In Search of Hidden Hearing Loss — Evidence and Diagnosis

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Learning Objectives

1. Physiological changes underlying noise-induced “hidden hearing loss”

2. The rationale behind recent attempts to improve audiology diagnostic methods

3. Currently available clinical measures that might improve diagnostic sensitivity

A Day in the Clinic

1. Jack is a retired engineer with moderate hearing loss. He wears a hearing aid sometimes but does remarkably well without his aid. He only has trouble when it's noisy.

2. Carol has the same amount of hearing loss but struggles to hear in the best of situations.

3. Marianne is a teacher. She has **normal hearing thresholds** but insists that her hearing has been getting worse in the last few years. She struggles to understand what the kids are saying.

Suprathreshold Loss

- Hearing problems can be:
  1. **disproportionate to hearing loss or**
  2. **present with normal thresholds!**

  (Grant et al., Ear Hear, 2013, Plomp, J Speech Hear Res 1986, Strelcyk & Dau, 2009)

- In the elderly we might call this "central presbycusis" — but it is central?

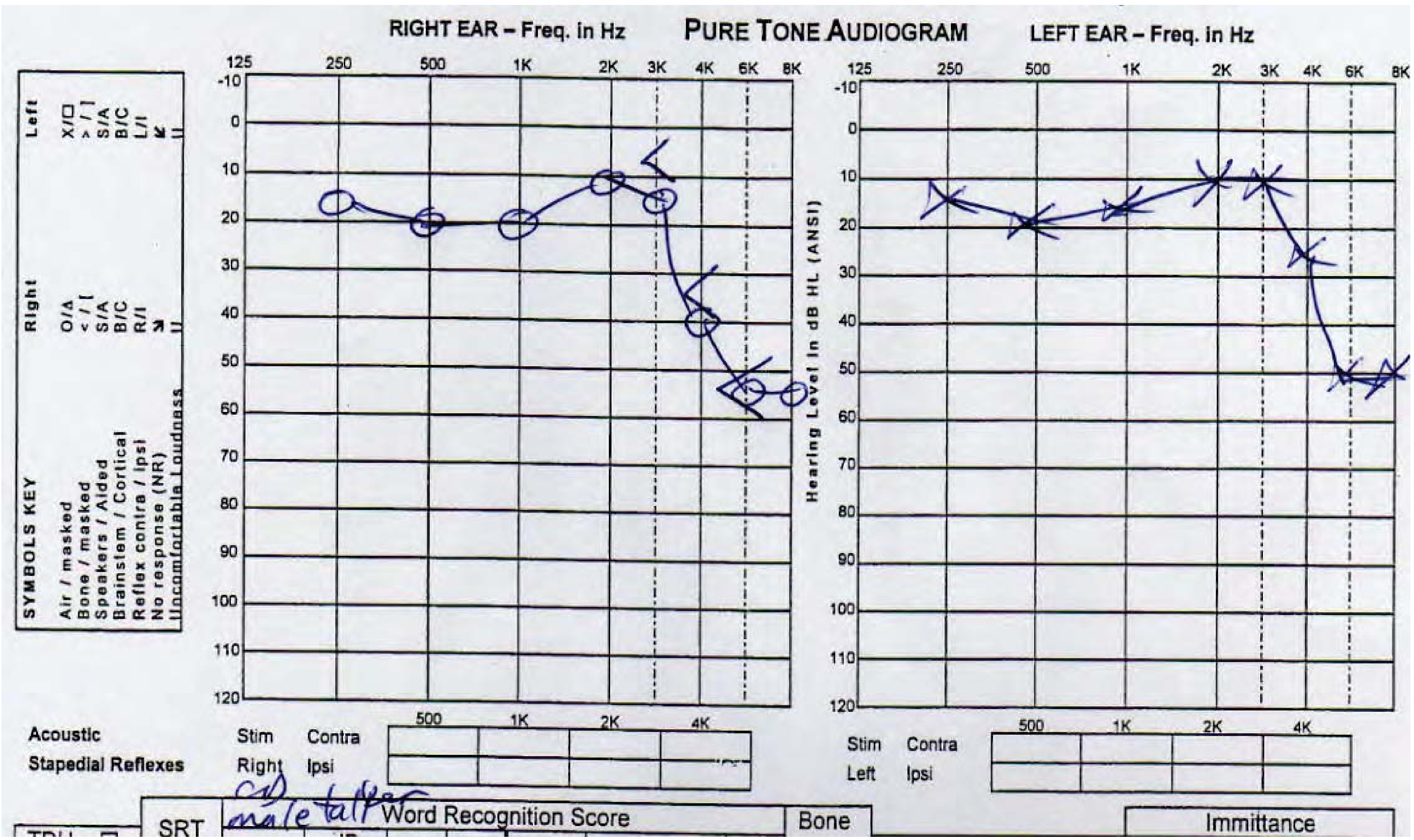
  (Humes et al., J Am Acad Audiol, 2012)

- In children we might call this (c)APD, but is it central?

  (Canadian APD Guideline, CISG, 2012)

How do we approach it?

- Measure thresholds—is a hearing aid warranted?
- But what is going on 'under the hood'?



The Missing Piece

e·ti·ol·o·gy

/ˌēdēˈäləjē/

noun

1. MEDICINE

   the cause, set of causes, or manner of causation of a disease or condition.

   "a disease of unknown etiology"

- prognosis
  - will this get worse?
  - does this entail poorer cognition?
- prevention
  - is this due to something that could be prevented e.g,. noise exposure? toxicity?
- treatment
  - a treatment could be developed to prevent further damage

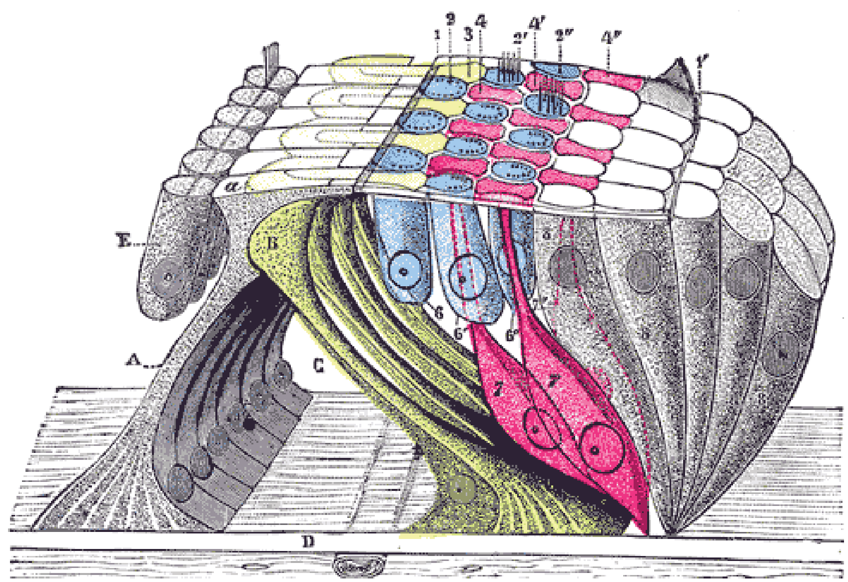
What Happens with Noise Exposure?

- Levels below about 80 dB SPL are considered safe or "Effective quiet"
  - above this level, threshold may shift as a function of intensity and duration—even @ 85 dBA (Seixas et al., 2012)
  - this is proportional to the log of exposure time

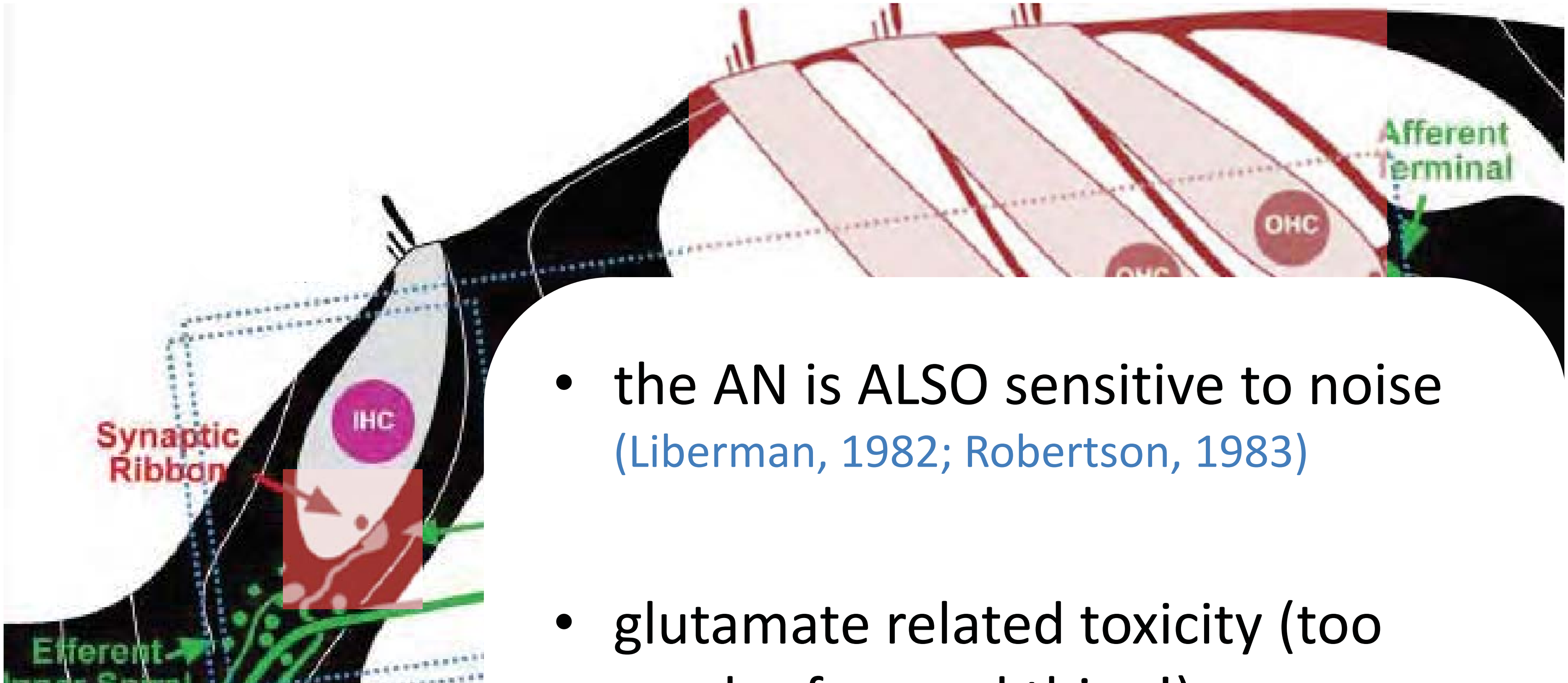
- Greatest for a particular neuron when the sound is one half-octave below it's characteristic frequency
  - damage tends to occur in higher frequency regions of the cochlea

What is really happening?

- **Temporary threshold shift is mainly <u>outer hair cell damage</u>**
  - IHCs are relatively insensitive to noise
  - hearing comes back with repair of the stereocilia and the tectorial membrane (Wang et al., 2011)
  - takes about 1000 minutes (16-17 hours); but variable
  - we can see this by measuring OAEs



This is only PART of the Picture



- the AN is ALSO sensitive to noise
  (Liberman, 1982; Robertson, 1983)

- glutamate related toxicity (too much of a good thin
  (Pujol et al., 1993; Sun et
  Oestreicher et al., 2002; P
  Ruel et al., 2007)

A Startling Finding in 2009

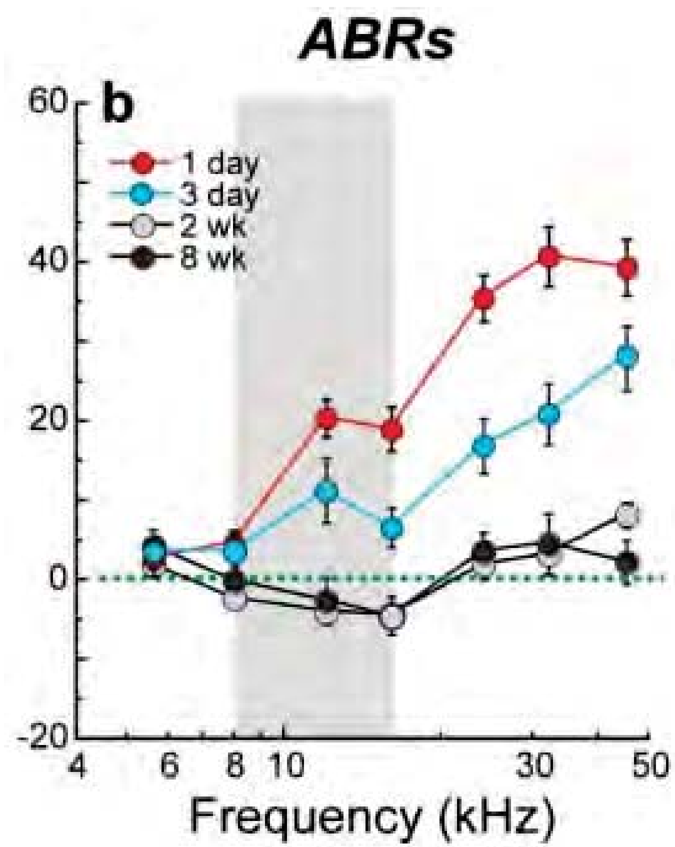
- A mouse walks into a bar...

A Startling Finding in 2009

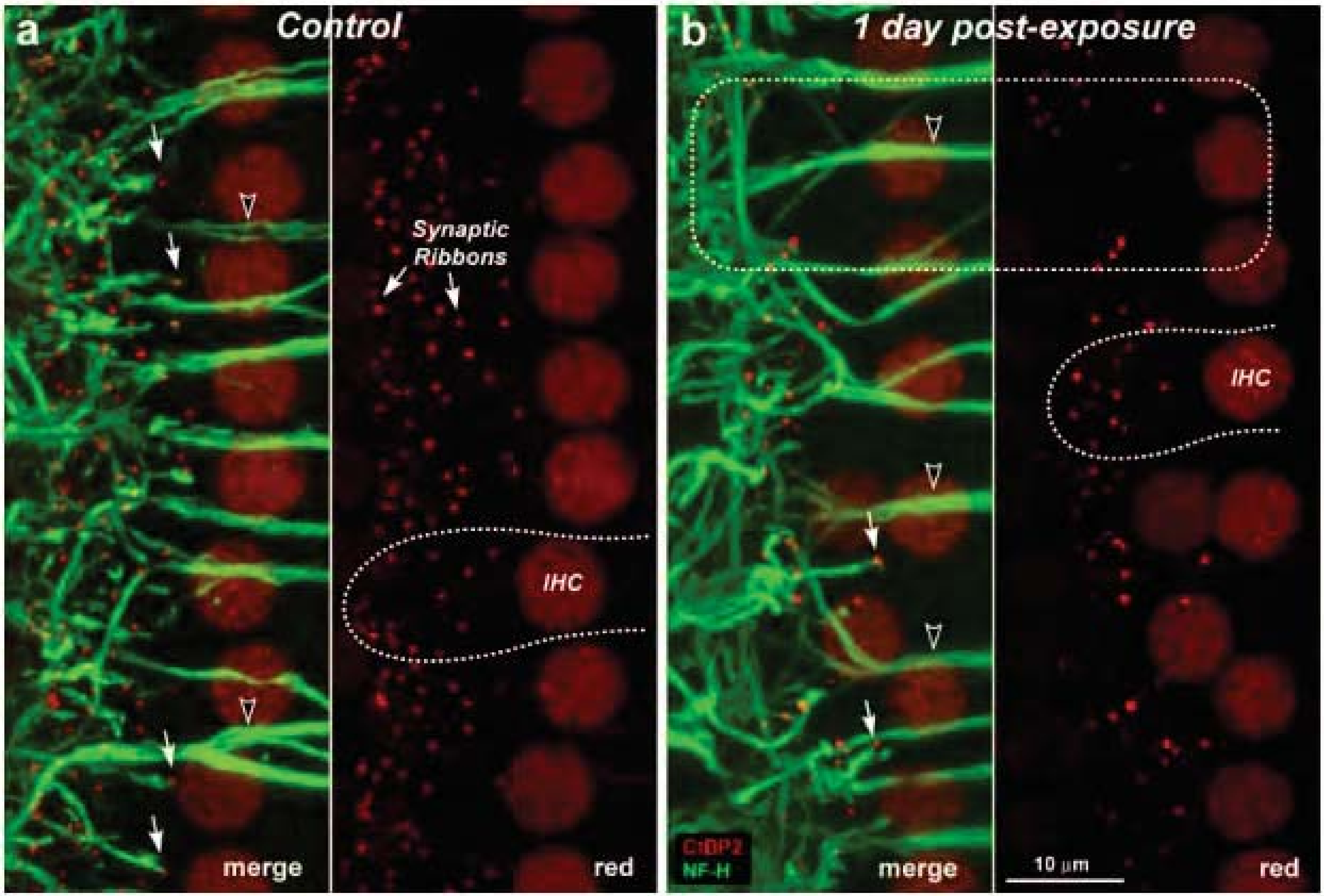
- Liberman and Kujawa exposed mice to moderate levels of noise… just enough to induce a TEMPORARY threshold shift
  - 100 dB SPL for 2 hours

