- If you are viewing this course as a recorded course after the live webinar, you can use the scroll bar at the bottom of the player window to pause and navigate the course.
- This handout is for reference only. It may not include content identical to the PowerPoint. Any links included in the handout are current at the time of the live webinar, but are subject to change and may not be current at a later date

Hidden Hearing Loss: Cochlear Synaptopathy in Noise-Induced and Age-Related Hearing Loss

M. Charles Liberman
Eaton-Peabody Laboratories
Massachusetts Eye and Ear Infirmary

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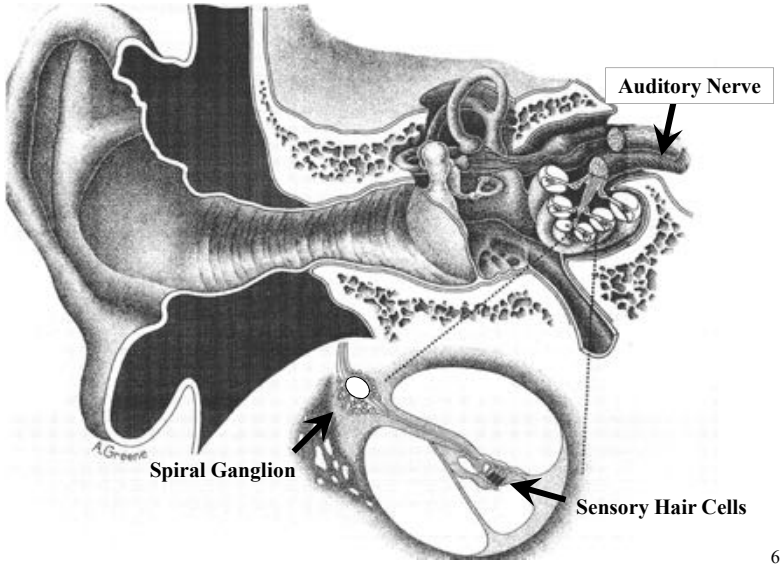
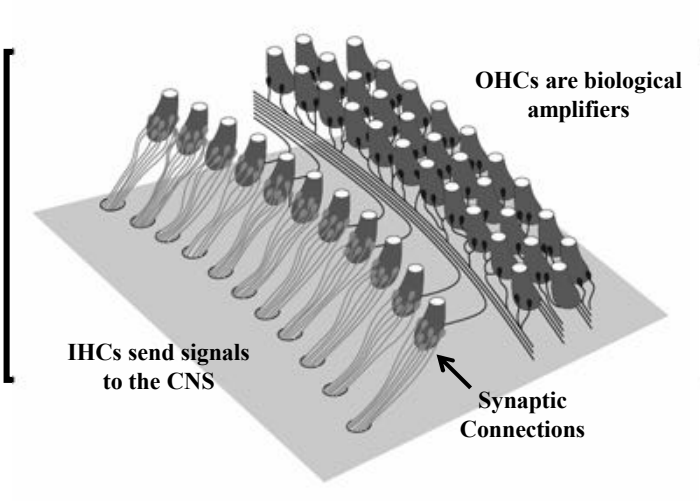
The Inner Ear and Sensorineural Hearing Loss



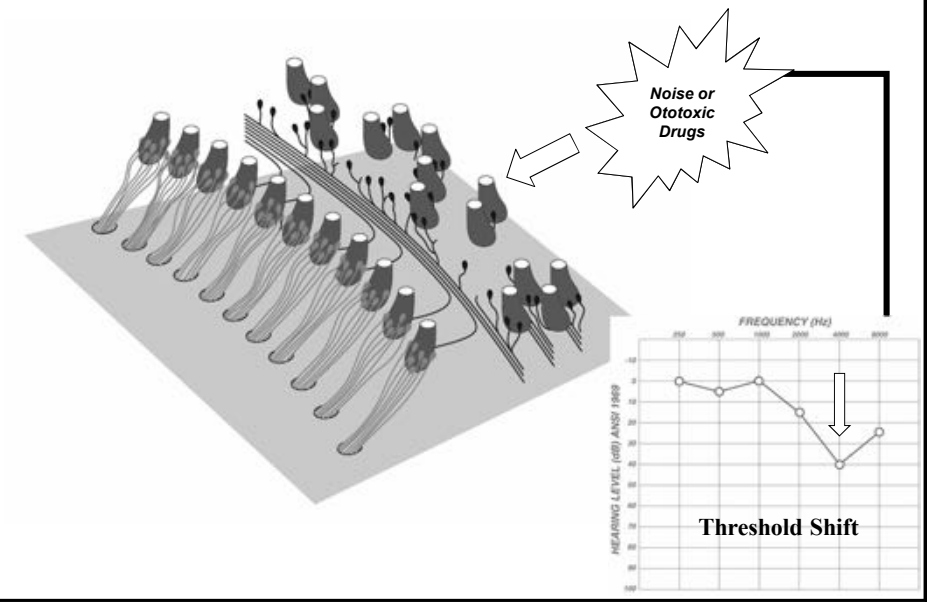
6

Hair cells & cochlear neurons are key to SNHL



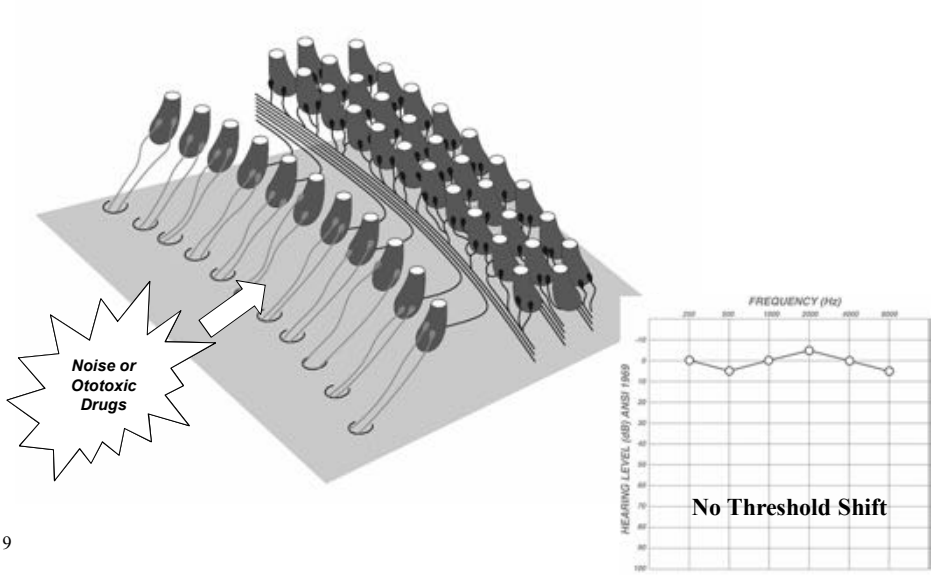
7

Hair cell death causes threshold shifts



8

Synapses, not hair cells, are most vulnerable



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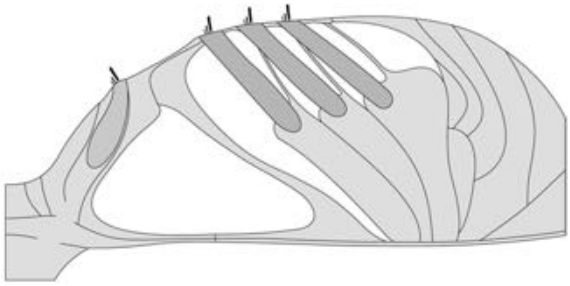
Synapses die before hair cells, but ganglion cell death is slow



