



## The search for noise-induced cochlear synaptopathy in humans

Mission impossible?

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1 **The search for noise-induced cochlear synaptopathy in humans: Mission**  
2 **impossible?**

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40 **ABSTRACT**

41 Animal studies demonstrate that noise exposure can permanently damage the synapses between  
42 inner hair cells and auditory nerve fibers, even when outer hair cells are intact and there is no  
43 clinically relevant permanent threshold shift. Synaptopathy disrupts the afferent connection  
44 between the cochlea and the central auditory system and is predicted to impair speech  
45 understanding in noisy environments and potentially result in tinnitus and/or hyperacusis. While  
46 cochlear synaptopathy has been demonstrated in numerous experimental animal models,  
47 synaptopathy can only be confirmed through post-mortem temporal bone analysis, making it  
48 difficult to study in living humans. A variety of non-invasive measures have been used to  
49 determine whether noise-induced synaptopathy occurs in humans, but the results are conflicting.  
50 The overall objective of this article is to synthesize the existing data on the functional impact of  
51 noise-induced synaptopathy in the human auditory system. The first section of the article  
52 summarizes the studies that provide evidence for and against noise-induced synaptopathy in  
53 humans. The second section offers potential explanations for the differing results between  
54 studies. The final section outlines suggested methodologies for diagnosing synaptopathy in  
55 humans with the aim of improving consistency across studies.

56

## 57 **Introduction**

58 Damage to the inner ear, and associated hearing loss, occurs from noise trauma, ototoxic drugs,  
59 aging and genetic factors. One form of cochlear pathology involves synaptic damage that perturbs  
60 the neurotransmission between the inner hair cell (IHC) and auditory nerve (AN) fibers. This type  
61 of pathology has been termed cochlear synaptopathy (Kujawa and Liberman, 2015) and popularly  
62 “hidden hearing loss” (Schaette and McAlpine, 2011) because it can occur without affecting  
63 hearing thresholds. However, the definition of the latter term has become inconsistent between  
64 articles, with some authors using it to refer more generally to hearing dysfunction in the presence  
65 of normal hearing thresholds. For this reason, we will avoid use of the term “hidden hearing loss”  
66 in the present review. The predicted functional consequences of these synaptic alterations are  
67 listening difficulties in noisy backgrounds, tinnitus and hyperacusis (Kujawa & Liberman 2015).  
68 Experimental work, primarily on noise-traumatized and ageing rodents, has clearly demonstrated  
69 that the afferent synapse is more vulnerable than hair cells. AN fibers with low and medium  
70 spontaneous rates (SRs) and higher response thresholds appear to be particularly vulnerable to  
71 noise damage (Furman et al. 2013). Since these fibers do not respond at low intensity levels, their  
72 loss does not impact measures of auditory threshold, such as the clinical audiogram. Although  
73 auditory brainstem response (ABR) thresholds are insensitive to these synaptic changes, and there  
74 is some evidence that low SR-fibers do not contribute to the amplitude of ABR wave 1 (Bourien et  
75 al., 2014), the amplitude of ABR wave 1 recorded to supra-threshold transients appears to be a  
76 sensitive indicator of synaptopathy (Kujawa and Liberman, 2015; Furman et al., 2013). The  
77 amplitude of the middle-ear muscle reflex (MEMR) and the envelope following response (EFR)  
78 also appear to be sensitive to synaptopathy in animal models (Shaheen et al. 2015; Valero et al.  
79 2016; Valero et al. 2018). An alternative explanation is that the low spontaneous fibers are more  
80 involved in efferent regulation than in high-intensity coding (Carney, 2018).

81         It has recently been questioned whether cochlear synaptopathy occurs in humans and if  
82 there is evidence for functional consequences of this phenomenon, as revealed by listening  
83 difficulties in noisy backgrounds, tinnitus or hyperacusis. The purpose of this article is to highlight  
84 the research that finds evidence supporting noise-induced human synaptopathy, contrast this with  
85 studies that have not provided supporting evidence, discuss possible reasons for null results and  
86 diverging outcomes, and provide guidance to the field regarding research protocols. To outline  
87 these inconsistencies, the existing data that either support or do not support that noise-induced

88 synaptopathy occurs in humans are summarized. Details of the cited studies can be found in Table  
89 1. Next, possible explanations for these inconsistencies are provided. Finally, the last part of the  
90 article discusses methodological considerations for diagnosing synaptopathy in humans in order to  
91 standardize future experimental approaches. This will facilitate the integration of data across  
92 studies and improve the overall understanding of cochlear synaptopathy in humans.

93  
94

## 95 **Data Consistent with Noise-Induced Synaptopathy in Humans**

### 96 *Post-mortem temporal bone studies*

97 There is little debate regarding the existence of age-related synaptic loss (or synaptopathy) in the  
98 human inner ear. Analysis of temporal bones harvested post-mortem demonstrate that both age-  
99 related synaptopathy (Viana et al. 2015) (**Figure 1**) and age-related neural degeneration can occur  
100 in humans (Makary et al. 2011). In the study by Makary et al., temporal bones were carefully  
101 selected to include only those with no overt loss of either IHCs or outer hair cells (OHCs),  
102 demonstrating that spiral ganglion cell numbers can decrease prior to hair cell loss. The results of  
103 Viana et al. suggest that synaptopathy can also occur independently of hair cell loss. The same  
104 study also included temporal bones with a combination of synaptic loss and hair cell (IHC and  
105 OHC) loss, with the most extreme hair cell loss observed in the cochlear base. Interestingly, a  
106 temporal bone from a female (age 67) donor had a notched OHC loss centered at 3000 Hz, which  
107 is suggestive of previous noise injury. Fewer type I fibers/IHC and fewer synapses/IHC were  
108 observed in this donor relative to a 54-year-old male and a 70-year-old female donors, which is  
109 consistent with noise-related neuronal/synaptic loss. These findings build on earlier observations  
110 of age-related AN fiber loss in temporal bones that also had “expected” age-related loss of OHCs  
111 (Felder & Schrott-Fischer 1995). Wu et al. (2018) also demonstrated significant age-related  
112 synapse and AN fiber loss in ears with expected age-related loss of hair cells. In addition, although  
113 spiral ganglion cell loss can occur independently of hair cell loss, neuronal loss is greater when  
114 hair cells are also missing (Otte et al. 1978). Thus, cochlear synaptopathy and neuropathy may be  
115 some of the earliest manifestations of future sensorineural hearing loss (SNHL) where  
116 synaptic/neuronal loss co-exists with hair cell loss.

117

118 ***Human auditory brainstem response studies of noise-induced synaptopathy***

119 To date, the electrophysiological metric for studying synaptopathy in humans has been the  
120 amplitude of wave I of the ABR, a measure of AN function that is associated with synaptopathy in  
121 rodent models (Kujawa & Liberman 2009; Sergeyenko et al. 2013). In a sample of young (age 19-  
122 35) military Veterans and non-Veterans with normal audiograms and good distortion-product  
123 otoacoustic emissions (DPOAEs), Bramhall et al. (2017) found a reduction in ABR wave I  
124 amplitude for Veterans with high levels of reported noise exposure during their military service  
125 and non-Veterans who reported firearm use compared to non-Veterans with less noise exposure  
126 **(Figure 2)**. Liberman et al. (2016) showed a reduction in the amplitude ratio of the ABR summing  
127 potential (SP) to the action potential (AP; equivalent to wave I of the ABR) in college music  
128 students (age 18-41) with high levels of reported noise exposure versus non-music students with  
129 lower reported noise exposure histories **(Figure 3)**. It must be noted that using the Wave I/SP ratio  
130 can be problematic as a normalizing strategy since the ratio is critically dependent on changes in  
131 the denominator. Stamper and Johnson (2015a) reported a reduction in ABR wave I amplitude for  
132 young people (age 19-28) with higher reported recreational noise exposure compared to individuals  
133 with lower exposure, but a reanalysis showed that this relationship held true only for female  
134 participants (Stamper & Johnson 2015b). In a group of older adults (aged 29-55) with pure tone  
135 thresholds ranging from normal to mild hearing loss, Valderrama et al. (2018) reported a significant  
136 relationship between lower ABR wave I amplitude and increasing lifetime noise exposure.

