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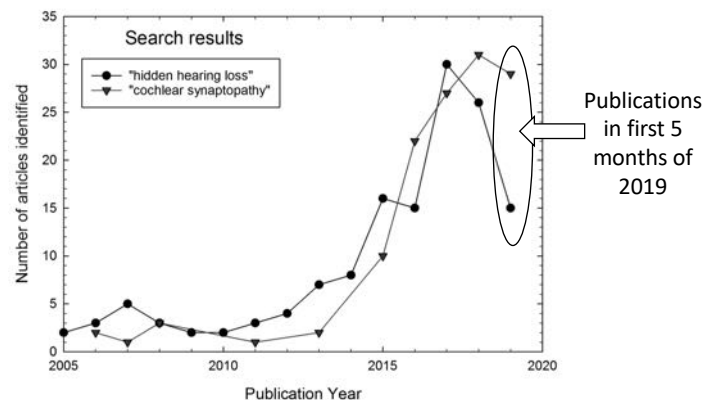
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# Cochlear synaptopathy: Potential functional implications for musicians and other performing artists

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Cochlear synaptopathy (aka “Hidden hearing loss”) is a hot topic with concerning implications for various human populations, including musicians



PubMed Search results, May 26, 2019

## Overview

- Cochlear synaptopathy in rodents: noise and aging
- Cochlear synaptopathy in humans: noise and aging
- Are ABR wave I deficits associated with supra-threshold deficits?
- Implications for musicians
- Diagnostics and clinical care

## Learning Outcomes

After this course, participants will be able to:

- Describe the pathology of cochlear synaptopathy in animals and in humans.
- Identify the causes of cochlear synaptopathy in animals and in humans.
- Discuss the potential consequences of synaptopathy in animals and humans.

## Cochlear synaptopathy in animal models

- Cochlear synaptopathy is a pattern of synaptic ribbon loss, resulting in disconnection of the synapses between inner hair cells and auditory nerve dendrites
- Synaptopathy and decreased ABR wave I amplitude shown after some but not all noise exposures
- Age-related cochlear synaptopathy documented in absence of noise exposure
- The effects of age and noise can be synergistic, with greater spiral ganglion cell loss during aging in animals that experience TTS at a young age
- Cochlear synaptopathy resulting in decreased wave I amplitude was specifically termed “hidden hearing loss” as the wave I amplitude deficit was “hidden” behind a normal pure tone audiogram

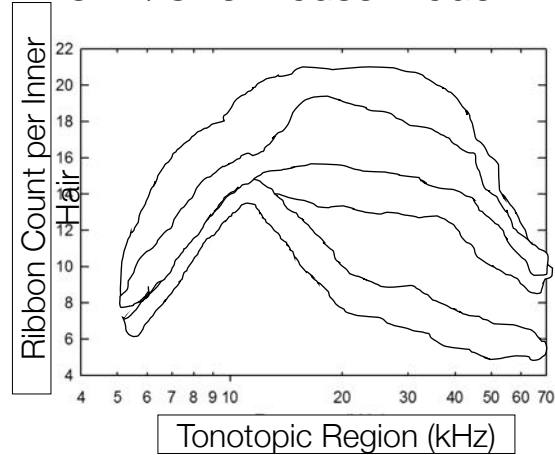
## Noise-induced cochlear synaptopathy

- When this decrease occurs in animal models:
  - It is immediate and permanent
  - Synaptopathy is located in the cochlear regions that respond to the frequencies at which the largest TTS was observed and other more basal locations (i.e., appears to be generally consistent with the “half octave shift”)
  - During subsequent aging, the region over which synaptopathy is located spreads to more apical regions of the organ of Corti
- Wave I deficits in the absence of DPOAE deficits are consistent with cochlear synaptopathy but do not confirm synaptopathy.

continued

- Gray shading illustrates range of published synapse count values from no-noise control mice
- Red shading illustrates range of published synapse count values in mice that developed noise-induced synaptopathy
- Green shading illustrates range of published synapse count values in mice exposed to shorter or lower level noise; no synapse loss at time of euthanasia