- thresholds returned to

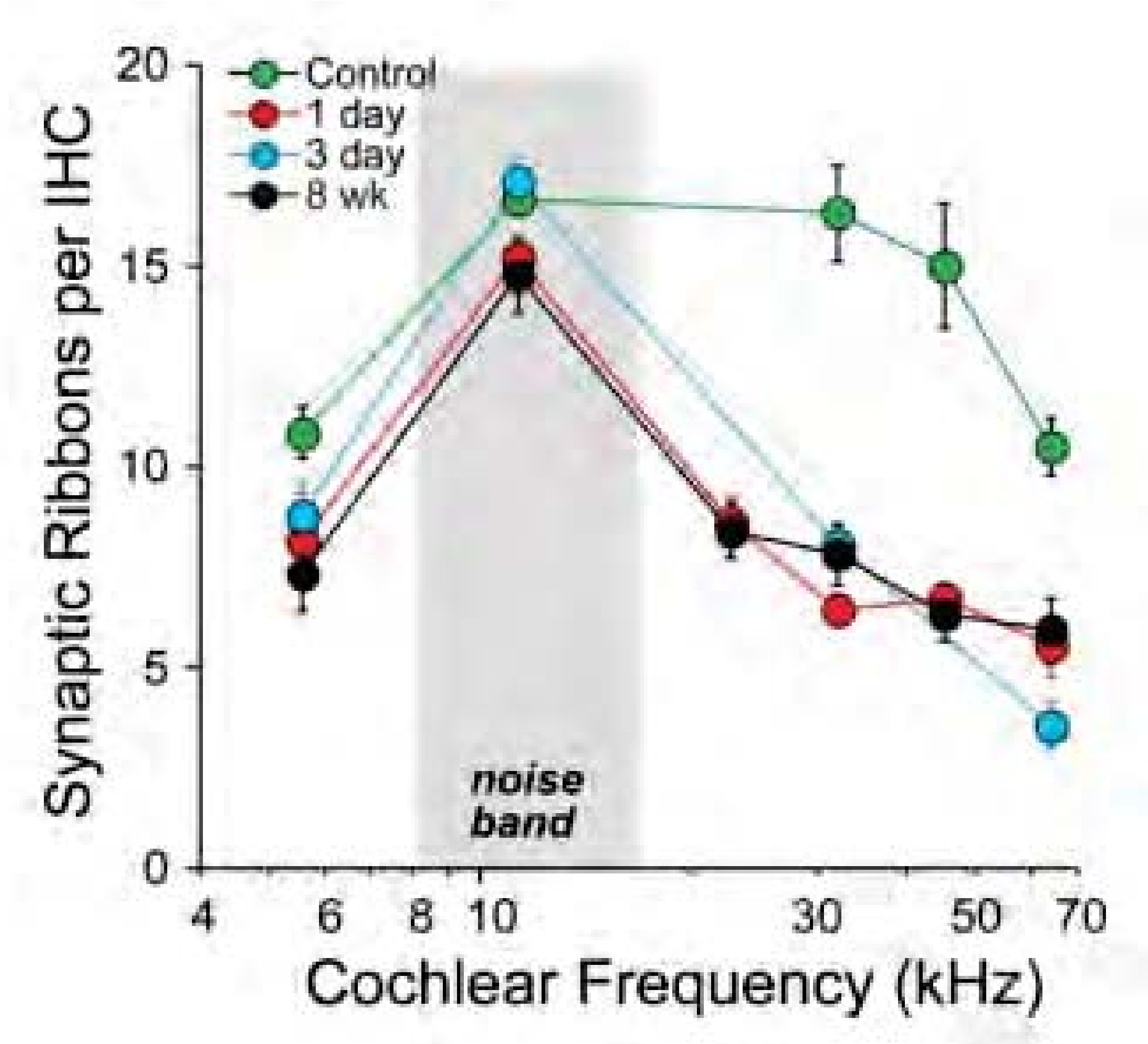
normal as expected



Staining to Show IHCs and Synaptic Ribbons



Do the synapses come back?



A Mechanism for Hidden Hearing Loss

- thresholds returned to normal; synapses did not
- this damage was **permanent**
  (Kujawa et al., 2009; Lin et al., 2011; Liu et al., 2012; Shi et al., 2013)
- this damage was followed by a delayed loss of auditory nerve fibres
  (Kujawa et al., 2009; Kujawa et al., 2015; Liberman et al., 2015; Lin et al., 2011)

In what sense did these mice have “normal hearing”??

Hidden Hearing Loss

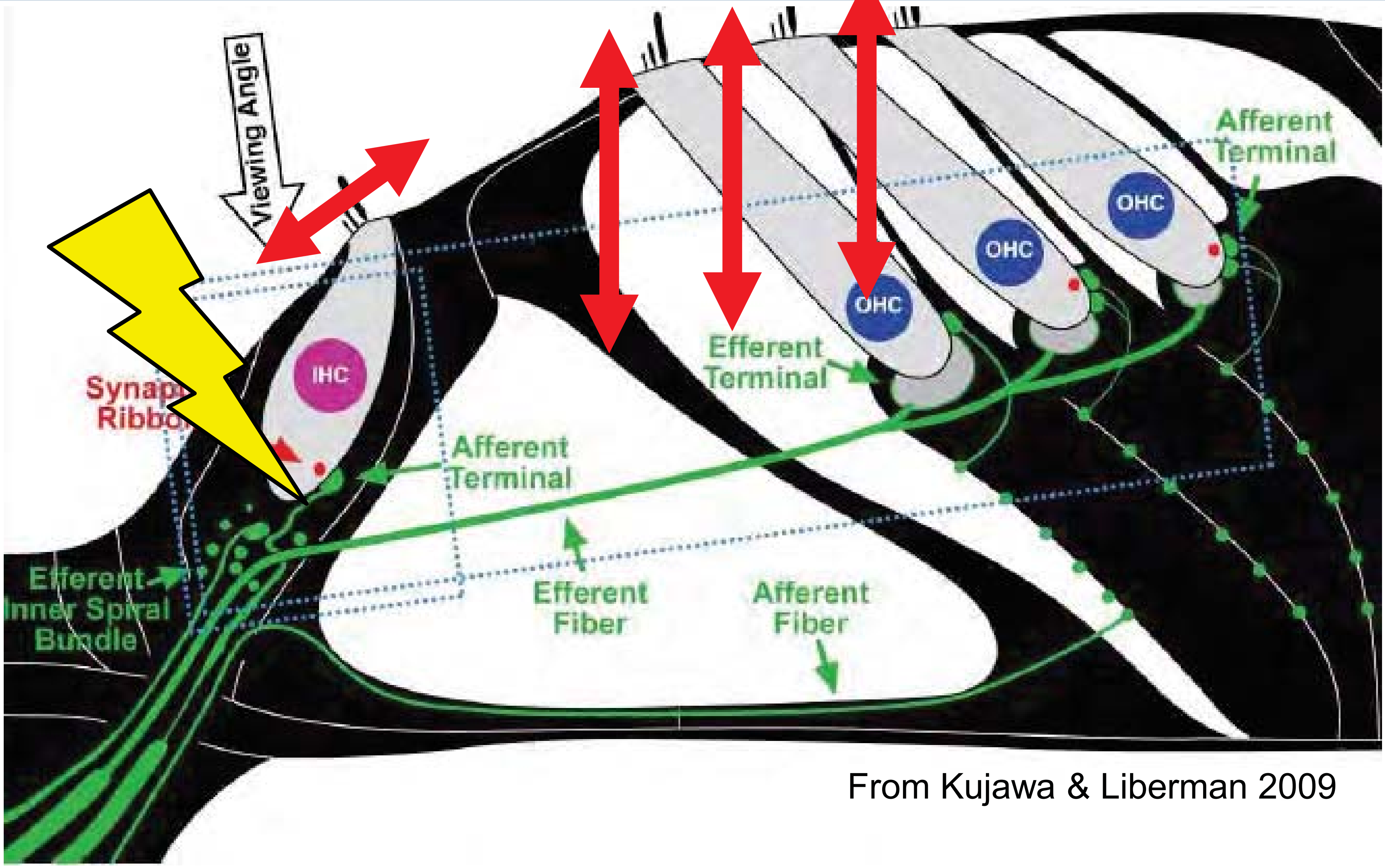
- they found **permanent noise-induced damage** (with **no permanent threshold shift)** for:
  - ribbon synapses
    (Kujawa et al., 2009; Lin et al., 2011; Liu et al., 2012; Shi et al., 2013)
  - auditory nerve fibers
    (Kujawa et al., 2009; Kujawa et al., 2015; Liberman et al., 2015; Lin et al., 2011)
- <u>this is 'hidden' hearing loss, because it happens without any change in thresholds</u>

Back to the Clinic

- Does this help us to understand what might be happening in our non-mice?
- Jack does pretty well in spite of his thresholds. Carol does not. And Marianne does not do well in spite of normal hearing thresholds.
- Could this be a loss of synapses and nerves?

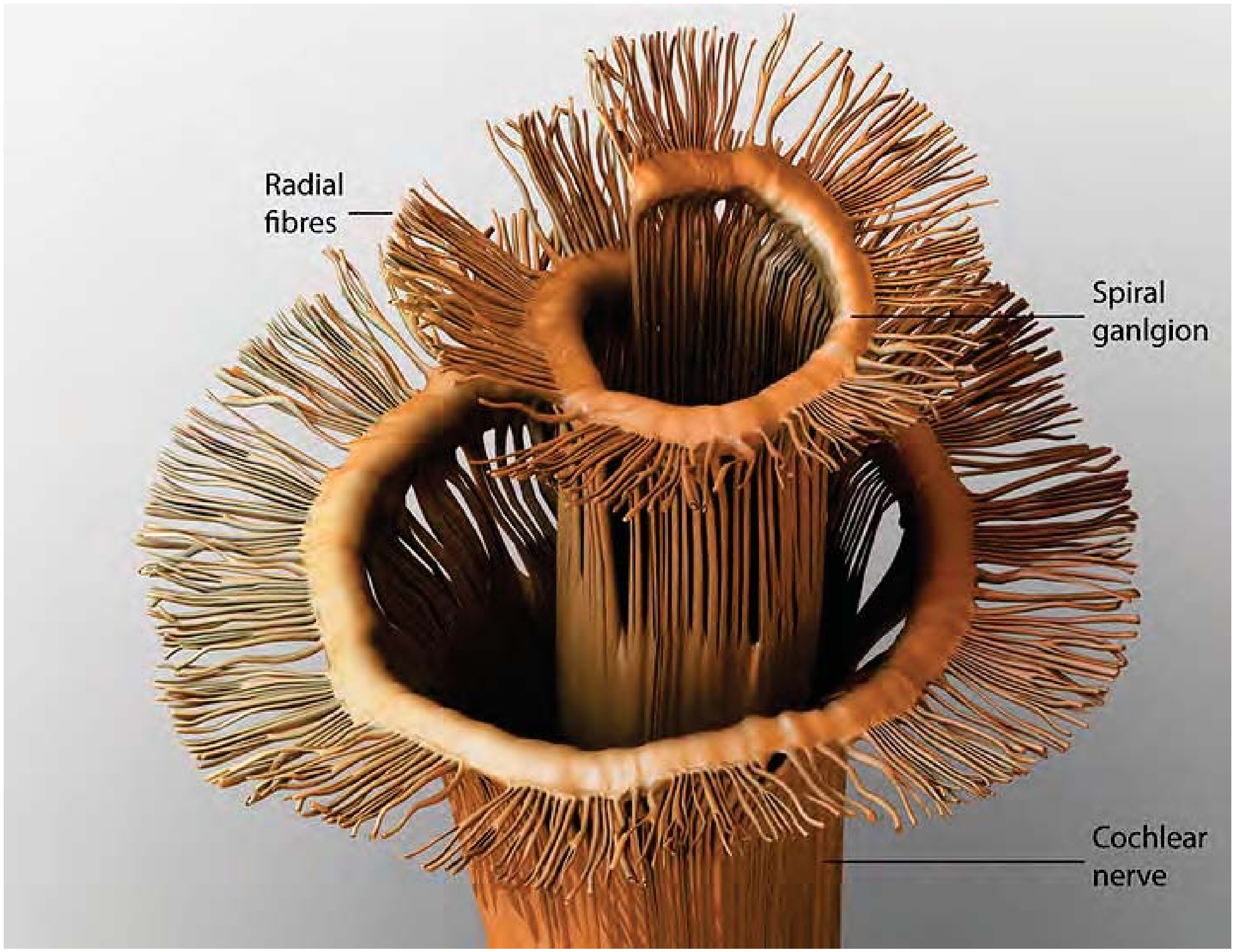
WHAT DOES SYNAPTIC DAMAGE DO?