137

138 ***Human envelope following response studies of noise-induced synaptopathy***

139 The envelope following response (EFR) is an evoked potential generated in response to  
140 amplitude modulated sounds (often a sinusoidally amplitude modulated pure tone) that can be  
141 measured from electrodes placed on the scalp. The EFR provides an indication of the fidelity  
142 with which the auditory system can follow the envelope of a stimulus (Dolphin & Mountain  
143 1992). Two studies demonstrated that EFR strength was reduced in mice with histologically  
144 confirmed synaptopathy that was either induced through ageing (Parthasarathy & Kujawa 2018)  
145 or noise exposure (Shaheen et al. 2015). The EFR was most sensitive to synaptopathy for  
146 stimulus modulation frequencies between 700 and 1000 Hz, which is consistent with the EFR  
147 being generated at the AN. However, it is unclear how these animal results will translate to  
148 humans, where the EFR is generally measured at much lower modulation frequencies (80-120

149 Hz), targeting EFR generators from the auditory midbrain. Bharadwaj et al. (2015) detected a  
150 marginally significant difference in the EFR slope and envelope interaural time difference (ITD)  
151 threshold when participants were grouped as “more” and “less” noise exposed, but argued this  
152 result should be interpreted with caution based on the crude characterization of noise-exposure  
153 history, small sample size, and cross-correlations among the temporal coding outcomes. While  
154 simulation studies based on functional models of the auditory periphery show a role for  
155 synaptopathy in reduced EFR strength (Bharadwaj et al. 2014; Paul et al. 2017; Verhulst et al.  
156 2018a; Verhulst et al. 2018b), it remains unclear whether the EFR is a robust marker for noise-  
157 induced synaptopathy in humans. One potential confound is that animal experiments have shown  
158 that EFR remains normal as long as there is the capacity to maintain neural gain suggesting that  
159 top-down activity, including cognition and memory capabilities, can influence neural responses  
160 in the brainstem (Möhrle et al. 2016). These findings suggest that future studies should consider  
161 how top-down mechanisms influence the periphery, especially for aged populations.  
162 Furthermore, with better detection tools, other factors that may contribute to impaired neural  
163 processing may become feasible to assess, such as potentially detrimental effects of  
164 corticosterones and/or potentially beneficial effects of systemic corticosteroids on auditory  
165 processing (Singer et al., 2018).

166

### 167 ***Data consistent with an impact of synaptopathy on auditory perception***

168 One advantage of looking at perceptual consequences of synaptic/neural dysfunction is that  
169 uncertainties about the reliability of noise exposure questionnaires and their comparability across  
170 studies can be taken out of the equation. Instead, a physiological measure (e.g. ABR wave I  
171 amplitude, ABR wave I/V amplitude ratio, EFR strength, middle-ear-muscle reflex (MEMR)  
172 strength) can be directly compared to, or correlated with, the perceptual measure.

173

174 **Tinnitus.** Consistent with animal models of cochlear synaptopathy, where ABR wave I amplitude  
175 is reduced (Kujawa & Liberman 2009; Furman et al. 2013; Sergeyenko et al. 2013), several studies  
176 have shown a relationship between reduced wave I amplitude (or reduced wave I/V ratio) and  
177 tinnitus (Schaette & McAlpine 2011; Gu et al. 2012; Bramhall et al. 2018; Valderrama et al. 2018).  
178 It is not completely clear why the amplitude of wave V remains close to normal despite the inferred  
179 synaptopathy in tinnitus patients, although enhanced central gain after IHC loss can be a possible

180 explanation for this phenomenon (for review see Salvi et al. 2016). Decreased responses for two  
181 other physiological measures that are sensitive to synaptopathy in mouse models, the MEMR and  
182 the EFR (Shaheen et al. 2015; Valero et al. 2016; Valero et al. 2018), have been associated with  
183 tinnitus in humans as well. In individuals with tinnitus who have normal or near-normal  
184 audiograms, Wojtczak et al. (2017) observed a weakened MEMR relative to age- and sex-matched  
185 controls. Paul et al. (2017) showed EFR reductions for individuals with normal audiograms and  
186 tinnitus compared to those without tinnitus. However, reanalysis after identification of a statistical  
187 error revealed that this was not a significant effect (Roberts et al. 2018).

188  
189 **Hyperacusis.** The lack of a uniform measure of hyperacusis makes this perceptual deficit difficult  
190 to assess. Bramhall et al. (2018) did not observe a relationship between loudness discomfort level  
191 (LDL) and ABR wave I amplitude, but this may be because LDL alone is not a good indicator of  
192 hyperacusis (Sheldrake et al. 2015; Zaugg et al. 2016). Liberman et al. (2016) showed that their  
193 high noise exposure group was more likely to report annoyance of everyday sounds and avoidance  
194 of noisy environments than their low noise exposure group. However, neither their noise exposure  
195 nor their hyperacusis questionnaire was validated. In addition, although they showed a reduction  
196 in SP/AP ratio in their high noise exposure group, they did not specifically analyze the relationship  
197 between responses on the hyperacusis questionnaire and ABR measures. Given that the high noise  
198 exposure group had significantly poorer extended high frequency (EHF) thresholds than the low  
199 noise exposure group, this may account for the increased reporting of sound tolerance problems in  
200 the high noise exposure group.

201  
202 **Speech-in-noise performance.** Theoretical reasoning predicts that synaptopathy should degrade  
203 the neural coding of speech, particularly in noise, and thus hinder the intelligibility of speech in  
204 noise (Lopez-Poveda & Barrios 2013; Lopez-Poveda 2014). Liberman et al. (2016) found a  
205 relationship between SP/AP ratio and speech-in-noise performance in young males, the significant  
206 differences in the EHF thresholds of the two groups could have impacted speech-in-noise  
207 performance (Badri et al. 2011; Yeend et al. 2017). Prendergast et al. (2018) reported the SP/AP  
208 ratio had considerably less test-retest reliability than wave I amplitude within their normal hearing  
209 cohort. In a sample that included participants up to age 55 with pure tone thresholds ranging from  
210 normal to mild high frequency hearing loss, Valderrama et al. (2018) observed an interaction effect



211 of the ABR wave I/V amplitude ratio and wave V-I interpeak latency on speech-in-noise  
212 performance, suggesting that slower neural conduction is associated with poorer performance.  
213 While average high-frequency and EHF auditory thresholds did not appear to be predictive of  
214 speech perception performance in this sample, this does not rule out the possibility that subclinical  
215 OHC dysfunction may have contributed to the relationship between the ABR metrics and speech  
216 perception performance. Although the impact of synaptopathy on speech perception in people with  
217 normal audiograms may be limited, it is important to remember that synaptopathy likely co-exists  
218 with audiometric loss in many cases of SNHL, and that in the context of OHC dysfunction,  
219 synaptic/neuronal loss may have a greater impact on speech perception. This is supported by the  
220 findings of Bramhall et al. (2015) showing an interaction effect of average pure tone thresholds (at  
221 0.5, 1, 2, and 4 kHz) and ABR wave I amplitude on performance on the QuickSIN intelligibility  
222 test, with a stronger relationship between ABR wave I amplitude and QuickSIN performance  
223 (poorer performance for lower wave I amplitudes) in individuals with elevated pure tone  
224 thresholds. In addition to these peripheral effects, central factors such as attention, working  
225 memory and language, are also important factors that affect speech-in-noise performance (Yeend  
226 et al. 2017) and likely interact with any peripheral encoding deficits, thus contributing to the wide  
227 variation observed in speech-in-noise performance across individuals with similar audiograms  
228 (Johannesen et al. 2016; Lopez-Poveda et al. 2017).

229  
230 **Performance on suprathreshold psychoacoustic tasks.** Synaptopathy likely degrades the neural  
231 coding of acoustic information, particularly in noise (e.g., Lopez-Poveda 2014). The relationship  
232 between auditory encoding of complex stimuli and performance on basic psychoacoustic tasks such  
233 as amplitude modulation detection, temporal fine-structure sensitivity, tone-in-noise detection,  
234 frequency and intensity discrimination, and binaural interaural time difference (ITD) or interaural  
235 level difference (ILD) sensitivity are not well understood. Numerous studies have investigated the  
236 relationship between these metrics over the years with mixed outcomes, even for listeners with  
237 clinically normal hearing (Strelcyk & Dau 2009; Hopkins & Moore 2011; Fullgrabe et al. 2014;  
238 Stone & Moore 2014; Prendergast et al. 2017a; Yeend et al. 2017; Valderrama et al. 2018). Without  
239 a better understanding of the relationship between physiological metrics (often representing a  
240 population response to a click or AM stimulus) and performance on a psychoacoustic task, we run  
241 the risk of comparing apples to oranges, as a single synaptopathy profile may have differing effects

242 on physiological measures versus psychoacoustic tasks. Numerical modelling approaches can  
243 improve our ability to compare potential metrics of synaptopathy by predicting the expected impact  
244 of synaptopathy and/or OHC/IHC deficits on each measure (Verhulst et al. 2016; Encina-Llamas  
245 et al. 2017; Paul et al. 2017; Carney 2018; Verhulst et al. 2018b).