### CBA/CAJ Mouse Model



For data points and discussion, see: Le Prell, C.G., and Brungart, D.S. (2016). Potential effects of noise on hearing: supra-threshold testing using speech-in-noise and auditory evoked potentials, *Otology & Neurotology*, 37: e295-e302.

continued

### Synaptopathic injury across species

- **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:** Multiple and ongoing efforts to assess risk using both retrospective and prospective designs

continued

## Sensitivity of ABR wave I in humans is unclear

- Sex differences well documented; may confound results if not controlled for Type of electrode (mastoid, earlobe, tiptrode) influences evoked potential amplitude and waveform; none of these will produce as “clean” a signal as the subcutaneous electrodes used in rodents
- Humans are typically tested awake; rodents are anesthetized
- Human skull and head size are much larger than rodents; electrodes are more distant from the brainstem ABR wave generators
- Human noise exposure (and other risk factors) are much more diverse than that of lab animals; noise exposure estimates are not precise or controlled
- Widespread discussion – has it been difficult to find results consistent with noise induced synaptopathy because the metric is inadequate, or because the populations assessed do not have significant pathology

## Other metrics of interest?

- Wave I amplitude normalized relative to wave V, based on the relative invariance of wave V after trauma due to central gain mechanisms within the central auditory system
- SP/AP ratio has been of interest, with neural AP response amplitude normalized to hair cell SP response amplitude; caution interpreting ratio changes is necessary as larger ratios will be driven by larger SP response as well as smaller AP response.
- Middle-ear-muscle reflex relies on the intact ascending pathway from the auditory nerve to the SOC and descending motor neuron pathways to the stapedius muscle; MEMR threshold and amplitude deficits have been associated with cochlear synaptopathy in the mouse model (Valero et al 2016, 2018)
- Envelope following response (EFR) and frequency following response (FFR) are also metrics of interest that have been used in some rodent and human studies

## The “ $L_{Aeq8760}$ ” approach in humans

- Survey approach used to estimate the total number of hours spent engaged in specific noisy activities during previous year (8760 hrs/year)
- A literature-based sound level is assigned to each of the noisy activities; a default level of 60 dBA is assigned to all hours not assigned to a noisy activity
- The annual exposure level ( $L_{Aeq8760}$ ) is calculated akin to an 8-hr time-weighted-average; this is the equivalent sound level if a single sound had been presented the entire 12-month period
- Recall of recent exposure likely to be most accurate, but recall may not be accurate, assigned exposure levels may not accurately reflect actual exposure levels, and most recent 12 months may differ from historic exposure

## Findings using the $L_{Aeq8760}$ approach

- Stamper and Johnson (2015a,b) reported a statistically significant correlation, with decreased ABR wave I amplitude as a function of increasing  $L_{Aeq8760}$ 
  - Relationships generally consistent for 70-90 dB nHL clicks and 4 kHz pure tones signals
  - Relationships detected using mastoid electrodes; not statistically significant using tympanic electrodes
  - Re-analysis revealed this pattern of results was limited to female cohort
- Spankovich et al (2017) reported no statistically significant relationships between ABR wave I amplitude and  $L_{Aeq8760}$  in healthy or diabetic young adults
- Fulbright et al (2017) reported no statistically significant relationship between ABR wave I amplitude and  $L_{Aeq8760}$

continued

## Findings using surveys of lifetime noise history

- Prendergast et al (2017a,b) reported no statistically significant relationships between ABR wave I amplitude and lifetime noise exposure in adults
- Guest et al (2018) reported no statistically significant relationships between ABR wave I amplitude and lifetime noise exposure in adults
- Valderamma et al (2018) reported statistically significant relationships between ABR wave I amplitude and lifetime noise exposure in adults, but the relationship was not significant after an outlier was omitted

continued

## Findings using cohort comparisons

- Bramhall et al (2015) reported that veterans with significant noise history and civilian firearm users had smaller wave I amplitudes than veterans with less noise exposure and civilians who do not shoot firearms.
- Liberman et al (2016) reported no statistically significant difference between AP amplitudes in high-risk (mostly music student; 7F, 15M) and low risk (mostly communication disorder student; 8F, 4M) participants, but SP amplitude and SP/AP ratio were significantly different with larger ratios in high risk than low risk groups (larger ratios driven by SP and/or smaller wave AP).
- Grose et al (2017) reported no statistically significant difference in Wave I or Wave V amplitudes, but wave I/V ratio was significantly different with larger ratios in controls than in extreme concert goers (larger ratios driven by larger wave I and/or smaller wave V). Extreme concert goers attended at least 40 concerts in past two years (range =40-500; 10F, 21 M) whereas controls attended an average of 4 concerts in past two years (range=0-30; 19F, 11M).

