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Relationships between Recreational Noise Exposure and Auditory Function

Colleen Le Prell, PhD &
Angela Fulbright, AuD, PhD, CCC-A

Learning Outcomes

- After this course, participants will be able to define hidden hearing loss.
- After this course, participants will be able to discuss evidence of neural pathology in human samples with diverse noise exposure history.
- After this course, participants will be able to identify monitoring strategies that may be more sensitive than the audiogram.
Overview

- Cochlear synaptopathy in rodents
- Translation to humans
  - Retrospective analyses
  - Cross-sectional comparisons
  - Prospective (longitudinal) data collection
- Prevention
- Where do we go from here, and what can you tell your patients today?

IHC/ANF Connections Decrease Post-Noise

- Synaptic ribbons (red dots) connect IHCs and auditory nerve dendrites (green)
- Noise induces decrease in synaptic ribbons

A closer look reveals:
- Swollen peripheral terminals of IHC/ANF synapse
- Missing, misshaped or misplaced auditory nerve dendrites


https://www.audiologyonline.com/articles/20946

Cochlear Synaptopathy after TTS

- TTS induced in mice; subsequent to threshold recovery and DPOAE amplitude recovery, there was a lasting decrease in ABR wave I amplitude at a subset of tested frequencies
- When synaptic connections were counted, there were lasting decreases in the number of synapses between the IHCs and the auditory nerve fibers
- Swollen peripheral terminals of IHC/ANF synapse and missing, misshaped, or misplaced auditory nerve dendrites observed
Cochlear synaptopathy

- Noise exposure that induces a TTS can result in immediate synapse loss, decreased ABR amplitude, and long-term spiral ganglion loss

- Not every noise is synaptopathic

- Critically important to determine dose relationship related to both a single acute exposure resulting in a perceived TTS as well as repeat lower level exposure, and contrast with aging alone

Where does risk of synaptopathic injury begin?

- Mouse: synapse damage observed with 100 dB SPL OBN x 2 hrs, but not 97 dB SPL x 2 hours
- Guinea Pig: synapse damage observed at 106 dB SPL OBN x 2 hrs, PTS observed at 109 dB SPL x 2 hours
- Rat: synapse damage observed at 109 dB SPL OBN x 2 hrs, but not 106 dB SPL x 2 hours
- Rhesus Macaque: synapse damage observed at 108 dB SPL narrow band noise x 4 hours (50 Hz noise band centered at 2 kHz), or, 120 dB SPL OBN x 4 hrs
- Human: We don’t know where risk begins, or how it grows, in humans; active efforts to assess risk using both retrospective and prospective designs
Susceptibility for TTS and synaptopathy is specie dependent

Different susceptibilities for TTS, HC loss (rank order):

1. Chinchilla, gerbil
2. Mouse (varies by strain)
3. Guinea pig
4. Human
5. Rats

Dobie & Humes (2017) suggest there is an approximate 14 dB difference for species susceptibility between humans and mice

1 > 3 (Drescher, 1974; Saunders, 1982)
1 > 4 (Mills, 1988)
2 > 3 (Burdick, 1978; Henry, 1982; Duan, 2008)
3 > 4 (Liang, 1992)
5 <= 3 but > 4 (Maanstrom et al., 2015; Duan et al., 2008; Lobarinas et al., 2016)

Adapted from slide from Dobie & Humes, NHCA 2016

Early Translation to Humans

- Stamper & Johnson, 2015: ABR wave I amplitude decreased as recreational noise exposure in past 12 months increased; follow-up with control for sex differences revealed differences limited to female participants
- Liberman et al., 2016: Summating Potential (and therefore SP/AP amplitude ratio) smaller in high-risk young adults (music students) vs low-risk young adults (communication disorders students); in addition, high-frequency thresholds poorer, and hearing in noise poorer
“Confirmation” of noise-induced synaptopathy in humans?

- Stamper and Johnson (2015, Ear & Hearing) reported decreased ABR amplitude as a function of self-reported noise exposure in the past 12 months
  - Relationship statistically significant for 90-dB nHL click signal when ABR assessed using mastoid electrodes
  - Similar trends detected at lower levels (>70 dB nHL) for clicks and 4-kHz pure tones and when using an electrode placed on the tympanic membrane

Synaptopathy limited to females?

