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Revealing the Phantom:

Electrophysiological measures for objective diagnosis and treatment of tinnitus

Presented by Victoria Duda, Ph.D., reg. OOAQ

October 13th 2023

Plan for the day

1. What do we know about tinnitus (10 mins)
2. The challenges associated with tinnitus (5 mins)
3. The gap paradigm: What is it? Why does it matter? (5 mins)
4. How electrophysiology is used to measure gap-detection responses (10 mins)
5. How EEG gap-elicited measures are used for tinnitus (20 mins)
6. Future directions (5 mins)

What do we know about tinnitus

Cortical hyperactivity

Who has Tinnitus?

- 37% (or 9.2 million) Canadians suffer from tinnitus[1]
- Tinnitus can impact one's emotions, reactions and concentration
- The statistics do not include those who are not capable of reporting the presence of tinnitus (ex. children, people who don't know what it is, those with intellectual, social or psychological disabilities)

1. Ramage-Morin, P. L., Banks, R., Pineault, D., & Atrach, M. (2019). Tinnitus in Canada. Health Reports, 30(3), 4–11. https://doi.org/10.25318/82-003-x201900300001-eng

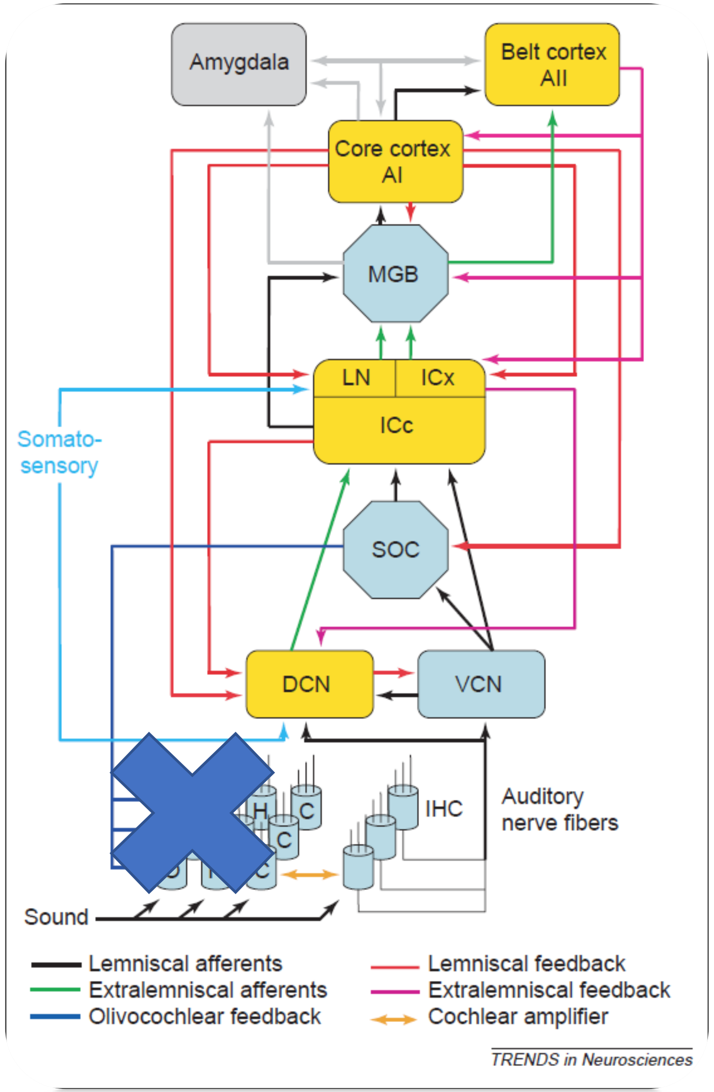
What is tinnitus?

1. **Subjective tinnitus:** a sound produced in the absence of an external auditory event.
2. **Objective tinnitus:** an internal sound that is heard by another person (ex. cardiovascular beating in the middle ear)
3. **Somatosensory tinnitus:** a sound modulated by other cranio-cervical regions that are outside of the auditory pathways (ex. tinnitus modulated by the movement of eyes or by touching certain parts of the body)

"roaring, whistling, static, high-tension wire, pure tones, ringing, beating, clicking… etc."

Where does tinnitus come from?

Response to the deprivation (efferent)

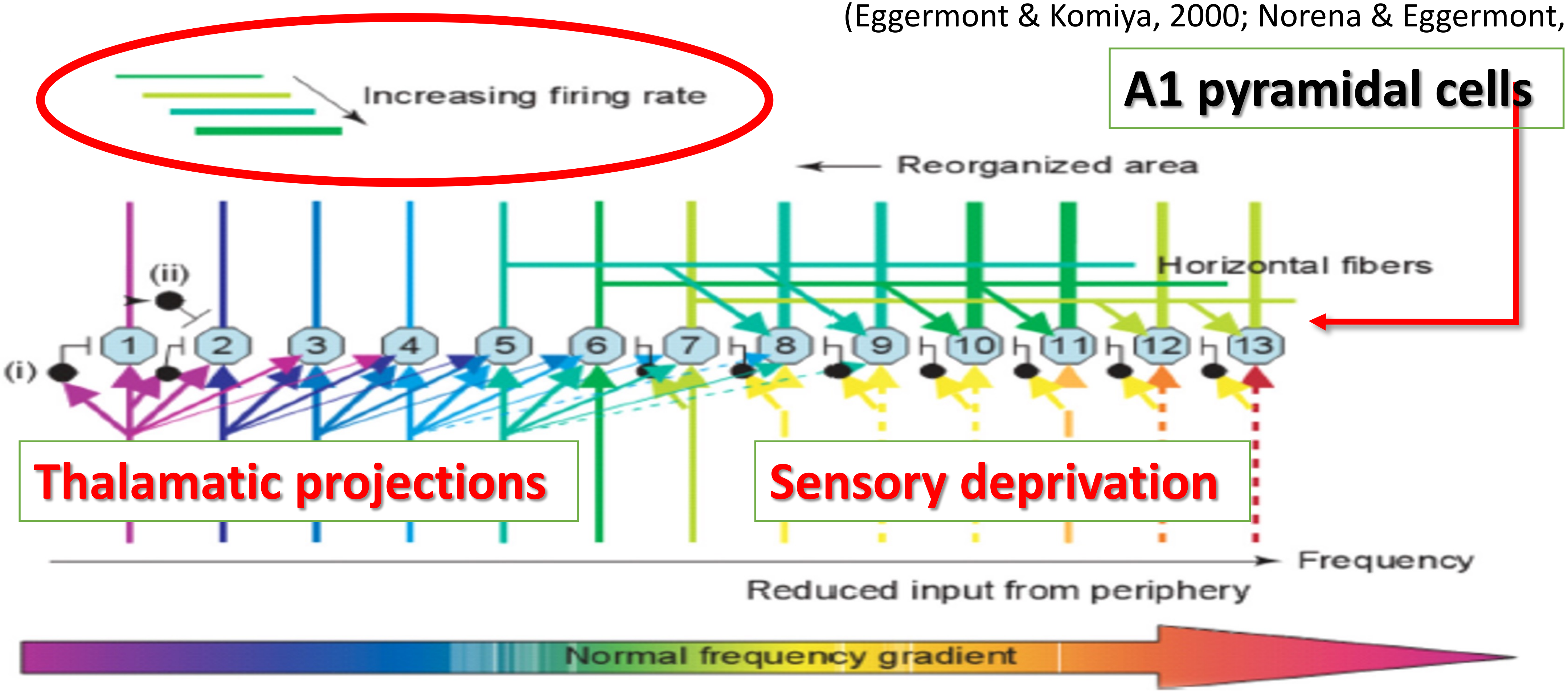


Sensory deprivation (afferent)

Eggermont et Roberts (2004)

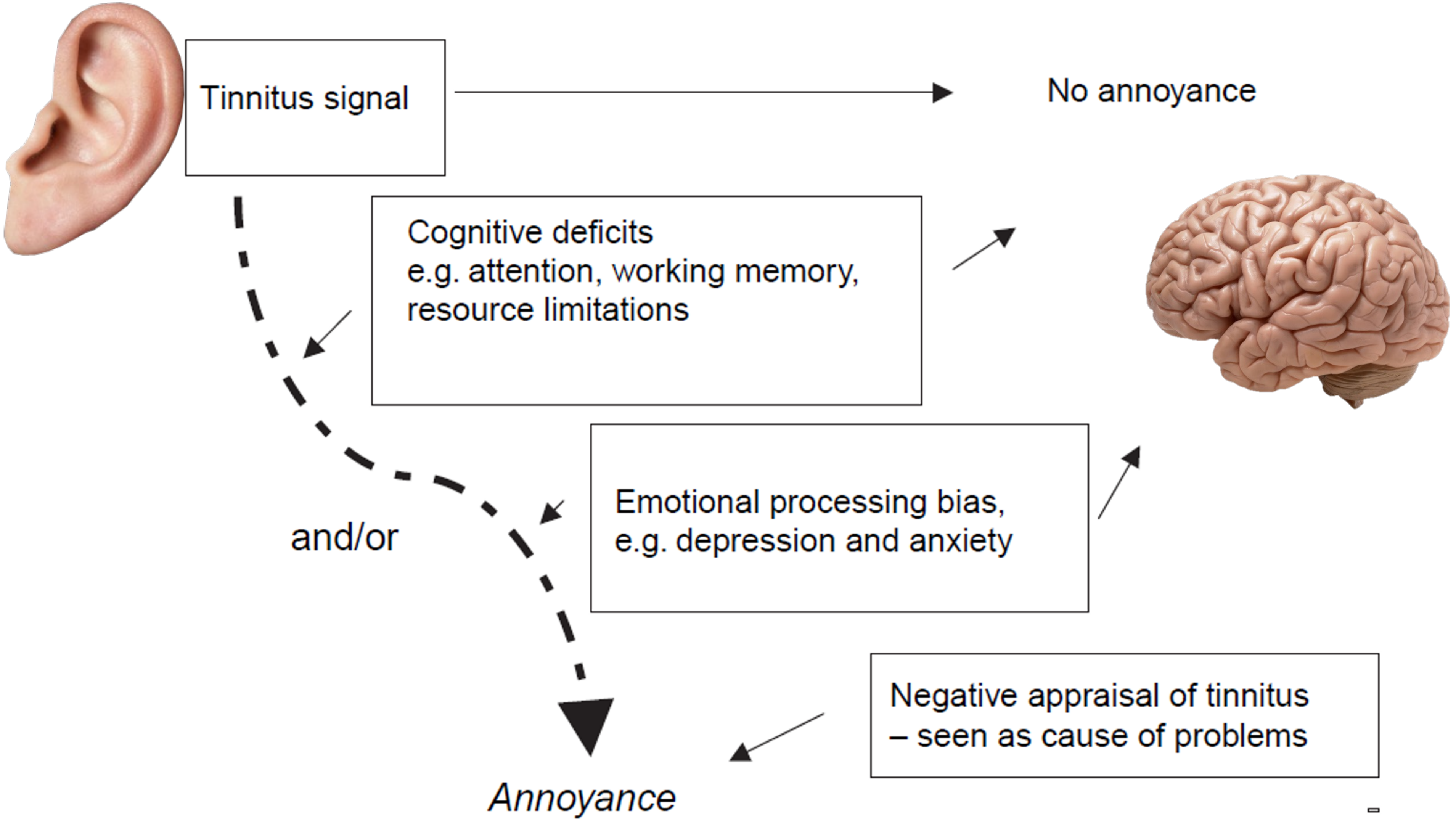
What happens when we deprive the ears of sound?