Peripheral axons survive for weeks

Cell body and central axons survive for years/decades

Kujawa and Liberman, 2009

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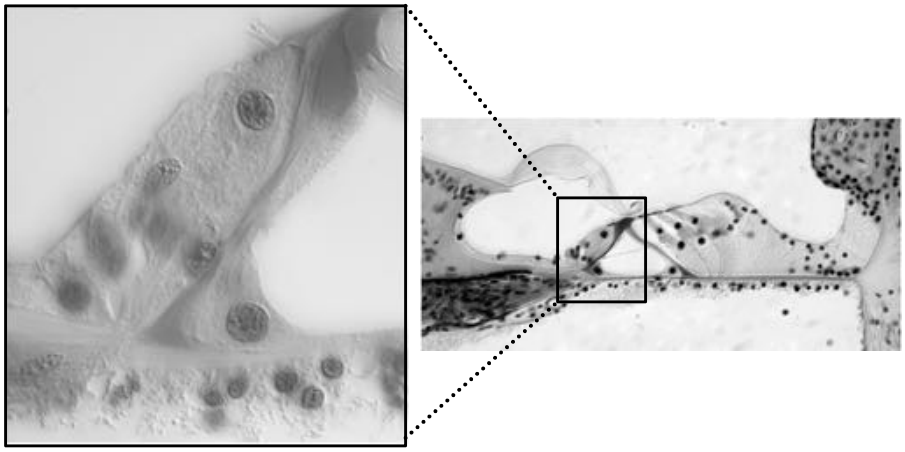
Cochlear synaptopathy is a “Hidden Hearing Loss”

Synapses and nerve terminals are invisible in routine histology



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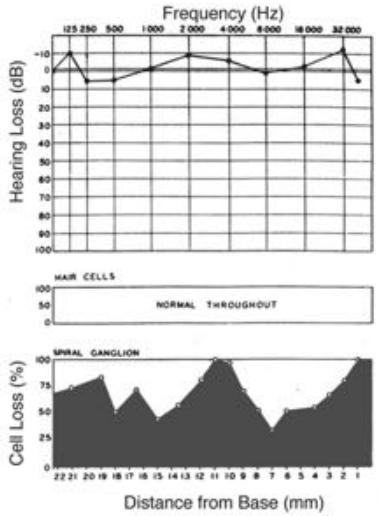
Cochlear synaptopathy is a “Hidden Hearing Loss”

Primary neural degeneration does not elevate thresholds

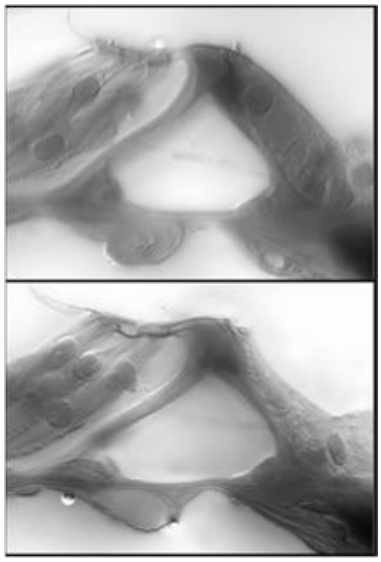


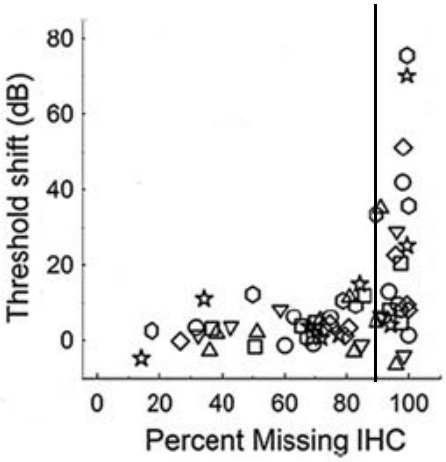
12

Schuknecht and Woellner, 1955

Neuropathy does not elevate thresholds

Behavioral thresholds in carboplatin-treated chinchillas





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Lobarinas, Salvi & Ding 2013

Cochlear Synaptopathy impairs understanding speech in noise

Impulse

5 - 15 min: TTS
50 - 150 min: PTS

Mammals: Chinchilla, Guinea Pig, Cat and Mouse

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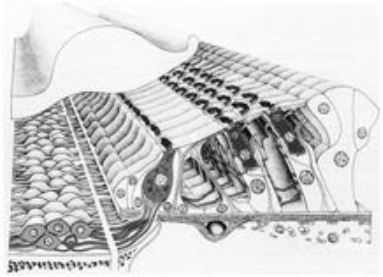
Outline

1. Cochlear synaptopathy in experimental animals: AHL and NIHL

3. Cochlear synaptopathy in aging humans: analysis of post-mortem inner ears



3. Cochlear synaptopathy in young humans: ECochG and speech in noise

4. Neurotrophins and the search for a therapy

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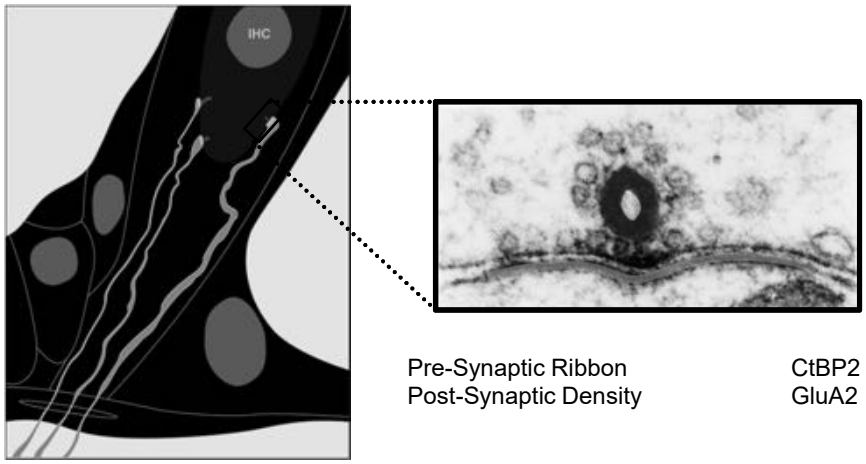
Quantifying Cochlear Synaptopathy

Use immunolabeling to see cochlear nerve terminals and synapses



Pre-Synaptic Ribbon	CtBP2
Post-Synaptic Density	GluA2

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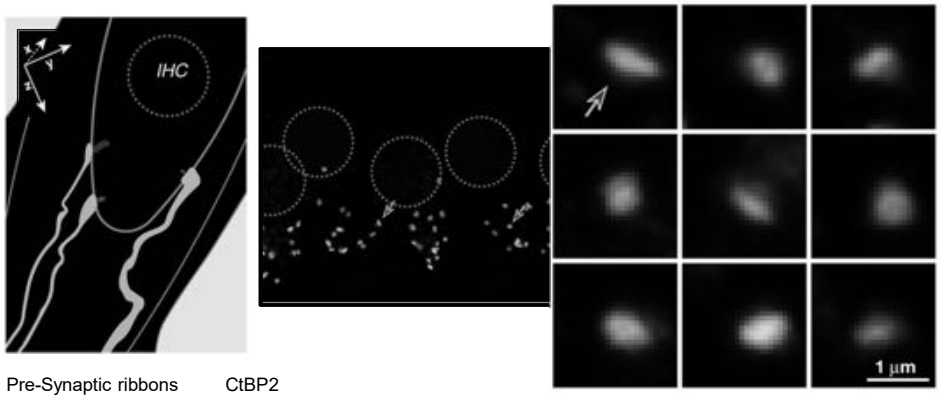
Quantifying Cochlear Synaptopathy