- Stamper and Johnson reanalyzed mastoid electrode data set to account for potential confound related to sex differences (2015 Letter to the Editor)
  - Relationship between Wave I amplitude and noise in past year statistically significant within female cohort
  - Opposite effect observed within males; ABR amplitude tended to grow larger with increasing 1-year noise history (n.s.)

continued
Early Translation to Humans

- Stamper & Johnson, 2015: ABR wave I amplitude decreased as recreational noise exposure in past 12 months increased; follow-up with control for sex differences revealed differences limited to female participants.

- Liberman et al., 2016: Summating Potential (and therefore SP/AP amplitude ratio) larger in high-risk young adults (music students) vs low-risk young adults (communication disorders students); in addition, high-frequency thresholds poorer, and hearing in noise poorer.

EHF thresholds poorer in music students; SP and SP/AP larger.

Poorer speech-in-noise results in music students


Vanderbilt University Cohort

- 40 participants (22F, 18M), 18-28 yrs of age, with ≤25 dB HL thresholds from 250-8000 Hz, with and without diabetes
- Participants with higher noise scores worked in the music industry, attended frequent live shows in Nashville, TN, or were hunters/shooters
- No statistically significant relationships between noise history and:
  - Conventional or EHF thresholds
  - DPOAE or TEOAE amplitude
  - ABR amplitude

### ABR wave-1 amplitude versus noise exposure

**Left ears**

- Supra-threshold wave I amplitude
- Wave I amplitude plotted as function of NEB at 27.7 clicks/sec and 77.7 clicks/sec
- Triangles: participants with diabetes; circles: no diabetes controls
- Linear regression analyses were not statistically significant (p's > 0.05)

**Right ears**


### University of Florida Cohort

- 60 participants (34F, 26M), 18-29 yrs of age, with <25 dB HL thresholds from 250-8000 Hz
- Participants had varied noise histories, non-occupational/recreational

- No relationship between noise history and:
  - Threshold (250 – 8000 Hz)
  - DPOAE amplitude
  - ABR amplitude
  - Performance on a variety of word-in-noise tests and other temporal resolution tasks

Retrospective Data on Noise Exposure

- Noise survey used to determine LAeq8760 and LAeqLife
  - Stamper and Johnson (2015) supplemental data for calculations
  - Conducted as an interview
  - Mean noise exposure scores not significantly different when males and females compared

Noise vs ABR Wave I amplitude: no statistically significant relationships w/earlobe electrodes and clicks

- Supra-threshold wave I amplitude measured using earlobe electrodes versus NEB in females (top panels) or males (bottom panels)
- 21.1/sec clicks
- Linear regression analyses were not statistically significant (p's > 0.05)

4000 Hz Tones
Noise vs ABR Wave I amplitude: no statistically significant relationships at 4000 Hz

- Wave I amplitude measured using earlobe/mastoid electrodes and clicks
- Linear regression analyses were not statistically significant (p’s > 0.05)

UT Dallas Cohort

- 32 participants (19F, 13M), 21-27 yrs of age, with ≤25 dB HL thresholds from 250-8000 Hz
- Participants had varied recreational noise histories, with no significant occupational exposure to noise
- No statistically significant relationships between noise history and:
  - Threshold (250-8000 Hz)
  - DPOAE amplitude
  - ABR amplitude


No reliable relationship between previous 12-months noise exposure and threshold sensitivity in normal hearing young adults exposed to loud recreational sound

No reliable relationship between previous 12-months noise exposure and DPOAE amplitude in normal hearing young adults exposed to loud recreational sound


No reliable relationship between previous 12-months noise exposure and Words-in-Noise (WIN) in normal hearing young adults exposed to loud recreational sound

Statistically significant male vs female difference in ABR wave I amplitude at 80 and 90 dB nHL

- Wave I amplitude was reliably larger in females than in males for clicks, 2000, 3000, and 4000 Hz tone bursts, at 80 dB nHL and 90 dB nHL.


No statistically significant relationship between ABR wave I amplitude and noise history

No reliable relationship between previous 12-months noise exposure and threshold sensitivity in normal hearing young adults exposed to loud recreational sound

Males
Click: R=0.0780, p=0.8095
2000 Hz: R=0.1096, p=0.7346
3000 Hz: R=0.0374, p=0.9081
4000 Hz: R=0.0106, p=0.9740

Females
Click: R=0.0858, p=0.7269
2000 Hz: R=0.1290, p=0.5987
3000 Hz: R=0.0877, p=0.7293
4000 Hz: R=0.1516, p=0.5355

Prospective Monitoring

- 28 of 31 participants attended recreational event they deemed loud, and returned the day after event for repeat testing.