246  
247 Biophysical models of the human auditory periphery have suggested an impact of synaptopathy on  
248 the encoding of suprathreshold sounds. Bharadwaj et al. (2014) modelled the effect of a complete  
249 loss of low-SR AN fibers on the population response of the inferior colliculus (IC) (a proxy for the  
250 dominant source generators of the EFR) (Melcher & Kiang 1996) for an 80 dB SPL 100%  
251 sinusoidally AM pure tone embedded in notched noise and found a 7 dB reduction in the magnitude  
252 of the response. This study did not consider the impact of this reduction on a specific  
253 psychoacoustic task, but degraded coding of AM information at the level of the IC is expected to  
254 impair performance on a psychoacoustic AM detection task. Verhulst et al. (2018b) expanded on  
255 these findings by using a numerical model of the human auditory periphery to compute the impact  
256 of synaptopathy and OHC loss on the EFR, AM and tone-in-noise detection threshold. Complete  
257 low-SR fiber loss was predicted to elevate the 4-kHz AM detection threshold by 2 dB, and an  
258 additional loss of 50% or 75% of the high-SR fiber population resulted in an AM detection  
259 threshold shift of 8 dB and 15 dB, respectively. The simulations also showed that individual  
260 differences in AM detection were well correlated to the EFR (in response to a 100% amplitude-  
261 modulated tone) and that synaptopathy, rather than OHC deficits, was the main factor driving  
262 individual differences in AM detection performance for listeners with normal audiograms and those  
263 with sloping high frequency hearing loss. The simulations furthermore predicted the need for a 4-  
264 dB stimulus signal increase for a synaptopathy model (100% low-SR loss and 50% high-SR fiber  
265 loss) to reach the same performance on a 4-kHz tone-in-noise detection task as a normal-hearing  
266 model. The simulated tone-in-noise detection differences on the basis of different degrees of  
267 synaptopathy were consistent with behavioural chinchilla tone-in-noise detection threshold shifts  
268 in the range of 5-10 dB when more than 60% of the IHC population was lost (Lobarinas et al.  
269 2016). Paul et al. (2017) showed that a simulated loss of low and medium SR fibers (based on the  
270 Zilany et al. (2014) model) was sufficient to account for individual differences in AM detection  
271 thresholds for a 5 kHz pure tone among individuals with normal hearing. In another simulation  
272 model, Carney (2018) suggested that synaptopathy may alter spectral contrasts across the cochlear

273 partition, which could impair encoding of speech. These studies suggest that model simulations are  
274 a promising method for disentangling the role of different AN fiber populations on suprathreshold  
275 auditory perception as well as the interaction between synaptopathy and OHC/IHC dysfunction.

276

277

### 278 **Data Inconsistent with Noise-Induced Synaptopathy in Humans**

279 As outlined earlier, there are two basic approaches to the search for noise-induced cochlear  
280 synaptopathy in humans. The first is to determine if noise exposure is associated with neural  
281 deficits (wave I amplitude changes) consistent with those observed in animals with histologically  
282 confirmed synaptopathy. The second is to determine whether or not noise exposure (with or without  
283 changes in evoked potential measurements) is associated with a measurable change in auditory  
284 function (difficulties understanding speech in complex listening situations).

285

286 A number of studies have used the first approach, specifically, seeking evidence of neural deficits  
287 that parallel those observed in rodent models. To reduce the probability of inclusion of participants  
288 with significant OHC loss, human studies have largely recruited listeners with hearing thresholds  
289 within the clinically normal range ( $\leq 20$  dB HL) and measured the amplitude of wave I of the ABR,  
290 the measure of AN function that is associated with synaptopathy in the rodent models (Kujawa &  
291 Liberman 2009; Sergeyenko et al. 2013). It needs to be mentioned that there are several  
292 morphological differences between rodent and human auditory neurons that could explain the  
293 difficulty in detecting synaptopathy in humans. For example, the total number of spiral ganglion  
294 cells and AN fibers differ and in contrast to rodents, nerve fibers in humans are rarely myelinated  
295 (Kimura et al. 1979; Nadol Jr 1988).

296

297 The majority of studies have failed to find a significant relation between questionnaire- or  
298 interview-based estimates of noise exposure and wave I amplitude, for participants with normal  
299 audiometric hearing (Fulbright et al. 2017; Grinn et al. 2017; Guest et al. 2017b; Prendergast et al.  
300 2017a; Spankovich et al. 2017; Prendergast et al. 2018; Johannesen et al. 2019) (**Figures 4 and 5**).

301 The largest study to date (126 participants) used a comprehensive lifetime noise interview to  
302 estimate noise exposure history but failed to detect significant decreases in wave I amplitude with  
303 increasing noise exposure, despite the presence of EHF hearing loss (Prendergast et al. 2017a),

304 raising questions about the prevalence of this pathology in humans with “typical” noise histories.  
305 Also of interest is the study of Fulbright et al. (2017), who collected data using the same  
306 methodology and stimulus conditions as the earlier study by Stamper and Johnson (2015a). A  
307 reanalysis of this earlier study by sex reported a significant correlation between noise exposure and  
308 wave I for female participants, but not males (Stamper & Johnson 2015b). However, when  
309 Fulbright et al. added their data to those of Stamper and Johnson, the effect was no longer  
310 significant for females either, suggesting that this original result may have been a statistical fluke.  
311 Several other groups have used the noise exposure questionnaire (NEQ) as used by Stamper and  
312 Johnson, without finding statistically significant relationships between NEQ scores and wave I  
313 amplitude (Grinn et al. 2017; Spankovich et al. 2017; Ridley et al. 2018). Skoe and Tufts (2018)  
314 did not detect differences in wave I amplitude, although they did report delayed latencies of waves  
315 I through V, with increasing delays for later waves. In this study, the participants were divided into  
316 low- and high-exposure groups based on noise dosimetry over a one-week period.

317  
318 As indicated earlier, another potential electrophysiological measure of synaptopathy that has  
319 received attention is the EFR, which has been suggested as a sensitive measure of low-SR fiber  
320 loss, especially at high stimulus levels and shallow modulation depths (Bharadwaj et al. 2014;  
321 Bharadwaj et al. 2015). Again, however, the evidence for an association with noise exposure is  
322 weak. Prendergast et al. (2017a), Guest et al. (2017b), and Grose et al. (2017) have all reported no  
323 significant relation between lifetime noise exposure and EFR amplitude.

324  
325 ***Studies failing to find evidence that noise-induced cochlear synaptopathy is functionally***  
326 ***significant in humans***

327 The second basic approach taken in studies of noise-induced cochlear synaptopathy in humans is  
328 to determine whether or not noise exposure (with or without changes in evoked potential  
329 measurements) is associated with a measurable change in auditory function. Recent studies that  
330 have taken this approach have provided little evidence that noise exposure is related to perceptual  
331 deficits for listeners with normal audiometric hearing. In a study of 138 participants aged 18-36  
332 with clinically normal hearing, Prendergast et al. (2017b) reported little relation between lifetime  
333 noise exposure and a range of perceptual measures, including frequency discrimination, intensity  
334 discrimination, interaural phase discrimination, amplitude modulation detection, auditory

335 localization, musical consonance perception, and speech perception in noise (SPiN). Similarly, in  
336 an older cohort of 122 participants aged 30-57, Yeend et al. (2017) reported no relation between  
337 lifetime noise exposure and a range of auditory processing and SPiN tasks. Le Prell et al. (2018)  
338 similarly failed to detect any statistically significant relations between common sources of noise  
339 exposure and performance on a word-in-noise test. These null results are consistent with several  
340 other studies (Fulbright et al. 2017; Grinn et al. 2017; Grose et al. 2017; Guest et al. 2018).

341  
342 Another approach that avoids issues with the unreliability of self-reported noise exposure is to  
343 determine whether or not perceptual deficits are associated with physiological measures assumed  
344 to reflect cochlear synaptopathy. Several recent studies have reported no relation between ABR  
345 wave I amplitude and SPiN (Fulbright et al. 2017; Grinn et al. 2017; Prendergast et al. 2017b;  
346 Bramhall et al. 2018; Guest et al. 2018), nor between EFR amplitude and SPiN (Prendergast et al.  
347 2017b; Guest et al. 2018) (**Figure 6**). With regard to tinnitus, Gilles et al. (2016), Guest et al.  
348 (2017a; 2017b), and Shim et al. (2017), have each reported no relation between presence of tinnitus  
349 and wave I amplitude for participants with normal audiometric hearing. Guest et al. (2017a; 2017b)  
350 also reported no significant reduction in EFR amplitude in their tinnitus participants compared to  
351 controls.

352  
353 **Possible explanations for null results and differences between studies.**

354 It is invalid to assume that a non-significant result implies that the null hypothesis has been proven.  
355 The following comments offer potential reasons for null results and differences in outcomes across  
356 studies. Many of the issues noted below have the net effect of reducing statistical power, as they  
357 introduce variability into the data.