The Sensory World—Movement and Electricity



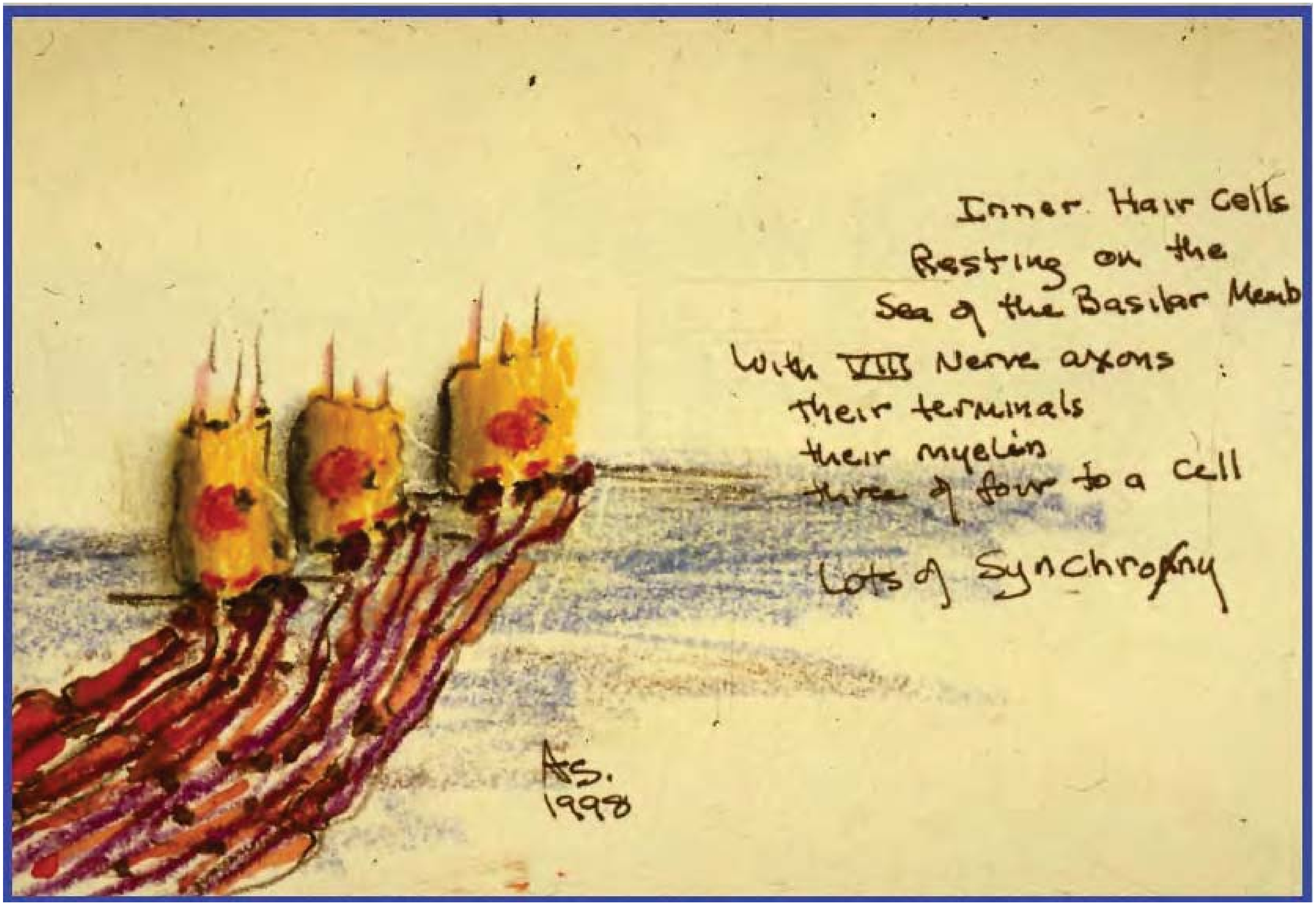
From Kujawa & Liberman 2009

The (Beautiful) Auditory Nerve

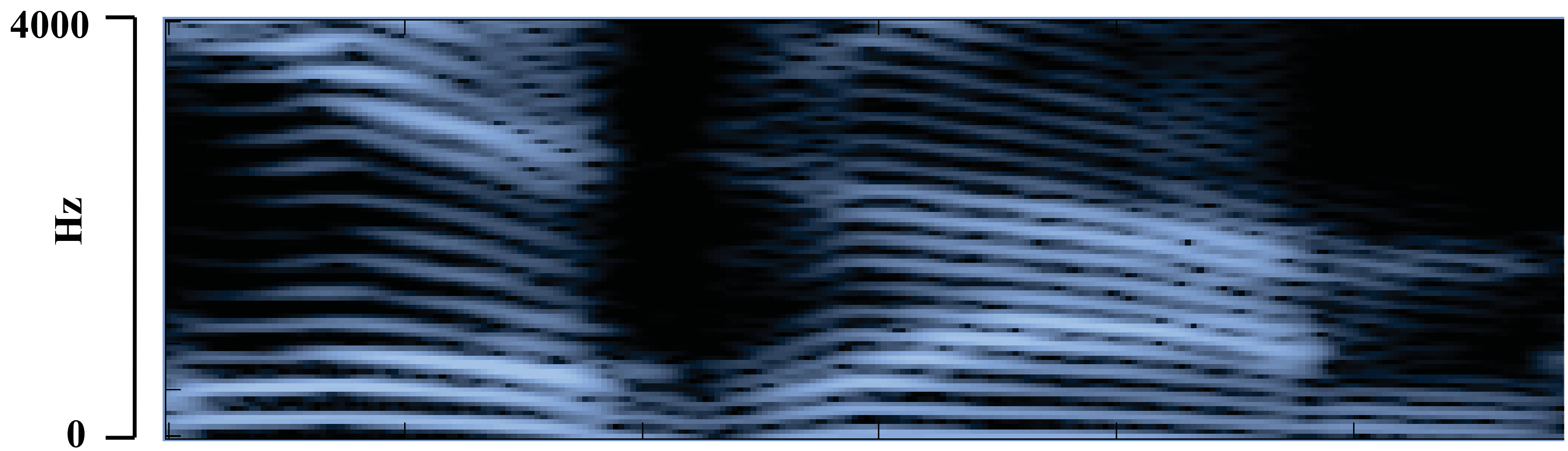


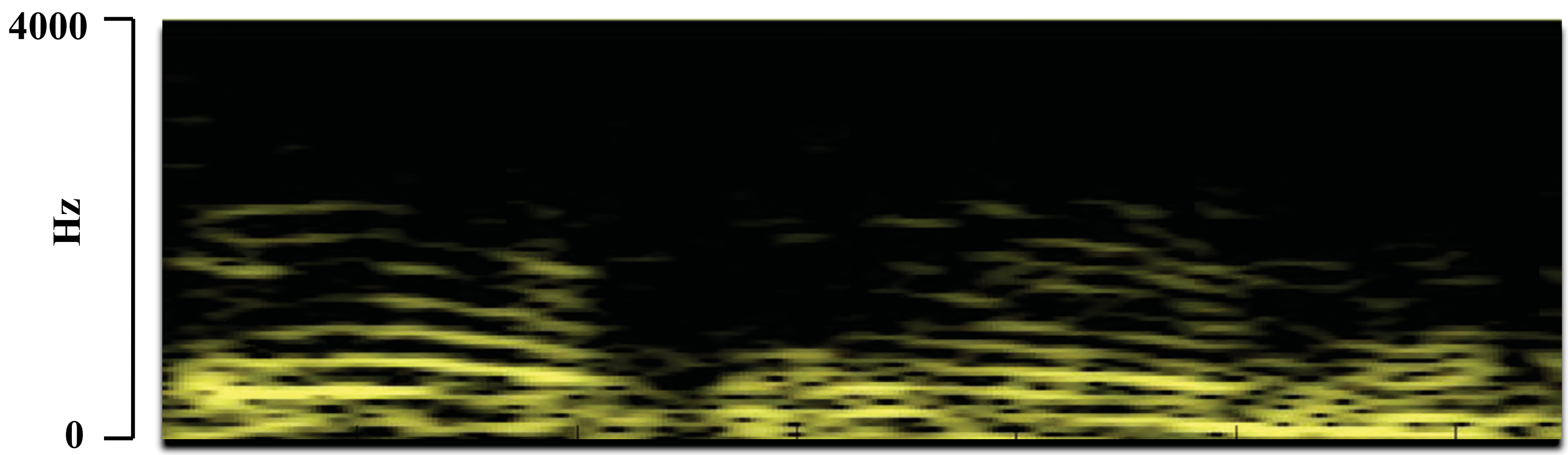
http://www.andreazariwny.com/#!cochlear-nerve-with-spiral-ganglion/c1sqe

Beautiful Synchrony in the Normal Ear



Precise Temporal Responses





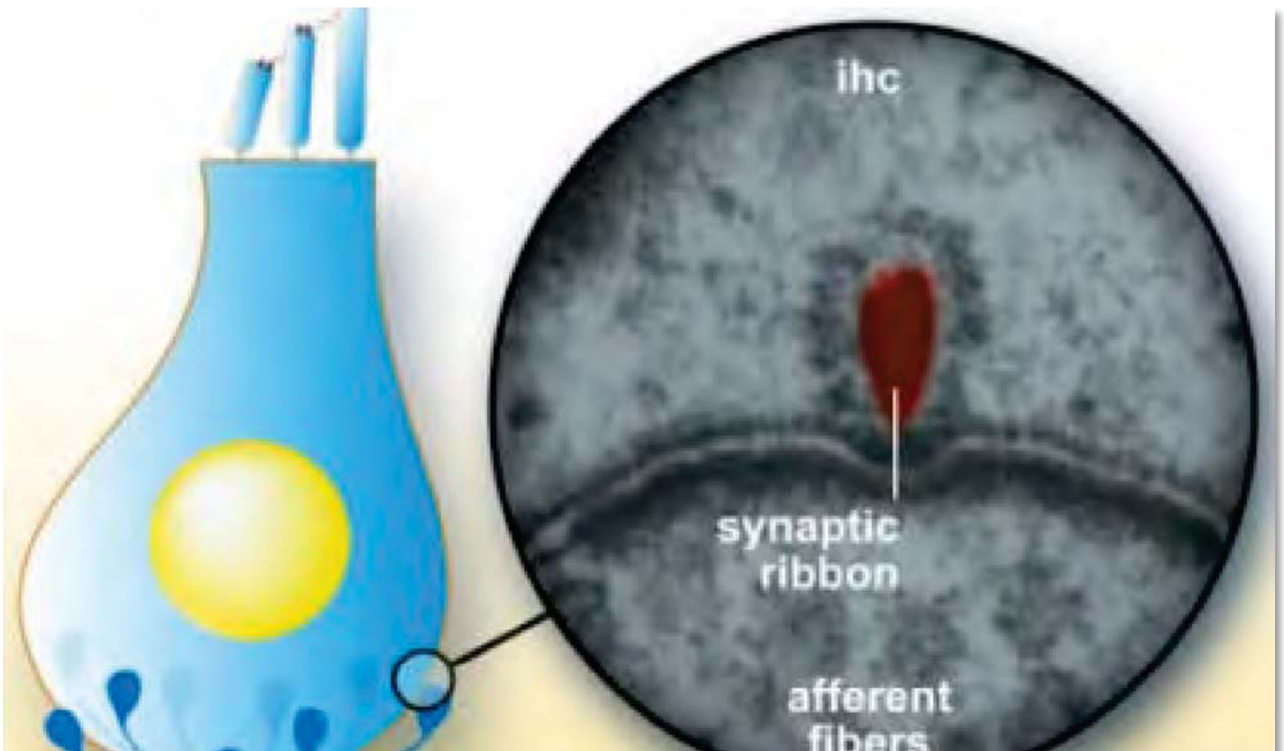
What Enables this Temporal Precision?

- Fast enough to digitally code sound waves!
- Is it normal for neurons to work this quickly?
- Magical elves?
- Magical ribbons?

Magical ‘Ribbon’ Synapses

– surrounded by synaptic vesicles which contain **glutamate** (the IHC neurotransmitter)

– ensure glutamate ready for quick firing

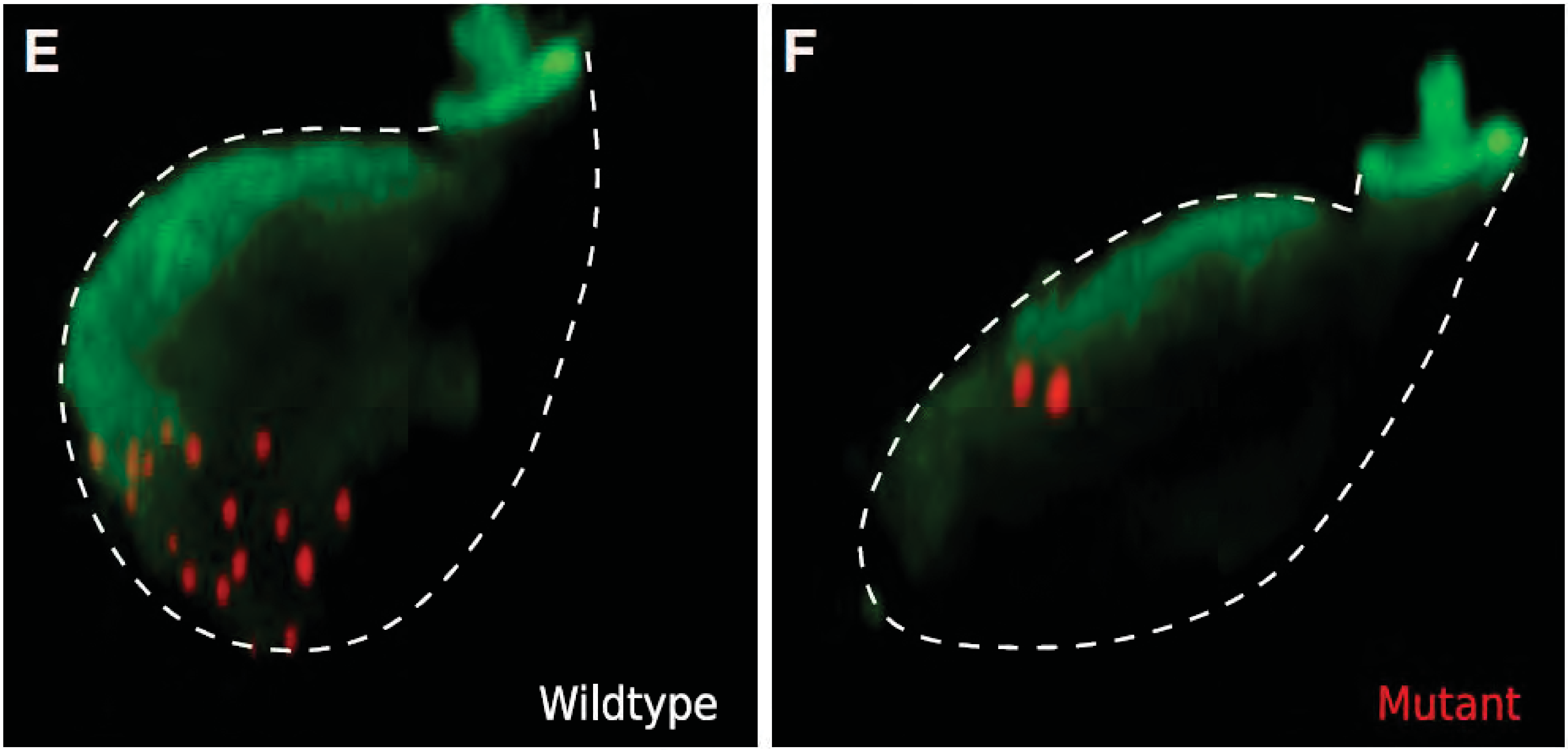


Régis Nouvian, Rémy Pujol Sam Irving

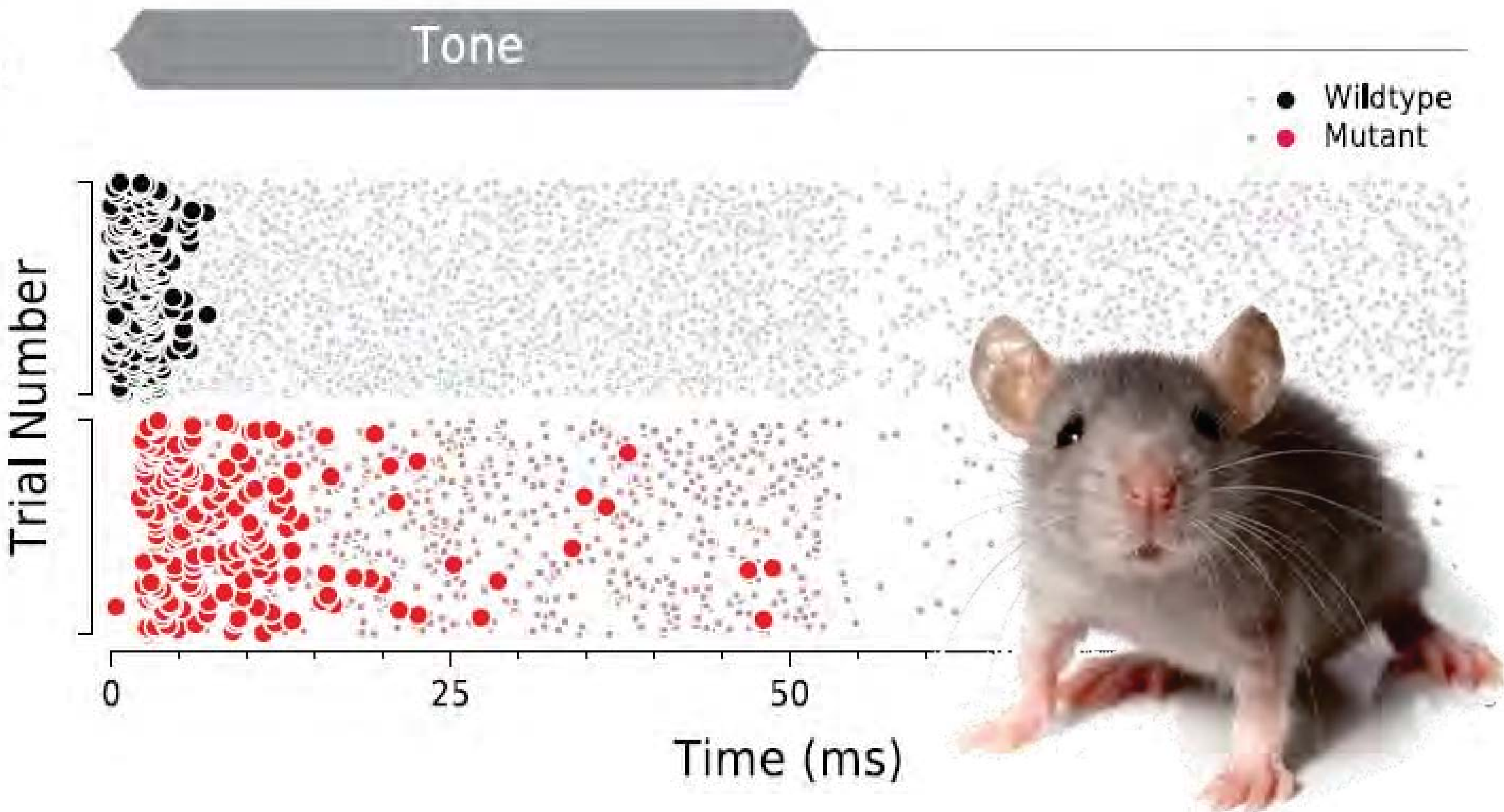
What happens when they’re gone?