Exposure Data:

- < 50% OSHA dose (4 male, 5 female)
- 50-100% OSHA dose (4 male, 6 female)
- > 100% OSHA dose (3 male, 6 female)

Event levels of 93.3 ± 7.8 dBA (range 73.1 – 104.2 dBA)

Event durations of 4.2 ± 3.5 hours (range 1.5 – 16.0 hours)

Calculated using 29 CFR 1910.95, average noise dose was 168.4% ± 276% (range 3.5% – 1,230.8%)

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<td>108.1</td>
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No reliable increase in TTS the day after recreational events; all TTS recovers by 1-wk post

No reliable TTS the following day within OSHA dose > 100% group

No reliable decrease in DPOAE amplitude the day after recreational events; all changes recover by 1-wk post
No reliable DPOAE decrease the following day within OSHA dose > 100% group


No reliable decrease in wave I amplitude the day after recreational events

No reliable change in ABR amplitude the following day within OSHA dose > 100% group

Temporary noise-dependent decrease in performance observed for Words-in-Noise (WIN) the day after recreational events; recovery observed at 1-wk test

Reliable noise-induced decrease in WIN score the following day, within OSHA dose > 100% group

![Graph showing number of correct responses per ear against OSHA Dose >100%]


Review of Acute Changes

- No reliable TTS
- Poorer Words in Noise
- DPOAEs unchanged?
- ABR unchanged

Word-in-Noise understanding was temporarily compromised, suggesting this was the most sensitive metric for transient noise injury.

Individuals are highly variable even if they have same exposure, and these were not equivalent exposures – are there relationships between max TTS and other changes?
2017 - “hidden hearing loss” was hot topic

- Bramhall et al., 2017: ABR wave I amplitude decreased in veterans with high noise exposure and civilians exposed to firearm noise
- Prendergast et al., 2017: No relationship between ABR wave I amplitude and lifetime noise exposure in young adults with normal audiograms; high frequency hearing loss detected
- Yeend et al., 2017: No relationship between hearing-in-noise outcomes versus lifetime noise exposure in young adults with normal audiograms; high-frequency hearing loss detected
- Yeend et al., 2017: No relationship between hearing-in-noise in young adults with normal audiograms; high-frequency hearing loss detected
- Prendergast et al., 2017: No relationship between lifetime noise exposure and hearing-in-noise in young adults with normal audiograms; high-frequency hearing loss detected
- Grose et al., 2017: No relationship between extreme concert attendance (40 concerts in past two years) vs low concert attendance (4 concerts in past two years) and ABR wave I amplitude or hearing-in-noise outcomes in young adults with normal audiograms; high frequency hearing loss detected

- N = 35
- 14 out of 16 high noise were male

Bramhall et al., 2017
Impulse Noise & Hidden Hearing Loss?

Noise Exposure  AIBS, 2010

Clinical Hearing Tests Normal

Difficulty Hearing and Communicating in Noisy Environments

Portable audiology and speech in noise tests

Goal: Identify TTS and speech-in-noise performance changes

2018 - “hidden hearing loss” still a hot topic

- Skoe and Tufts, 2018: No relationships between ABR amplitude and exposure, but latencies delayed
- Guest et al., 2018: No relationship between self-reported or lab-validated hearing-in-noise deficits and lifetime noise exposure
- Valderrama et al., 2018: ABR wave I amplitude decreased in association with lifetime noise exposure; longer ABR interpeak latencies and reduced central gain (less growth of Wave-V amplitude relative to Wave-I amplitude) was associated with poorer performance on listening in noise test
- Ridley et al., 2018: No relationships between ABR amplitude and exposure, but thresholds in noise varied more than expected after adjusting for threshold and OAE amplitude
Other data assessing noise and function

- 74 participants (14 male, 60 female), 18 - 27 years of age, recruited via advertisements posted throughout campus.
- Hearing not required to be normal, but most participants had thresholds < 25 dB HL, present DPOAEs, and normal WIN scores.
- The two most common exposures included bars and dance clubs, followed by music player use.
- No statistically significant relationships between threshold, DPOAE amplitude, or WIN and individual or composite measures of recreational sound exposure, including preferred listening level, years of music player use, number of reported sound exposures, previous impulse noise exposure, or previous noise-induced change in hearing.