358  
359 **Humans may be less vulnerable to noise-induced synaptopathy than rodents.**

360 Cochlear synaptopathy is observed with ~100 dB SPL two-hour octave band exposures in the  
361 mouse (Kujawa & Liberman 2009), ~106 dB SPL two-hour octave band exposures in the guinea  
362 pig (Lin et al. 2011), and ~109 dB SPL two-hour octave band exposures in the rat (Lobarinas et al.  
363 2017). Decreasing sound levels by 3 dB can eliminate synaptopathic injury (see Fernandez et al.  
364 2015), whereas increasing sound levels by 3 dB can intensify the injury to include permanent  
365 threshold shift (Lin et al. 2011). Macaque monkeys are more resistant to cochlear synaptopathy

366 than rodents (Valero et al. 2017), resulting in predictions that humans are less susceptible to noise-  
367 induced synaptopathy than rodents (Dobie & Humes 2017). Given the high intensity levels needed  
368 to produce acoustic trauma resulting in significant temporary threshold shift and bordering on a  
369 permanent threshold shift, there may be few human exposures that will result in the large reductions  
370 in ABR wave I seen in the original mouse study (Kujawa & Liberman 2009). If so, this would  
371 make selective noise-induced cochlear synaptopathy harder to detect in humans. Indeed, when  
372 Dobie and Humes adjusted for inter-species differences in susceptibility to noise-induced  
373 temporary threshold shift, they found that the noise exposures that cause neuropathy in rodents,  
374 when translated to the equivalent levels predicted to be needed to induce cochlear synaptopathy in  
375 humans, exceed the OSHA permissible exposure limits. This suggests that the noise exposure  
376 levels that are synaptopathic for humans may already be addressed by current noise exposure  
377 guidelines.

378

379 **The range of exposures inducing selective cochlear synaptopathy may be narrow.**

380 In a recent macaque study, noise exposures producing a temporary threshold shift were  
381 associated with only a 12-27% loss of synapses (Valero et al. 2017) versus 40-55% loss in rodent  
382 models (Kujawa & Liberman 2009; Lin et al. 2011; Hickox et al. 2017). Given that primates  
383 appear more resistant to noise-induced synaptopathy than mice (Kujawa & Liberman 2009;  
384 Valero et al. 2017), there may only be a narrow “sweet spot” where noise-induced cochlear  
385 synaptopathy can occur while hearing thresholds are still clinically normal. This sweet spot  
386 would be characterized by sufficient synaptopathy to be detectable via ABR amplitude  
387 measurements (or another less variable, more reliable metric), but with overall cochlear damage  
388 low enough that OHCs are intact and hearing thresholds are normal. It is possible that this “sweet  
389 spot” is often the result of a combination of noise- and age-related synaptopathy. Support for this  
390 suggestion comes from the observation that several studies investigating young people with  
391 recreational noise exposure or tinnitus have failed to find evidence for synaptopathy in ABR  
392 wave I amplitude measurements (Fulbright et al. 2017; Grinn et al. 2017; Guest et al. 2017b;  
393 Prendergast et al. 2017a; Guest et al. 2018), whereas studies in slightly older cohorts (Schaeffe &  
394 McAlpine 2011; Gu et al. 2012; Valderrama et al. 2018) did find reductions in ABR wave I  
395 amplitude in the experimental group. There is also the possibility that partial synaptic repair may  
396 occur in humans following noise exposure. This phenomenon has been observed in noise-

397 exposed guinea pigs (Liu et al. 2012; Shi et al. 2016) and if also prevalent in humans, it would be  
398 yet another source of variation impacting our ability to find evidence for synaptopathy.

399  
400 **Sound evoked potentials are more variable in humans than in rodents.** In the study of  
401 Prendergast et al. (2018), the coefficient of variation in wave I amplitude was 25% in the low noise  
402 exposure group, which may indicate a large degree of variability compared to the effect being  
403 measured. One of the factors that may contribute to the between-subject variability and reduced  
404 statistical power for detection of differences in human electrophysiological measures is head size  
405 and geometry (Mitchell et al. 1989; Don et al. 1994); this may contribute to differences in the average  
406 ABR wave I amplitude for males and females, with smaller average wave I amplitudes in males than  
407 in females. Cochlear duct length also varies with sex, with longer duct length in males than in females  
408 (Sato et al. 1991; Thong et al. 2017). The higher noise floor of human ABR wave I amplitude  
409 measurements is another potential source of variability. Humans are tested while unanesthetized  
410 (with a variable sleep state) and with dermal or ear canal electrodes, while rodents are tested while  
411 anesthetized using subcutaneous needle electrodes. An additional aspect that needs further  
412 investigation is the possibility that top-down regulation might be playing a role.

413  
414 **The sensitivity of the auditory brainstem response to human synaptopathy might be**  
415 **inadequate.**

416 Most human studies have employed ABR amplitude measurements to assess cochlear synaptopathy  
417 (Schaette & McAlpine 2011; Gu et al. 2012; Stamper & Johnson 2015a; Liberman et al. 2016;  
418 Bramhall et al. 2017; Fulbright et al. 2017; Grinn et al. 2017; Grose et al. 2017; Guest et al. 2017b;  
419 Prendergast et al. 2017a; Shim et al. 2017; Bramhall et al. 2018; Guest et al. 2018; Valderrama et  
420 al. 2018). In these studies, a decrease in the amplitude of ABR wave I relative to wave V has been  
421 interpreted as evidence for cochlear synaptopathy and based on speculation that wave V amplitude  
422 is “normal” as a consequence of the compensatory central gain observed in animal models (see  
423 Salvi et al. 2017). The interpretation of wave I/V ratios must be considered hypothetical at this  
424 time, as central gain as a compensatory mechanism subsequent to the loss of synapses in the cochlea  
425 is highly speculative and not well understood. It is possible that not all cases of synaptopathy lead  
426 to increased central gain. Using ABR wave I amplitude as an indicator of synaptopathy is further  
427 complicated by the fact that high frequency OHC loss also reduces the wave I ABR amplitude by

428 decreasing the contribution of high frequency AN fibers to the ABR generation (e.g., Lewis et al.  
429 2015; Verhulst et al. 2016). In addition, it must be remembered that the OHCs provide significant  
430 level-dependent amplification of the cochlear response, and loss of the OHCs decreases the input  
431 to the IHCs (Dallos et al. 2006; for recent review see Le Prell 2019). This makes it difficult to use  
432 ABR wave I amplitude to diagnose synaptopathy when OHC dysfunction is also present. Thus,  
433 synaptopathy might remain “hidden” even if ABR amplitude measurements are added to the  
434 audiometric test battery.

435 In addition, the results of Bourien et al. (2014) suggest that ABR wave I amplitudes might not be  
436 a particularly sensitive measure of low-SR synaptopathy. In a series of measurements in gerbils,  
437 Bourien et al. showed that low-SR AN fibers have a minimal contribution to the amplitude of ABR  
438 wave I. This suggests that the sensitivity of wave I amplitude to low-SR synaptopathy is limited.  
439 There are, however, indications, that low-SR fibers might be more important in controlling the  
440 efferent system than in encoding of high-intensity sound levels (Carney 2018). This is also  
441 consistent with the modeling work in Encina-Llamas et al. (2017) where the EFR is dominated by  
442 off-frequency high-SR fibers. Removing all low-SR fibers shows hardly any contribution in a  
443 model based on AN responses. Interestingly, when Furman et al. (2013) demonstrated particular  
444 vulnerability of low-SR fibers to synaptopathy, they binned the low- and medium-SR fibers  
445 together in their analysis. Therefore, the possibility for a significant contribution of medium and  
446 high-SR fiber loss to synaptopathy (and ABR wave I amplitude) should also be considered.

447  
448 **The sensitivity of the envelope following response to human synaptopathy might be**  
449 **inadequate.** In addition to the concerns noted above, there are other factors that suggest the second  
450 main electrophysiological measure of synaptopathy in rodents, EFR amplitude, may also be  
451 insensitive to synaptopathy in humans, consistent with the lack of a clear reduction in EFR strength  
452 in individuals with a history of noise exposure. Modelling of AN activity suggests that low-SR  
453 fibers have limited contribution to the EFR at high stimulus levels and that amplitude fluctuations  
454 in the stimulus are coded by the activity of high-SR fibers at frequencies basal to the frequency of  
455 the stimulus (Encina-Llamas et al. 2017). Accordingly, low-SR fiber loss will not impact the EFR  
456 due to the large population of high-SR fibers contributing to the response. Empirical data will be  
457 necessary to resolve these questions, given discrepancies in predictions across the various modeling  
458 efforts. Furthermore, as noted earlier, in the mouse model, the EFR is sensitive to synaptopathy at



459 high modulation rates (around 1 kHz and above) but does not seem to be sensitive to synaptopathy  
460 at the lower rates (typically 100 Hz) used in the human studies (Shaheen et al. 2015).