(Eggermont & Komiya, 2000; Norena & Eggermont, 2005)



Tinnitus and cognition

Andersson et McKenna (2006)



Can sensory deprivation be linked to a sound hypersensitivity?

Adaptive plasticity of loudness induced by chronic attenuation and enhancement of the acoustic background[a] (L)

C. Formby,[b] L. P. Sherlock, and S. L. Gold
Division of Otolaryngology—HNS and The University of Maryland Tinnitus and Hyperacusis Center, University of Maryland School of Medicine, Baltimore, Maryland 21201

Can we induce hyperacusis on those with normal hearing?

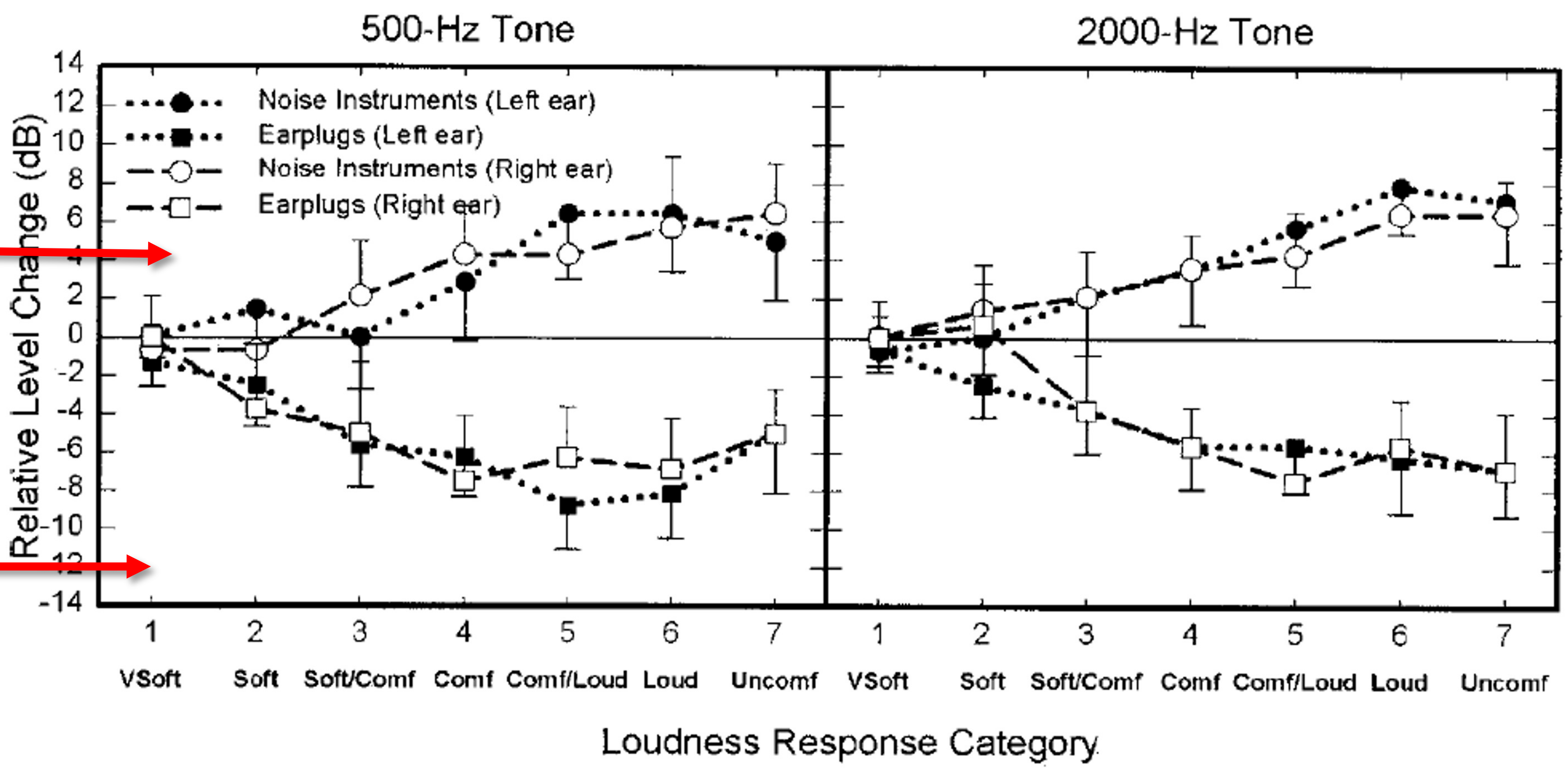
Earplug group (sensory deprivation)
vs.
Sound generator group

.... Intensity testing .... 2 weeks .... Intensity testing

A rescaling of intensity …

Generator effect using a sound that was 1-8 kHz at 50 dB HL

Earplug effect after 2 weeks of use (24h per day)



Key points:

1. Patients with hyperacusis or a hearing loss should avoid using ear plugs
2. Patients with hearing loss who purchase hearing aids for the first time will find amplification too loud in the beginning
3. Sound generators can be used to treat not only tinnitus but hyperacusis as well

Generally, the evidence suggests that stimulating the auditory system can inverse the effects of auditory deprivation

The challenges associated with tinnitus assessment and treatment

UdeM Assessment Protocol and Verification; other literature

How do we evaluate tinnitus?

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- Detailed case history
- Questionnaires on tinnitus and hyperacusis
- Tinnitus evaluation (i.e. pitch-, intensity-matching, IR)
- Hyperacusis evaluation (i.e. Cox test)

The challenges associated with tinnitus

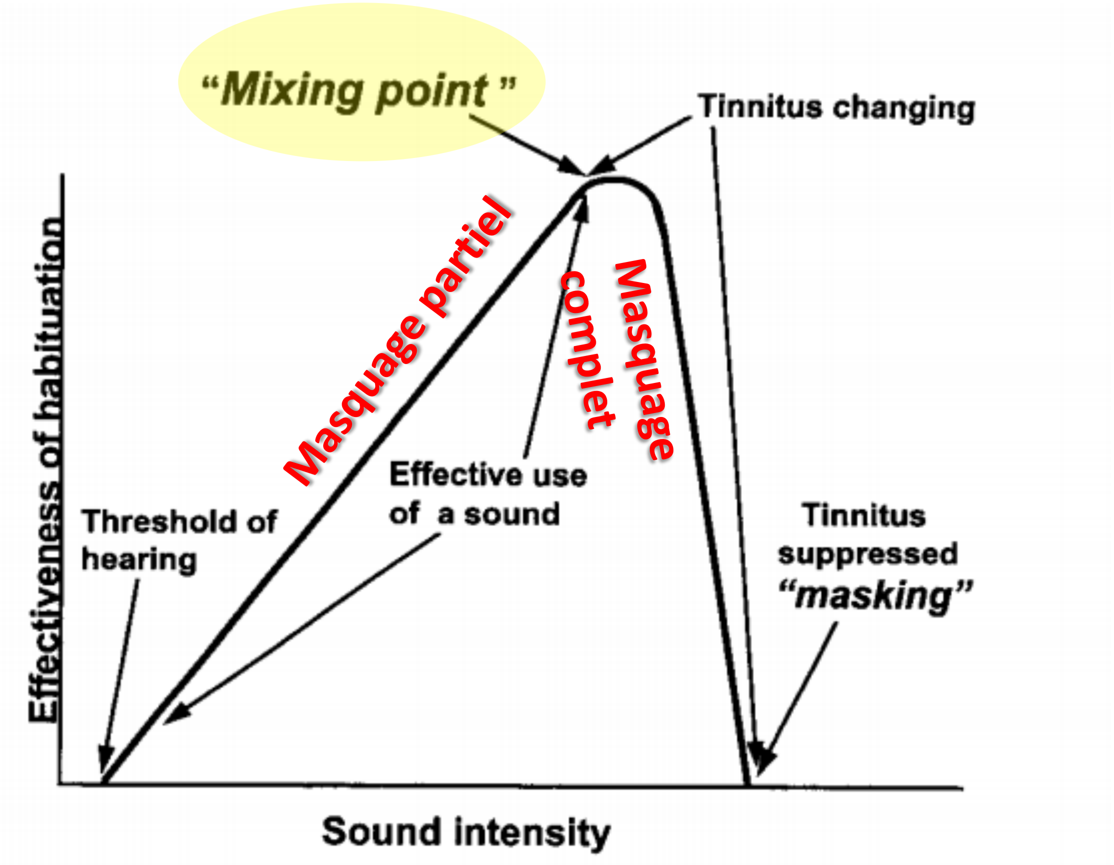
- **Requires patients respond to a stimulus**
- Limits tinnitus assessment among non-responsive patients:
  - Pediatric populations
  - Individuals with developmental/intellectual disabilities
- Risks influence by patient motivation, malingering, false reporting (i.e. insurance cases, compensation, lawsuits)
- There is no single pathophysiology