- Buran et al. 2010 (J Neurosci): create ’Bassoon’ mutant mice that didn’t have connected ribbon synapses (the ‘Bassoon’ gene codes for the protein which anchors the synapses), compared them to normal ‘wild-type’ mice

Missing Anchored Ribbon Synapses in Mutants



Slower & less precise without Ribbon Synapses



Interim Summary—Effects of Noise Damage

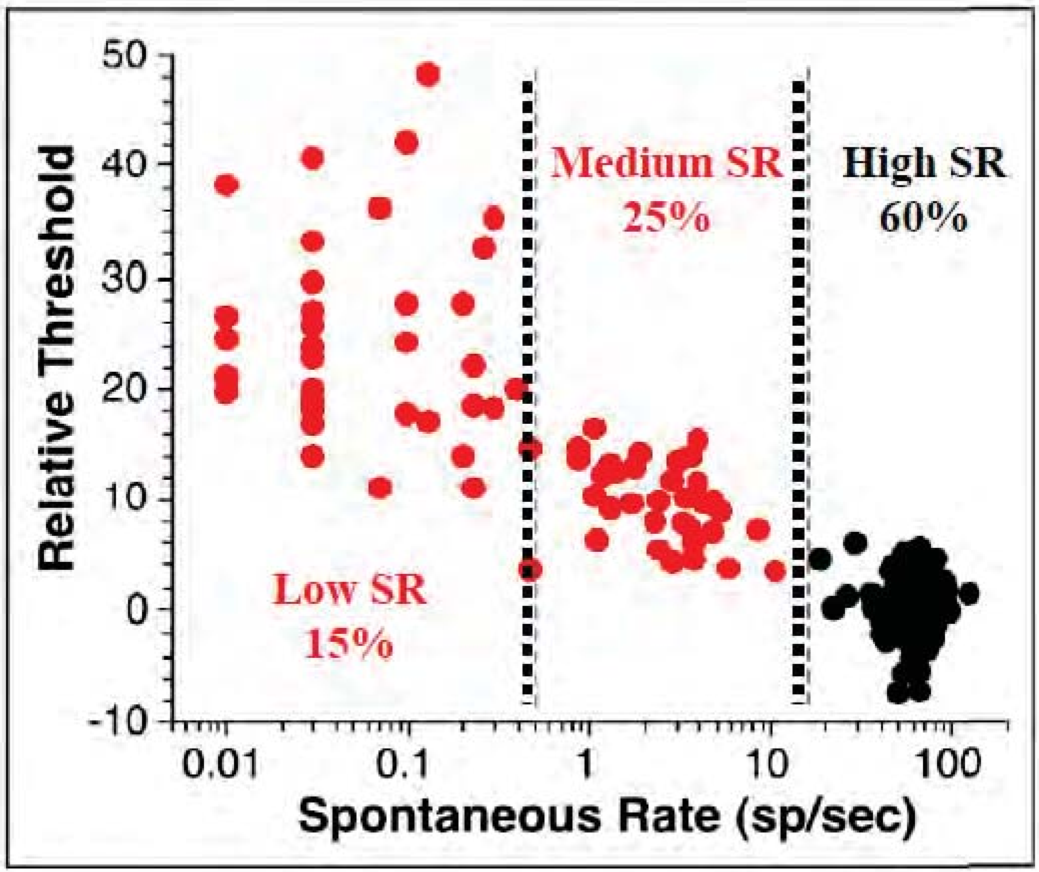
- Noise exposure that only causes temporary threshold shift (primarily temporary OHC damage) may also cause:

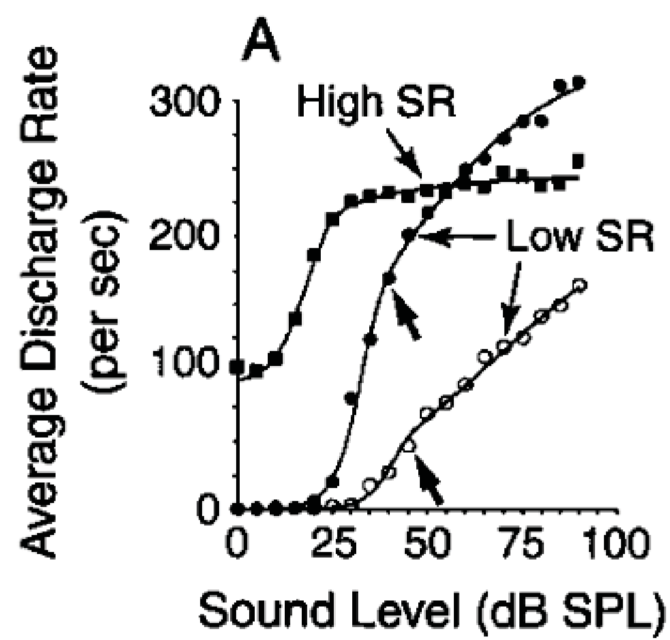
  1. <u>Permanent</u> loss/damage of synapses (and then fibres) → that should result in <u>poor temporal processing</u>

  2. Disproportionate loss of synapses for low spontaneous rate fibres (Furman et al., 2013)

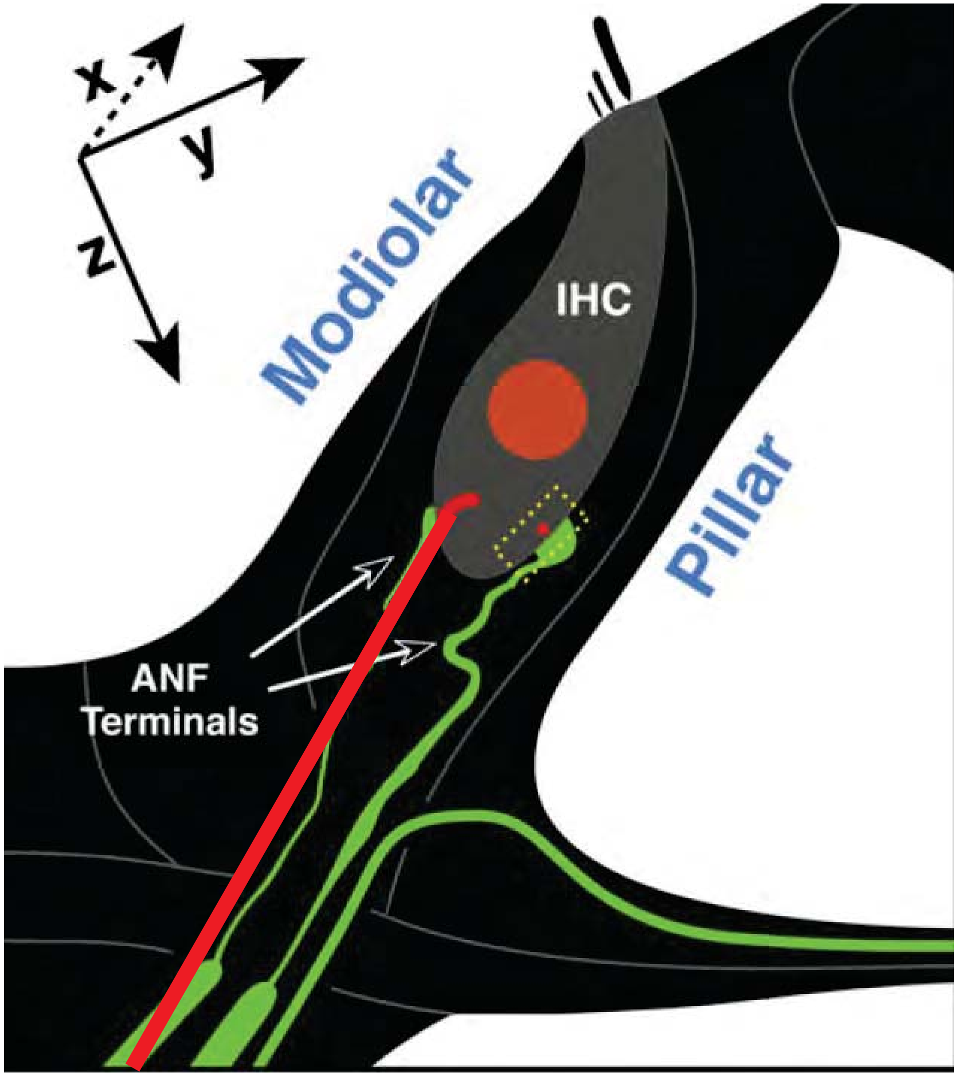
Auditory Nerve Fibre Spontaneous Rates

- Low Spontaneous Rate (high threshold)
- Medium Spontaneous Rate
- High Spontaneous Rate (low threshold)





AN Classification and Ribbon Synapses



- "modiolor" synapses to low SR / high threshold nerve fibres
  - can code high levels (e.g., speech in noise)

- "pillar" synapses to high SR / low threshold nerve fibres
  - code for thresholds

- low SR / high threshold fibres appear to be **more sensitive** to noise damage (Furman et al., 2013)

Interim Summary—Effects of Noise Damage

- Noise exposure that only causes temporary threshold shift (primarily temporary OHC damage) may also cause:

1. <u>Permanent</u> loss/damage of synapses (and then fibres) → that should result in <u>poor temporal processing</u>

2. Disproportionate loss of synapses for low spontaneous rate fibres (that code for higher levels)
   - will affect high level sounds (e.g., speech, especially in background noise), but NOT thresholds

Can we assume the same for humans?

What about guinea pigs?

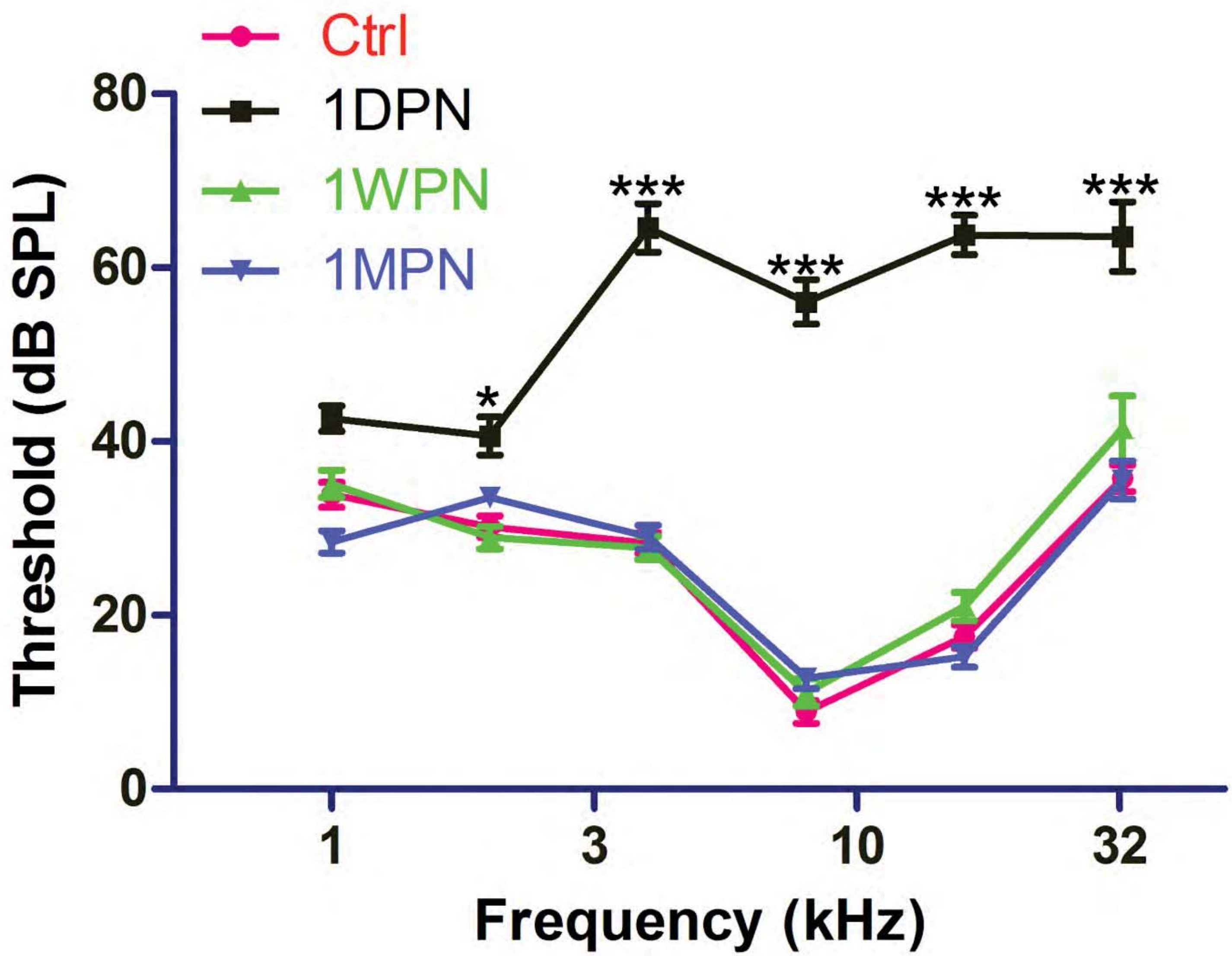
- A guinea pig walks into a bar…
  - 30 guinea pigs tested after two hours of exposure to 105 dB SPL noise

Silent Damage of Noise on Cochlear Afferent Innervation in Guinea Pigs and the Impact on Temporal Processing

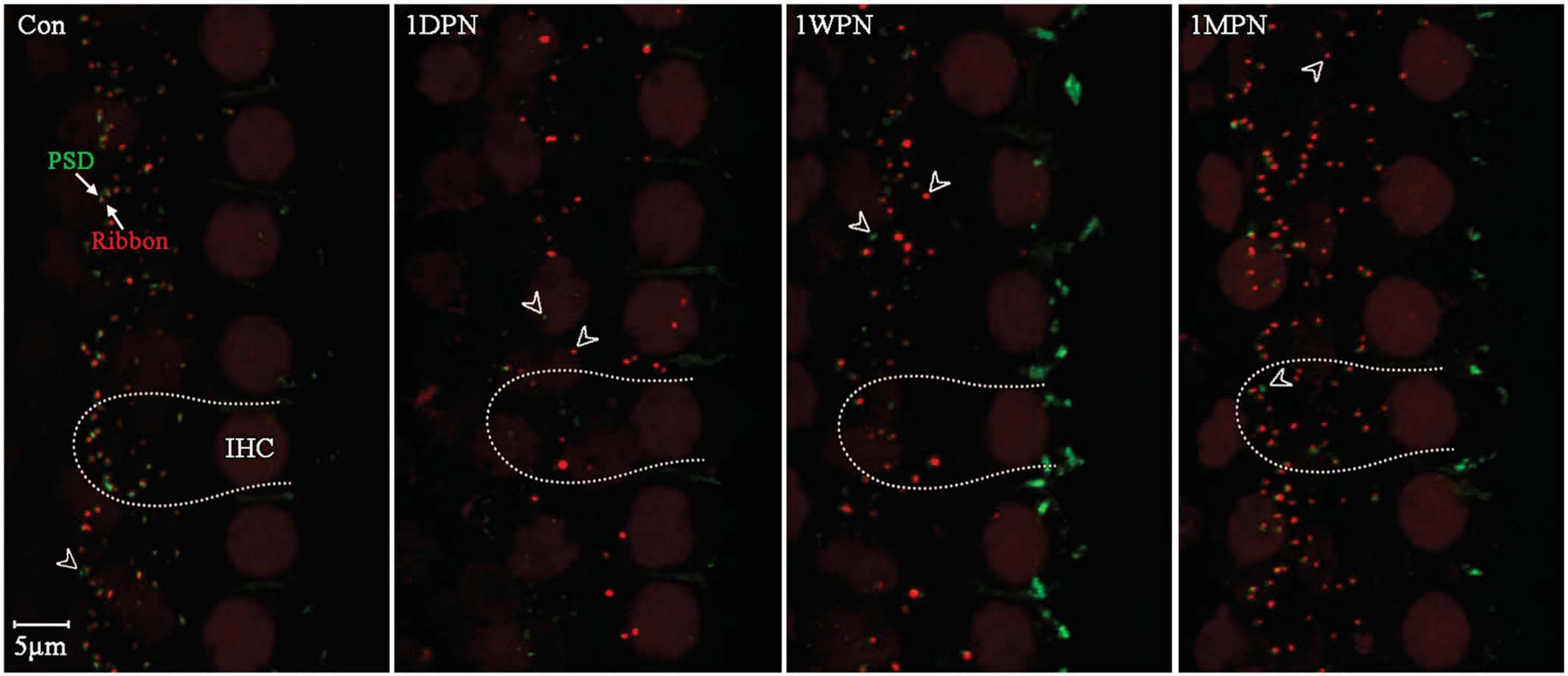
Lijie Liu[1], Hui Wang[2], Lijuan Shi[1], Awad Almuklass[3], Tingting He[1], Steve Aiken[4], Manohar Bance[4,5], Shankai Yin[2*], Jian Wang[1,4*]

1 Department of Physiology and Pharmacology, Medical College of Southeast University, Nanjing, China, 2 Department of Otolaryngology, 6th Affiliated Hospital, Jiaotong University, Shanghai, China, 3 Department of Physiology & Biophysics, Dalhousie University, Halifax, Canada, 4 School of Human Communication Disorders, Dalhousie University, Halifax, Canada, 5 Division of Otolaryngology, Head and Neck Surgery, Department of Surgery, Dalhousie University, Halifax, Canada

105 dB SPL (2 hours)