Previous TTS (Yes/No) was not associated with threshold, DPOAE amplitude, or WIN threshold

Previous impulse noise (Yes/No) was not associated with threshold, DPOAE amplitude, or WIN threshold.


---

**Important Questions Remain**

- Do Hearing-in-Noise tests reveal cochlear synaptopathy and provide a sensitive early warning for effects of noise on the inner ear?
  - Most difficult tests appear to have greatest sensitivity
  - Is this neural damage? Or, is pathology in humans more likely to be a mixture of OHC loss and neural damage?

- Where does human risk for synaptopathy begin?
  - “Typical” recreational exposure vs extreme concert goers vs music students vs firearm users

- How does risk grow as a function of repeated exposure?
- Can TTS be prevented?
Do Hearing-in-Noise tests provide a sensitive early warning for effects of noise on the inner ear?

- Rat data
- Synaptopathy model – if you have a permanent reduction in wave I amplitude, and you have a difficult listening task, listening in noise can be compromised

Effect of noise on ABR threshold

- Rats exposed to octave band noise, 8-16 kHz, 2h at 106 or 109 dB SPL
- TTS of 20-25 dB after 106 dB
- TTS of 30-40 dB after 109 dB

Effect of noise (109 dB) on ABR Wave I amplitude

- Large TTS (30-40 dB) resulted in permanent decrease in ABR Wave I amplitude in 75% of exposed animals (4 of 6 animals).

Lobarinas E, Spankovich C, Le Prell CG. Evidence of “hidden hearing loss” following noise exposures that produce robust TTS and ABR wave I amplitude reductions. Hear Res. 2017 Jun; 349:155-163

Noise burst prepulse inhibition

No prepulse condition

BBN Carrier Noise

Startle Stimulus (airpuff)

Startle Response

Prepulse condition

50 ms NBN cue

BBN Carrier Noise

Startle Stimulus (airpuff)

Startle Response

The presenters acknowledge and thank Edward Lobarinas for generously sharing this slide.
Baseline Assessment Prior to Noise Exposure

- Pre-pulse inhibition using an acoustic cue (50 ms, 70 dB) and an airpuff stimulus was used to assess hearing in noise.
- At easy ("high") SNR, the pre-pulse reduces the startle response.
- At hard ("low") SNR, the pre-pulse less effectively reduces the startle response.
- Once SNR is too difficult, startle no longer affected.


No Effect of Noise Exposure on High SNR performance

Noise Reduced Performance at 16 kHz at Low SNR

Lobarinas E, Spankovich C, Le Prell CG. Evidence of “hidden hearing loss” following noise exposures that produce robust TTS and ABR wave-I amplitude reductions. Hear Res. 2017 Jun; 349:155-163

Summary and Conclusions

- Noise exposures that do not result in permanent threshold shift can cause ABR amplitude decrease and “hidden” hearing loss
- Functional deficit only after large TTS (30-40 dB at 24h in rats)
  - This large TTS much greater than expected in most occupational and recreational settings
  - But this may be highly relevant to blast over exposure (work by Brungart at Walter Reed, Boston Marathon victims)
- When deficits in noise did occur in rats, it was only at the poorest SNR tested and only at 16 kHz (where greatest TTS was observed)
- These data consistent with the limited deficits in chinchillas after carboplatin
- Data urgently needed in order to provide data-based on relationship between noise exposure, TTS, neural loss, and functional deficits
Real-World Guidance

- Deficits hearing in noise may be one of the earliest symptoms of noise injury to the inner ear
  - Data from musicians and those with occupational and other exposures are needed
- It is not clear if deficits in noise are related to outer hair cell damage, neural damage, or a combination of these two pathologies
- Some clinicians are now dispensing hearing aids with digital noise reduction algorithms and others are advocating auditory training programs for those with speech in noise deficits
- Multiple pharmaceutical companies are tackling synaptogenesis as a target for improving hearing in noise
- The best advice is to limit exposure to loud sound to prevent hearing loss, hearing in noise difficulties, and other dysfunction

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- Sound Pharmaceuticals, Inc.
- Edison Pharmaceuticals, Inc.
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