In normal ear: every ribbon is opposite a receptor patch and vice versa



Pre-Synaptic ribbons CtBP2
Post-Synaptic Receptors GluA2

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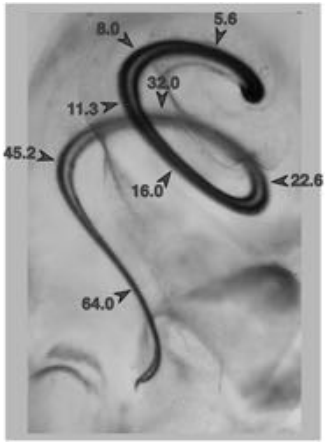
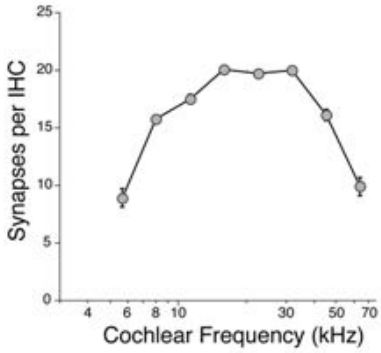
Maison and Liberman, 2013

Quantifying Cochlear Synaptopathy

In normal ear: synapse counts peak in the middle of the cochlea





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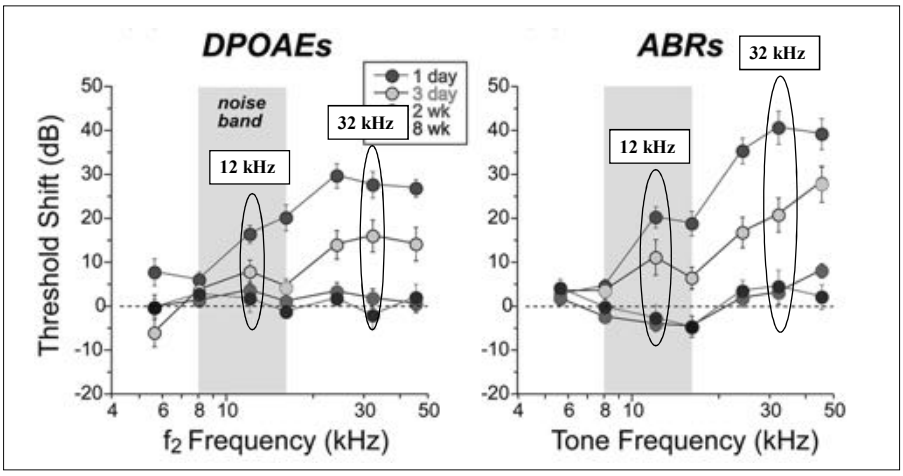
Maison and Liberman, 2013

Cochlear Synaptopathy and Temporary Threshold Shift

Mouse: ABR and DPOAE thresholds recover from initial 30-40 dB shift



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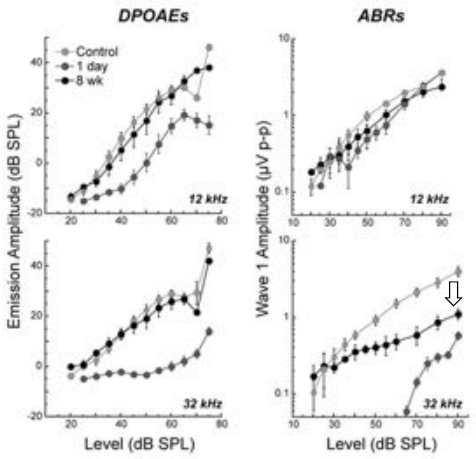
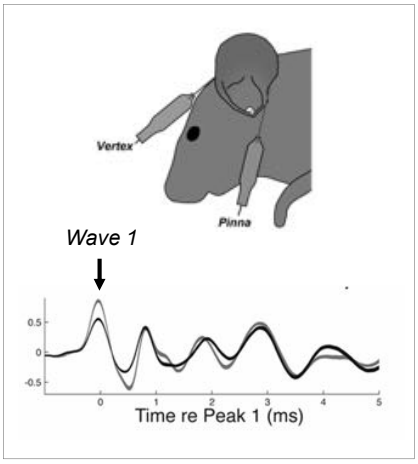
Kujawa & Liberman, 2009

Cochlear Synaptopathy and Temporary Threshold Shift

ABR Wave 1 does not recover

ABR Wave 1 = auditory nerve





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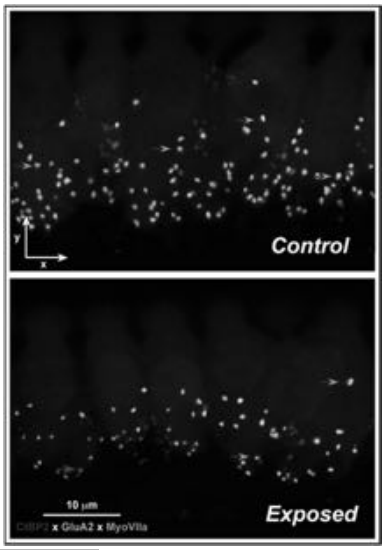
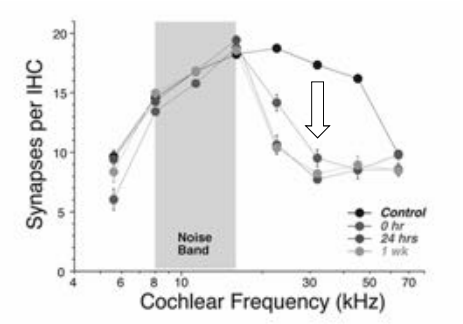
Kujawa & Liberman, 2009

Cochlear Synaptopathy and Temporary Threshold Shift

Cochlear nerve synapses disappear immediately– hair cells remain intact





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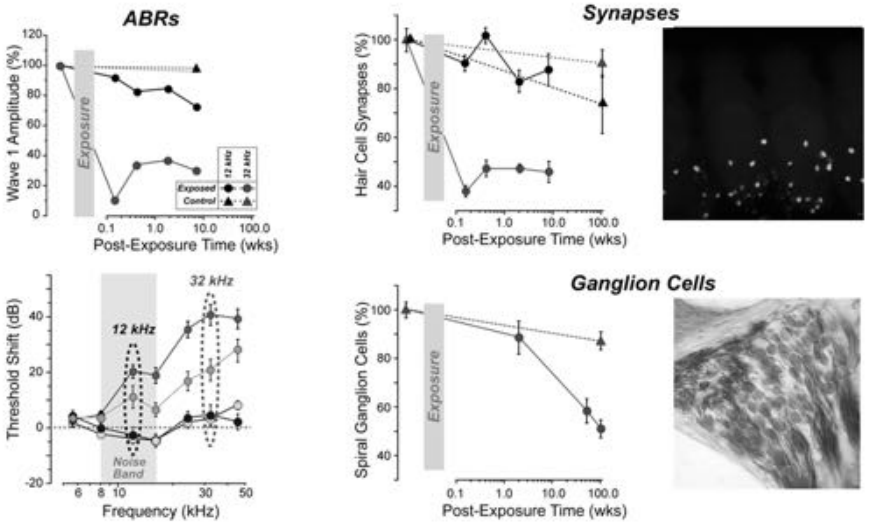
Liberman et al, 2015