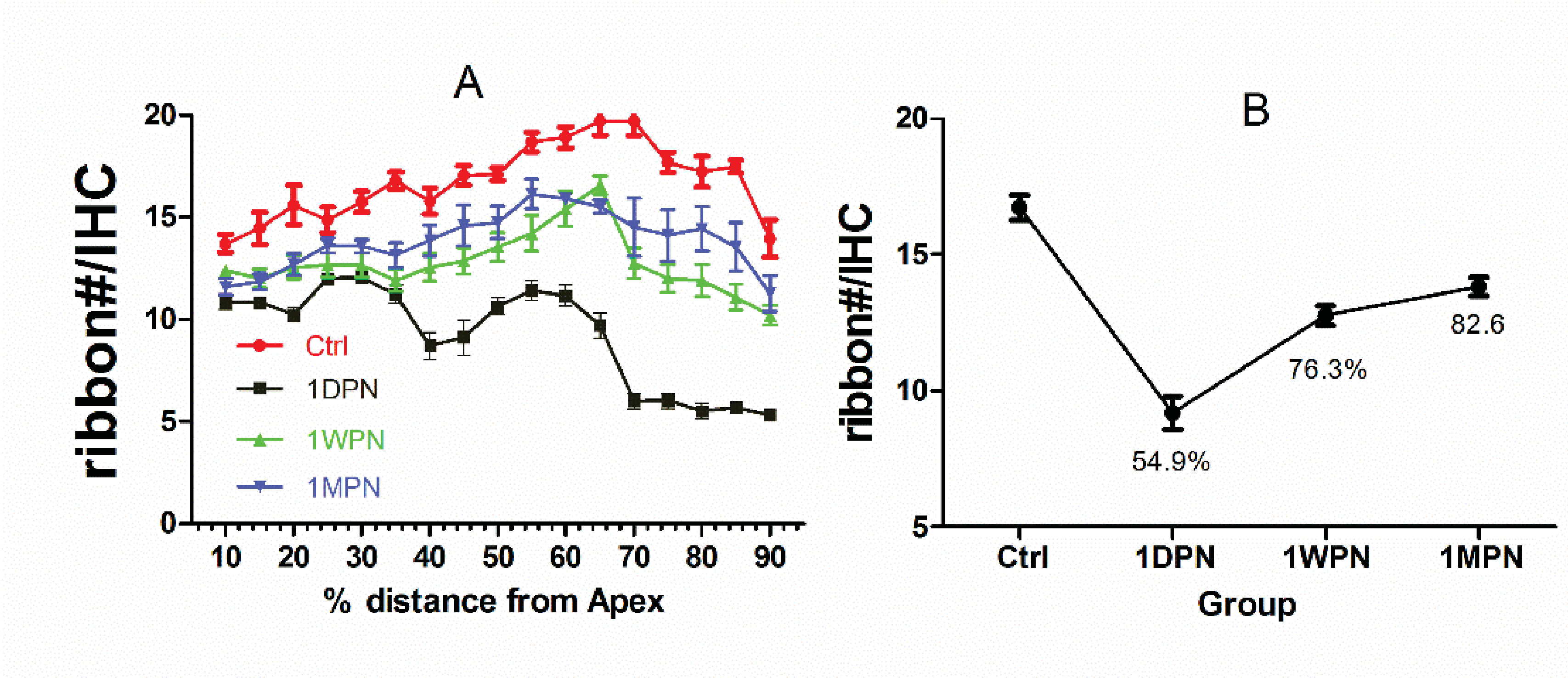


Ribbons Lost and Partially Recovered



- Ribbons are present but not in the right place
- This is different than what we saw in mice, but still problematic

Ribbon Counts after Noise Exposure



A: ribbon density cochleogram
B: averaged density

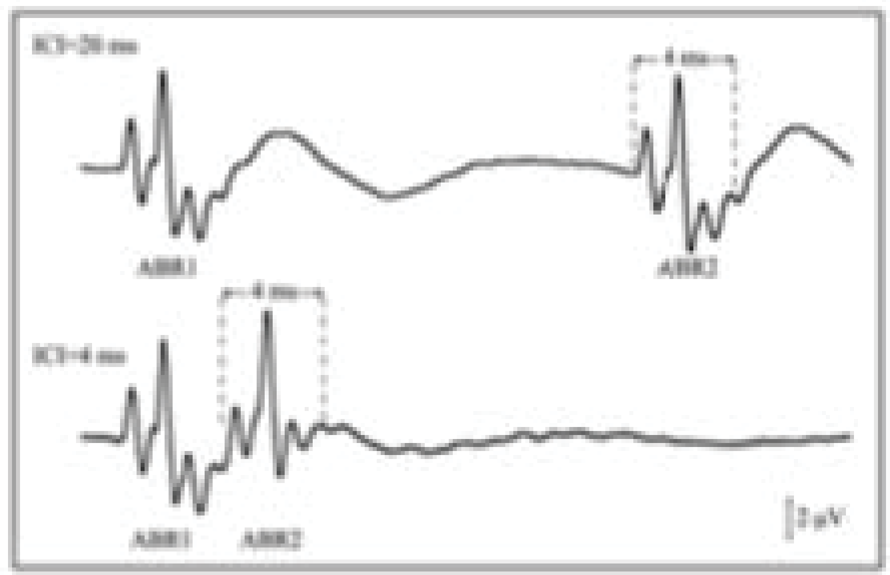
- Ribbon synapses partially recovers @ 1 mo, unlike in mice

What are the Effects?

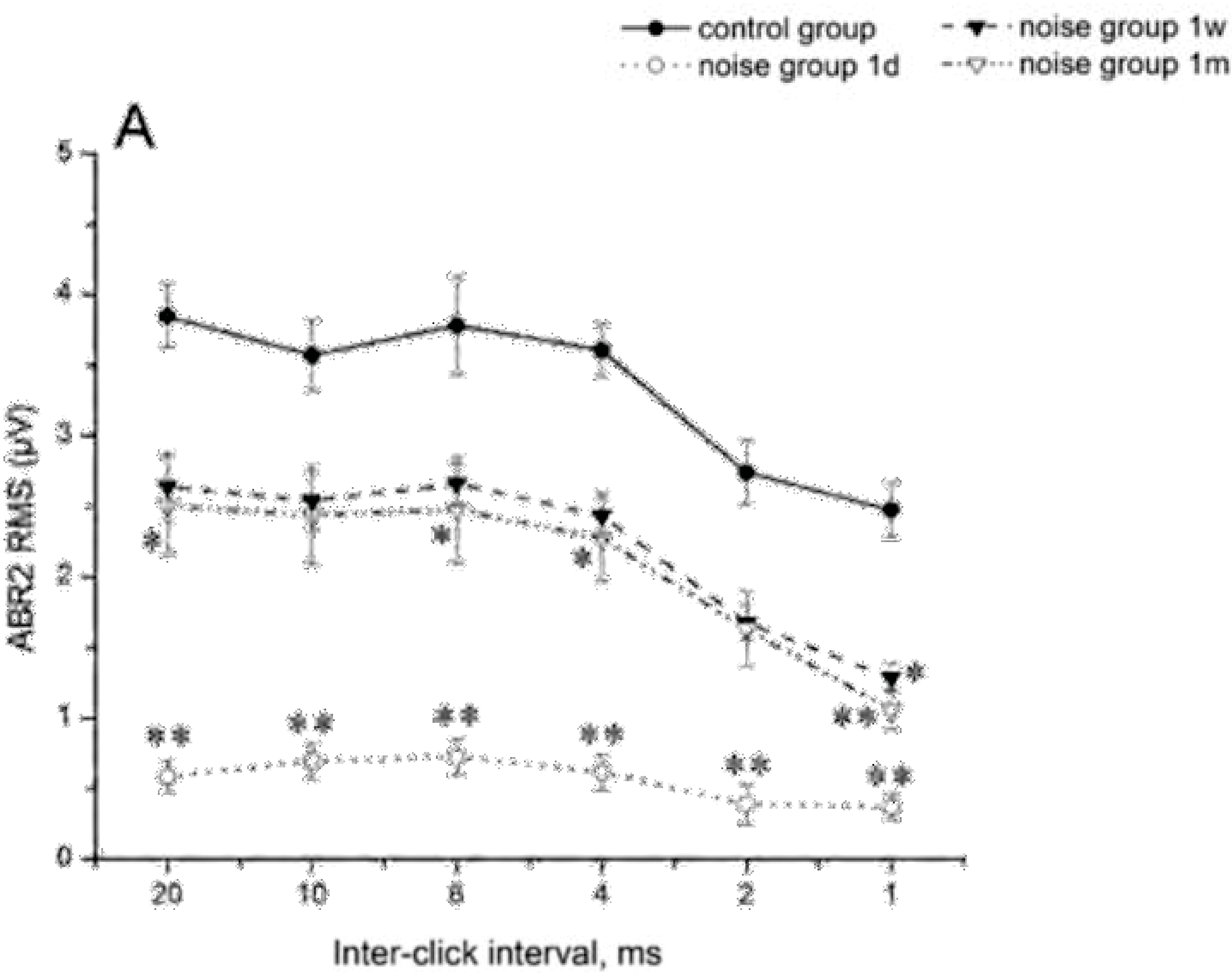
- Paired-click ABR—Get two nerve responses in a row
- How quickly does the response recover?
- Recall Buran’s mutant mice

Long Gap Between Clicks

Short Gap Between Clicks

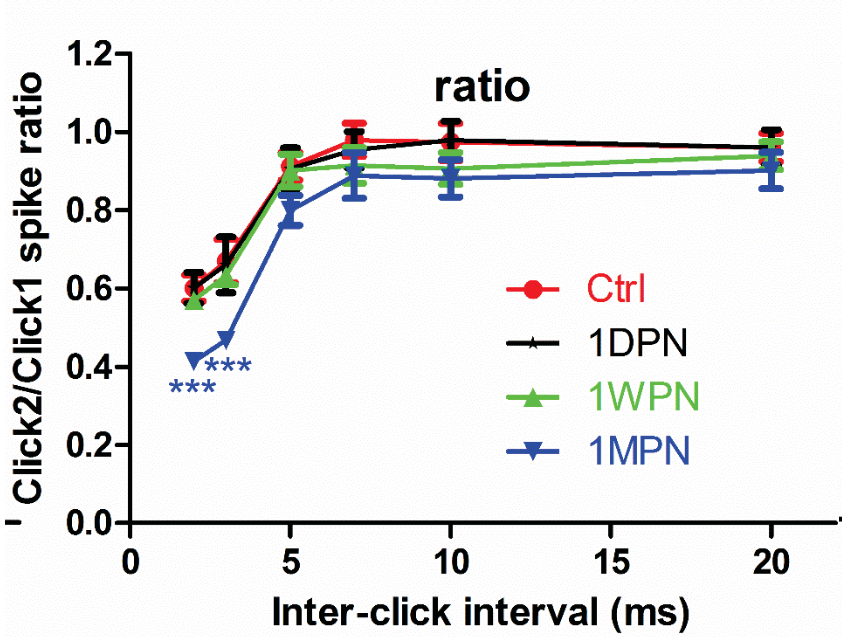


Response to Second Click in the Guinea Pigs

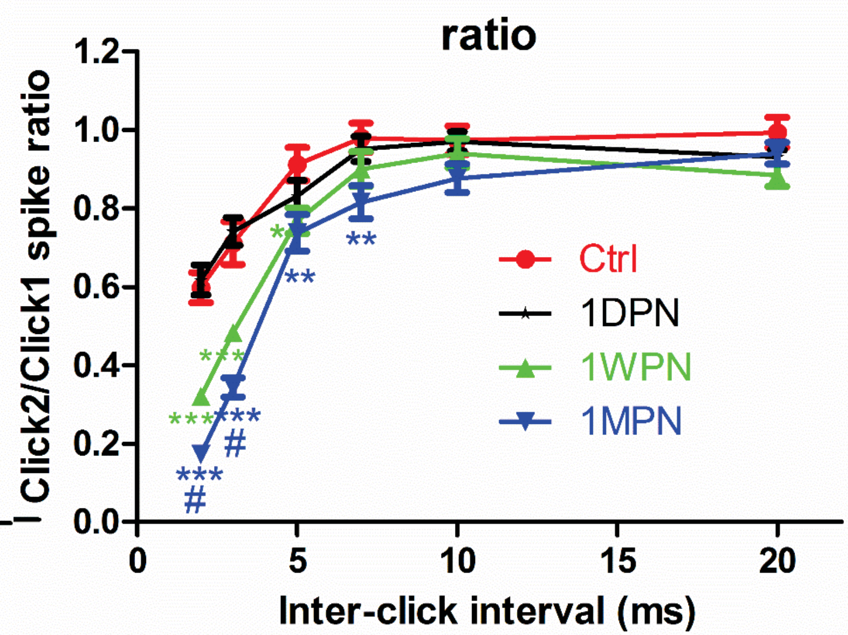


Recovery Functions–2nd Click Resp / 1st Click Resp

High SR Fibres



Low SR Fibres



- for shorter inter-click intervals, damage actually increases in the weeks and months after exposure—especially for Low–SR fibres (important for high levels)

Hidden Hearing Loss → Poor Temporal Processing

- incomplete recovery of ribbon synapses in spite of recovered hearing thresholds **i.e., “hidden” hearing loss**

- even though thresholds have returned to normal, response to second click is impaired, even for inter-click interval of 20 ms (equivalent to 50 Hz)
  - greater abnormalities at intervals < 10 ms (i.e., > 100 Hz)

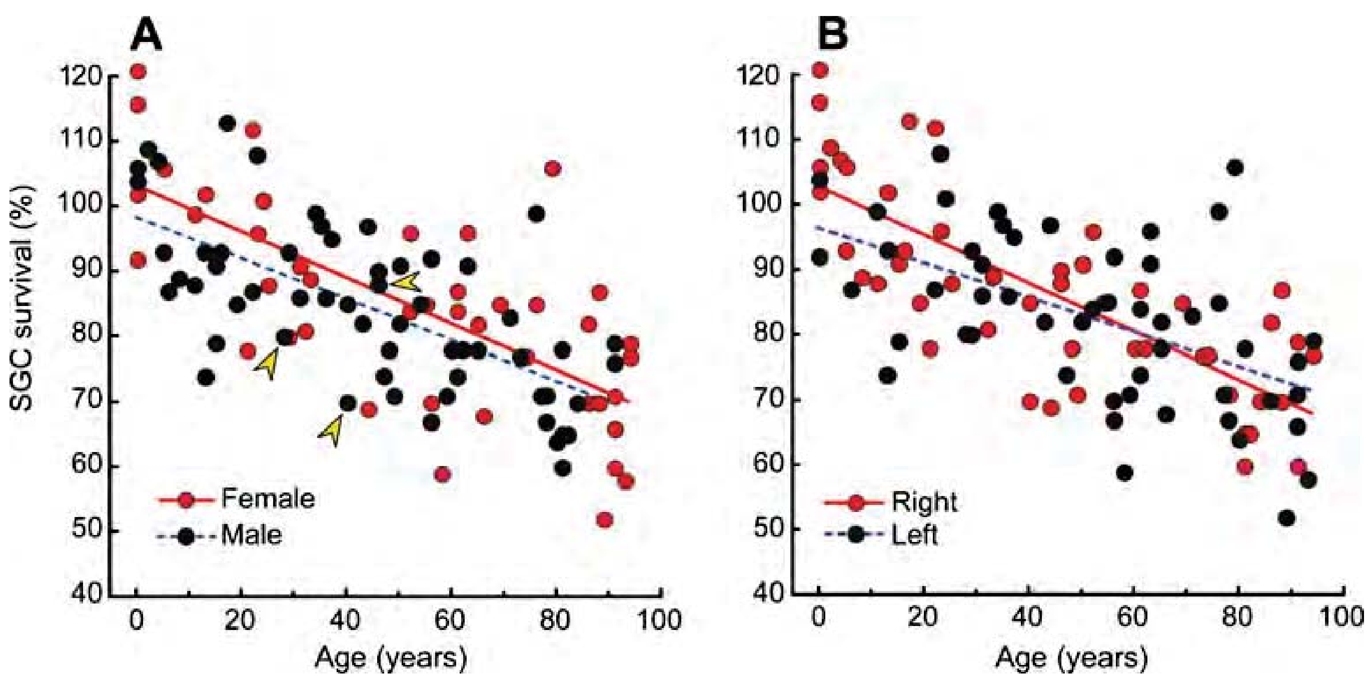
- temporal response (esp. for fibres that code high levels) decreases over time, suggests an imperfect repair process

- this is <u>ABNORMAL TEMPORAL PROCESSING, especially for high level sounds (e.g., speech)</u>

Is there any evidence in humans?

