Hidden Hearing Loss? Effects of Recreational Noise on Evoked Potential Amplitude and Other Auditory Test Metrics

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Overview

• 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?
Long-Term Post-Noise Neural Response Depression

- DPOAEs measure OHC function
- ABR is neural response
- DPOAEs intact post-noise
- ABR amplitude depressed at supra-threshold levels


IHC/ANF Connections Decrease Post-Noise

- Synaptic ribbons (red) connect IHCs and auditory nerve dendrites (green)
- Noise induced decrease in contacts

Changes in Neural Connections are Permanent

- Explanation for age/noise interactions?
- What happens in other species?
- What is critical level of TTS?
- Robust TTS may be much more harmful than previously assumed, BUT, what are functional correlates?


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 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

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**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 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

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

- 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)


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

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)


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

- 4000 Hz, 90-dB nHL
- 27.1/sec rate
- Supra-threshold wave I amplitude measured using earlobe (left panels) and tip trode (right panels) electrodes
- Linear regression analyses were not statistically significant (p’s > 0.05) in females (top) or males (bottom) for either electrode type

Combined data sets increase sample size and power

- 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 in 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


No systematic evidence of risk “boundary” at $L_{Aeq8760}=79$ dBA for ABR wave I amplitude

- Relationships between Wave I amplitude and noise history assessed within sex
- No reliable relationships between noise (those with less than 100% noise dose and those with 100% or greater noise dose) and amplitude revealed by ANOVA analyses.

### 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%)

### “Low-Risk” Cohort (OSHA Dose < 50%)

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<th>Level</th>
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<th>NIOSH TWA</th>
<th>OSHA Dose (%)</th>
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### “High-Risk” Cohort (OSHA Dose > 100%)

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No reliable increase in TTS the day after recreational events as noise dose (TWA) increases; 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 as noise dose (TWA) increases; 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 as noise dose (TWA) increases; all TTS recovers by 1-wk post


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.

Review of Acute Changes

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?

6 kHz DPOAE amplitude reliably related to observed TTS

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
- 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

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
Can we accurately estimate noise exposure without dosimetry?

- Listening levels vary from person to person, so plugging in a single level for anyone reporting music player use will not be very accurate
Do listeners consistently report their preferred listening level?

- **Top:** highly consistent level preference across 19 songs
- **Middle:** the average SD was 4.4 dB SPL
- **Bottom:** highly variable preferences across 23 songs


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**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

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
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
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.

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

No Effect of Noise Exposure on High SNR performance

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 Reduced Performance at 16 kHz at Low SNR

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

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
Can TTS be prevented?

• Human TTS paradigm development
  • These are much smaller TTS’s, which is necessary for obvious ethical reasons
• Data on TTS prevention

4-hr iPod exposure induces dose-dependent TTS

93 dB: N=10 subjects. 98 dB: N=11 subjects. 100 dB: N=12 subjects.

Mouse vs Human at 24 hrs

- Little, if any, TTS at 24 hrs
- This is dramatically different from TTS in animal models in which ABR deficits have been documented

iPod® studies

- Randomized placebo-controlled, double-blind, between-subjects design
TTS protection varies with experimental agent

• Co-inventor on patents owned by the University of Michigan.


TTS protection varies with experimental agent

• NCT01444846 funded by Sound Pharmaceuticals, Inc.
• NCT02779192, not yet recruiting, will expand enrollment criteria, and includes data collection at multiple study sites

Human Clinical Trials: Why TTS?

- Most pre-clinical studies measure reduction of PTS but most human trials have assessed reduction of TTS

Why use TTS models?

- Shorter duration, reduced cost, decreased attrition, no permanent damage expected in any subjects
- DoD has high interest in drugs that prevent TTS – temporary compromise in communication compromises lethality, increases mortality
- “proof of concept” – drug was available in cochlea at concentration that was sufficient to attenuate biological response to noise
  - Most (if not all) agents that have reduced TTS (in animals) have also reduced PTS (in animals)
- Confirmatory data in PTS trials will be required for PTS claims
  - Access to populations in which extent, prevalence, variability, and rate of change are documented is challenging

WIN shift is limited to immediate post-music tests

TTS after 4-hours of music player use shown for 19 normal hearing listeners (thresholds from 0.25-8 kHz < 25 dB HL), tested at the University of Florida; Funded by Sound Pharmaceuticals, Inc.
WIN shift is \(~1.5\) words, in most difficult listening conditions

WINT changes after 4-hours of music player use shown for 19 normal hearing listeners (thresholds from 0.25-8 kHz \(<25\) dB HL), tested at the University of Florida; Funded by Sound Pharmaceuticals, Inc.

Where does risk begin?

- **Vulnerability:**
- Mouse > Guinea Pig > Rat > Rhesus macaque ?? Human
- Within species, risk grows with exposure intensity
- Within species, risk grows with exposure duration
Reducing noise level decreases TTS

- Octave band noise at 100-dB SPL for 2h produces 40-50 dB TTS
- Octave band noise at 91-dB SPL for 2h produces 30 dB TTS
- Both noise exposures result in TTS, neither resulted in PTS, only the higher level exposure resulted in synapse loss


Increasing noise duration increases damage

- 91-dB SPL exposure becomes synaptopathic when the exposure duration is extended from 2 hrs to 8 hrs
- We don’t know damage-risk relationship, but clearly there is a time x intensity trade

Many unanswered questions

- Final answer will not be as simple as “size of the TTS”
- Panel A shows identical TTS at 22.6 kHz
- Panel B shows pathology is only observed for the group with increasing TTS at higher frequencies


How does risk grow with repeated exposure?

- First exposure results in robust TTS, synapse loss, decrease in wave I amplitude
- Second exposure results in robust TTS, but no additional synapse loss or decrease in wave I amplitude
- Third exposure results in PTS, additional synapse loss, and additional decrease in wave I amplitude
Repeat Exposure

- Single exposure: 30-40 dB TTS at 24 hrs, no PTS
- Second exposure: same TTS developed, and recovered
- Third exposure: TTS increased (45 dB TTS at 24 hrs) and PTS developed (~10-20 dB)


Repeat TTS/PTS Exposure

- Single exposure: ABR wave I amplitude is reduced
- Second exposure: No additional decrease in ABR amplitude with second robust TTS
- Third exposure: ABR amplitude drops again, in parallel with PTS

Synaptic decrease observed with both TTS and PTS

- Single exposure: Synapses per IHC decreased
- Second exposure: No additional decrease in synapses per IHC
- Third exposure: Additional decrease in synaptic density after 3rd exposure


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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