Cochlear Neuropathy after Temporary Threshold Shift

Spiral ganglion cell death follows - after months to years



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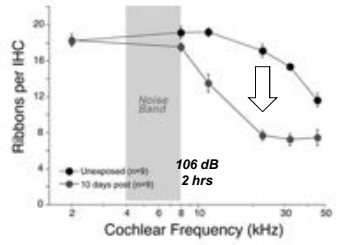
Kujawa & Liberman, 2009

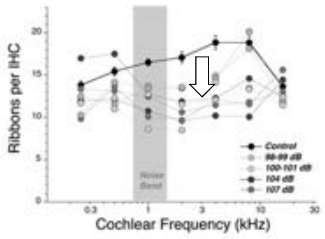
Cochlear Synaptopathy and Temporary Threshold Shift

Noise-induced synaptic loss is observed in other mammalian species

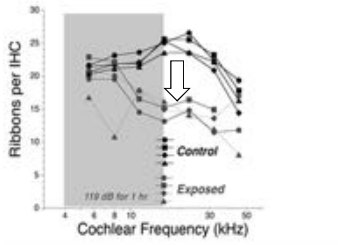
Guinea Pig

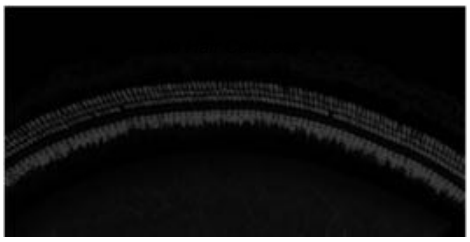


Chinchilla



Rat





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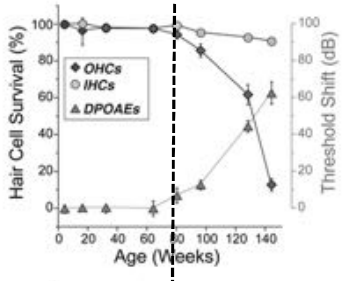
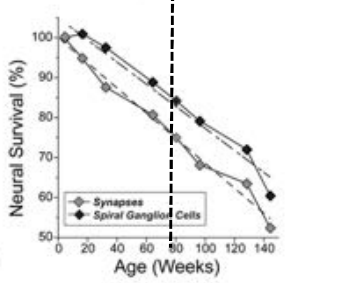
Cochlear Synaptopathy in Aging Mice

In aging mice,synaptopathy precedes hair cell loss and threshold shifts



Hair Cells



Nerve Terminals

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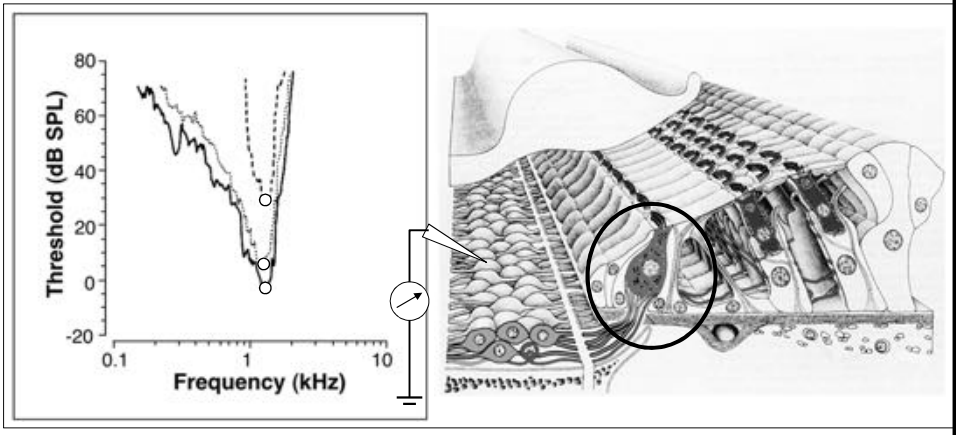
Sergeyenko et al. 2013

Cochlear synaptopathy is selective for Low-SR fibers

Auditory nerve fibers have different threshold sensitivity



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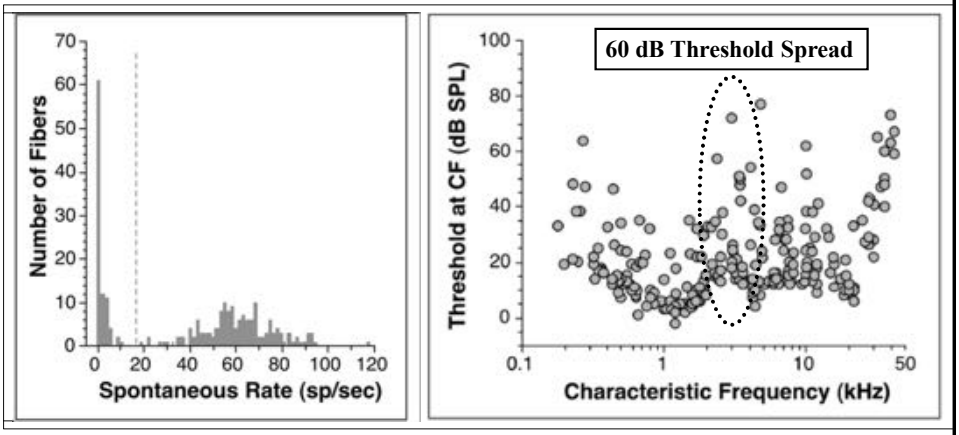
Cochlear synaptopathy is selective for Low-SR fibers

Low-SR neurons have high thresholds and vice versa



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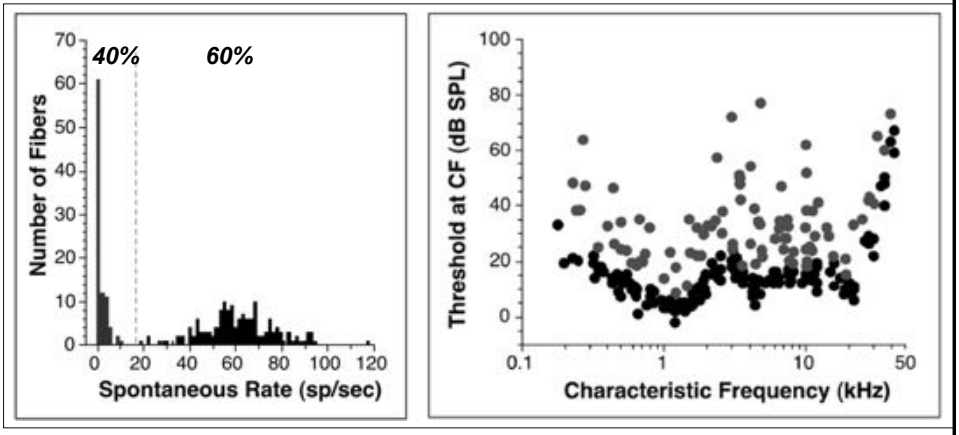
Cochlear synaptopathy is selective for Low-SR fibers