Hearing aids adjustments for tinnitus

- With or without amplification… presence of hearing loss?
- Width of the masker frequency band… multi-tonal tinnitus?
- Intensity level… the MML
- The masker center frequency … the tinnitus pitch-matched frequency

The Masking Level

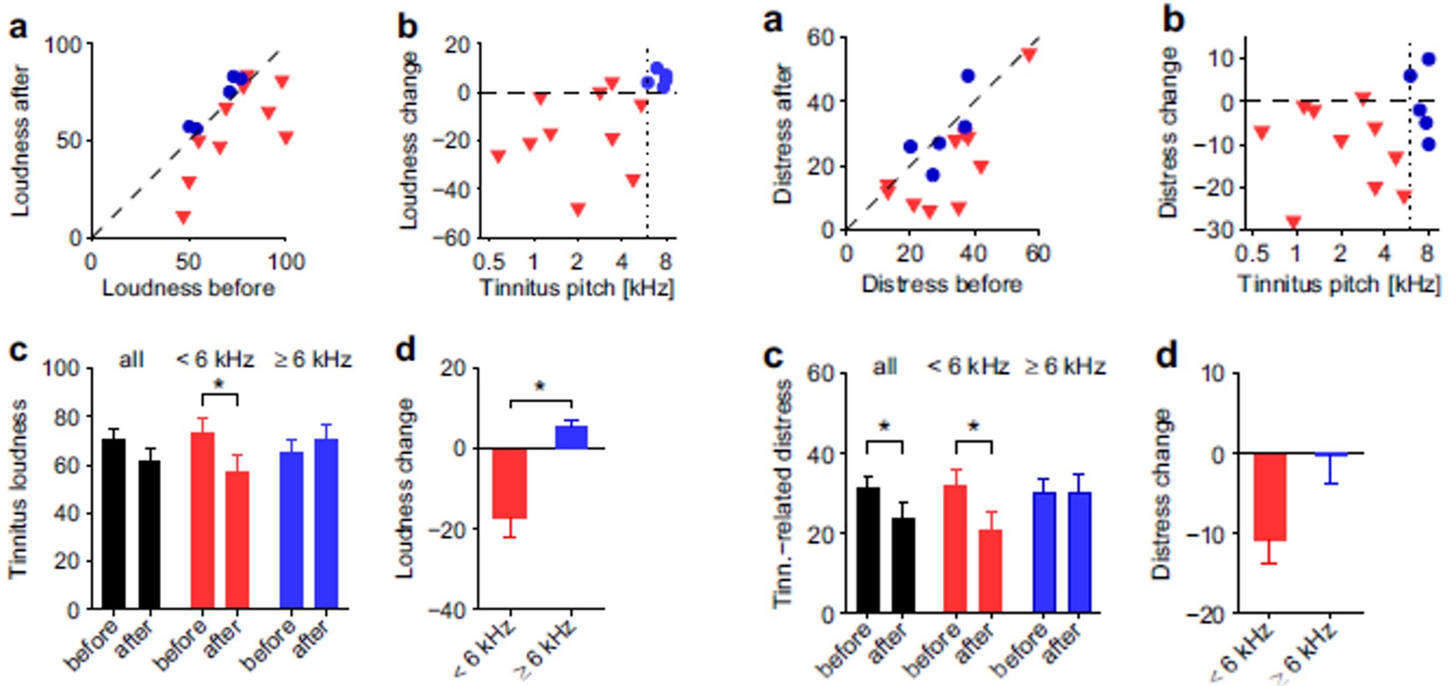
Jastreboff and Jastreboff (2000)



The pronosis?

Schaette, König, Hornig, Gross et Kempter (2010): The pitch of the noise generator matters

- Group 1: tinnitus ↓ 6kHz
  Group 2: tinnitus ↑ 6kHz
- Siemens Hearing aids and the Connexx software
- Patients adjusted their noise generators to the pitch of the tinnitus at a level just above hearing threshold
- 6 hour per day for 6 months



Current clinical practice vs. future?

Current methods used in clinic

- Validated questionnaires
- Intensity and Pitch-matching
- Residual inhibition testing
- Tinnitus-retraining therapy
- Sound generators
- Verification

Methods under investigation

- Use of EEGs as biomarkers for tinnitus
- The gap-prepulse inhibition acoustic startle reflex test

Clinical EEG tests: could they be a compliment to psychoacoustic measures?

Functional Problem	Questionnaire	Psychoacoustic measure	Clinical EEG tests

What is the “gap” paradigm?

Gap-prepulse inhibition

“Fill-in” hypothesis: Tinnitus can “fill” gaps?

- Tinnitus “fill-in” hypothesis (Turner et al. 2006)
- Gap Pre-Pulse Inhibition Acoustic Startle Reflex

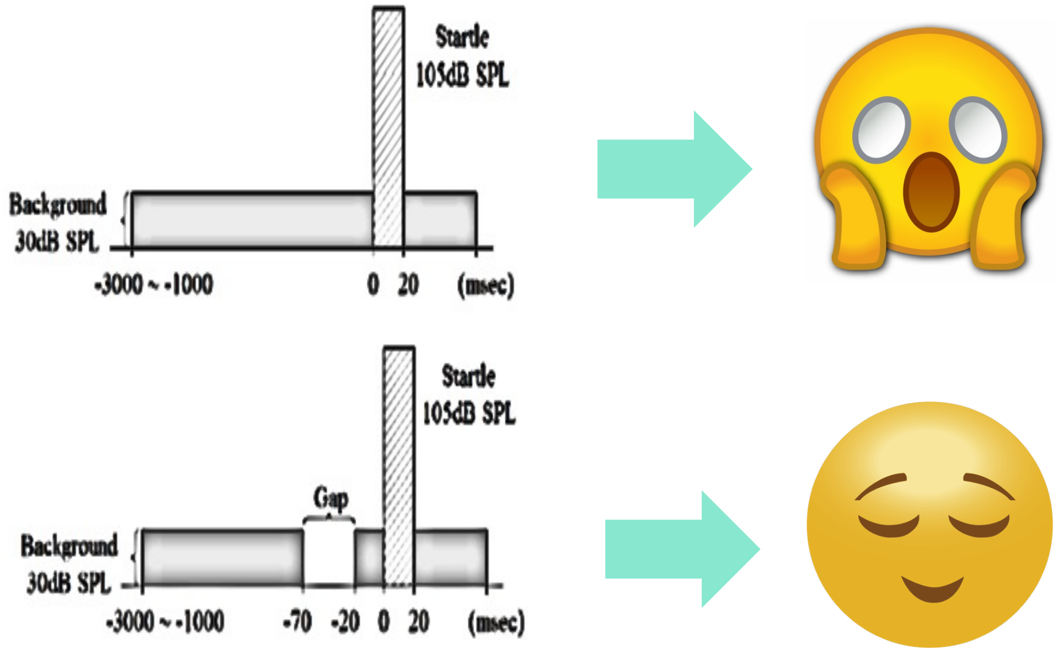


Image from Ku et al. (2014)

Behavioural Gap detection

Objective gap detection has been studied using the startle reflex:

- Turner et al. (2006), mice, ↓16 kHz
- Fournier and Hébert (2012), humans, ↓ HF and LF
- Berger (2017 and 2018), guinea pigs, ↓ HF

↓

Psychoacoustic gap detection in humans with tinnitus:

- Campolo, Lobarinas, & Salvi (2013), no difference
- Boyen, Baskent, & van Dijk (2015), no difference

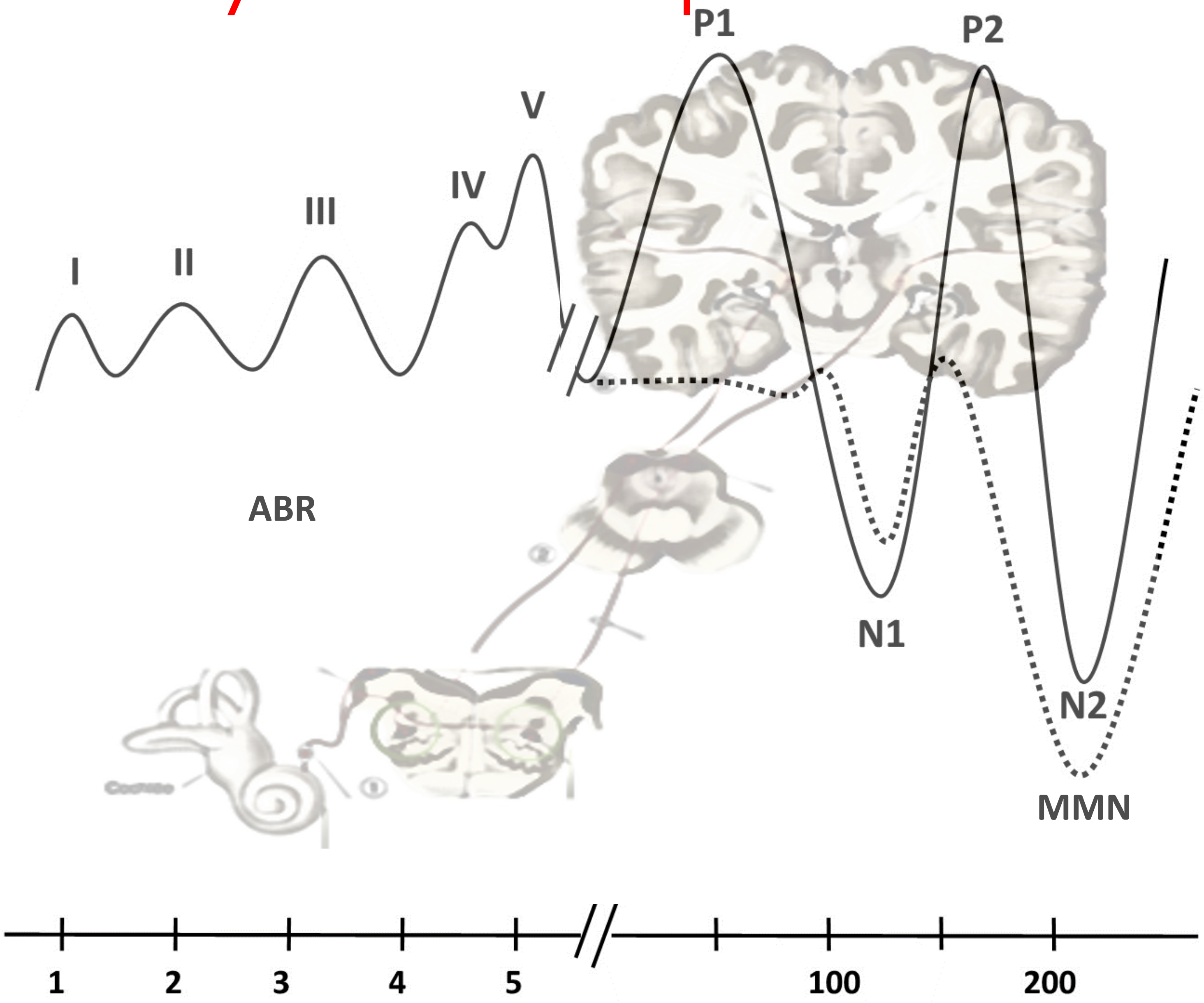
≠

How can electrophysiology be used to detect gaps?

