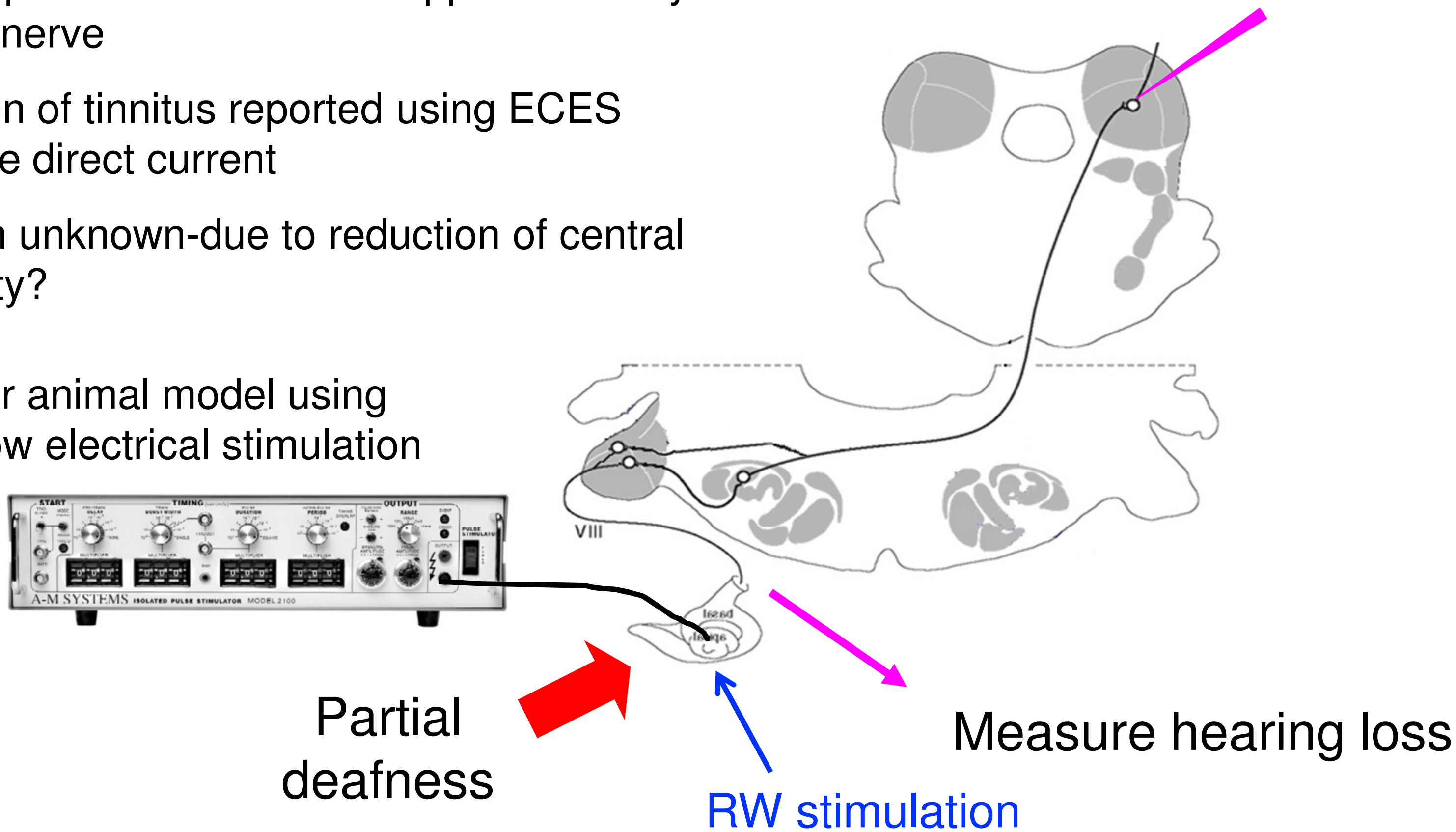
What's next?