continued

## Additional findings using cohort comparisons

- Skoe and Tufts (2018) collected 1-week of noise dosimetry data and divided participants into high exposure (>100% NIOSH REL on at least 2 days; 22F, 4M, primarily music students participating in ensemble performances) and low exposure (<20% daily NIOSH REL per day; 19F, 10M) groups; they reported no significant group differences for ABR waves I, III or V amplitude and noise exposure but ABR wave latencies were delayed in the high-noise group.
- Smith et al (2019) divided participants based on answers to a yes/no question in which participants were asked whether they had experienced excessive noise exposure; if they replied yes, the type of exposure and estimated duration and/or frequency of the exposure were queried. They reported no significant group differences in SP or AP amplitude.

## Human noise-induced “hidden hearing loss”?

- Across  $L_{Aeq8760}$  approaches, participant  $L_{Aeq8760}$  scores highly consistent, but results mixed with single study revealing wave I deficits only in females
  - These studies are largely normal hearing young adult populations primarily with recreational music exposure but with some other exposures
- Across studies using lifetime noise approaches, results mixed with single study revealing deficits that depend on inclusion of one outlier
- Across studies using cohort (including high noise/low noise) approaches:
  - Firearm use associated with wave I deficits (Bramhall et al 2015)
  - Music student status associated with AP/SP amplitude decreases (Liberman et al, 2016), and wave I, III, and V latency increases (Skoe and Tufts, 2018)
  - Concert attendance associated with decreases in wave I/V ratio (Grose et al 2017)
  - Excessive noise (yes/no) questionnaire did not reveal differences (Smith et al 2019)

continued

## Age-related cochlear synaptopathy in animal models

- When this decrease occurs in animal models:
  - It is the first pathology to emerge, preceding outer hair cell loss
  - It begins in the more basal regions of the cochlea
  - It is progressive, with increasing loss of synapses across rest of the lifespan
  - During subsequent aging, synapse loss in the base increases, and the region over which synaptopathy is located spreads to more apical regions of the organ of Corti
- Age-related synapse loss and age-related decrease in ABR wave I amplitude are highly correlated
  - These data suggest that when DPOAE responses are confirmed to be unchanged, ABR wave I is a reliable diagnostic tool for synaptopathy, at least in rodent models

continued

## Age-related cochlear synaptopathy in humans

- Cochlear synaptopathy has been documented in human temporal bones
  - Synaptopathy observed both alone and in combination with outer hair cell loss
  - Synaptopathy greater in temporal bones from older donors than younger donors
    - See reports by Viana et al 2015; Wu et al 2019
- ABR wave I amplitude and or ABR wave I amplitude growth rate decreases documented have been documented in aging humans
  - Konrad-Martin et al 2012: All ABR waves decrease with age
  - Bramhall et al 2015: ABR wave I decreases with age
  - Johanneson et al 2019: ABR wave I amplitude growth rate (slope) significantly decreases with age (i.e., in older individuals, wave I amplitude does not grow as quickly as sound level increases)
    - Relationships observed after adjusting for lifetime noise exposure; no relationships observed between ABR wave I growth rate and noise exposure history

continued

## Does synaptopathy cause suprathreshold deficits?

- Three deficits proposed and investigated
- Tinnitus
  - Perception of sound when there is no external sound source
  - Can disrupt sleep, result in anxiety and/or depression, reduce music enjoyment, compromise music performance
- Hyperacusis
  - Heightened sound sensitivity often resulting in decreased sound tolerance
  - Can result in fear of sound, sound avoidance, and/or overuse of HPDs
- Difficulty understanding speech in background noise
  - The most common issue is difficult listening environments such as restaurants or areas with fans or other equipment running; sound is audible, but not understandable