ABR-gap study; MMN1, 2, 3; High-frequency-gap;

Scoping review on HL and EEG-gaps

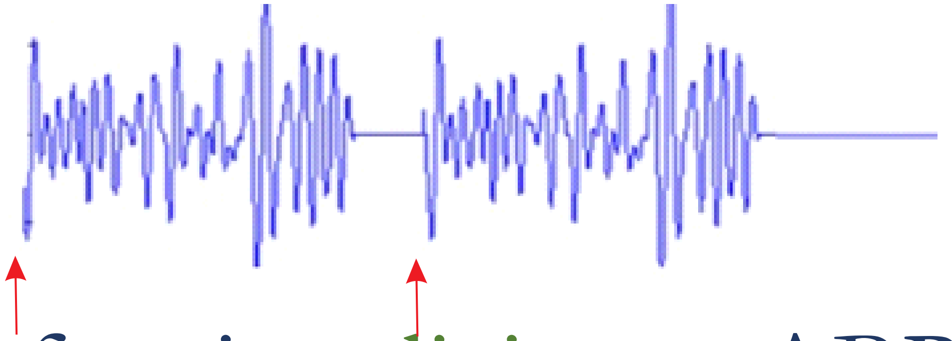
Auditory evoked potentials



Tracé moyen

Tracé de différence

Can we detect the presence of a gap using the ABR?

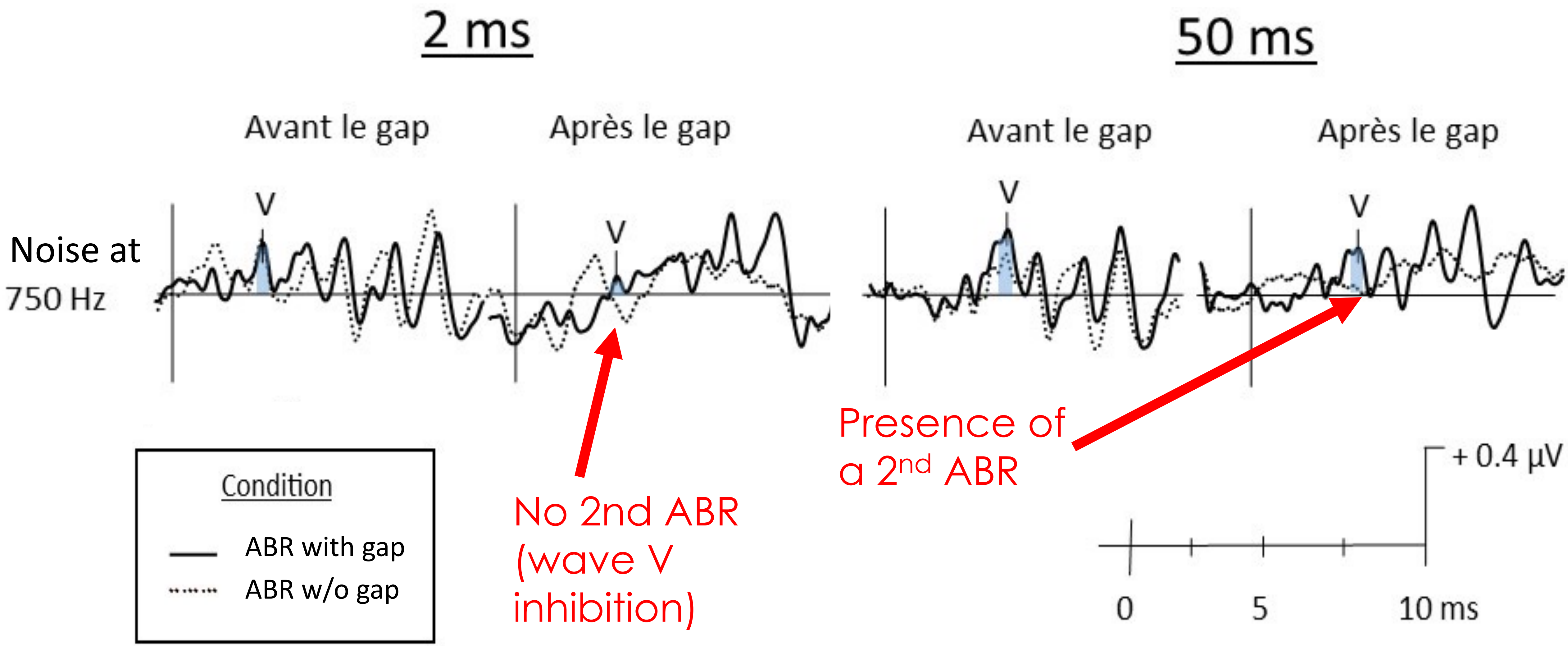


(1) The onset of noise elicits an ABR

(2) After a period of silence, the 2nd noise onset elicits a second ABR, *if the gap is detected by the auditory system*

Duda-Milloy et al. (2019), *Canadian Acoustics*

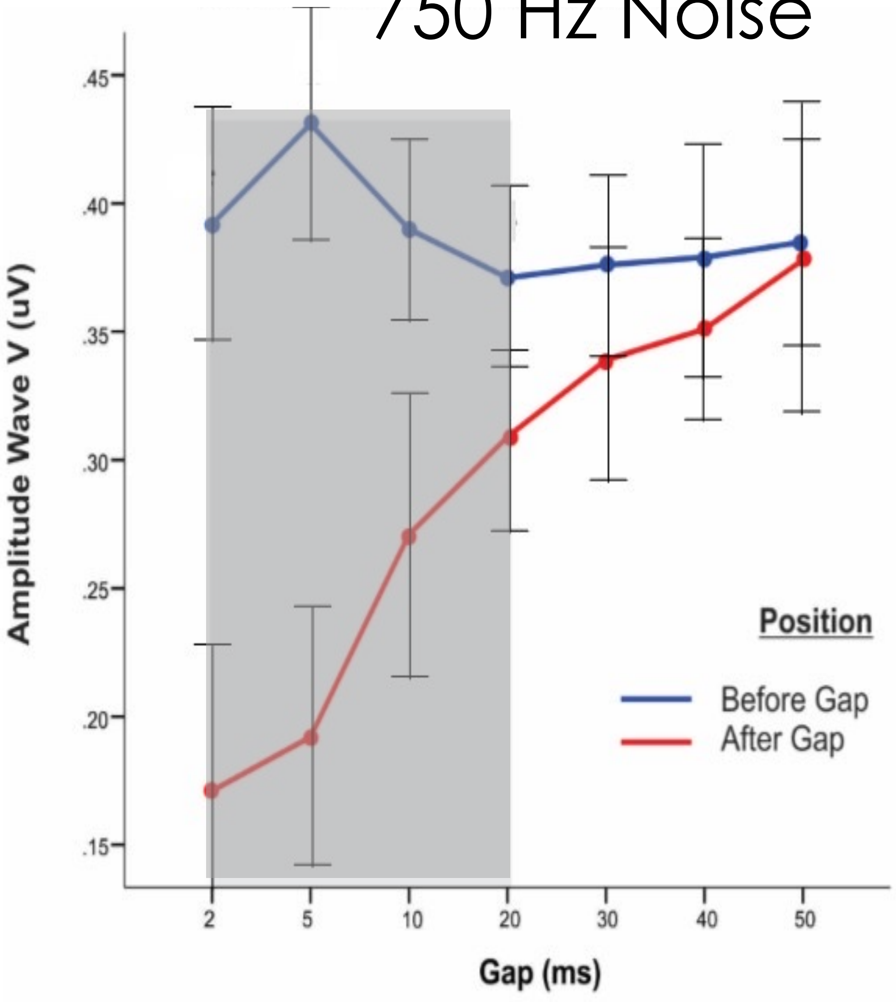
For long gaps, we can observe a second ABR