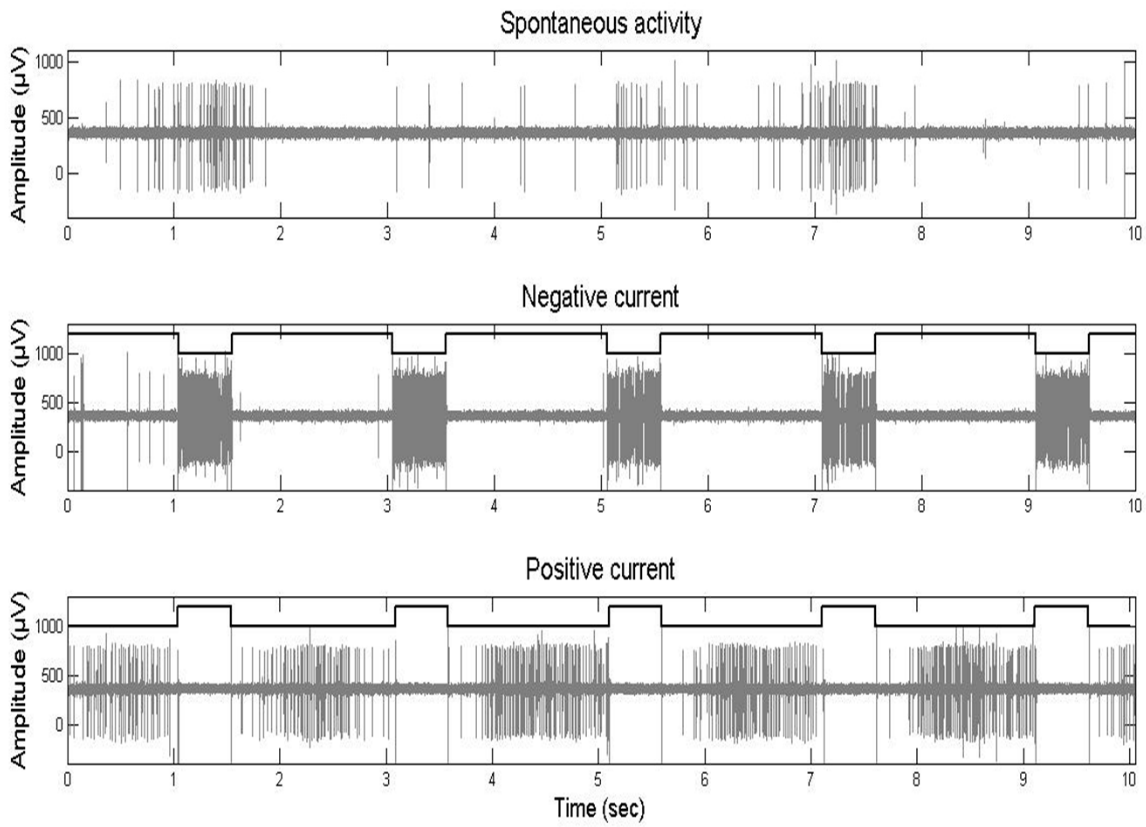
- **Can we show proof of principle in human tinnitus sufferers?** (collaboration Prof Friedland; Ear Science Institute Australia)
- **Investigations into more chronic effects of furosemide on tinnitus.** (Mulders et al. 2014 Frontiers in Neuroscience)
- **Other options beside furosemide?**
- **What about treatments for centralized tinnitus?**

A different way to modulate activity in the cochlea: Extra-cochlear electrical stimulation (ECES)

- ECES with positive current can suppress activity of auditory nerve
- Suppression of tinnitus reported using ECES with positive direct current
- Mechanism unknown-due to reduction of central hyperactivity?

Tested in our animal model using round window electrical stimulation





ECES with negative current hyperactivity in IC ↑

ECES with positive current hyperactivity in IC ↓

Only small effect on thresholds and tone-induced activity of IC neurons.
ECES may be a viable approach for suppressing some forms of (peripheral-dependent) tinnitus.

Acknowledgements:

Action on Hearing Loss (UK)

Neurotrauma Research Program

NHMRC

MHRIF

Auditory lab members

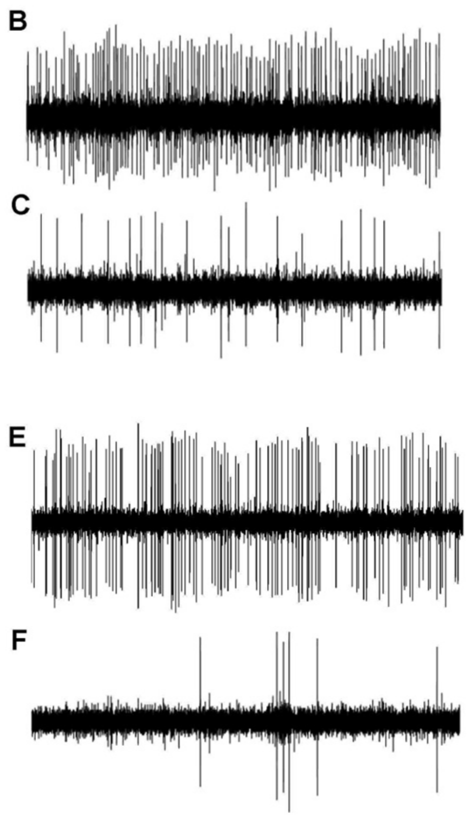
A/Prof. Jenny Rodger (University of Western Australia)

Dr Arnaud Norena (Universite de Marseille, France)

Prof Tony Paolini (RMIT, Australia)

Prof Richard Salvi (University of Buffalo, USA)

1-6 weeks recovery: Acute but temporary silencing of auditory nerve after recovery period eliminates hyperactivity



Single neuron recordings in midbrain 2 weeks after acoustic trauma:

Cochlear perfusion with

kainic acid or

$CoCl_2$

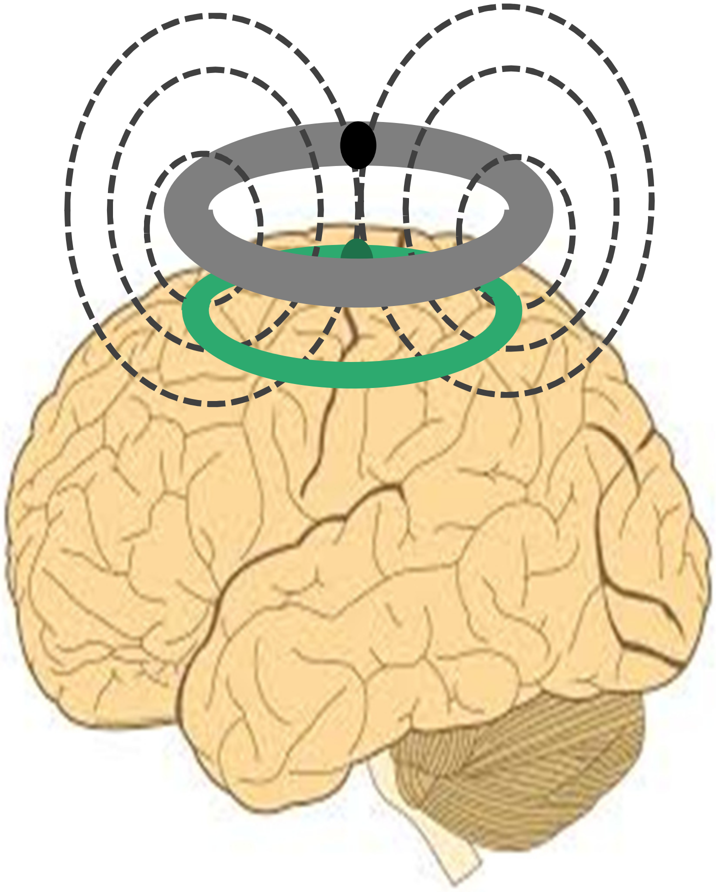
suppresses spontaneous activity

Mulders et al. 2009 Neurosci

What's next?

- **Can we show proof of principle in human tinnitus sufferers?** (collaboration ESIA)
- **Investigations into more chronic effects of furosemide on tinnitus.**
- **Other options beside furosemide?**
- **What about treatments for centralized tinnitus?**

Repetitive Transcranial Magnetic Stimulation (rTMS)



- Therapeutic effects on many neurological and psychiatric disorders
- Non-invasive
- Some success reported in tinnitus patients

Vooys 2014; Huerta and Volpe, 2009; (Khedr et al., 2008, Langguth et al., 2008, Khedr et al., 2010

rTMS frequency protocol

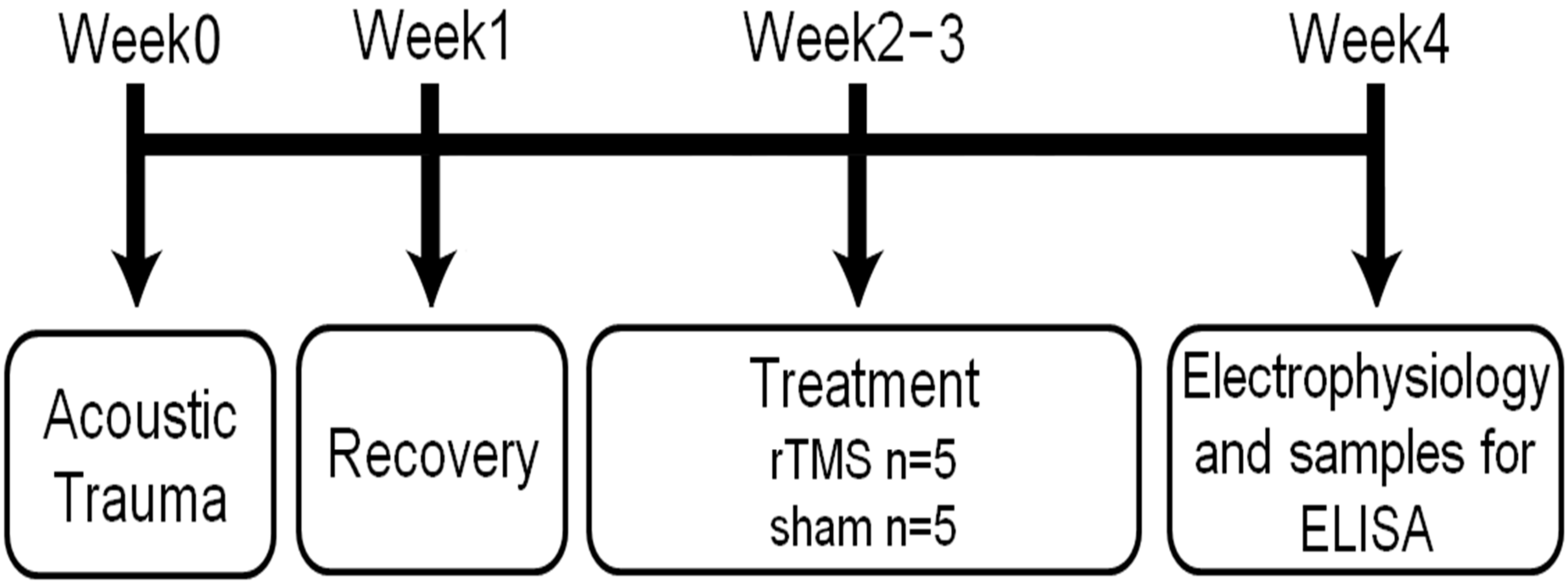
- ⬆ High frequency rTMS – excites neuronal activity
- ⬇ Low Frequency rTMS – inhibits neuronal activity

Low-frequency rTMS:
Ideal treatment for disorders involving excessive cortical excitability

Hallet (2000); Huerta and Volpe (2009); Hoffman (2002); Eichhammer et al. (2003)