continued

## Musicians, tinnitus, and synaptopathy

- The prevalence of tinnitus in various musician populations is higher than that in the control populations
  - College student musicians (Bhatt 2018)
  - Rock musicians (Størmer 2017)
  - Professional musicians (Halevi-Katz et al 2015; di Stadio et al 2018)
- Schaette and McAlpine (2011) reported tinnitus was associated with reduced wave I amplitude
- Systematic review and meta-analysis by Milloy (2017) revealed reduced wave I amplitude and delayed wave I latency were the most common findings within tinnitus studies, with articles from 1980-2016 included.
  - Differences statistically significant within patients with tinnitus and hearing loss; differences not statistically significant within normal hearing patients with tinnitus

continued

## Tinnitus and synaptopathy: other recent findings

- Significant relationships:
  - Wojtczak et al 2017: Tinnitus associated with reduced middle-ear-muscle reflex
  - Bramhall et al 2018: Tinnitus associated with reduced wave I amplitude
- No significant relationships:
  - Liberman et al 2016: No significant differences in tinnitus for high-risk and low-risk groups
  - Gilles et al 2017: No significant relationships between tinnitus and wave I amplitude
  - Guest et al 2017: No significant relationships between tinnitus and wave I amplitude
  - Shim et al 2017: No significant relationships between tinnitus and wave I or V amplitude, or wave I/V ratio
  - Guest et al 2018: Tinnitus associated with lifetime noise but not wave I amplitude
  - Guest et al 2019: No significant relationships between middle-ear-muscle reflex and tinnitus
  - Valderamma et al 2018: No significant relationships between lifetime noise and tinnitus
  - Smith et al 2019: No significant relationships between tinnitus and noise exposure history

## Musicians, hyperacusis, and synaptopathy

- Hyperacusis is commonly reported in musician populations
  - Professional musicians (Halevi-Katz et al 2015; di Stadio et al 2017)
- Significant relationships with wave I amplitude:
  - Liberman et al 2016: High-risk group had significantly greater annoyance to everyday sounds and were more likely to report sound avoidance behaviors
- No significant relationships with wave I amplitude:
  - Shim et al 2017: Participants with tinnitus had lower uncomfortable loudness levels (UCLs); however, tinnitus was not associated with smaller wave I or wave V amplitudes
  - Bramhall et al 2018: Loudness tolerance not associated with wave I amplitude

## Hearing-in-noise: Musician performance

- Comprehensive review by Coffee (2017)
  - Recent evidence musicians advantage led to suggestion that musical training might be used to improve or delay decline of speech-in-noise (SIN) function.
  - However, musicians advantage has not been universally reported.
  - If there is a real effect of experience, what exactly is its nature, and how might future training-based interventions target the most relevant components of cognitive processes?
  - Important differences in study design and uneven coverage of neuroimaging modality complicate understanding.
  - This review systematically reviews recent results from studies that have specifically looked at musician-related differences in SIN by their study design properties, to summarize the findings, and to identify knowledge gaps for future work.

## Musician advantage (MA) on hearing-in-noise tests?

	Sentences	Words	Phonemes	Tones
Multi-talker babble	5 MA, 2 NA	3 MA, 1 NA	2 MA	
Single talker babble	4 MA, 3 NA			
Speech-like				
Tone				4 MA, 1 NA
Broadband	6 MA, 5 NA	1 MA	3 MA	
Quiet		1 MA, 1 NA	11 MA	5 MA
<b>Total</b>	<b>15 MA, 10 NA</b>	<b>5 MA, 2 NA</b>	<b>16 MA</b>	<b>9 MA, 1 NA</b>

- MA=Musician Advantage; NA=No Advantage
- Summary of the results reported by Coffey EBJ, Mogilever NB, Zatorre RJ. (2017). Speech-in-noise perception in musicians: A review. Hear Res. 352:49-69.