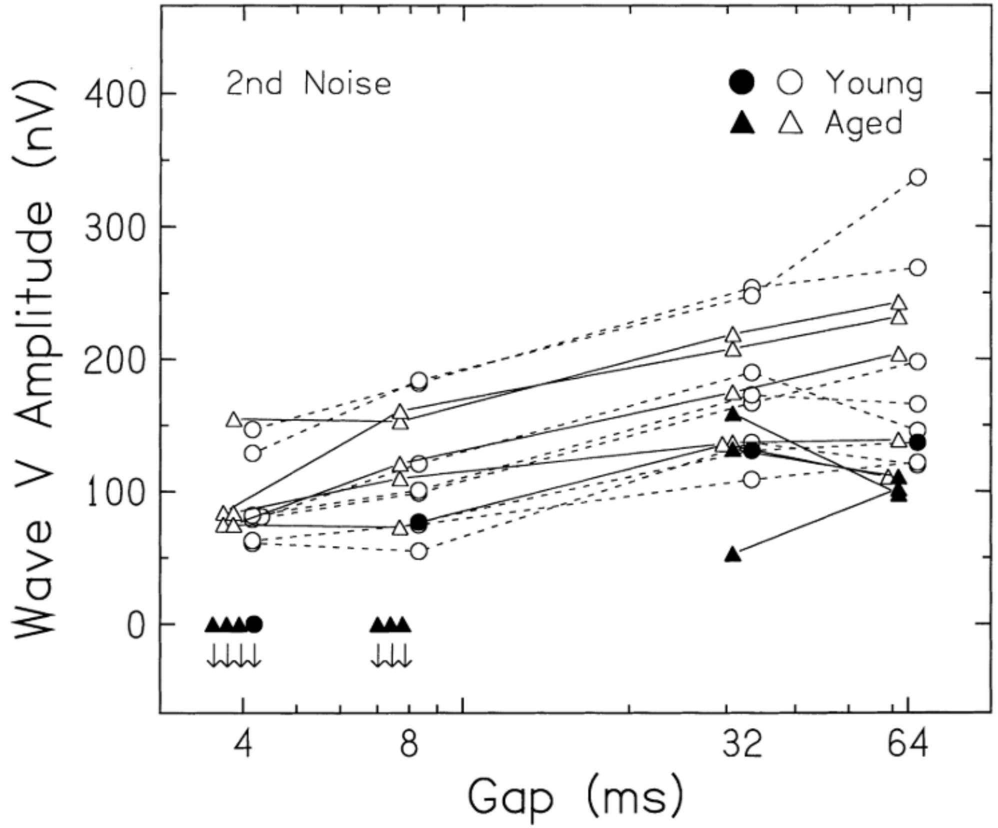
Duda-Milloy et al. (2019), *Canadian Acoustics*

We observe wave V for variable durations as a function of frequency

750 Hz Noise



Same tendencies as with wide band noise (Poth et al. 2001)

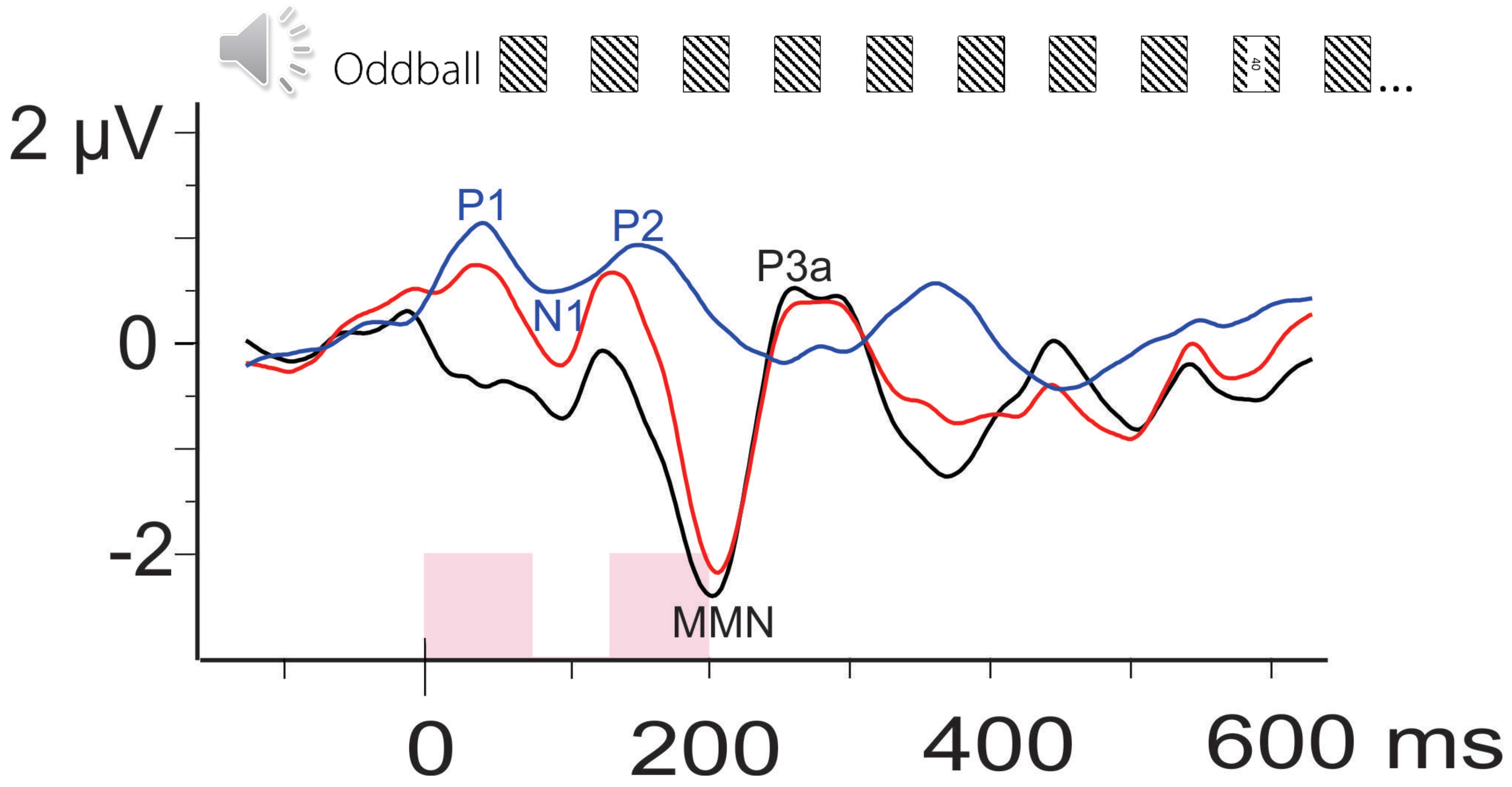


Conclusion: gap-ABR

- The gap-ABR works for gaps 30 ms or larger
- But, 5 or 10 ms gaps are less clear

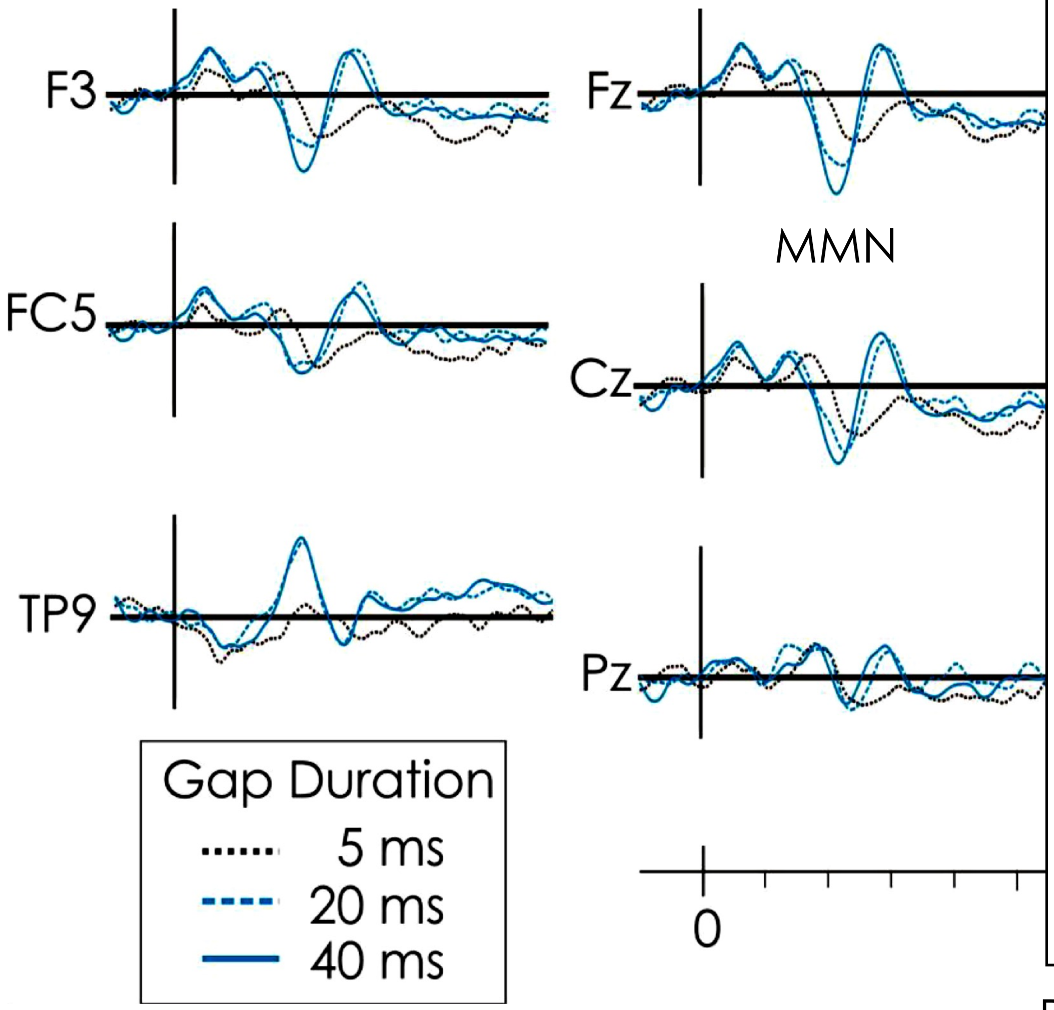
Duda-Milloy et al. (2019), *Canadian Acoustics*

Oddball paradigm: the classic

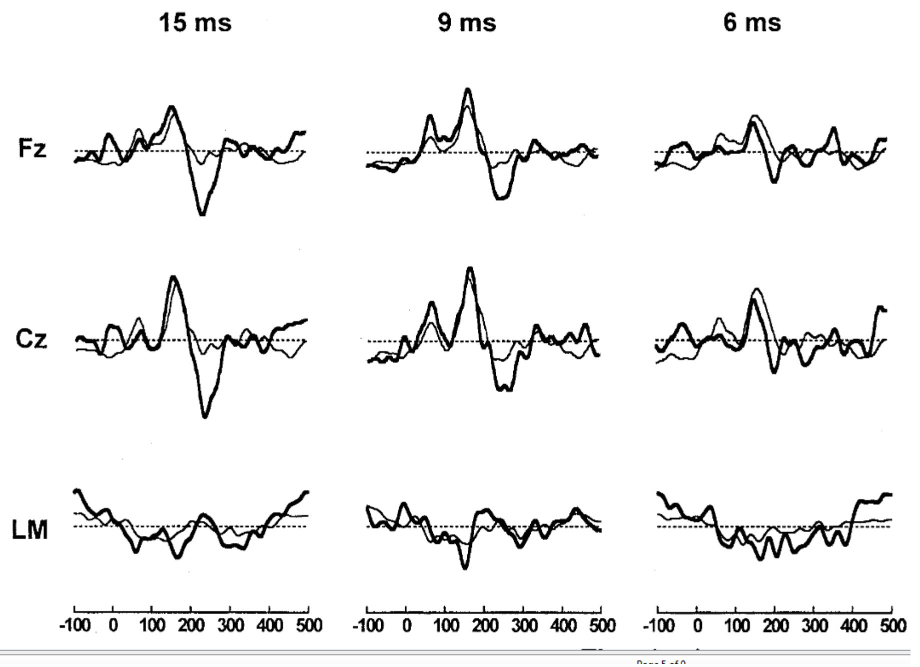


Duda-Milloy et al. (2019), *Hearing Research*

Can the MMN be used to detect gaps? Yes!