High-SR neurons have low-thresholds and vice versa



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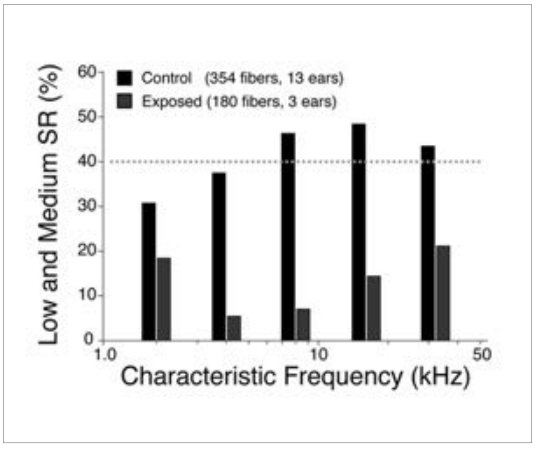
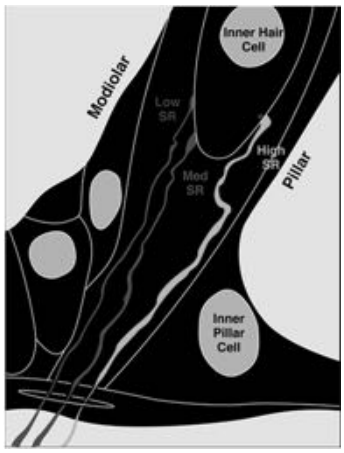
Liberman, 1978

Cochlear synaptopathy is selective for Low-SR fibers

Low- and medium-SR fibers comprise 40% of the cochlear nerve





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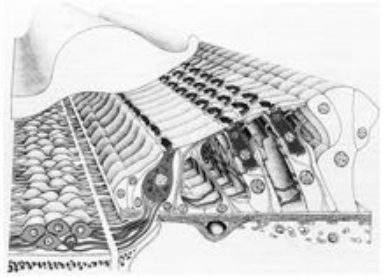
Lin, Furman, Kujawa & Liberman, 2011

Outline

1. Cochlear synaptopathy in experimental animals: AHL and NIHL

3. Cochlear synaptopathy in aging humans: analysis of post-mortem inner ears



3. Cochlear synaptopathy in young humans: ECochG and speech in noise

4. Neurotrophins and the search for a therapy

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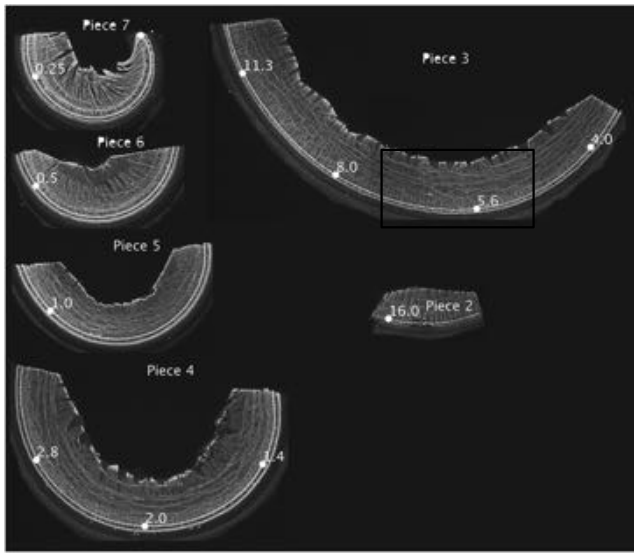
Cochlear Synaptopathy in Aging Humans

Dissect the cochlear spiral, measure length and convert to frequency



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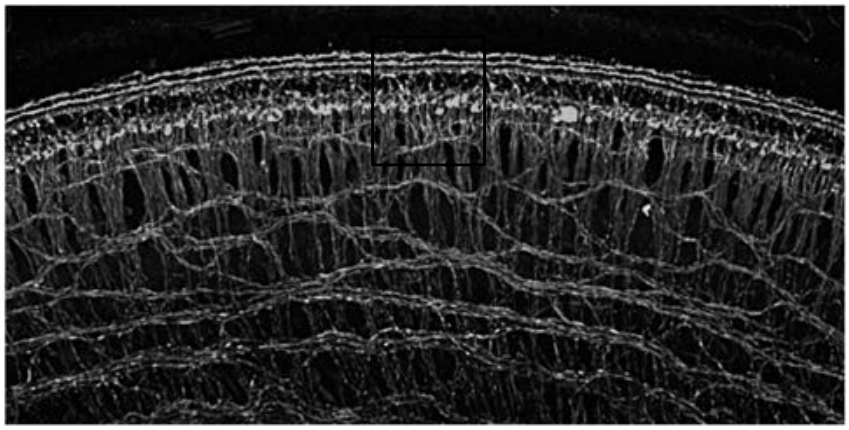
Cochlear Synaptopathy in Aging Humans

Anti-Neurofilament stains all cochlear axons and terminals

Anti-ChAT stains all cochlear efferent axons and terminals



Viana et al 2015

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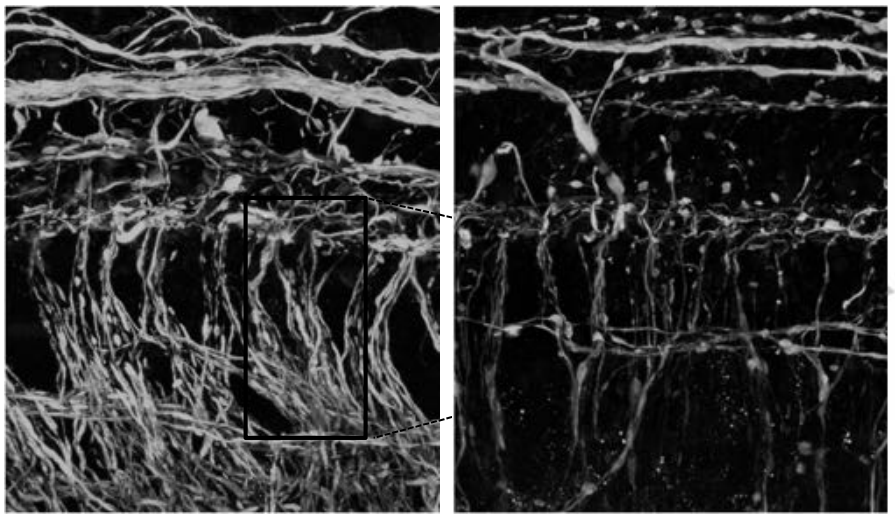
Cochlear Synaptopathy in Aging Humans