461  
462 **Variability in the noise-exposed populations studied could underlie observed differences in**  
463 **results and conclusions.** Most studies of noise-induced synaptopathy have investigated young  
464 people with clinically normal hearing and high versus low recreational noise exposure (e.g.  
465 concerts, personal music player use, etc.). Many of these studies have not found an effect of noise  
466 exposure on suprathreshold ABR wave I amplitude, either using the noise exposure survey scores  
467 as a continuous variable or when participants are sorted into high and low exposure groups using  
468 survey data (Fulbright et al. 2017; Grinn et al. 2017; Prendergast et al. 2017a). Similarly,  
469 Holtegaard & Epp (2018) found no difference in ABR wave I amplitude for individuals with a  
470 history of occupational noise exposure (musicians and flight attendants) compared to controls with  
471 less reported noise exposure. In contrast, studies of young music students (Lieberman et al. (2016)  
472 and young female adults (Stamper & Johnson 2015a, 2015b) have found electrophysiological  
473 differences as a function of noise exposure history, consistent with synaptopathy. The few studies  
474 that have included older participants or individuals with higher levels of noise exposure have found  
475 noise exposure-related reductions in ABR wave I amplitude (Bramhall et al. 2017; Valderrama et  
476 al. 2018). Common recreational exposures and many occupational exposures are very different  
477 from the high-intensity military noise and firearms to which Bramhall et al.'s participants were  
478 exposed. If it is the case that humans are not as susceptible as rodents to noise-induced  
479 synaptopathy (Dobie & Humes 2017; Valero et al. 2017), then it is likely that the intensity levels  
480 of many common sources of recreational noise exposure are simply not high enough to cause  
481 synaptopathy.

482  
483 **Differences in OHC function between control and experimental groups could confound**  
484 **results and interpretation.** Even among young people with normal audiograms, subclinical OHC  
485 dysfunction is more likely in those with noise exposure than those without. This could affect  
486 electrophysiological and perceptual measures, leading to between-group differences that are not  
487 solely related to synaptopathy.

488

489 **Variability in the tinnitus populations used across studies could underlie observed differences**  
490 **in results and conclusions.** Recruitment strategies across studies investigating ABR wave I  
491 amplitude and tinnitus have varied (Schaette & McAlpine 2011; Gu et al. 2012; Guest et al. 2017b;  
492 Shim et al. 2017; Bramhall et al. 2018), which may contribute to the differing results. Tinnitus is a  
493 heterogeneous disorder with noise exposure as one possible cause. Other etiologies of tinnitus  
494 include head/neck trauma, medications, thyroid problems, cardiovascular disease, acoustic  
495 neuroma, Meniere's disease, etc. (Henry et al. 2014). When subjects are recruited specifically based  
496 on their report of tinnitus, it is expected that there will be a mix of underlying etiologies for the  
497 tinnitus. However, if a study recruits for noise exposure and then looks at the subgroup of noise-  
498 exposed participants that have tinnitus, that tinnitus group is more likely to have predominantly  
499 noise-induced tinnitus.

500  
501 **Functional metrics are variable; some tests may not have adequate sensitivity or specificity.**  
502 It is also perhaps unsurprising that it has proven difficult to find evidence that synaptopathy leads  
503 to deficits in behavioral performance. Oxenham (2016) has argued, from a signal detection theory  
504 perspective, that the effects of even 50% deafferentation may be insignificant perceptually. Other  
505 perceptual (Lopez-Poveda & Barrios 2013; Marmel et al. 2015) and computational models,  
506 however, suggest larger effects (4-7 dB) (Paul et al. 2017; Verhulst et al. 2018b) depending on the  
507 stimulus characteristics and the amount of deafferentation. Empirical data are needed to assess  
508 these varied model predictions. However, the models recently described by Carney (2018) suggest  
509 an even more fundamental paradigm change may be necessary, arguing against a direct role of low-  
510 and medium-SR fibers in coding sounds at moderate to high sound levels.

511  
512 Many auditory and non-auditory factors, such as memory and attention, are known to contribute to  
513 behavioral tasks such as SPiN (Yeend et al. 2017), and the contribution of synaptopathy may be  
514 relatively small, at least for listeners with clinically normal audiograms. Additional research is  
515 needed to determine the relative contributions of OHC function, cochlear synaptopathy, memory,  
516 attention, and other factors on auditory perception. If associations between cochlear synaptopathy  
517 and perceptual issues cannot ultimately be reliably measured, even in individuals with significant  
518 synaptic loss, such results would raise questions as to whether noise-induced cochlear synaptopathy  
519 should be regarded as a major hearing health issue. While cross-sectional retrospective study

520 designs are useful and powerful, longitudinal studies allowing the trajectory of change to be  
521 established in parallel across a detailed test battery would be helpful in more completely answering  
522 these questions.

523  
524 **Noise exposure history metrics are variable and imprecise exposure measurements introduce**  
525 **variability.** Different groups have used a variety of measures of self-reported noise exposure  
526 history in their studies of noise-induced synaptopathy (Bharadwaj et al. 2015; Stamper & Johnson  
527 2015a; Liberman et al. 2016; Bramhall et al. 2017; Grinn et al. 2017; Grose et al. 2017; Paul et al.  
528 2017; Prendergast et al. 2017a; Yeend et al. 2017; Holtegaard & Epp 2018). Although synaptopathy  
529 can theoretically be induced by noise exposure experienced at any point in an individual's lifetime,  
530 some of these metrics assess noise exposure only during the previous year or two rather than over  
531 their lifetime. Although participants were excluded if they reported that the previous year was not  
532 representative of historic exposure, surveys based on the previous year have not been validated  
533 against lifetime surveys. Except for Bramhall et al. and Yeend et al., these noise exposure measures  
534 either do not specifically ask about firearm use or they do not incorporate firearm exposure into  
535 the overall noise exposure score because they use a scoring system that does not allow for both  
536 continuous and impulse/impact noise exposures. However, this is probably not a significant  
537 confound for the European studies, where firearm use is minimal. In addition, all self-report  
538 measures are dependent on the recall ability of the participants. This makes noise exposure history  
539 questionnaires a relatively crude metric that is prone to measurement error. There is no consensus  
540 on which noise exposure questionnaire should be used for studying synaptopathy or how to score  
541 it, making comparisons across studies difficult.

542  
543 It has been argued that the imprecision of the self-report noise exposure metrics is small compared  
544 to the range of noise exposures in the sample of participants used in some studies. For example, in  
545 one study reporting a null result for ABR wave I, the low- and high-exposure groups differed by  
546 an *average* of a factor of 340 in terms of estimated lifetime energy of exposure (Prendergast et al.  
547 2018). The mean exposure for the low-noise group in this study was equivalent, in terms of total  
548 energy, to that for an individual who goes to a nightclub or live music event for 1.5 hours, once per  
549 year, for 5 years. The mean high-noise exposure was equivalent to going to the same event for 3  
550 hours, three times per week, every week of the year, for 5 years. It seems unlikely that participants'

551 recollection of exposures would be so poor as to be unable to distinguish between these.  
552 Furthermore, the lifetime noise-exposure measure used by Prendergast, Guest, and colleagues, was  
553 significantly correlated with 16-kHz thresholds (Prendergast et al. 2017a) and with the presence of  
554 tinnitus (Guest et al. 2017b), suggesting that this measure is reliable. However, measurement error  
555 in estimates of noise exposure remains a significant concern. The potential for errors associated  
556 with the assignment of sound intensity levels to recreational exposures is highlighted by Le Prell  
557 et al. (2018), who measured preferred music player listening levels across multiple songs per  
558 subject. Even within a quiet lab setting, individual subjects had significant variability in their level  
559 selections on a song-to-song basis. These data raise questions about the validity of assigning a  
560 relatively arbitrary intensity level for calculating accumulated noise exposure over the past year or  
561 longer periods of time. Differences in accumulated noise dose are highly variable across events  
562 and individuals, as a function of differences in event intensity level, distance from the sound source,  
563 and duration of event attendance (see for example, the event specific exposure data in Grinn et al.,  
564 (2017)).

565  
566 **Control groups may differ across studies.** In group comparisons, it is vital that the control  
567 population has limited noise exposure, otherwise the presence of people with synaptopathy in the  
568 control group will make it difficult to detect differences between the control and experimental  
569 groups. Ensuring a control group with limited noise exposure is difficult due to the inherent  
570 limitations of using noise exposure questionnaires. An in-depth noise exposure questionnaire with  
571 specific questions about a variety of potentially noisy activities rather than a questionnaire that uses  
572 more general questions to assess noise exposure history may be necessary to aid recall of noise  
573 exposures in potential study participants, particularly for infrequent exposures. Given the results  
574 from Bramhall et al. (2017) suggesting that firearm users have reduced ABR wave I amplitudes,  
575 even individuals with a single episode of firearm exposure should not be included in a control  
576 group. Confirming good OHC function by screening for otoacoustic emissions (OAEs) and/or EHF  
577 thresholds will also help ensure this population does not have noise exposure history that they have  
578 forgotten to report. It is also possible that most adult humans have some degree of age-related  
579 and/or noise-induced synaptopathy, making it difficult to identify a true control population, and  
580 obscuring variation between groups.