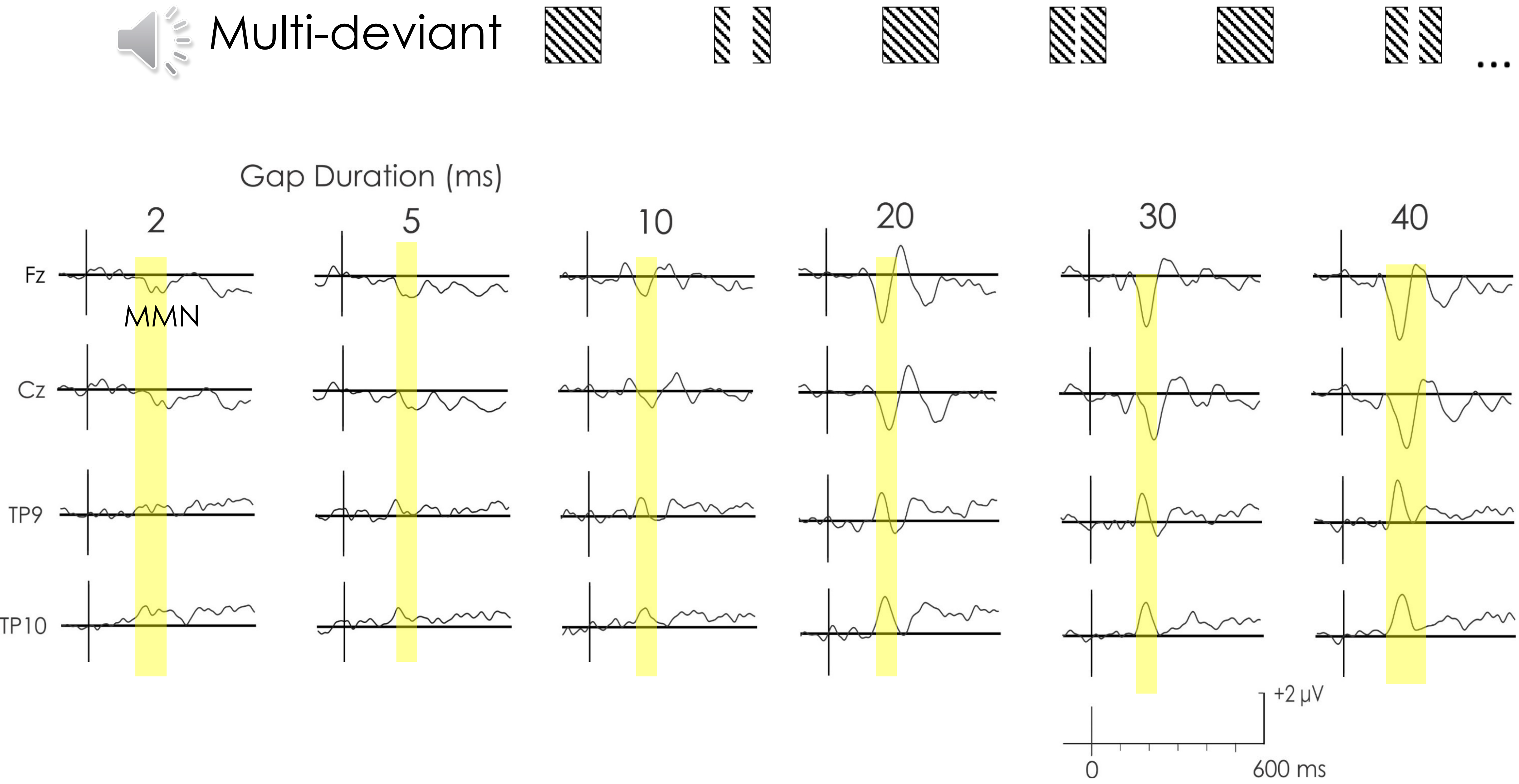


MMN-oddball reproduced in Bertoli et al. 2001!



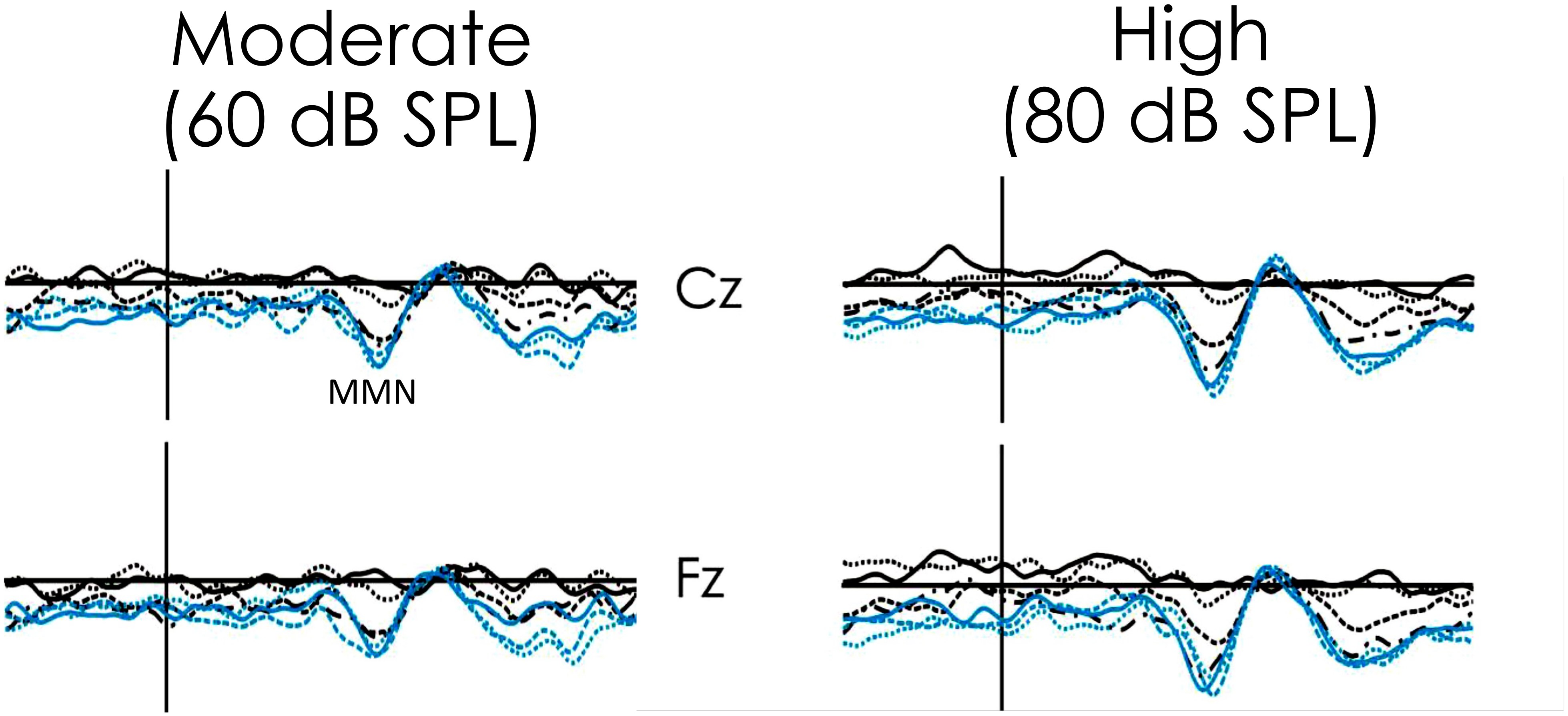
Duda-Milloy et al. (2019), *Hearing Research*

Multi-deviant



Duda-Milloy et al. (2019), *Hearing Research*

Yes! Intensity effects…



Duda et al. (2020), Brain Research

<u>In summary</u>: The MMN is an evoked potential that is sensitive to detecting gaps in various carrier signals:

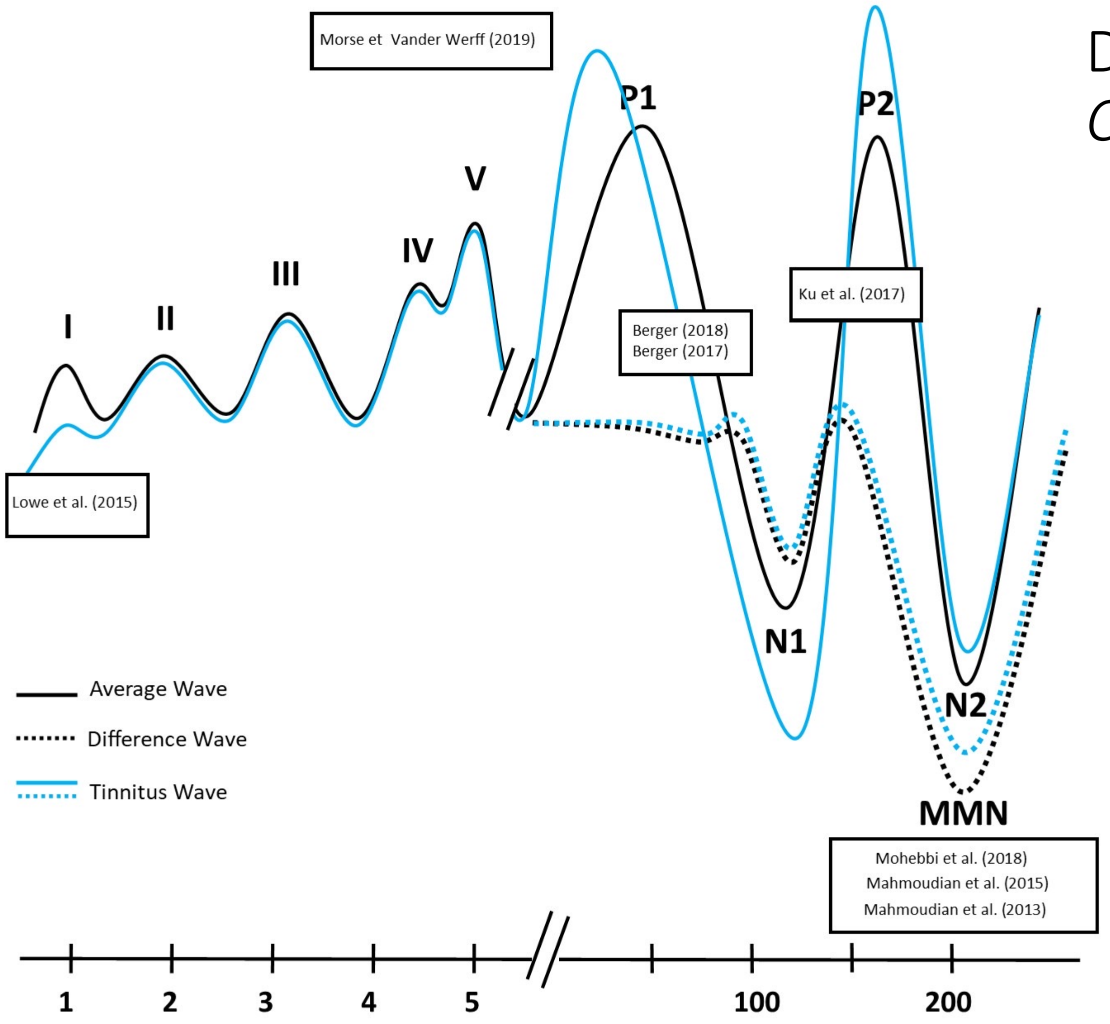
- Using the multi-deviant paradigm (~30 minutes)
- For gap durations of 2 ms (subthreshold) to 40 ms: monotonic pattern
- Can reflect psychophysical performance (detects anormalities)
- Using noise bursts, pure tones, clicks, and using phonemes
- From low to high intensities
- Even in moderate to high background noise intensities

This offers a rich tool for testing the central auditory system

How is the EEG gap-detection protocol used to detect tinnitus?

Scoping review on EEG and tinnitus, N1-gap study

Do other studies show EEG-gaps change in tinnitus? Yes.



Duda, Scully, Baillargeon, Hébert, *Clinics (2020)*

Can the N1 be used to detect tinnitus using pitch- and intensity-matched gapped stimuli?

Victoria Duda, Brandon Paul, Charlotte Bigras, Olivia Scully, Boutheina Jemel, Sylvie Hébert





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Toronto Metropolitan University

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Duda et al. (in preparation)

Objective

- Determine whether the N1 changes for 20 ms gaps (silent periods) when the stimulus is matched in intensity and frequency to tinnitus.
  - What is the effect of the gap?
  - What is the effect of pitch/frequency?

Duda et al. (in preparation)

Design

- 15 tinnitus participants and 15 non-tinnitus controls (matched by audiogram, age and sex)

- Three conditions:
    1) Below tinnitus pitch ↓ T
    2) At tinnitus pitch = T
    3) Above tinnitus pitch ↑ T

Duda et al. (in preparation)

Procedure

Tinnitus
n=15

Non-tinnitus
Controls
n=15

Pre-assessment

1- Standard audiogram
2- High frequency audiometry

Tinnitus Psychoacoustic Tests

1- Tinnitus questionnaire (THI)
2- "Tinnometer" (pitch-matching)
3- "Tinnitus maker" (intensity-matching)

EEG-Gap Test

Using stimulus matched to tinnitus pitch (-T, T or +T)

Duda et al. (in preparation)

What does all this mean?

- We are working on new methods that target gap-EEG alterations
- These new methods could become future treatments for people with atypical hearing abnormalities that are not detected in a conventional audiogram
- These methods would potentially divide the population between those who benefit from hearing aids and auditory therapies, such as tDCs, pharmacological treatments, or other forms of aural rehabilitation. The gap-EEG could therefore provide sound objective information on the progress of such treatments.

Future directions in EEGs and tinnitus

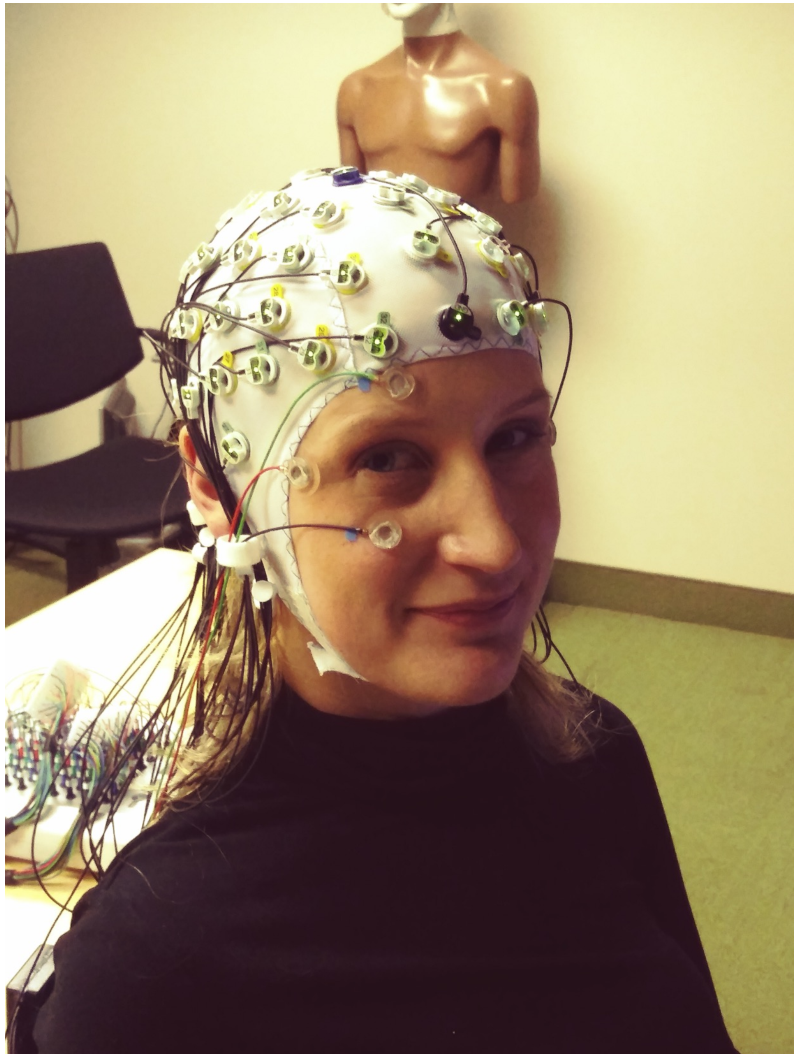
Neurofeedback and EEG-hearing aids

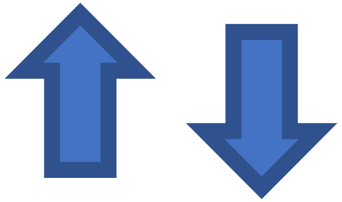
Neurofeedback and tinnitus (Güntensperger et al., 2017)

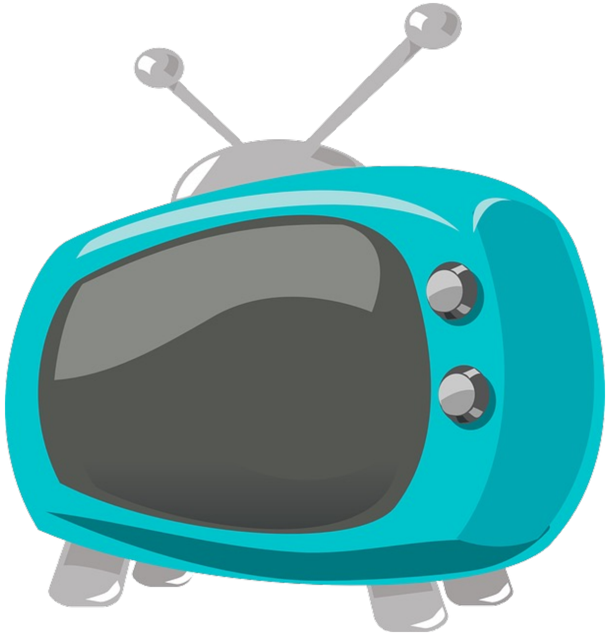
Authors	Tinnitus patients	Neurofeedback	Electrodes/Sources	Feedback	Behavioral findings	Neuronal findings
Crocetti et al., 2011	$N = 15$	α↑ δ↓ 12 sessions	F3, F4, Fc1, Fc2	Plane moving up and down (with audio-visual reinforcement)	Distress ↓ Loudness ↓	α/δ-ratio ↑ (not all participants were able to manipulate α and δ successfully)
Dohrmann et al., 2007a,b	Group 1 ($n = 11$) Group 2 ($n = 5$) Group 3 ($n = 5$) Controls ($n = 27$)	Group 1: α↑ δ↓ Group 2: α↑ Group 3: δ↓ Control: FDT 10 sessions	F3, F4, Fc1, Fc2	Fish moving up and down	All groups: Distress ↓ Loudness↓ Group 1: strongest relief Controls: no reduction	All groups: α↑ and δ↓ Correlation with decrease in loudness
Gosepath et al., 2001	$N = 40$ Controls ($n = 15$)	α↑ β↓ 15 sessions	P4	Auditory and visual (not further explained)	Distress ↓	Group 1 ($n = 24$): α↑ Group 2 ($n = 16$): β↓ Controls: no effect
Hartmann et al., 2013	$N = 8$ Controls ($n = 9$)	α↑ 10 sessions Controls: rTMS	Source space projection on two temporal sources	Smiley	Distress ↓ Controls: no reductions	α↑ estimated over r PAC
Schenk et al., 2005	Group 1 ($n = 23$) Group 2 ($n = 13$)	Group 1: α↑ Group 2: β↓ Group 3: α↑ β↓	Group 1: P4 Group 2: C3	Floating ball and melody	Distress ↓	Both groups: α↑
Vanneste et al., 2016	Group 1 ($n = 23$) Controls 1 ($n = 17$) Controls 2 ($n = 22$)	Group 1: α↑ β↓ γ↓ 15 sessions Controls 1: α↑ β↓ γ↓ Controls 2: passive	sLORETA Group 1: PCC Controls 1: LG	Green bar moving up and down	Group 1: distress ↓ Controls: no reduction	No alterations in target areas for α, β and γ Changes in functional and effectivity connectivity
Weiler et al., 2002	$N = 1$	α↑ β↑ δ↑ θ↑	19 electrodes	Varying	Depression ↓ Anxiety ↓ Tinnitus ↓	No analysis