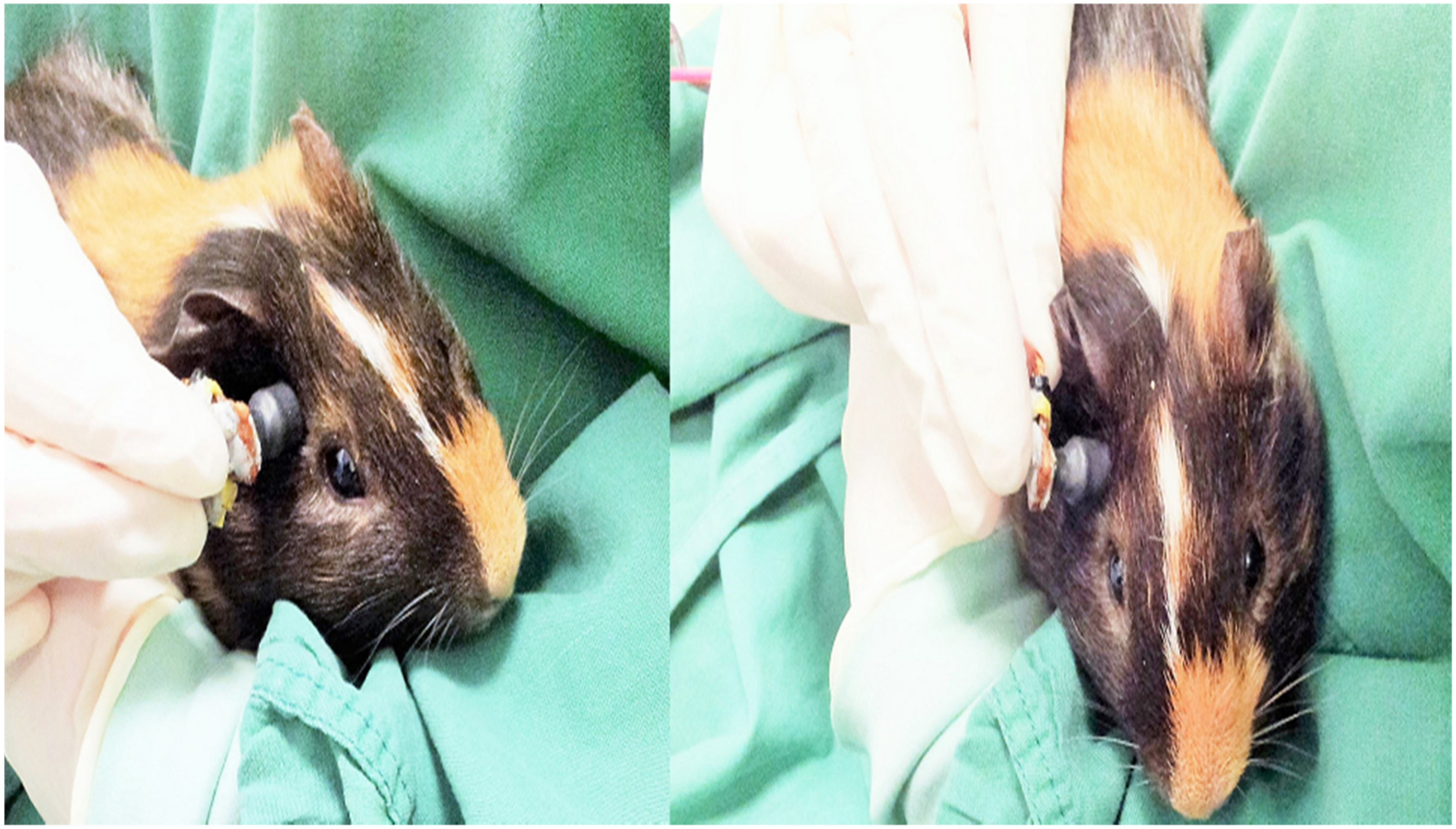
Can rTMS suppress hyperactivity after hearing loss?