581

582 **Positive results may be due to audiometric confounds unrelated to synaptopathy.** Several  
583 studies have provided intriguing evidence that could support an interpretation of an underlying  
584 synaptopathic injury. However, there are potential confounds in some of these studies that should  
585 be considered. Some studies that have reported a relation between ABR measures of synaptopathy  
586 and noise exposure have either reported high-frequency audiometric differences between low-noise  
587 and high-noise groups (Liberman et al. 2016; Bramhall et al. 2017), or have not measured  
588 audiometric thresholds at extended high frequencies above 8 kHz (Stamper & Johnson 2015a,  
589 2015b). Bramhall et al. (2017) reported a 2-6 kHz threshold elevation compared to controls for one  
590 of their high-noise groups (“veteran high noise”), but not the other (“non-veteran firearms”).  
591 However, they controlled for variability in OHC function in their analysis by statistically adjusting  
592 for DPOAE differences between the groups. It is unclear the extent to which small audiometric  
593 differences might influence the electrophysiological measures of synaptopathy, although it is  
594 known that ABR wave I amplitude is dependent on basal cochlear generators (Don & Eggermont  
595 1978). Valderrama et al. (2018) reported a weak but significant relation between lifetime noise  
596 exposure and ABR wave I amplitude, even after controlling for audiometric thresholds. Although  
597 this was a relatively large sample with careful documentation of lifetime exposure to noise, the  
598 authors note that if a single outlier with extremely low noise and an extremely robust ABR wave I  
599 amplitude was excluded from the analysis, the observed association between lifetime noise  
600 exposure and ABR wave I amplitude was no longer statistically significant.

601  
602 Some of the positive findings with respect to tinnitus and synaptopathy may also have been affected  
603 by audiometric differences. In the Gu et al. (2012) study the groups were not audiometrically  
604 matched for the click level (120 dB peSPL) at which a significant effect on wave I amplitude was  
605 observed, with higher thresholds in the tinnitus group at frequencies of 8 kHz and above. In the  
606 Bramhall et al. (2018) study there were also audiometric differences between the groups, although  
607 the authors controlled for DPOAE differences in the analyses. In the Schaette and McAlpine (2011)  
608 study there was a small audiometric threshold elevation (3.5 dB) in the tinnitus group at 12 kHz,  
609 and thresholds at higher frequencies were not reported. Wojtczak et al. (2017), who reported a large  
610 reduction in the acoustic MEMR amplitude in their tinnitus participants compared to controls, also  
611 observed substantial audiometric differences between groups. Although the effect of group was  
612 still highly significant after controlling for audiometric threshold, the pure tone threshold

613 measurements were limited to a minimum of 0 dB HL, which may have biased thresholds for the  
614 controls upwards. It is unclear, however, if this could account for the large group differences in  
615 MEMR amplitude they observed.

616

617 **Reproducibility is a major concern.** Finally, we should be aware of the crisis in the wider  
618 neuroscience community regarding reproducibility (Colquhoun 2017). Many of the human  
619 studies of synaptopathy have used a large number of outcome measures. Studies have often  
620 reported positive effects for one measure but not others, and the statistical significance of the  
621 positive effects has often been marginal (and usually uncorrected for multiple comparisons). In  
622 these circumstances, the rate of statistical Type I errors is very high.

### 623 **Suggestions for Methodological Approaches to Investigate Synaptopathy in Humans**

624 With the current state of technology, synaptopathy is a pathology that can only reliably be revealed  
625 using histological techniques post-mortem. Because across-study differences in results may be due  
626 to methodological differences, researchers around the world are working to identify the “best”  
627 (most sensitive) non-invasive measures for detecting synaptopathy in humans. Ultimately, a test  
628 battery should be sensitive to synaptopathy both when auditory thresholds are normal, as well as  
629 when other auditory deficits are present. However, given that most studies of synaptopathy in  
630 humans have used samples with clinically normal or near normal hearing thresholds, it is difficult  
631 to recommend the best test measures for diagnosing synaptopathy in individuals with abnormal  
632 auditory thresholds. Therefore, the following recommendations are oriented towards diagnosis of  
633 synaptopathy in people with normal audiograms. Many of the essential components of the test  
634 battery may be necessary in order to have confidence in inferences regarding synaptopathy. The  
635 recommendations are as follows:

636

- 637 ○ Noise exposure measurement tools: At this time, a variety of retrospective self-report tools are  
638 being used to investigate noise-induced synaptopathy. Some are survey based and emphasize  
639 the past year; others are interview based and emphasize lifetime noise exposure history. The  
640 strongest approach would include prospective monitoring of changes in the auditory measures  
641 described below as a function of noise exposure documented via dosimetry, but such data will  
642 be difficult to collect over an individual’s lifetime. The more practical goal should be the

643 development of standardized survey tools that can be used across laboratories, although these  
644 are inevitably subject to recall bias. An alternative approach is the recruitment of subjects with  
645 specific risk factors (e.g. frequent exposure to very high-intensity amplified music, exposure to  
646 firearm discharge, work in a high-level noise environment) with planned comparisons with  
647 lower-exposure control subjects matched for age and sex.

648 ○ Otoscopy: inspection of the ear canals is necessary to exclude participants with potential  
649 obstruction of the ear canal or other pathology that may confound the results.

650 ○ Tympanometry: measurement of ear drum mobility while the pressure in the sealed ear canal is  
651 systematically changed; this is necessary to document a correctly functioning middle ear system.

652 ○ Distortion product otoacoustic emissions (DPOAEs): a measure of OHC function, necessary for  
653 differential allocation of deficits to OHC or AN damage. Note that if sound conduction through  
654 the middle ear is compromised, DPOAEs will be reduced or absent even if the OHC population  
655 and function are intact.

656 ○ During screening tests, DPOAEs are often scored as pass/fail based on whether their  
657 levels are at least 6 dB above the noise floor. This is inadequate and more stringent  
658 criteria should be used to guarantee normal OHC function.

659 ○ When DPOAEs are used diagnostically, they are more commonly defined as present  
660 and normal, present but abnormal, or absent, with present but abnormal used to  
661 identify DPOAE responses that are present but at a reduced amplitude. Empirical  
662 research is necessary to identify whether use of these three categories has adequate  
663 specificity and sensitivity for sorting participants in these studies.

664 ○ DPOAE testing with  $f_1$  and  $f_2$  primary tone levels of 65 dB SPL and 55 dB SPL are  
665 common. A DP-gram obtained at these stimulus levels can be compared to  
666 normative values (Gorga et al. 1997, Table A1). Restricting study participation to  
667 individuals with DPOAE levels above the 95<sup>th</sup> percentile for Gorga et al.'s impaired  
668 sample will greatly limit OHC dysfunction. However, in noise-exposed samples,  
669 this may make it difficult to meet recruitment targets.

670 ○ Testing at lower SPLs should also be considered; noise-induced deficits may  
671 emerge at lower SPLs prior to higher SPLs and thus subtle changes in OHC function  
672 can be missed.

- 673           ○ As the availability of clinical equipment capable of measuring high-frequency  
674 DPOAEs continues to improve, the ability to adjust for OAE amplitude may  
675 continue to improve, and it may be advisable to require “normal” OAEs of all study  
676 participants at all tested frequencies (Bramhall et al. 2017). Although inclusion of  
677 OAEs might improve the ability to interpret study outcomes, it must also be  
678 remembered that normal DPOAEs can be recorded even in the presence of OHC  
679 damage and thus normal DPOAEs do not necessarily imply the OHC population is  
680 not damaged (Subramaniam et al. 1994a; Subramaniam et al. 1994b; Chen &  
681 Fechter 2003). In addition, OAEs are not sensitive to IHC function, and therefore  
682 controlling for OAEs will not guarantee perfect matching between groups.  
683
- 684           ○ Pure-tone air conduction thresholds, including EHF assessment: Conventional threshold  
685 assessment is necessary, including 3 and 6 kHz, and it is essential that EHF assessment be  
686 completed up to 12-16 kHz. Multiple studies have provided evidence of deficits in the high  
687 frequency range related to noise exposure history, with or without corresponding changes in  
688 ABR wave I amplitude. As described earlier, ABR wave I is sensitive to basal cochlear function,  
689 so it may be important to control for EHF thresholds when making comparisons between  
690 participants using this metric.
- 691           ○ ABR: a measure of the sound evoked neural response, evoked by tones or clicks. Protocols vary  
692 significantly across laboratories; in the absence of more sensitive metrics, this is the current gold  
693 standard in animal models and should be included in human studies.
- 694           ○ Clicks will activate larger regions of the cochlea than tones; some laboratories  
695 record responses to both clicks and tones while others only report responses to  
696 clicks. In order to reduce the potential impact of OHC loss in subjects with EHF  
697 hearing loss, low-pass filtered clicks could be used. At high intensities, ANFs at  
698 high CFs will only contribute through their tails, which are not affected by OHC  
699 loss. To facilitate comparisons across studies, clicks should be included in all  
700 investigations, and tones, chirps, and other shaped signals should be considered as  
701 optional additions. Because the original data from Kujawa and Liberman (2009)  
702 reveal frequency specific effects with both more cochlear synaptopathy in basal  
703 regions and greater wave I deficits at higher frequencies, it is reasonable to predict



704 that non-click signals may provide insight into patterns of damage within the human  
705 cochlea but we do not yet have sufficient evidence to recommend specific protocols.  
706 If data emerge documenting increased sensitivity with non-click signals, these  
707 recommendations should be re-evaluated.