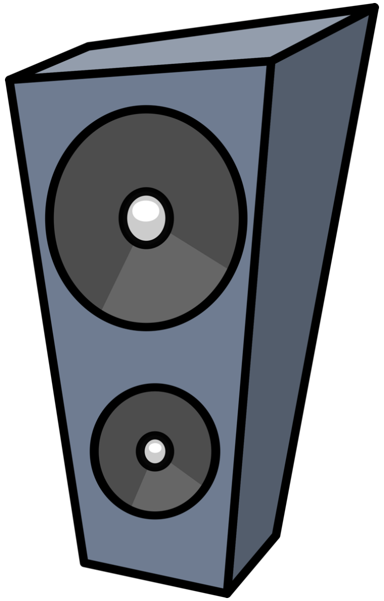
↑, increase; ↓, decrease; r PAC, right primary auditory cortex; PCC, posterior cingulate cortex; LG, lingual gyrus.

Future clinical practice?

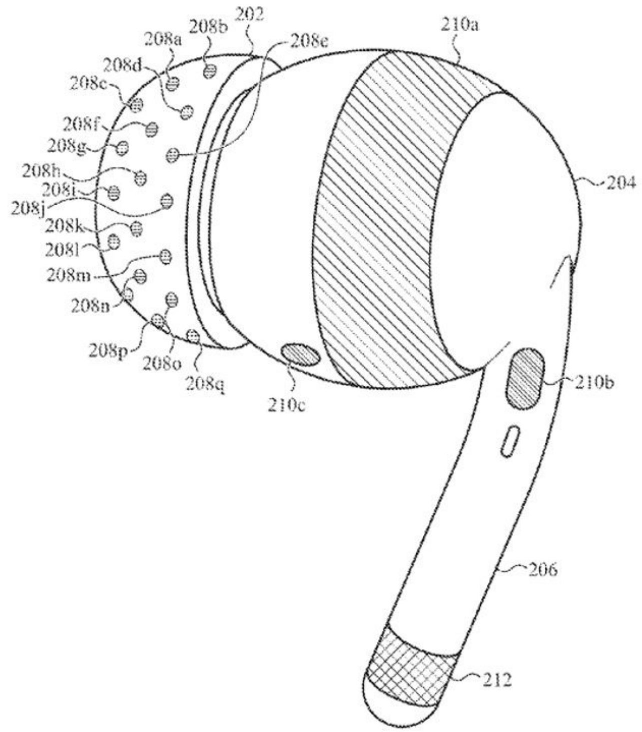


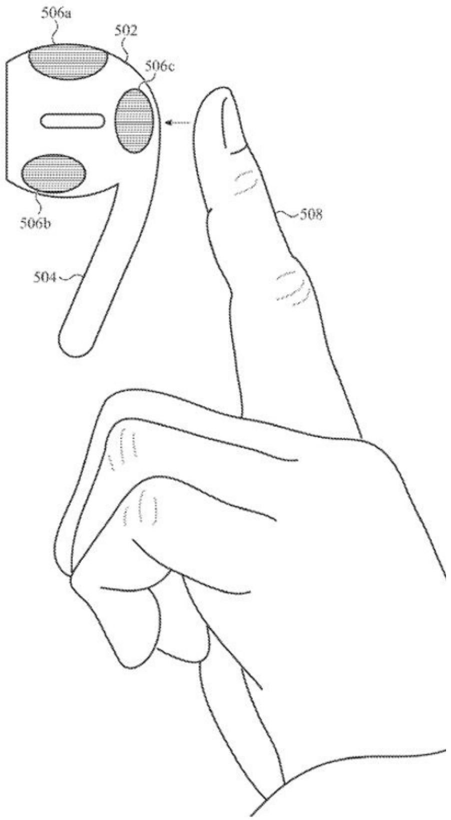






What this might mean in the advent of hearables…





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(12) **Patent Application Publication**
Azemi et al.

(10) **Pub. No.: US 2023/0225659 A1**
(43) **Pub. Date: Jul. 20, 2023**

(54) **BIOSIGNAL SENSING DEVICE USING DYNAMIC SELECTION OF ELECTRODES**

(71) Applicant: **Apple Inc.**, Cupertino, CA (US)

(72) Inventors: **Erdrin Azemi**, San Mateo, CA (US); **Ali Moin**, San Mateo, CA (US); **Anuranjini Pragada**, Cupertino, CA (US); **Jean Hsiang-Chun Lu**, Sunnyvale, CA (US); **Victoria M. Powell**, San Francisco, CA (US); **Juri Minxha**, Seattle, WA (US); **Steven P. Hotelling**, Los Gatos, CA (US)

(21) Appl. No.: **18/094,841**

(22) Filed: **Jan. 9, 2023**

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(57) **ABSTRACT**

A wearable electronic device includes a housing, and an electrode carrier attached to the housing and having a nonplanar surface. The wearable electronic device includes a set of electrodes, including electrodes positioned at different locations on the nonplanar surface. The wearable electronic device includes a sensor circuit and a switching circuit. The switching circuit is operable to electrically connect a number of different subsets of one or more electrodes in the set of electrodes to the sensor circuit.

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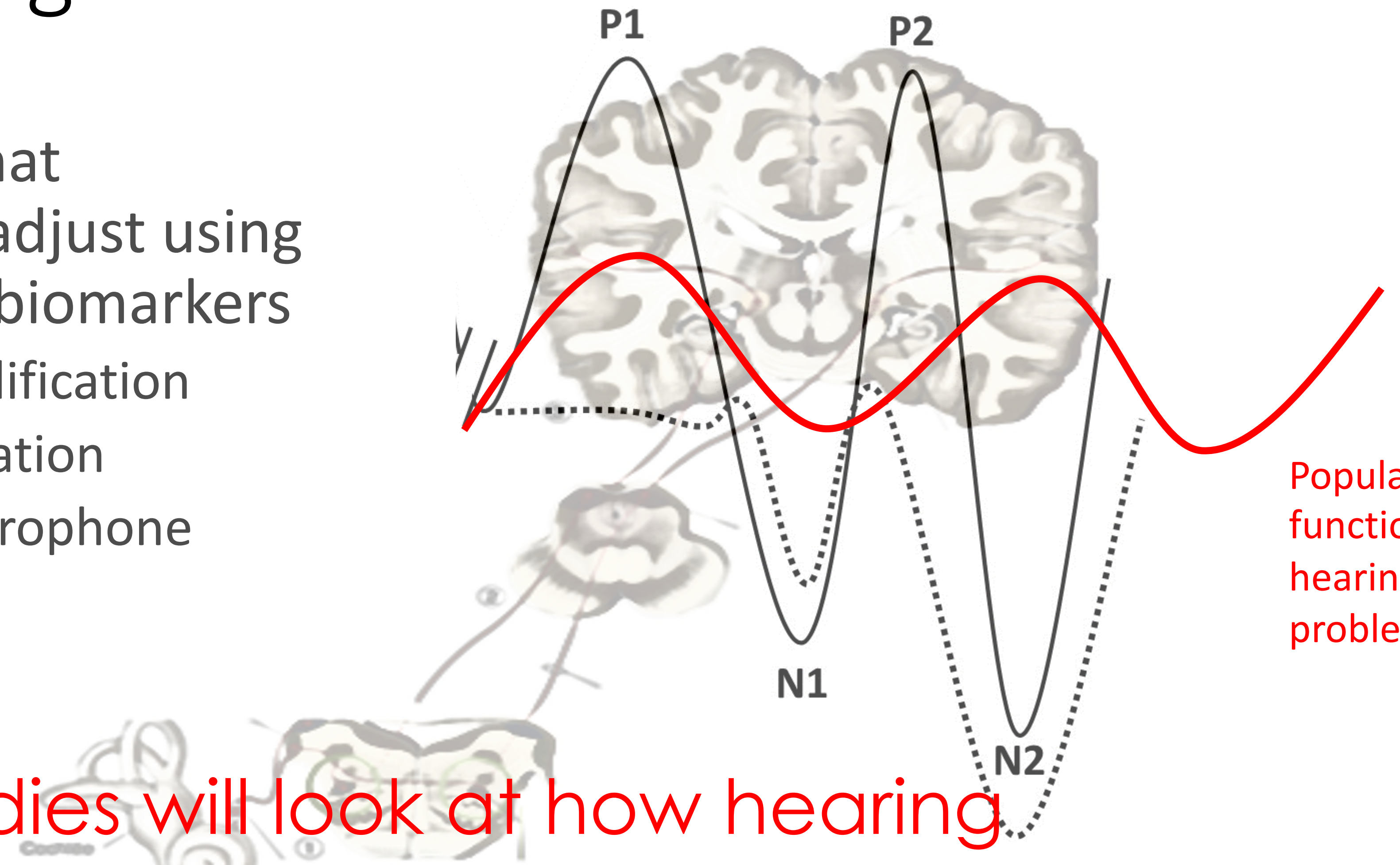
EEG-hearing aids…

- Hearing aids that automatically adjust using EEG signals as biomarkers
    - Intensity modification
    - Pitch modification
    - Changing microphone sensitivity?



Populations with functional hearing problems?

Next studies will look at how hearing aids modify the EEG-gap response.

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