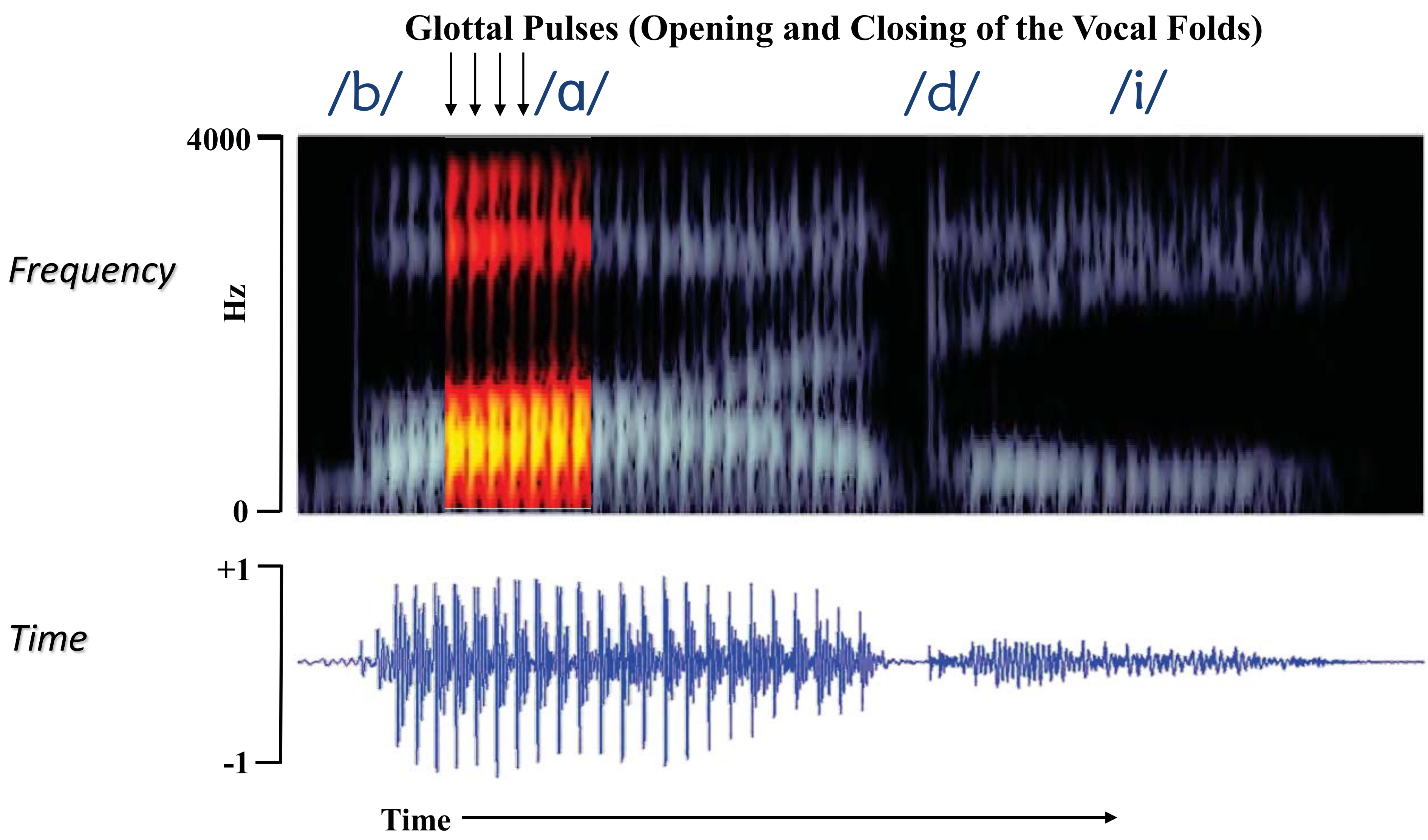
Human Physiological Evidence

- Makary et al. 2011
  - 100 temporal bones, with 8–12 for each decade 0–100 yrs
  - no significant IHC or OHC loss
  - SGN counts decreased with age (for both sexes & ears)

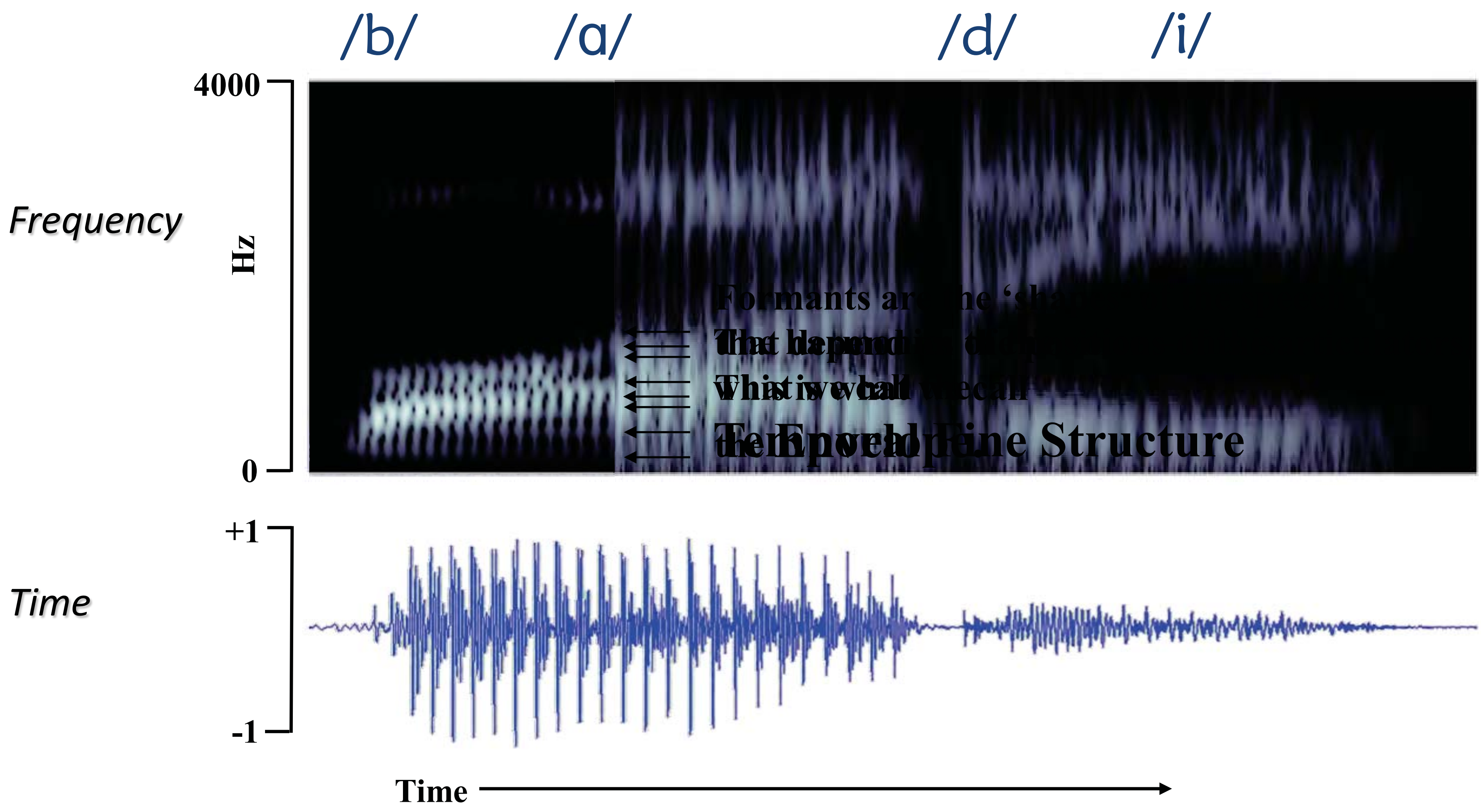


ROLE OF TEMPORAL CODING IN SPEECH

Role of Temporal Details in Speech



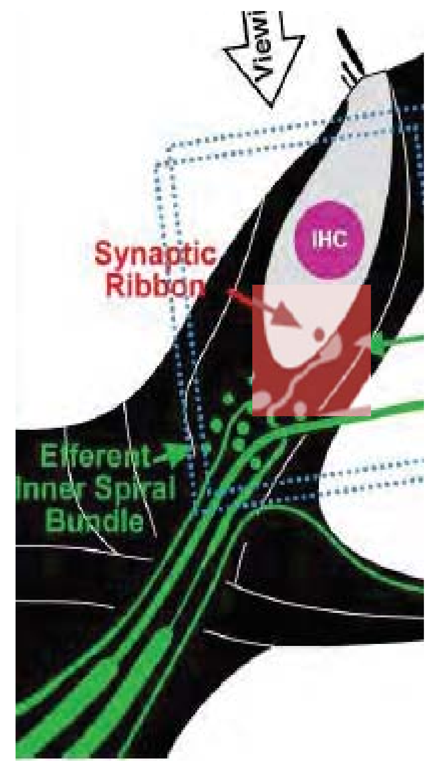
Role of Temporal Details in Speech



Poor Temporal Processing

- There is evidence that SNR loss is related to problems with temporal fine-structure (TFS) processing
  (Buss et al., Ear Hear 2004; Hopkins & Moore, J Acoust Soc Am, 2009; Lorenzi et al., Proc Nat Acad Sci USA, 2006; Strelcyk & Dau, J Acoust Soc Am, 2009; Summers et al., Ear Hear 2013)

- Auditory neuropathy / synaptopathy may be a common feature of speech-in-noise problems—at least after noise exposure



Checking in with our clients…

- Jack has a hearing loss, but his suprathreshold abilities suggest good temporal processing

- Carol has a hearing loss and likely has a loss of temporal processing (i.e., normal hearing loss **+ hidden hearing loss**)

- Marianne may have “hidden hearing loss”—synapse/nerve damage without any shift in threshold

Are we jumping to conclusions??

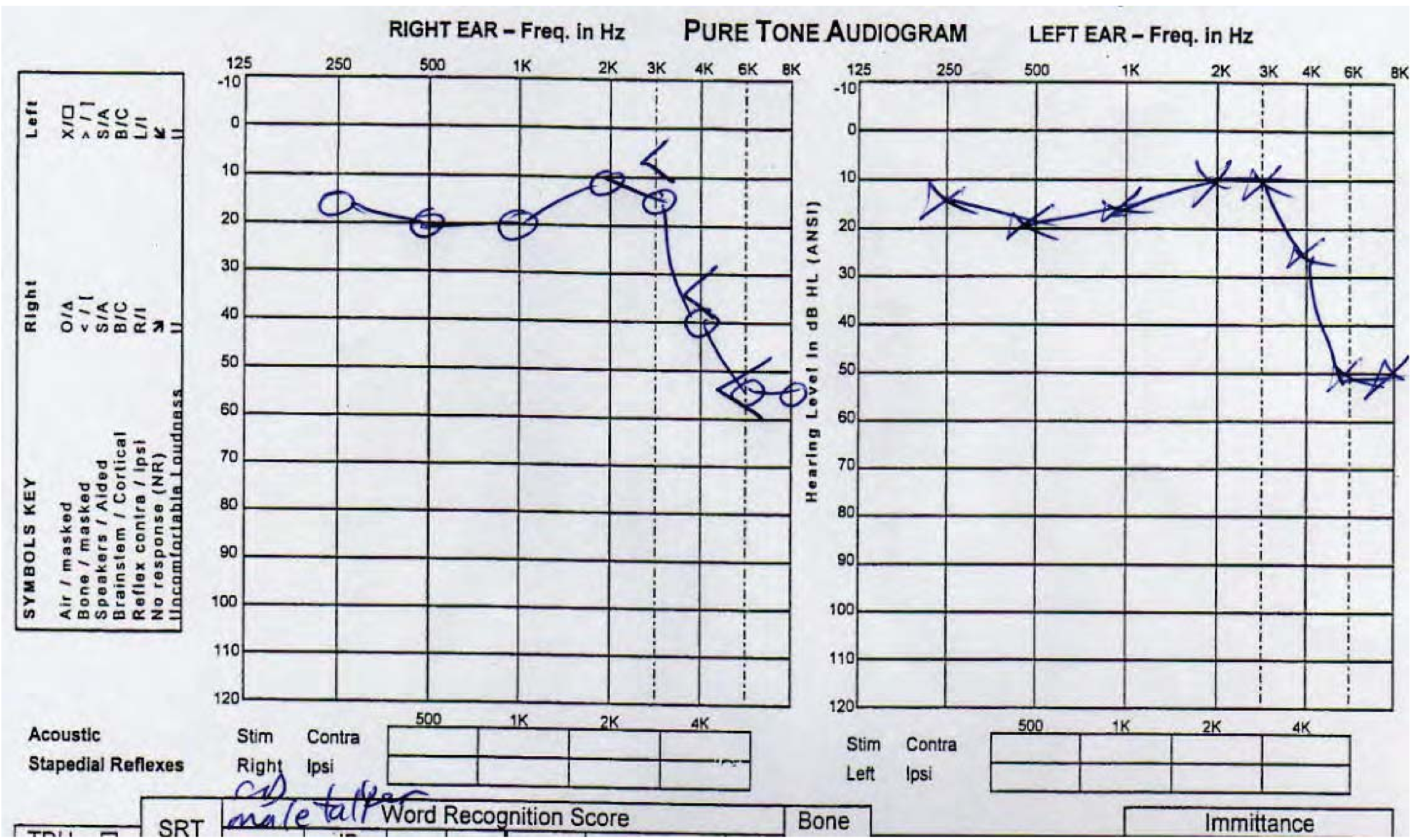
- Lin et al. (2013) studied 1162 individuals with hearing loss, 818 normal hearing over 6 years → **hearing loss independently associated with cognitive decline**

- Lin et al. (2011) studied individuals who had had a hearing test between 1990 and 1994, and incidence of dementia up to 2008. **Risk of dementia increases by 20-30% per 10 dB of hearing loss.**

- **Suprathreshold hearing problems could be the result of 'higher level problems' with cognition**
  Humes et al., J Am Acad Audiol, 2012; Moore et al., Int J Audiol, 2013; Sharma et al., JSLHR, 2009

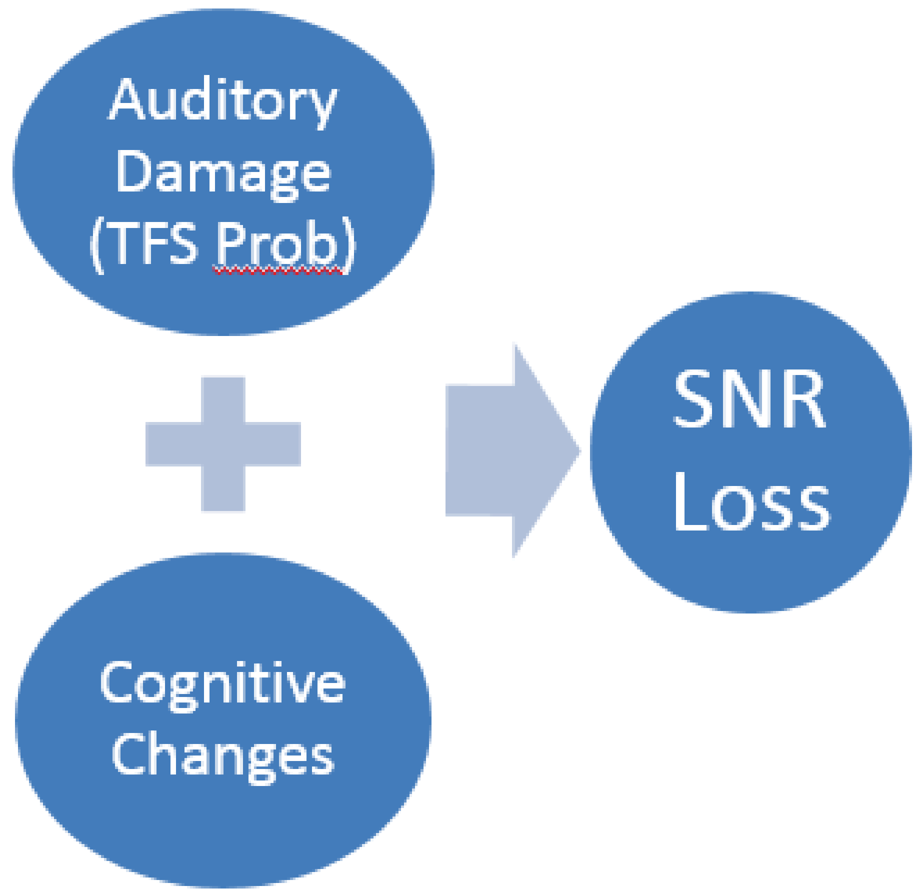
The Etiology Problem

- How do we diagnose noise-induced synaptopathy / neuropathy?