Fiber counts at 0.5 kHz

Fiber counts at 4 kHz



Viana et al 2015

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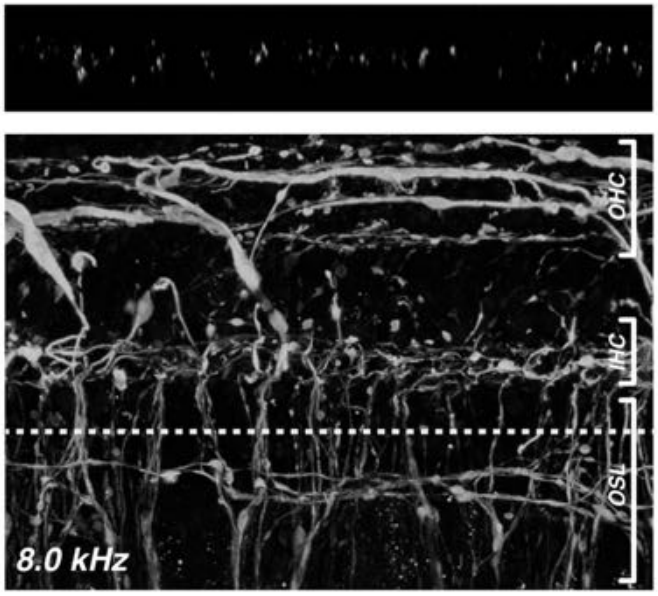
Cochlear Synaptopathy in Aging Humans



Viana et al 2015

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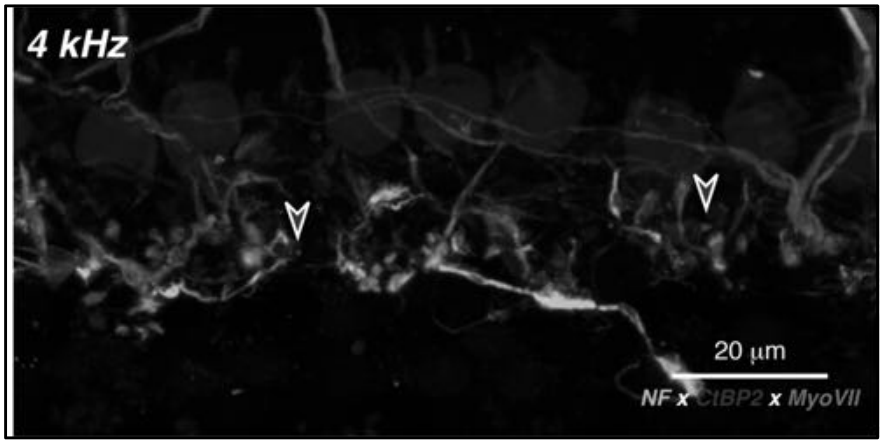
Cochlear Synaptopathy in Aging Humans

Immunostaining IHC synapses



Viana et al 2015

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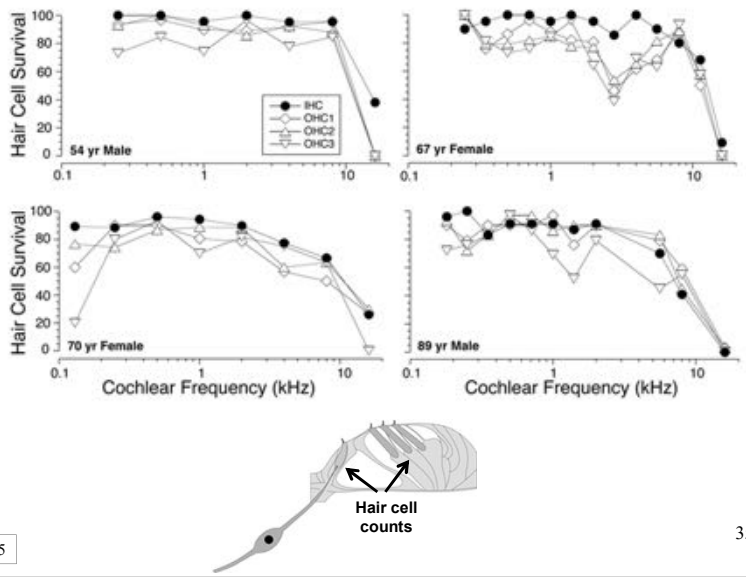
Cochlear Synaptopathy in Aging Humans

Hair cell counts in aging humans



Viana et al 2015

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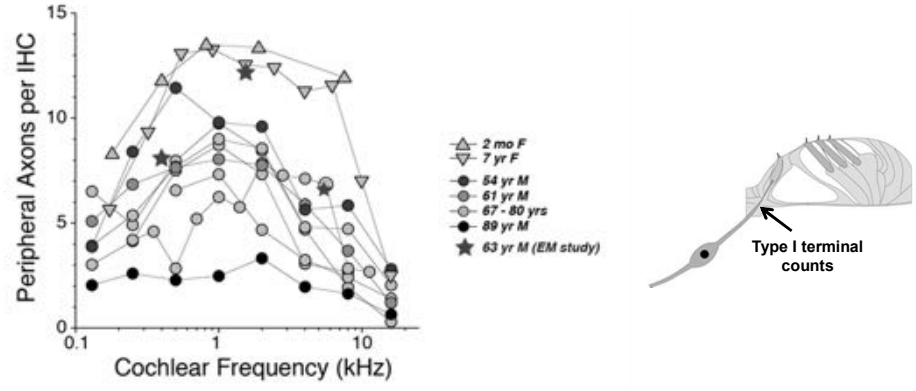
Cochlear Synaptopathy in Aging Humans

Nerve counts in humans with no hair cell loss



Viana et al 2015

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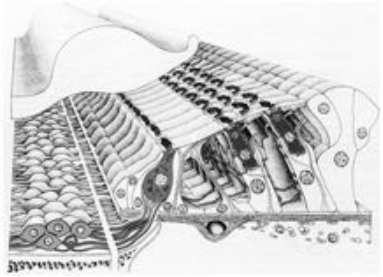
Outline

1. Cochlear synaptopathy in experimental animals: AHL and NIHL

3. Cochlear synaptopathy in aging humans: analysis of post-mortem inner ears



3. Cochlear synaptopathy in young humans: ECochG and speech in noise

4. Neurotrophins and the search for a therapy

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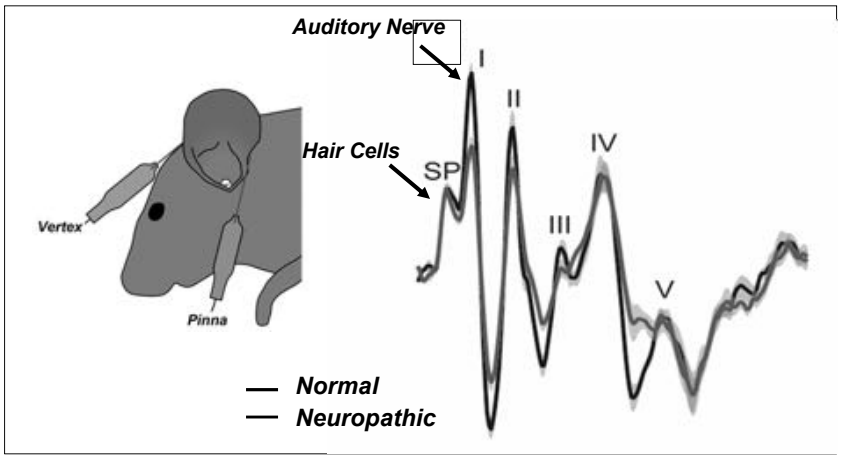
Diagnosing Cochlear Synaptopathy