## Does synaptopathy cause hearing-in-noise deficits?

### No statistically significant relationships

- Fulbright et al., 2017:  $L_{Aeq8760}$  vs word-in-noise (WIN) and tone-in-noise tests
- Grinn et al., 2017:  $L_{Aeq8760}$  vs word-in-noise (WIN) test
- Prendergast et al., 2017: Lifetime noise vs coordinate-response-measure (CRM) hearing-in-noise test
- Yeend et al., 2017: Lifetime noise vs on LiSN-S (listening-in-spatialized noise) test
- Grose et al., 2017: Concert attendance vs modified BKB-SIN sentences-in-noise
- Guest et al., 2018: Lifetime noise vs self-reported and lab-validated (CRM) hearing-in-noise deficits
- Smith et al., 2019: Excessive noise vs QuickSin sentence-in-noise deficits
- Johanneson et al., 2019: Lifetime noise vs deficits with disyllabic words-in-noise and Castilian Spanish hearing-in-noise test sentences

## Does synaptopathy cause hearing-in-noise deficits?

### Statistically significant relationships

- Liberman et al., 2016: High risk group had poorer performance on custom word-in-noise test (35 dB HL, 0 or 5 dB SNR, 45 or 65% time compression, 0.3 sec reverberation)
- Valderrama et al., 2018: longer ABR interpeak latencies and reduced central gain (less growth of Wave-V amplitude relative to Wave-I amplitude) associated with poorer performance on LiSN-S (listening-in-spatialized noise) test
- Ridley et al., 2018: Thresholds in noise varied more than expected after adjusting for threshold and OAE amplitude [TEN (HL) Threshold equalizing noise test]
- Johanneson et al., 2019: Age related deficits with disyllabic words-in-noise and Castilian Spanish hearing-in-noise test sentences

continued

## Other variables that impact hearing-in-noise

- Outer hair cell integrity
- MOC reflex strength
- Language
- Cognition
- Memory

continued

## Review

- Exposure to loud sound can result in temporary threshold shift, loss of synaptic connections between IHCs and AN dendrites (cochlear synaptopathy), decreased ABR wave I amplitude
  - Smaller TTS injury not accompanied by cochlear synaptopathy or decreased ABR wave I amplitude, but there have been few efforts to assess repeated injuries
  - We do not know if repeated small TTS injuries will eventually result in permanent synaptopathy, or if there may be some “toughening effect” as observed for OHCs
  - Musicians may be an at-risk population based on all of the above
- Aging appears to result in synaptopathy across species, including humans
  - Aging and noise exposure can interact synergistically in the mouse (Kujawa and Liberman 2006) and perhaps in the human (Gates et al 2000)
  - Musicians are at risk for age-related pathology and may be at risk for synergistic interactions between aging and loud sound exposure

## Basic Test Battery for Musicians and Others

- In-vivo test batteries that allow cochlear synaptopathy to be correctly inferred are needed
- To infer cochlear synaptopathy in the absence of middle ear and OHC pathology, the test battery must document:
  - Detailed case history establishing risk factors
  - Normal otoscopy
  - Middle ear conduction within normal limits, typically accomplished using tympanometry
  - OHC function within normal limits, typically accomplished using diagnostic DPOAE
  - Normal pure-tone thresholds, including function at extended high frequencies
  - Compromised neural response integrity, inferred using one or more evoked potential tests
- If cochlear synaptopathy occurs in parallel with middle ear dysfunction or OHC loss, diagnosis will be more difficult

## Evoked potential metrics to be considered

- ABR: wave I amplitude, wave I/V or V/I ratio, wave V latency
- ECoChG: AP and SP/AP ratio
- Middle ear reflex has been useful in animal models but data in humans are limited, and evidence is mixed
  - Wojtczak et al 2017; Guest et al, 2018
- Envelope following response has been useful in animal models, but statistically significant differences have not been detected as a function of lifetime noise exposure (Prendergast et al. 2017a) or frequent concert attendance (Grose et al. 2017)
- See consensus document by Bramhall et al 2019 for detailed discussion and minimum agreed on standards for testing currently including 80-100 msec click signals at 90 or 100 dB peSPL; 4000 repetitions at 21/sec