- 708 ○ In general, click levels vary from as low as 70 dB nHL to as high as 100 dB nHL.  
709 Some groups report these stimulus levels in dB nHL, while others report them in  
710 dB peSPL. To facilitate comparisons across studies, both dB nHL and dB peSPL  
711 should be included in all reports. Based on both animal data and the studies  
712 reporting ABR wave I deficits consistent with synaptopathy, 90 and 100 dB peSPL  
713 stimuli are likely to be the most sensitive in revealing wave I deficits; at least one  
714 of these higher-level conditions should be included.
- 715 ○ Most human studies consider click durations of 80-100  $\mu$ s (see Table I) to  
716 characterize the onset response of the population of AN fibers. It should be noted  
717 that adopting longer duration click or tone-burst stimuli with different windowing  
718 properties are known to alter the frequency-dependent sources which contribute to  
719 the ABR amplitude (Rasetshwane et al. 2013). The exact stimulus specifics for the  
720 ABR might thus also have an impact on their sensitivity to synaptopathy and/or on  
721 the AN fibers types which contribute to the population response.
- 722 ○ Responses may be measured using dermal electrodes or ear canal electrodes; ear  
723 canal electrodes are increasingly used in more recent studies to improve resolution  
724 of wave I.
- 725 ○ Overall configuration for recordings may be one-channel or two-channel  
726 configurations. In a one-channel configuration, the active electrode is placed at the  
727 high forehead (Cz or Fpz), the reference electrode is placed at the ipsilateral earlobe  
728 or the mastoid, and the ground is placed at the contralateral earlobe or mastoid. In a  
729 two-channel configuration, the active electrodes for both channels are placed on the  
730 high forehead (Cz or Fpz), reference electrodes are placed on both earlobes or both  
731 mastoids, and the ground is placed at the center of the forehead.
- 732 ○ The number of samples averaged has ranged from 500 (Grinn et al. 2017) to 12,500  
733 (Valderrama et al. 2018). Increasing the number of samples averaged will reduce  
734 noise in the ABR waveform, making it easier to resolve wave I, but data collection

735 time is increased. It has been indicated that there is little improvement between 1000  
736 and 2000 averages, except near threshold where as many as 4000 averages may be  
737 needed (Hall 1992). It appears that 1000 averages is probably adequate when  
738 measuring responses to high level (90-100 dB SPL) click signals in a normal-  
739 hearing population, but increased averaging may be required when including  
740 participants with abnormal pure tone thresholds. A conservative approach would be  
741 to average a minimum of 4000 responses; additional data would be helpful in  
742 guiding the minimum protocol requirements.

- 743 ○ Increasing the stimulus rate reduces neural recovery time between stimuli, reduces  
744 the ability to resolve wave I, and increases wave V latency. Stimulus presentation  
745 rates vary widely across studies. Hall (1992) shows that wave I amplitude is constant  
746 up to 21/sec rates and the amplitude decreases at 31/sec and at higher rates. Thus, a  
747 21/sec rate would be recommended for a standard test rate; additional stimulus rates  
748 can be included to probe the rate of wave I amplitude decrease as stimulus rate  
749 increases.
- 750 ○ Although ABR measurements are a necessary element of the test battery, it must be  
751 noted that the field is not yet at a point where it is feasible to agree on whether wave  
752 I amplitude is the best metric or not, with some data suggesting that wave I is  
753 insensitive to low-SR fiber loss (Bourien et al. 2014).

754 Wave I has good test-retest reliability (low measurement error) but large between-subject  
755 variance (Mitchell et al. 1989; Don et al. 1994; Prendergast et al. 2018). A differential measure  
756 that reduces between-subject variance due to factors unrelated to synaptopathy is recommended  
757 for improved sensitivity. As discussed above, the use of a ratio derived from wave I (i.e., wave  
758 V/I, or SP/AP amplitude) or other metrics such as wave V latency may be problematic because  
759 (1) the value of the ratio critically depends on changes in the denominator and (2) wave V  
760 features reflect response characteristics from central auditory nuclei, which may or may not  
761 correlate with synaptopathy. The growth of ABR wave I with increasing stimulus intensity may  
762 be a useful differential wave I measure with reasonable test-retest reliability (Johannesen et al.  
763 2019), but the data do not allow recommendation for a single best differential measure at this  
764 moment.

- 765           ○ In the absence of OHC deficits, it is not clear whether ABR latencies are impacted  
766           by synaptopathy. Delayed and temporally-smearred first-spike latencies of LSR  
767           fibers compared to HSR fibers, make that the ABR wave-I is mostly dominated by  
768           the temporally precise HSR fibers (Bourien et al., 2014). A selective loss of LSR  
769           fibers or different degrees of HSR fiber loss is thus not expected to impact the ABR  
770           wave-I latency much (see also simulations in Verhulst et al., 2018a). However, there  
771           is a suggestion that the degree to which the ABR wave-V latency shifts when  
772           background noise is added can be a marker of selective low/medium-SR fiber loss  
773           (Mehraei et al. 2016). In contrast to suggestions that ABR latencies reflect cochlear  
774           synaptopathy, it must also be noted that ABR latencies are very sensitive to OHC  
775           deficits and the shape of the audiogram (Gorga et al. 1985; Lewis et al. 2015). This  
776           means that ABR latencies for constant SPL stimulation can be used as a control  
777           measure to verify whether EHF loss contributed to the degraded ABR wave I  
778           amplitude. Specifically, the ABR waves would be delayed in listeners with OHC  
779           loss, when compared to listeners without OHC loss but with or without  
780           synaptopathy.
- 781           ○ It is important to control for any potential confounds due to high-frequency hair cell  
782           damage, which may impact wave I in particular (and more so than wave V given  
783           that wave-V generators are more low-frequent than the wave-I generators (Don and  
784           Eggermont, 1978)). EHF testing and/or high-frequency DPOAE measurements  
785           provide critical insight into peripheral damage and one or both of these measures  
786           should be included. Even in a sample with normal audiograms, it is advisable that  
787           ABR measures are statistically adjusted for between-subject differences in OAEs.  
788           OAEs are more sensitive to noise exposure than pure tone thresholds (Engdahl &  
789           Kemp 1996; Seixas et al. 2005; Marshall et al. 2009) and OAEs measured in the  
790           high frequencies (4-8 kHz) are correlated with pure tone thresholds in the extended  
791           high frequencies (11-20 kHz, Arnold et al. 1999). Given that OAEs are reflective of  
792           peripheral auditory function, adjusting ABR wave I amplitudes for OAEs may be  
793           preferable to adjusting for pure tone thresholds, which theoretically could be  
794           impacted by high levels of neuronal loss. Another potential method of limiting the  
795           impact of high frequency hair cell damage is to add notched noise to the ABR

796 stimulus. It should also be noted that wave I can be impacted by sub-clinical IHC  
797 dysfunction, and distinguishing synaptopathy from IHC dysfunction is problematic  
798 using wave I amplitude in isolation. It will also be problematic to distinguish  
799 synaptopathy (loss of synapses) from deafferentation (loss of nerve fibers) using  
800 wave I. In the absence of histopathology, which cannot be collected from live  
801 participants, we recommend that authors reporting results remain cognizant of these  
802 limitations and specifically acknowledge the imprecision of wave I results.

803  
804 In summary, it is reasonable to infer there is a pathology of the IHCs, the synapses, or the ascending  
805 neural pathway, if middle ear conduction, OHC function, and threshold sensitivity (including EHF  
806 thresholds) are all normal, but there is decreased amplitude of the AP or wave I of the ABR. If  
807 middle ear conduction, OHC function, or threshold sensitivity is suspected to be compromised, the  
808 inference of selective synaptopathy is drawn into question. This does not mean synaptopathy has  
809 not occurred, but that functional deficits and/or supra-threshold complaints cannot be attributed to  
810 a selective neural pathology as there are other potentially contributing pathologies present.

811  
812 There are a number of optional (experimental) elements of the test battery that labs may consider  
813 adding; it is possible that one or more of these elements will ultimately be identified as essential  
814 components to include in future investigations. These are described below.