SP is from Hair Cells; Wave 1 (AP) is from Cochlear Nerve



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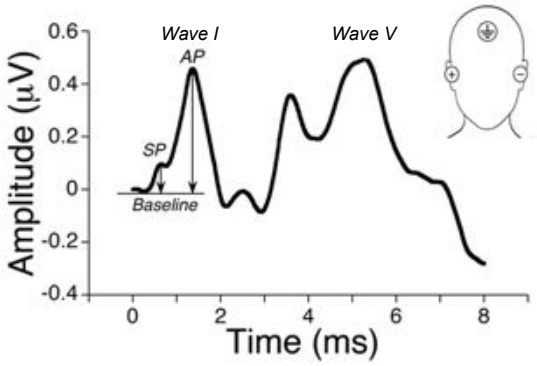
Shaheen et al., 2015

Diagnosing Cochlear Synaptopathy

SP : AP (Wave 1) ratio from tiptrode electrodes in the human ear canal



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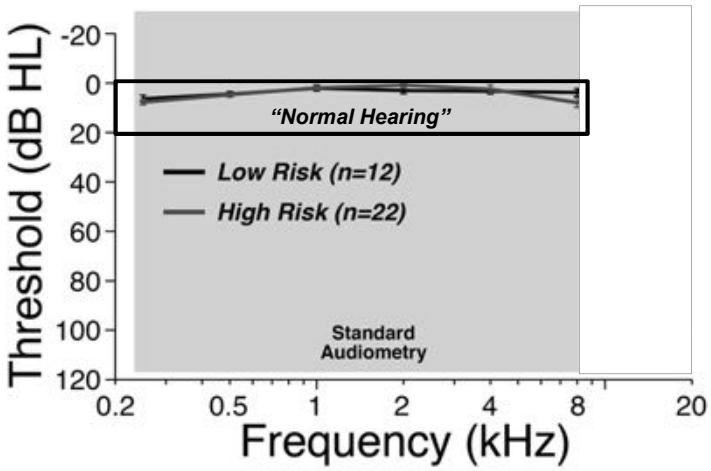
Liberman et al., 2016

Diagnosing Cochlear Synaptopathy

College students: High-risk vs. Low-risk based on self report



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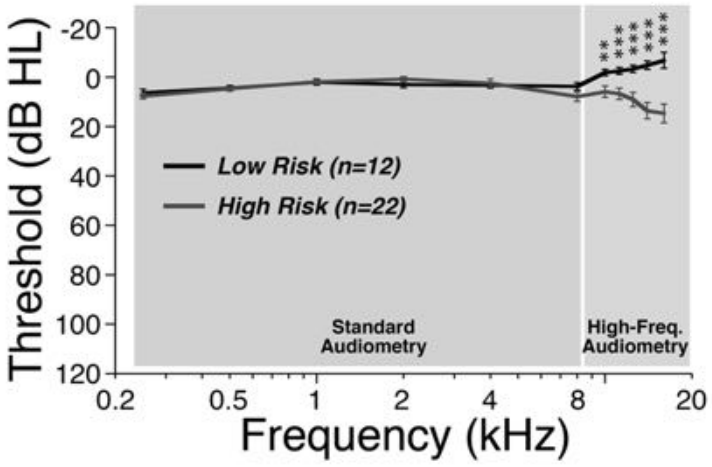
Liberman et al., 2016

Diagnosing Cochlear Synaptopathy

College students: High-risk vs. Low-risk based on self report



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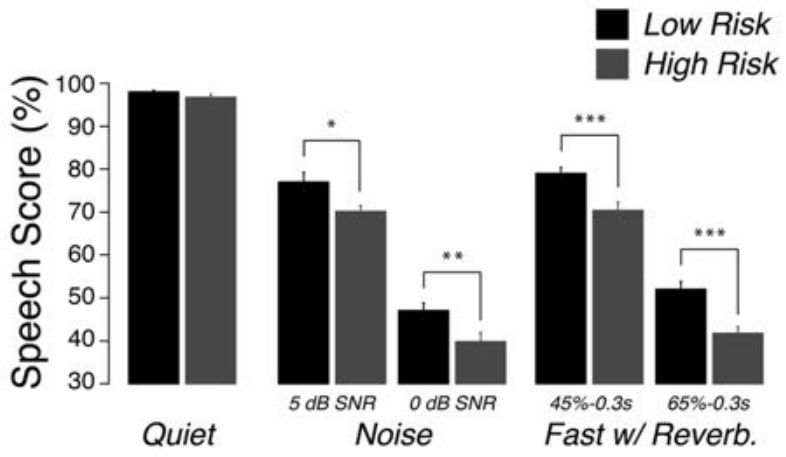
Liberman et al., 2016

Diagnosing Cochlear Synaptopathy

High-risk group shows reduced word recognition scores



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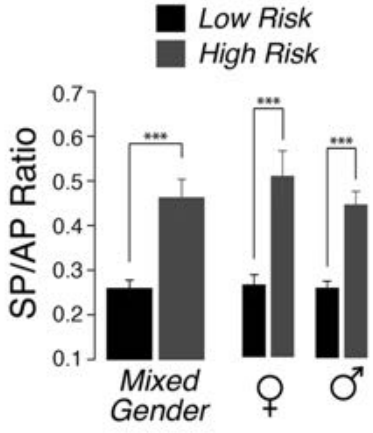
Liberman et al., 2016

Diagnosing Cochlear Synaptopathy

High-risk group shows pathological SP/AP ratios in ABR



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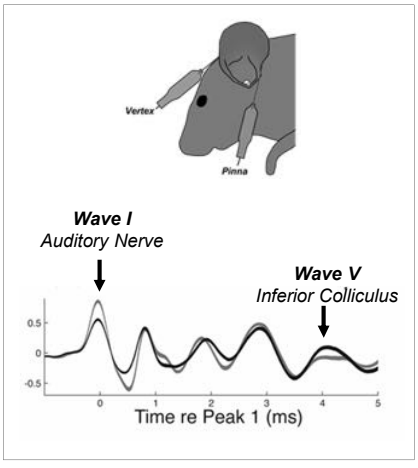
Liberman et al., 2016

Synaptopathy may also cause tinnitus

Signs of Central Hyperactivity



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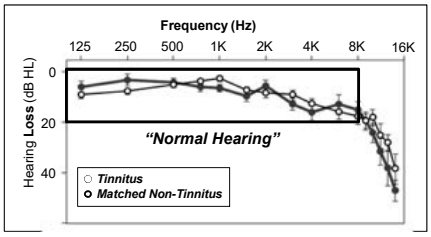
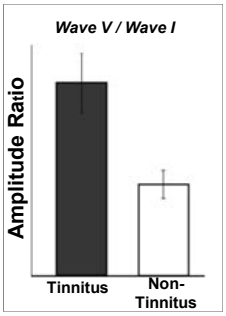
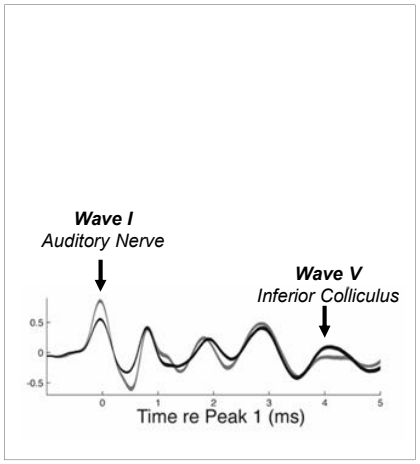
Synaptopathy, Central Hyperactivity & Tinnitus