10 Guinea Pigs



Vooys 2014

Coil size and position

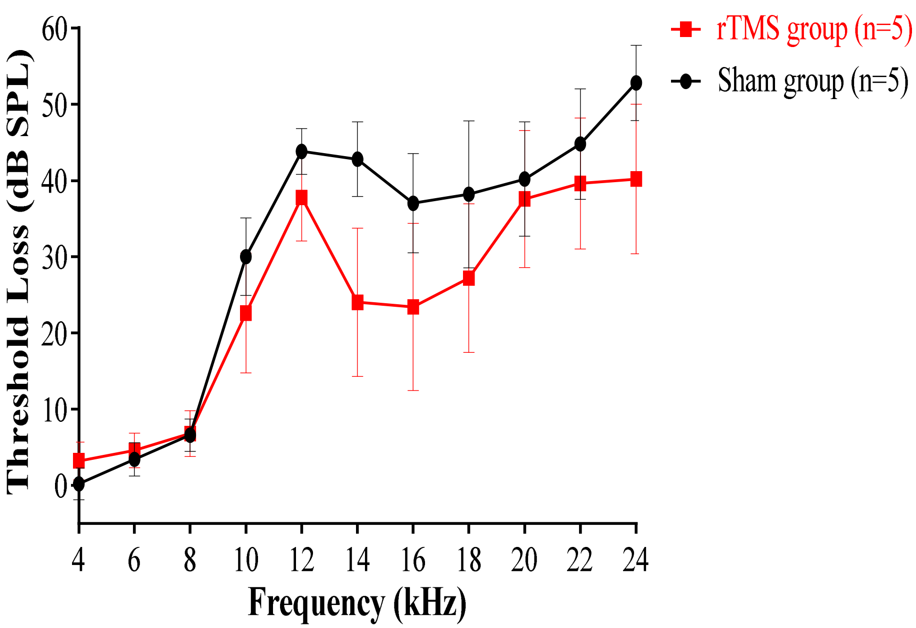


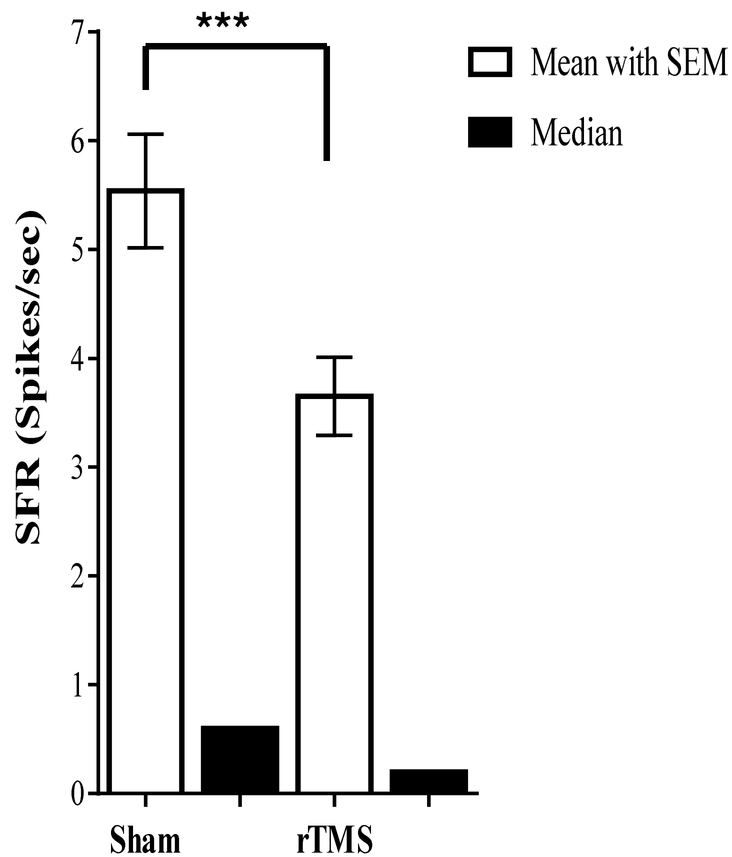
10minute sessions, 1 Hz, Monday – Friday for 2 weeks