Detecting Hidden Hearing Loss

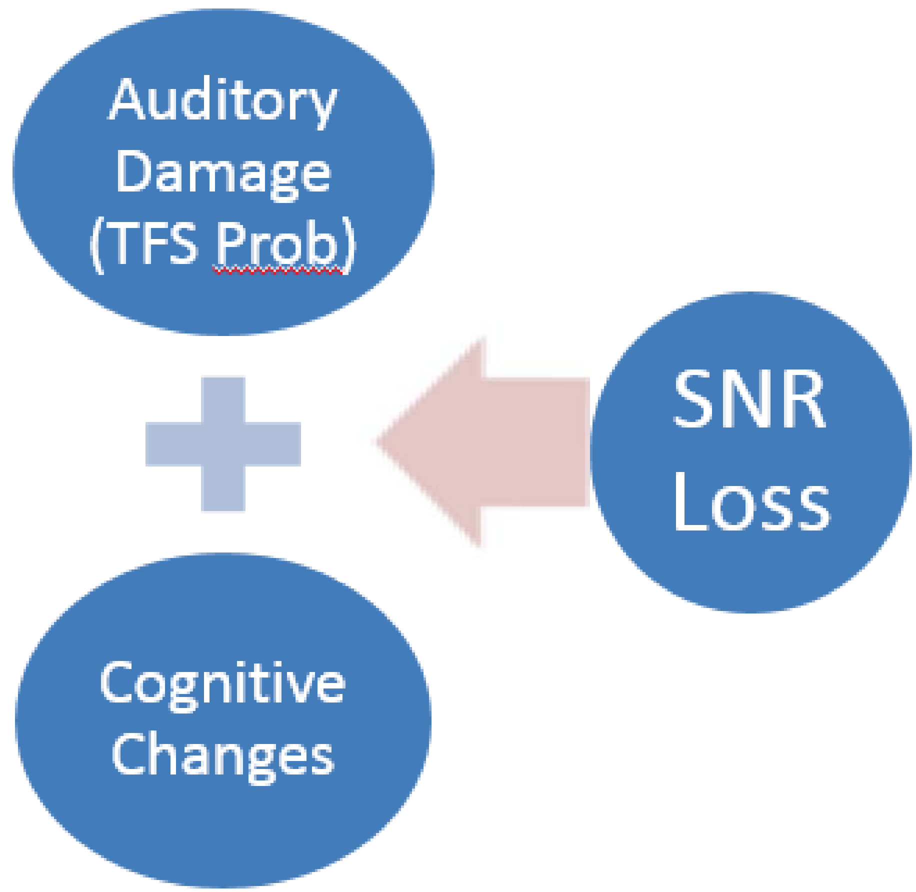
- Consider that SNR loss may relate to peripheral damage (e.g., synaptopathy) but also to central dysfunction



Detecting Hidden Hearing Loss

- As a first step, we should confirm that there is a functional problem

- Speech-in-noise testing is sensitive to neuropathy (Berlin et al., 2010)



A Way Forward

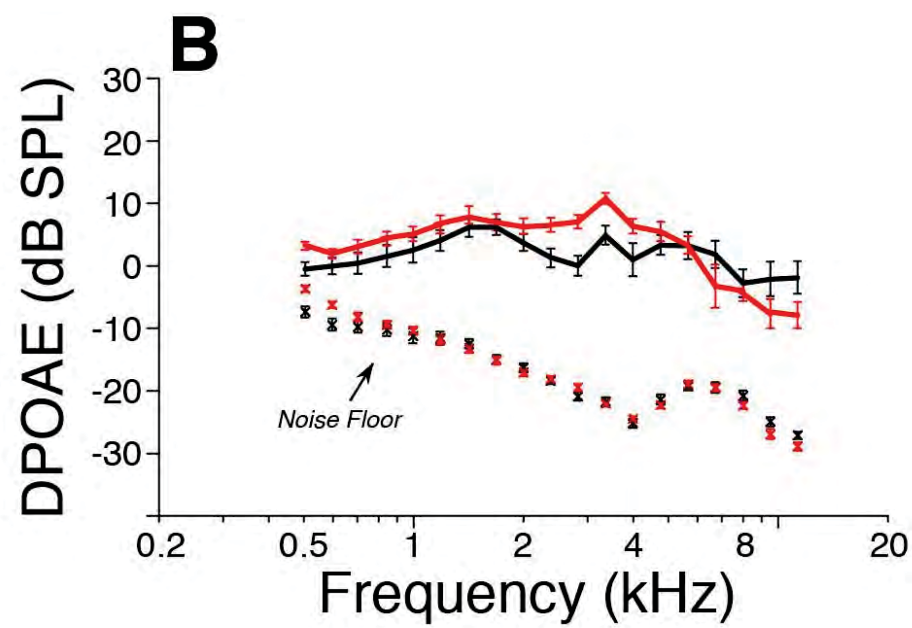
1. Test speech in noise (e.g., the QuickSIN test) to determine whether there is a functional problem
   - note that this might occur with normal thresholds

How can we determine if the problem is related to noise damage?

Relating SIN Problems to Noise - OAEs

- OAEs
  - Many papers show a relationship between noise exposure and OAE amplitude change (Dhar and Hall, 2012)
  - outer hair cell damage results in threshold shifts but OAEs may be better early indicators of damage than threshold (Lapsley Miller, 2006; Shupak et al., 2007, but see Seixas et al., 2012)

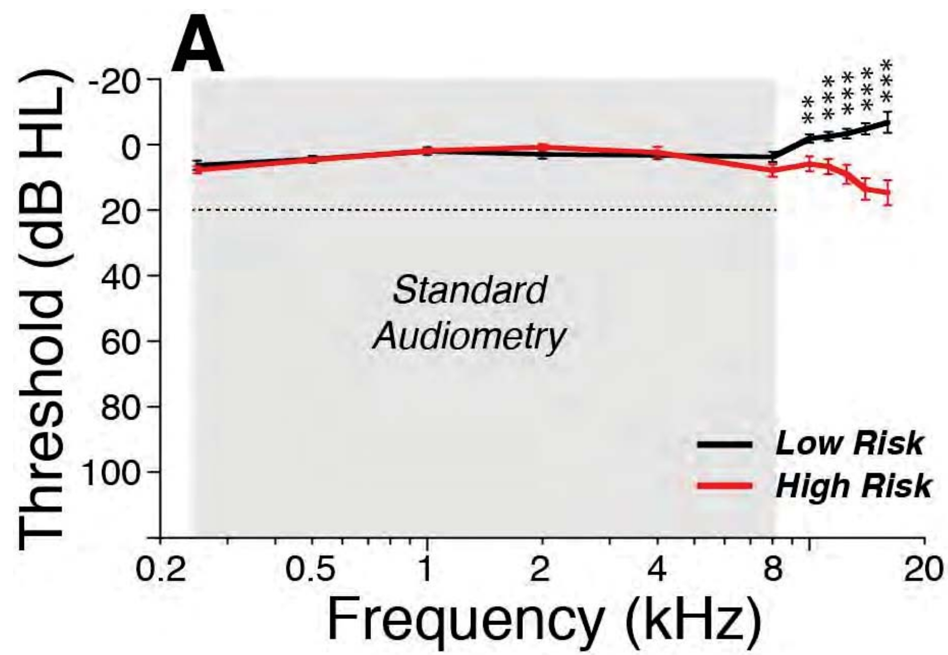
- Liberman et al., 2016
  - those who self-reported more noise exposure **did not** have different DPOAEs



Relating SIN Problems to Noise - exHFA

- Extended High-Frequency Audiometry (exHFA)
  - noise exposure may impact high-frequency thresholds earlier than frequencies 250–8000 Hz

- Liberman et al., 2016
  - those who self-reported more noise exposure **did** have poorer exHFA



A Way Forward

1. Test speech in noise (e.g., the QuickSIN test) to determine whether there is a functional problem
   - note that this might occur with normal thresholds

2. Self-Report measures and exHFA thresholds may help to determine likelihood of noise damage

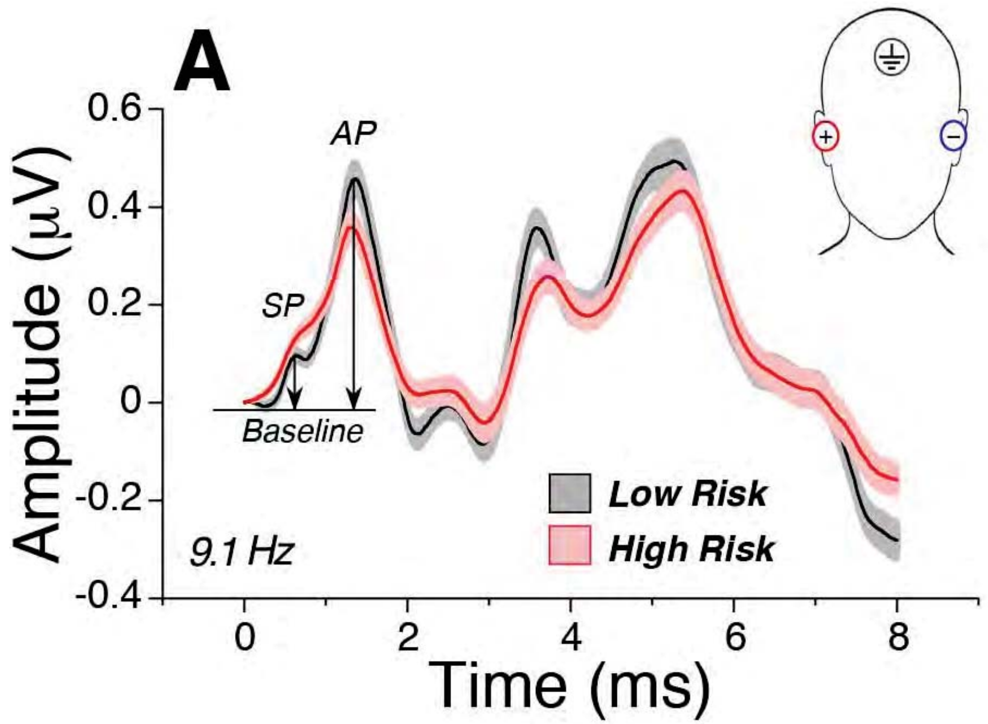
Can we go farther and measure it directly?

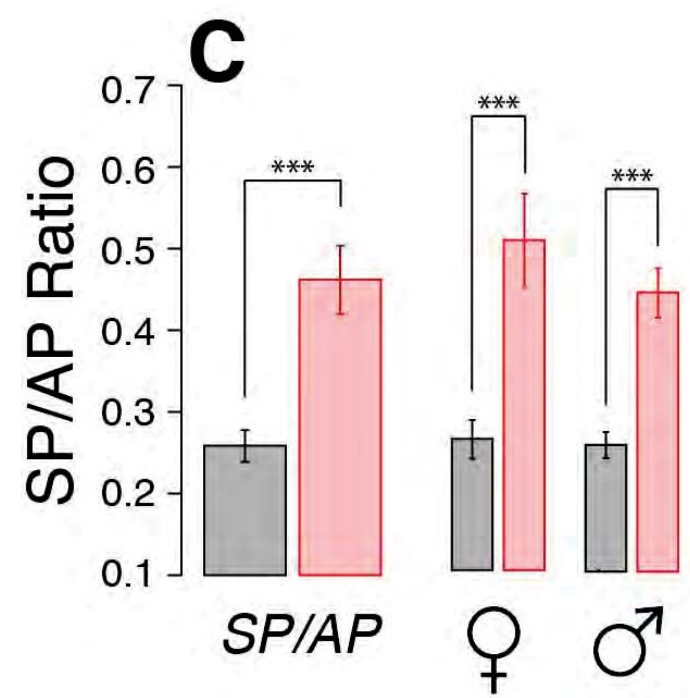
Direct Measurement

- Studying brain activity from the scalp is like studying the earth from orbit

Near-Field Measures in Humans

- Electrocochleography measures (e.g., TipTrode)
  - compound action potential <u>for high level click stimuli</u> (this is the ABR Wave I, but measured in the near field)
  - can normalize by measuring the SP/CAP ratio (Liberman et al., 2016)





A Way Forward

1. Test speech in noise (e.g., the QuickSIN test) to determine whether there is a functional problem
   - note that this might occur with normal thresholds

2. Self-Report measures and exHFA thresholds may help to determine likelihood of noise damage

3. The SP/AP ratio can tell us about nerve function

Can we record responses that reflect poor TFS encoding?

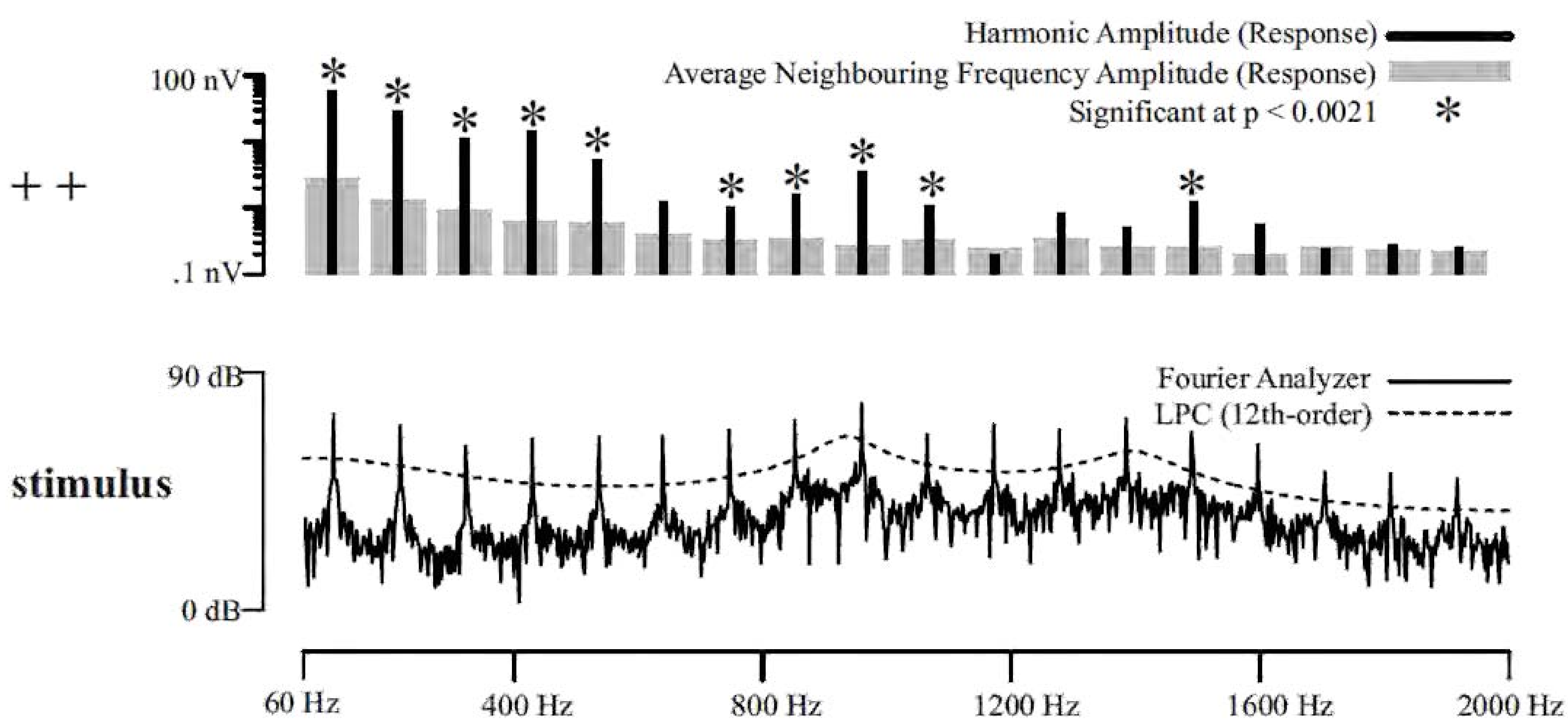
Can we record responses to TFS directly?