Tinnitus sufferers have high Wave V : Wave I ratio in ABR







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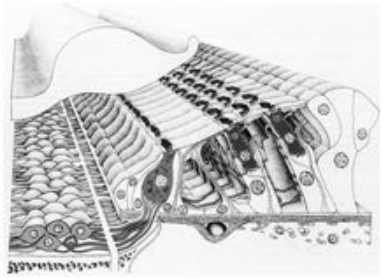
Gu, Herrmann, Levine, Melcher, 2012

Outline

1. Cochlear synaptopathy in experimental animals: AHL and NIHL

3. Cochlear synaptopathy in aging humans: analysis of post-mortem inner ears

3. Cochlear synaptopathy in young humans: ECochG and speech in noise



4. Neurotrophins and the search for a therapy

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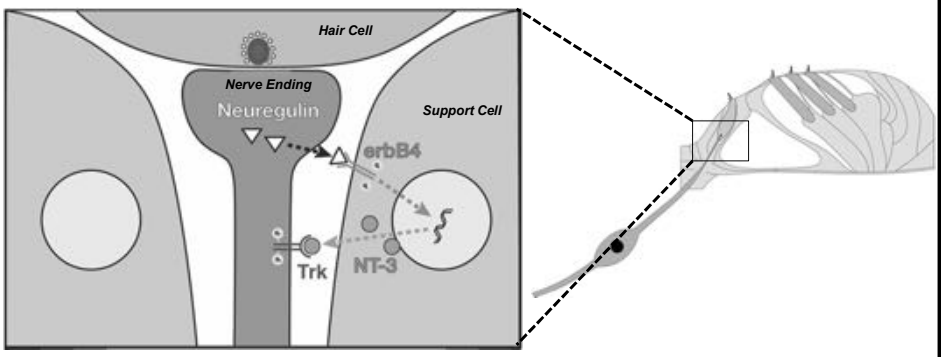
Neurotrophins are key to nerve survival

NT-3 *signaling from supporting cells keeps nerve cells alive*



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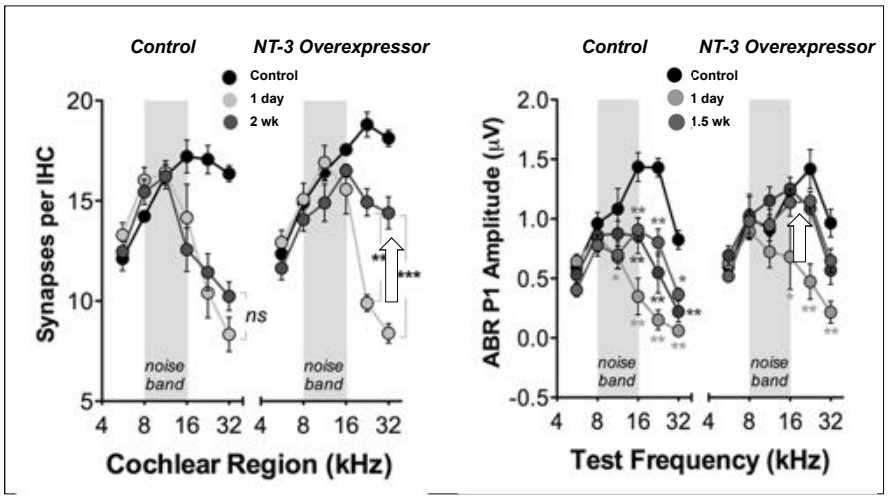
Stankovic et al., 2004

Neurotrophin-3 regenerates synapses after noise

Transgenic mouse with ***NT-3*** *overexpressed in support cells*

Synapse recovery ***Functional Recovery***



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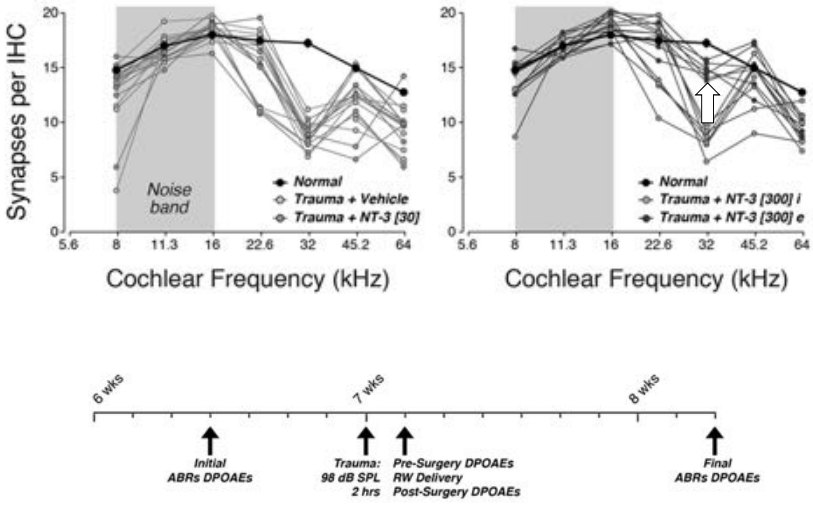
Wan et al 2015

Neurotrophin therapy to regenerate nerve fibers ?

*Direct **NT-3** delivery to inner ear via the RW*



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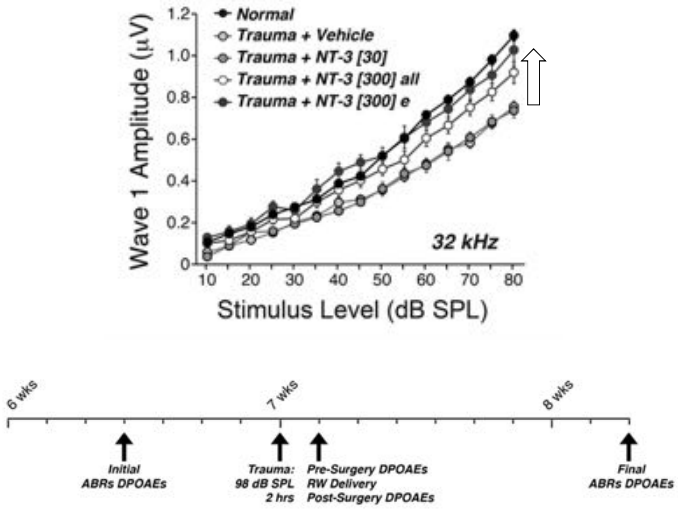
Neurotrophin therapy to regenerate nerve fibers ?

*Direct **NT-3** delivery to inner ear via the RW*



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Conclusions

Noise and ototoxic drugs causes rapid synaptic loss and slow cochlear nerve degeneration, even if hair cells recover

Aging causes slow synaptic loss, long before hair cell loss

Initially, synaptic loss is selective for high-threshold, low-SR fibers

Cochlear synaptopathy does not elevate audiometric thresholds but causes deficits in more complex hearing tasks and maybe tinnitus

Slow degeneration of spiral ganglion offers a therapeutic window; NT-3 can regenerate missing synapses

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noise- and age-induced neuropathy

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immunostaining protocols and cochlear histology

Stephane Maison – MEEI
human ECochG study

Jen O'Malley, Diane Jones, Lucas Viana, Felipe Santos – MEEI
human temporal bone work

Jun Suzuki – MEEI; Leslie Shinobu – Decibel Therapeutics
Round window NT-3 delivery in mouse

Gabriel Corfas & Guoqiang Wan – Kresge Hearing Research
NT-3 overexpression in mouse models

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