Vooys 2014 In preparation

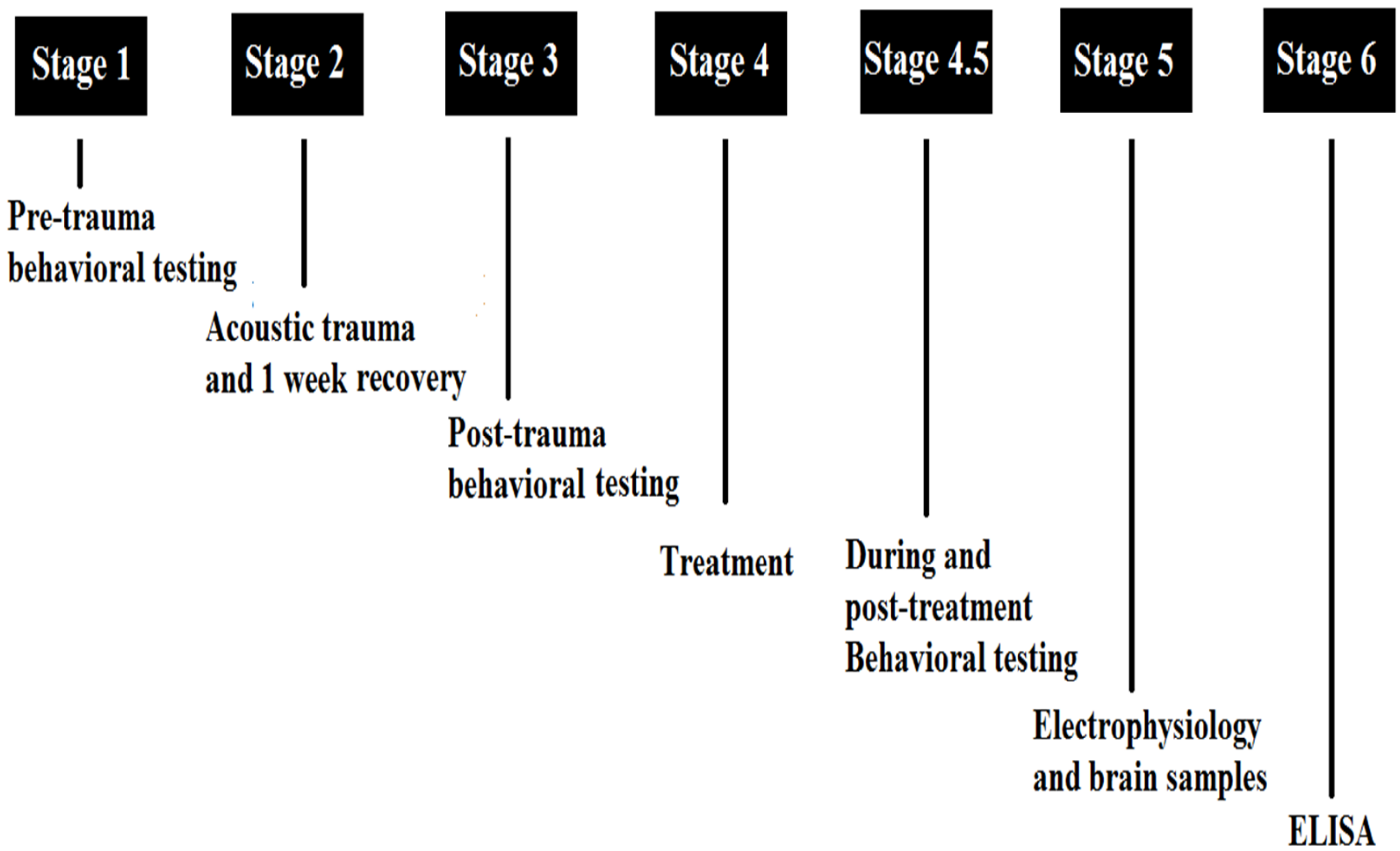
THE UNIVERSITY OF WESTERN AUSTRALIA

rTMS does not affect hearing loss but reduces hyperactivity

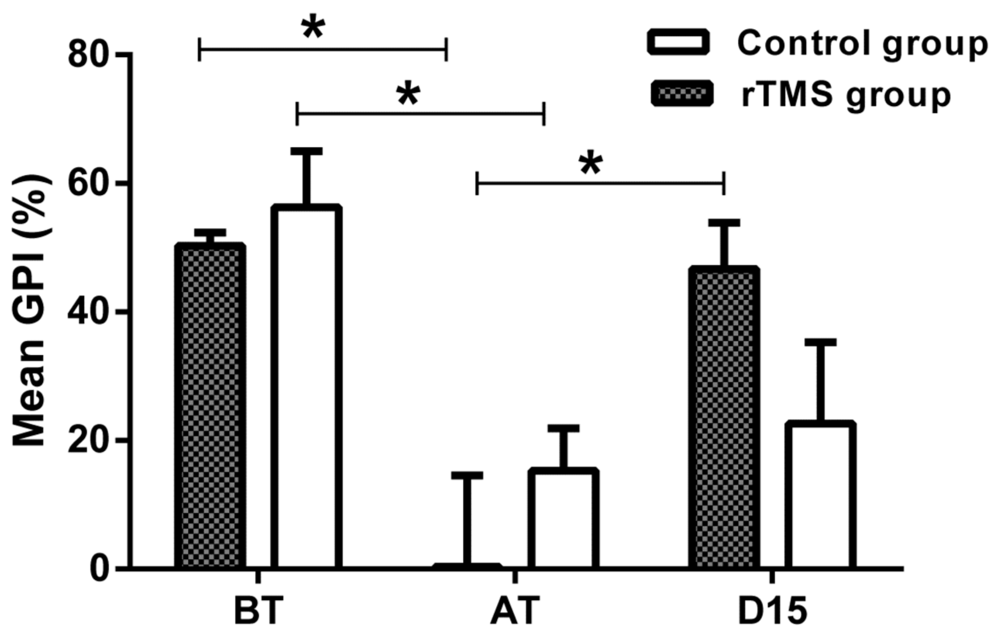




Can rTMS reduce the behavioural signs of tinnitus in our animal model?



Preliminary data: possible effect rTMS on tinnitus?



N=3/group

- Is rTMS affecting descending pathways from the cortex?
- Direct effect on IC?

Further ongoing studies

- Modulation of hyperactivity by paraflocculus (Darryl Vogler)
- Modulation of hyperactivity and tinnitus by limbic system (Kristin Barry and Prof Tony Paolini RMIT University Melbourne)
- Projection patterns of descending auditory systems (Ahmaed Bashaar)
- Effects of cochlear electrical stimulation on hyperactivity and tinnitus
- Testing validity of GPIAS in human subjects (Prof. Geoff Hammond, ESIA)
- Effects of rTMS on hyperactivity and tinnitus (A/Prof. Jenny Rodger)
- Proof of principle experiment effect of furosemide in tinnitus subjects (ESIA and Prof Peter Friedland)

Neural substrates of tinnitus

Human studies:

Neuroimaging data: Excessive spontaneous activity in auditory structures

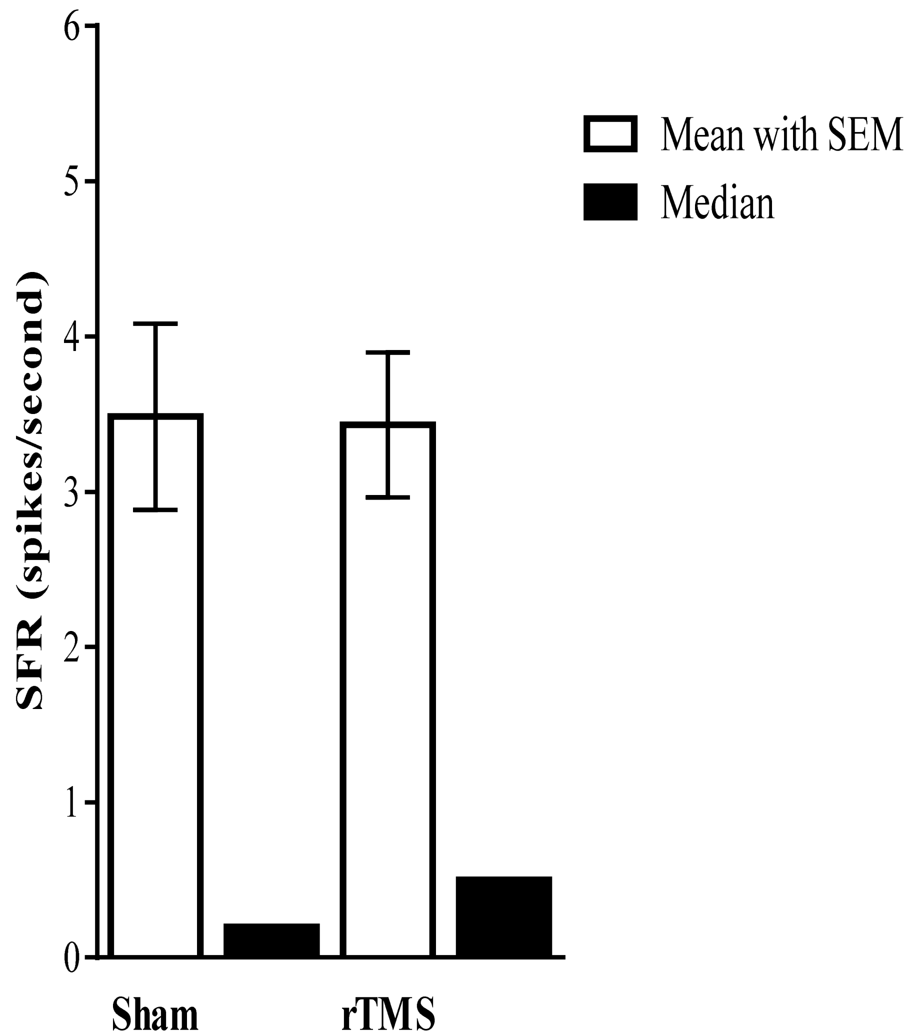
Audiogram vs tinnitus pitch: frequencies of hearing loss closely match pitch of perceived tinnitus

Animal studies: (models of hearing loss)

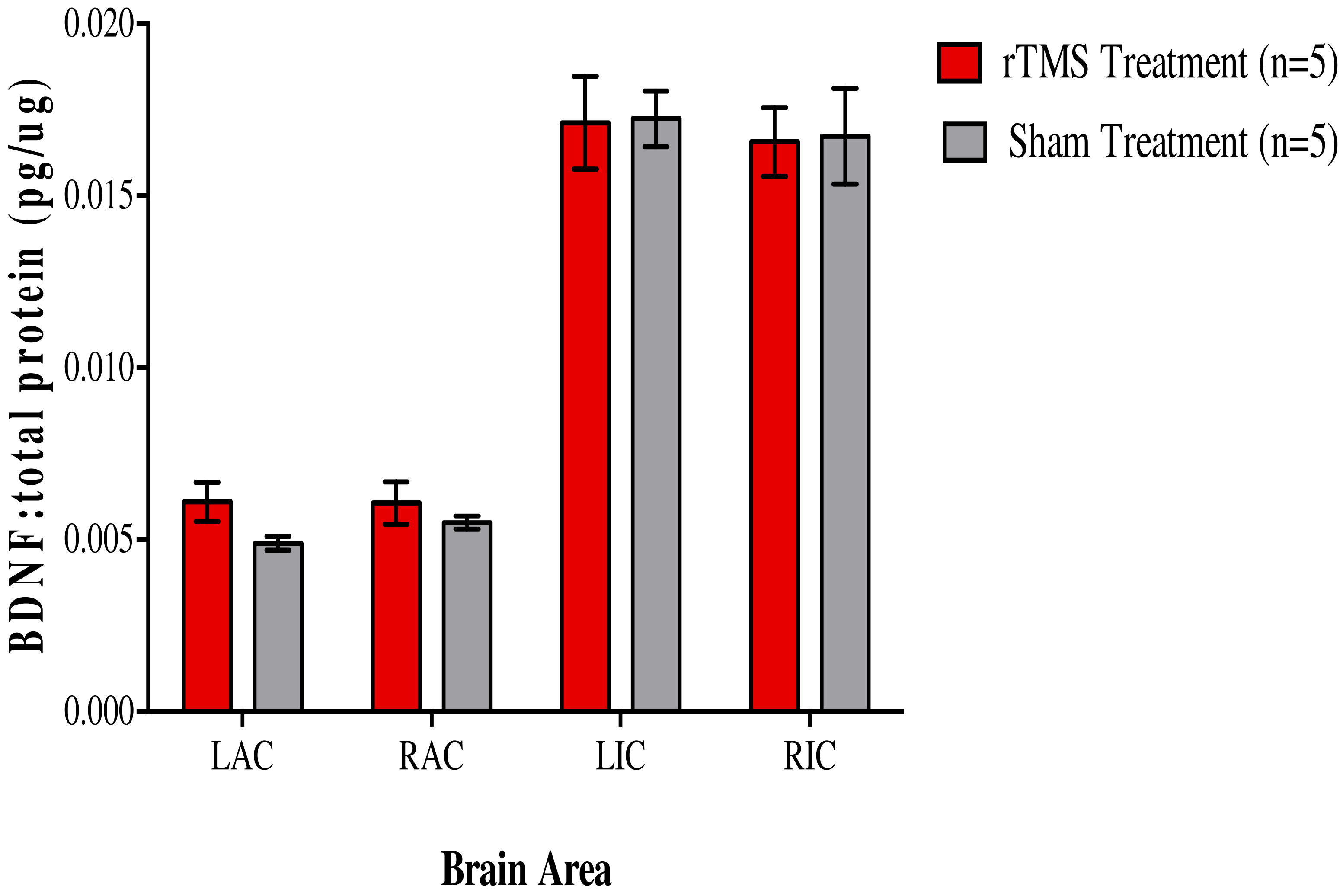
Electrophysiology: Increased spontaneous activity in auditory structures