- If synaptic damage is impairing speech-in-noise perception because of poor TFS encoding, a direct measurement may be helpful

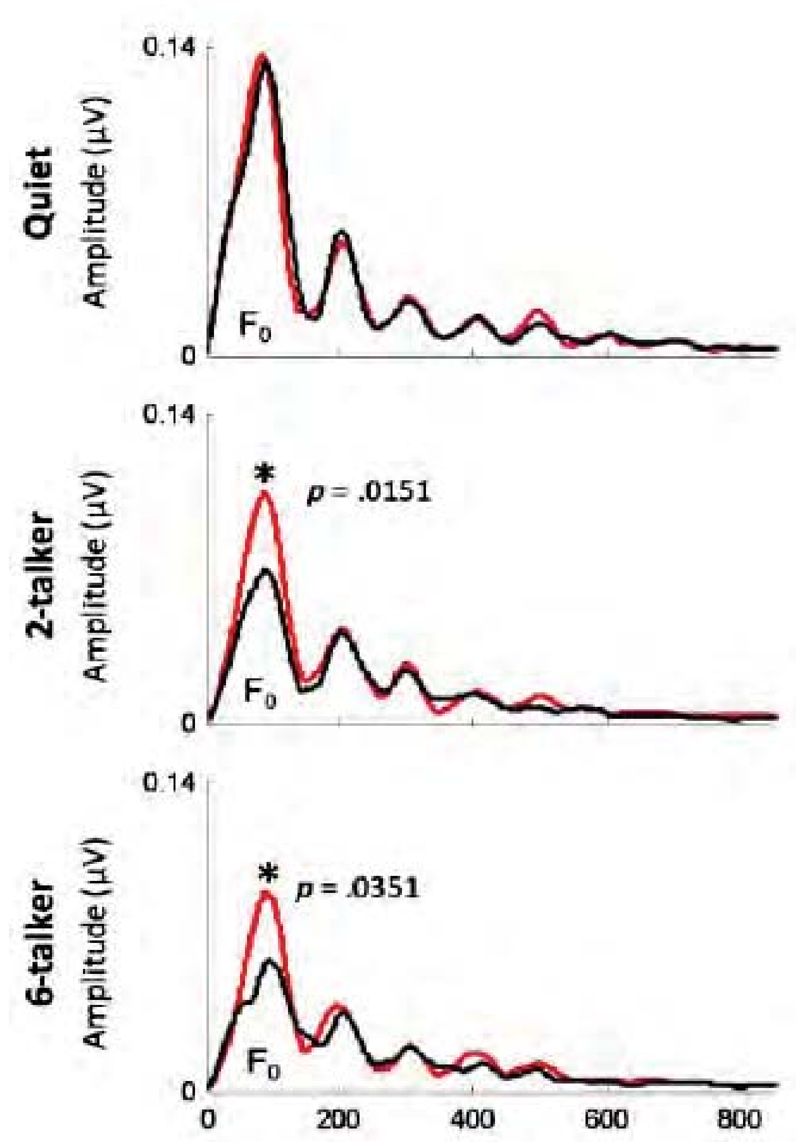
- We can do this with the steady-state response
  - also known as the auditory steady-state response (ASSR) or envelope-following response (EFR)
  - these may be more sensitive to low SR fibre damage than click responses such as SP/AP (Bharadwaj et al., 2014)

Steady-State Responses to /a/

- Steady-state responses to the envelope and harmonics of speech (TFS) (Aiken & Picton, 2008)



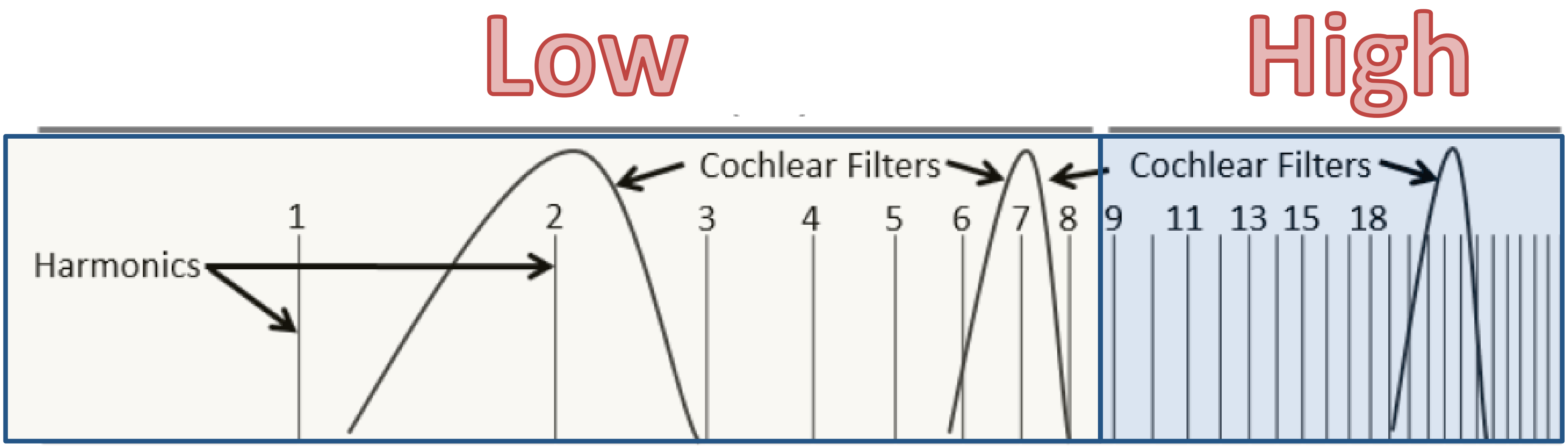
Does the response relate to hearing in noise?



- Song et al., 2011
  - measured responses to fundamental in /da/ syllables presented in quiet and in two- and six-talker babble
  - divided listeners into top performers (red) and bottom performers (black)
  - response was significantly higher in top performers

Low vs High Frequency Steady-State Responses

- Below 1500 Hz, significant representation of speech harmonics (phase-locking to TFS)
- Above 1500 Hz, representation only of envelope



Basilar Membrane of Inner Ear (log spacing)

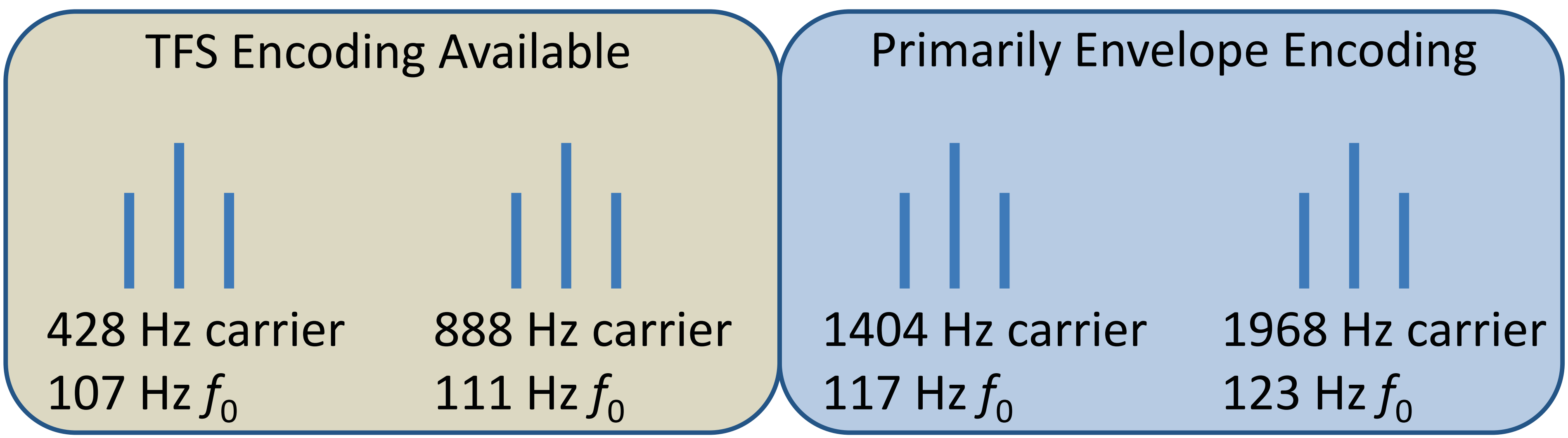
Low vs High Frequency EFR—relationship to SIN

Participants

- 29 young (19-40 yrs); 16 older (60+ yrs); ≤ 30 dB HL (250–4000 Hz)

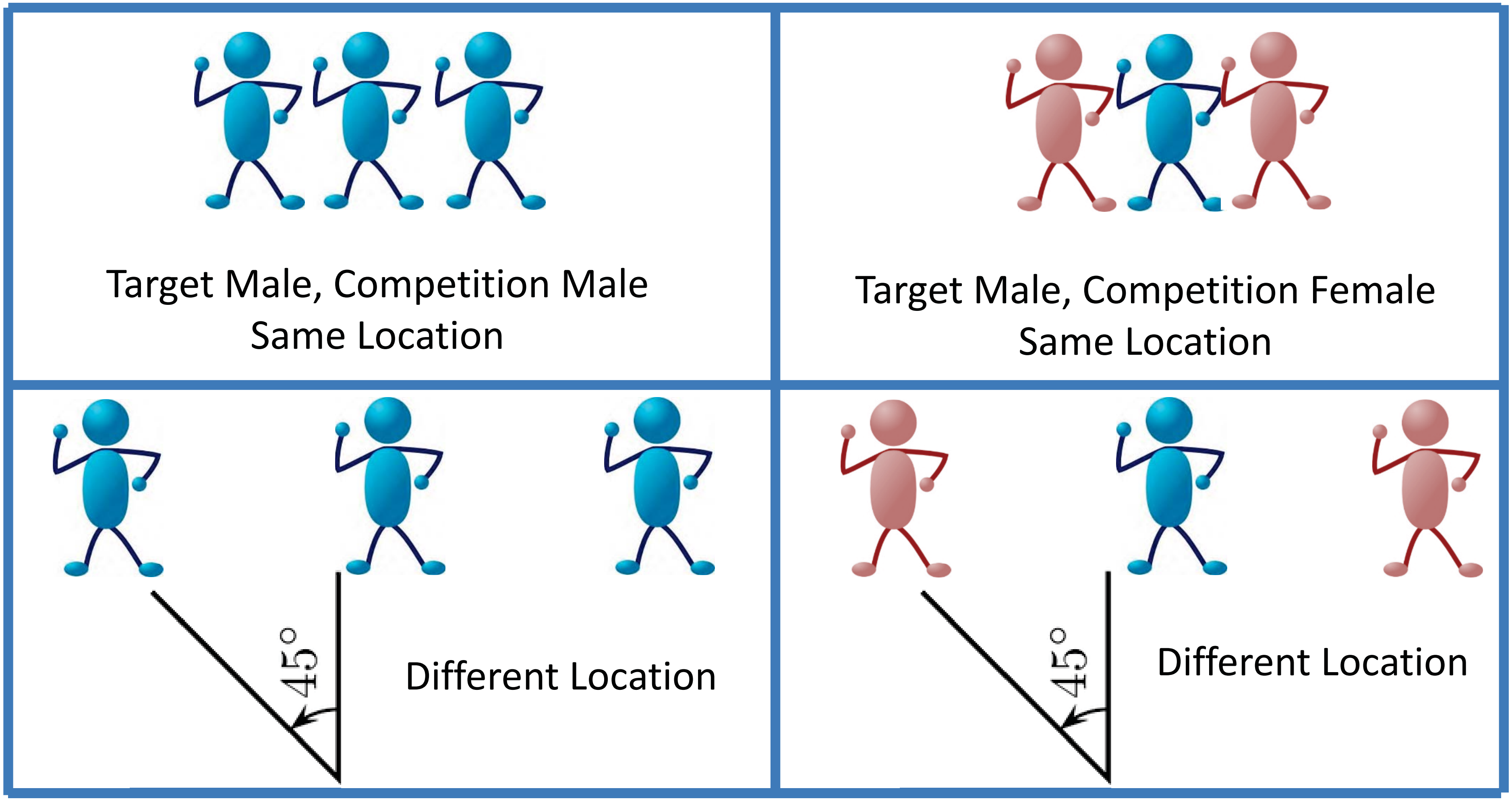
Measures

- steady-state responses to low (< 1500 Hz) and high frequency stimuli (modulated tones and speech sounds)
- speech perception in noise (CRM)

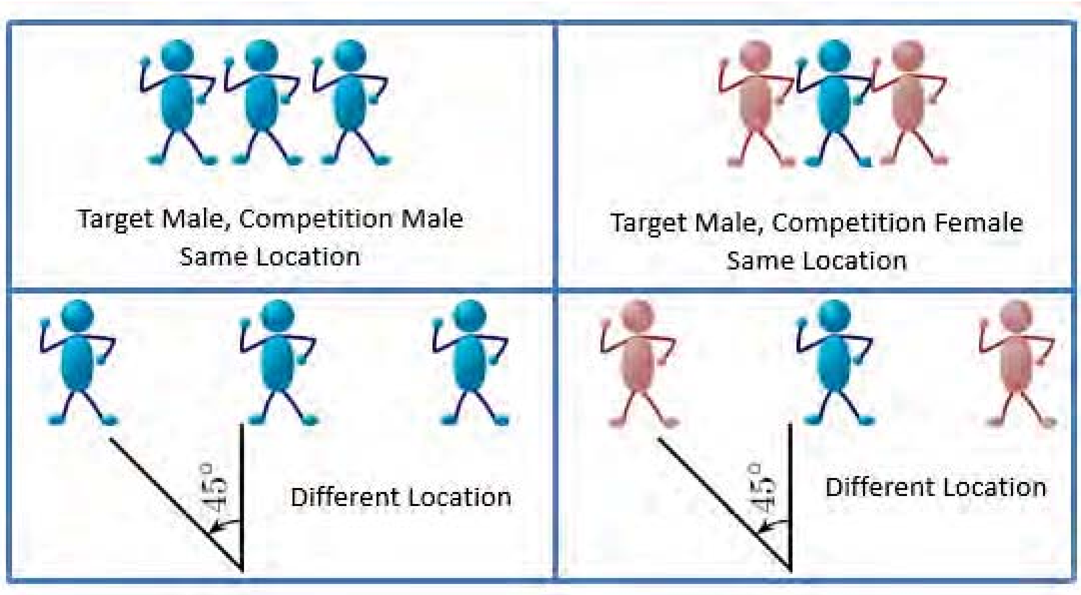


Pitch and Spatial Advantages

- Four conditions



Three Measures of Auditory Function

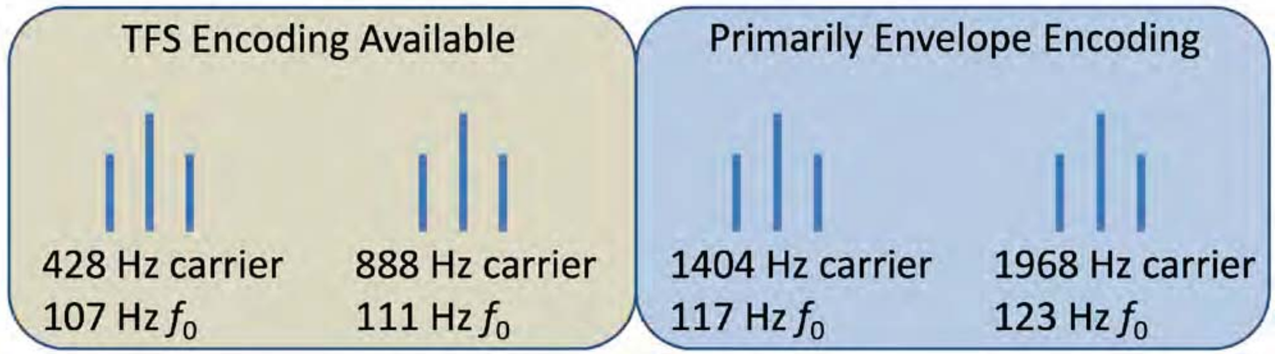


Spatial

Voice Pitch

Overall Speech in Noise Score

Results >> EFR and Speech Perception



	Quiet / Noise	Quiet / Noise
Speech in Noise	–.29 / *ns*	*ns* / *ns*
Pitch Benefit	–.32 / *ns*	*ns* / *ns*
Spatial Benefit	*ns* / *ns*	*ns* / *ns*

- only low-frequency EFR—which likely reflects peripheral TFS encoding—was related to speech-in-noise thresholds and pitch benefit

The jury is still out!

- Plack et al., 2014
  - steady-state response to low frequency tone (~200 Hz) and to high-frequency modulation (~modulation at 200 Hz)
  - response to high frequency modulated stimulus was reduced in noise-exposed group, but **not** response to low-frequency tone

- Prendergast et al., 2017
  - reduction of high-frequency EFR in males but not females

- We are seeing stronger results for tonal stimuli ~1000 Hz (i.e., higher frequency phase locking)

A Way Forward

1. Test speech in noise (e.g., the QuickSIN test) to determine whether there is a functional problem
   - note that this might occur with normal thresholds

2. Self-Report measures and exHFA thresholds may help to determine likelihood of noise damage

3. The SP/AP ratio can tell us about nerve function

4. Steady-state responses may provide information about TFS encoding problems at the physiological level

A Way Forward

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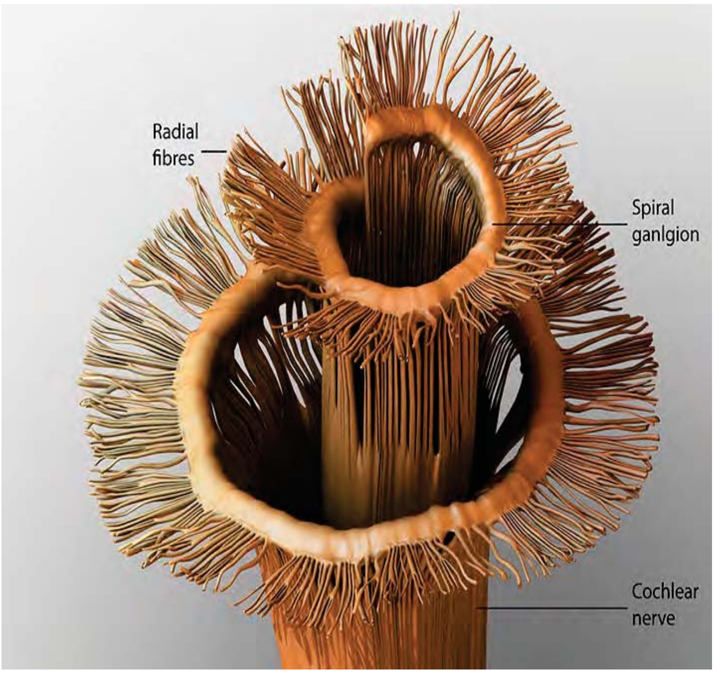
4. Steady-state responses may provide information about TFS encoding problems at the physiological level
5. Stapedius reflexes? Possibly! (Hickox et al., 2017)

Take-Out Messages



1. Synaptopathy and neuropathy may be occurring as a result of noise exposure, even when thresholds are normal

2. This may explain <u>some</u> difficulties with speech-in-noise

3. Differential diagnosis research is underway, but there are things that can be done now!

A New Era in Clinical Practice!

- Tests that are more sensitive than the audiogram to early damage
- Tests that provide clearer information about etiology

- May lead to:

→ better prevention and intervention

→ early treatment to save or reverse damage

With Thanks

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