## Advanced Test Battery for Use with Musicians

- Tinnitus, hyperacusis, and speech-in-noise deficits are commonly reported by musicians; likely occur as a consequence of loud sound exposure during practice, rehearsals, and other activities; and may be a consequence of either synaptic injury or other cochlear pathology
- Comprehensive care for musicians should include questions regarding tinnitus, hyperacusis, and speech-in-noise understanding as part of the detailed case history.
  - If deficits are reported, quantitative surveys or testing should be used to establish a baseline against which the success of hearing conservation interventions can be measured (i.e., do deficits progress over time or not)
  - These data should be used as part of the counseling process, to educate and motivate the musician to protect against new or increased deficits

## Speech-in-Noise tests

- Test vary with respect to background babble levels, signal to noise ratios, and memory requirements; some tests may prove to be more sensitive in revealing early deficits than others
- Some patients self-report difficulty, but do not have speech-in-noise test results outside test-specific clinically normal limits
  - Do testing conditions reflect conditions where patients have difficulty?
  - Does patient have realistic expectations for performance in a given environment?
- Diagnosis of a speech-in-noise deficit does not by itself provide insight into cochlear pathology but does provide insight into patient difficulties and a baseline against which can be quantitatively measured

continued

## When Speech-in-Noise tests reveal problems?

- No “gold standard” for treatment of speech in noise problems in individuals with otherwise normal hearing thresholds
  - Some clinicians are dispensing low-gain hearing aids with digital noise reduction algorithms
  - Some clinicians are advocating auditory training programs
  - Some clinicians provide counseling on good listening practices
- Scientists and companies are searching for

continued

## Other major challenges

- Tinnitus treatment remains elusive
  - Many tinnitus therapies emphasize counseling, maskers, and habituation, to decrease the stress and anxiety associated with tinnitus
  - Such therapies may not reduce the extent to which tinnitus interferes with music quality
- Hyperacusis treatment remains elusive
  - Many patients rely on ear plug use and sound avoidance strategies to decrease the pain and/or fear of pain associated with hyperacusis
  - Such therapies may not be feasible for musicians and other performing artists and personnel

## Education and Prevention are Critical to Success

- Given the host of challenges successfully “treating” tinnitus, hyperacusis, and speech-in-noise deficits, prevention is critically important
- Baseline audiometric testing, education about the audiogram and supra-threshold effects of noise are critical
- Education about safe listening and sound measurement strategies that empower safe listening decisions are critical
- Education about musician hearing protection products is critical; dispensing of ear plugs should include verification of the product attenuation

## In-ear monitors

- In-ear monitors allow the musician to customize the sound mix delivered behind the sound isolating earpiece
  - Mix can include self-generated sound, other instrumental sections, crowd noise, ambient sound, etc.
- When the mix is delivered at safe levels, these are a powerful hearing conservation tool for musicians
- They have the potential to be set at dangerously high sound levels, and training is necessary for musicians to learn to accept decreased sound levels
- Most AuD programs do not include the level of education necessary to achieve proficiency with these devices and additional continuing education must be sought to assure good advice is provided

## Take Home Message

- A comprehensive test battery is necessary to detect the earliest effects of noise on auditory function; high frequency hearing, hearing-in-noise, tinnitus, and hyperacusis should be assessed and documented
- Education to empower and motivate safe listening strategies is necessary; training is now required in music schools and the audiologist must repeat and reinforce the urgency and importance of hearing conservation strategies
- Hearing protection products for musicians require verification and training of the musician; audiologists should verify fit and obtain product specific training for any devices they dispense to assure best practices are met

## References

- Complete references provided as handout
- For recent reviews related to this presentation, see:
  - Beach, E., Bramhall, N., Epp, B., Le Prell, C. G., Lopez-Poveda, E. A., McAlpine, D., Plack, C., Schaette, R., and Verhulst, S. (2019). The search for noise-induced synaptopathy in humans: Mission impossible? *Hear Res*, 377:88-103.
  - Coffey EBJ, Mogilever NB, Zatorre RJ. (2017). Speech-in-noise perception in musicians: A review. *Hear Res*. 352:49-69.
  - Le Prell, C. G. (2019). Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature. *Int J Audiol*, 58(sup1):S3-S32.
  - Milloy V, Fournier P, Benoit D, Noreña A, Koravand A. (2017). Auditory brainstem responses in tinnitus: A review of who, how, and what? *Front Aging Neurosci*. 9:237.