Audiogram vs tinnitus pitch: Increased spontaneous activity associated with frequency range of hearing loss and behavioral signs of tinnitus correlate with Increased spontaneous activity/ frequency range of hearing loss

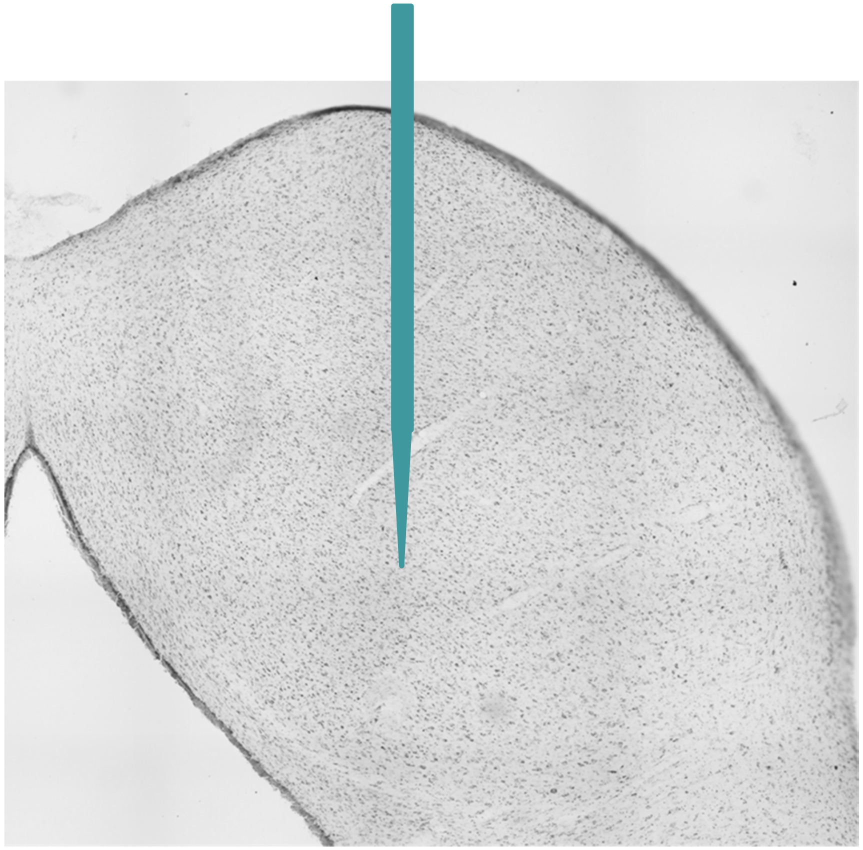
RESULTS (STUDY2): SPONTANEOUS FIRING RATE



RESULTS (STUDY1): BDNF ELISA



Measuring brain activity



Picture courtesy C. Bester

- Depth
- CF (characteristic frequency) and threshold
- Spontaneous firing rate
- 90-120 neurons per animal

THE UNIVERSITY OF WESTERN AUSTRALIA

Experiment 1:

Guinea pig model

↓

Establish hyperactivity in the brain

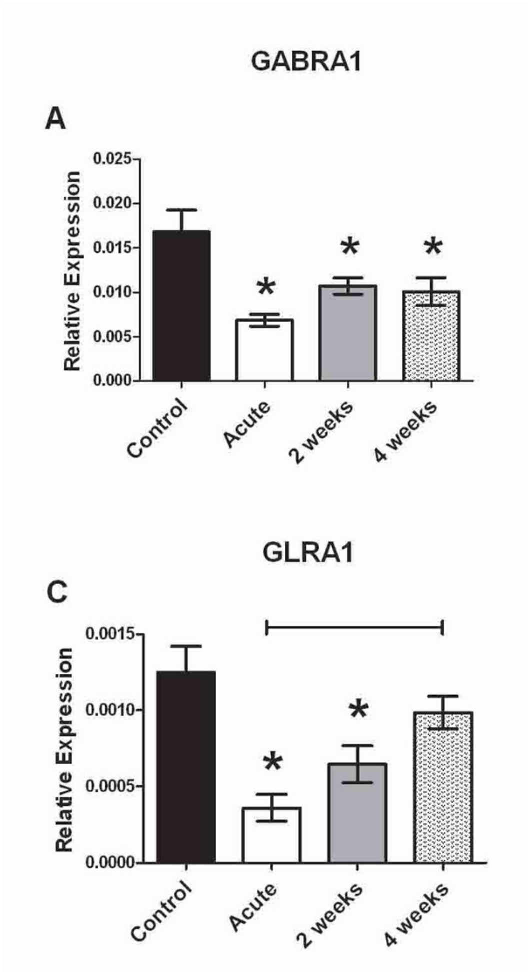
↓

Measure excitatory and inhibitory systems in the brain:

Gene products and brain chemicals

↓

Main result: Inhibitory systems ↓



Dong et al. Neurosci. 2009

Dong et al. Eur. J. Neurosci. 2010

Dong et al. Brain Res. 2010