815  
816 • Middle ear muscle reflex (MEMR): also termed the acoustic reflex, stapedius reflex, or auditory  
817 reflex; this is an involuntary muscle contraction which can be triggered by either ipsilateral or  
818 contralateral sound. The AN must be intact to initiate the acoustic reflex; the strength of the  
819 acoustic reflex is reduced in mice with synaptopathy (Valero et al. 2016; Valero et al. 2018)  
820 and this may prove to be a useful metric in humans as well. MEMRs are known to be weak, or  
821 absent, in a subset of the population (Flamme et al. 2017; McGregor et al. 2018), and it has  
822 been suggested that synaptopathic injury could underlie this observed individual variability  
823 (Wojtczak et al. 2017). Use of a wideband probe and a broadband activator stimulus has been  
824 shown to lower MEMR thresholds compared to the standard 226 Hz probe tone used clinically,  
825 which could perhaps improve the ability to reliably detect MEMR responses in future studies  
826 (Feeney et al. 2017).

827 • Signal-in-Noise/Speech-in-Noise testing: Various labs are using different clinical tests,  
828 including the QuickSin, WIN, Matrix test, and others. The custom manipulation of the NU-6  
829 words by Liberman et al. (2016) revealed significant differences in performance for high risk  
830 and low risk participants. However, this test is not readily available to others, complicating  
831 replication of the testing and reproduction of the results by other laboratories. Furthermore,  
832 task difficulty can be defined simply in terms of percent correct performance, which is easily  
833 manipulated in any speech-in-noise test by changing the signal-to-noise ratio. Making a test  
834 more “complex” with respect to the cues available would be expected to make the test more  
835 cognitively demanding (for example, requiring increased attention and listening effort). This is  
836 likely to make performance more reliant on central rather than peripheral factors, reducing  
837 sensitivity to synaptopathy.

838 • Testing audiometric thresholds for brief tones (<20ms) has been suggested as a possible method  
839 for detecting synaptopathy. Theoretical reasoning by Lopez-Poveda and Barrios (2013) and  
840 perceptual model simulations by Marmel et al. (2015) suggest that synaptopathy involves a  
841 substantial loss of low-threshold AN fibers in addition to the larger loss of high-threshold  
842 fibers, which is predicted to elevate the detection threshold for brief tones, without significantly  
843 elevating the thresholds for longer sounds. The results of Wong et al. (2019) in the budgerigar  
844 undermine this approach and the experimental data currently available are not adequate to allow  
845 a recommended protocol for this test.

846 • Supra-threshold temporal tasks: Basic psychoacoustic tasks such as amplitude-modulation  
847 detection, temporal fine-structure sensitivity tasks, tone-in-noise detection, frequency and  
848 intensity discrimination as well as basic binaural ITD or ILD sensitivity tasks have been  
849 completed by some laboratories, but there is only limited theoretical development relating  
850 synaptopathy to specific deficits of interest. In those cases where deficits are present on only a  
851 subset of temporal processing tasks, interpretation is challenging. Some of these tests will be  
852 compromised by OHC pathology, highlighting the need for careful DPOAE assessment, if  
853 deficits are to be attributed to selective neural injury.

854 Hyperacusis tools: There are no uniform measures of hyperacusis; loudness discomfort levels  
855 could be considered for inclusion (following Bramhall et al. 2018), although this measure may  
856 not be a good predictor of hyperacusis. Alternatively, a measure of loudness growth, such as the  
857 Contour Test of Loudness Perception (Cox et al. 1997), or categorical loudness scaling (Brand &

858 Hohmann 2002), might be a better metric. Annoyance related to everyday sounds and avoidance  
859 of noisy environments (following Liberman et al 2016) could be considered for inclusion as well.

- 860 • ABR amplitude versus latency plots can be derived from the raw data and may be considered  
861 as per Verhulst et al. (2016) to further disentangle the contribution of OHC and synaptopathy  
862 aspects to SNHL.
- 863 • Envelope following response (EFR): The EFR is a steady-state sound evoked response which  
864 follows the envelope of an AM stimulus. The carrier and modulation frequency can be  
865 manipulated, as well as the depth of amplitude modulation. Some studies have also included  
866 masking noise (e.g., Bharadwaj et al. 2015; Paul et al. 2017). However, as described above, the  
867 EFR cannot be measured in humans easily at the high modulations rates (~1 kHz) that are  
868 associated with synaptopathy in animal models. Even though model simulations suggest that  
869 EFRs to lower modulation rates may also be sensitive to synaptopathy, the interpretation of the  
870 EFR metric in terms of synaptopathy might depend critically on the stimulus characteristics  
871 and masking noise applied.

872 Ultimately, to reach a definitive differential diagnosis of synaptopathy, we may need to turn to  
873 novel brain imaging techniques, perhaps variations of magnetic resonance imaging (MRI), positron  
874 emission tomography (PET) or magnetoencephalography (MEG), or some future technique not yet  
875 developed. For example, a new molecular imaging technique to detect changes in the  
876 neurotransmitter dopamine in the human brain has been described by Badgaiyan (2014). It may be  
877 that research efforts into other neurological conditions, such as Alzheimer's disease, may yield  
878 viable techniques which hearing scientists can adopt for the detection of abnormal synaptic  
879 transmission at the AN.

880  
881 The above list of suggestions for assays to detect synaptopathy is quite lengthy and would not be  
882 clinically feasible for diagnostic purposes due to time constraints. However, at this point in time it  
883 is not possible to minimize the number of assays because of the many uncertainties within the  
884 literature. A more concise battery of assays can only be suggested when the number of studies  
885 related to human synaptopathy increase and the combinations of assays become validated.

886

## 887 **Conclusions**

888 Despite a concerted international research effort over the past several years, conclusive evidence  
889 for noise-induced cochlear synaptopathy in humans remains elusive. In this commentary, we have  
890 discussed some of the possible reasons behind this. We have described how each of the various  
891 experimental approaches, including electrophysiological, questionnaire and behavioural measures  
892 have proved to be imperfect metrics. Although there may be techniques we can use to control  
893 variability, improve robustness, and increase statistical power, we seem far from reaching a  
894 satisfactory diagnostic approach. There are also important questions to be answered about the  
895 extent to which human synaptopathy mirrors the animal models, particularly in relation to the  
896 intensity of noise that is needed to induce synaptic damage in humans, the relative susceptibility of  
897 low-, medium- and high-SR fibers, and the possibility that structural repair at the synapse may  
898 occur following early auditory insults. Given that aging and cumulative noise exposure are  
899 necessarily correlated and associated with peripheral and central damage in addition to  
900 synaptopathy, disentangling noise-induced synaptopathy from deterioration of other auditory  
901 structures may prove to be an insurmountable challenge. Nevertheless, it is important to continue  
902 our efforts to determine whether synaptopathy occurs in humans, and to better understand its  
903 potential perceptual effects. As one of several peripheral and central factors that may contribute to  
904 suprathreshold hearing deficits in humans, we need to be able to characterize its relative influence  
905 on an individual's overall auditory function. Understanding these relationships is essential if we  
906 are to move beyond the audiogram towards a holistic model of person-specific hearing care that  
907 diagnoses and treats both the "hidden" and "unhidden" components that underlie human hearing  
908 impairment.

909

910

## 911 **Figure Legends**

### 912 **Figure 1.**

913 **Histological evidence of synaptopathy in human temporal bones.** Figure shows analysis of  
914 orphan ribbons in the IHC area. **A:** Thumbnail re-projections of the voxel space immediately  
915 surrounding 12 selected synaptic ribbons from z-stacks. Some ribbons are clearly juxtaposed to  
916 nerve terminals (left two columns) while others are not (right column). Only the red (anti-CtBP2)  
917 and green (anti-neurofilament) channels are shown for clarity. **B:** Percentage of orphan ribbons,

918 i.e. those not closely juxtaposed to post-synaptic terminals, as assessed by evaluating thumbnail  
919 arrays such as those illustrated in A, for each of the five completely reconstructed ears in the  
920 present study. Reprinted with permission from Viana et al., 2015, Hearing Research.

921  
922 **Figure 2. Evidence of noise exposure-related ABR wave I amplitude reduction in humans.**  
923 Mean ABR waveforms and peak amplitudes are plotted by noise exposure group. ABR wave I  
924 amplitude was reduced in the Veteran High Noise and non-Veteran Firearms groups compared  
925 with the non-Veteran control and Veteran Low Noise groups, while waves III and V were similar  
926 across groups. A: Waveforms were generated in response to a 110 dB p-pe SPL 4 kHz toneburst  
927 and averaged across all participants in each group. The peaks of waves I, III, and V are labeled.  
928 The inset shows the average wave V peak after correcting for variability in peak latency across  
929 participants. B: Wave amplitudes were measured from responses to a 110 dB p-pe SPL 4 kHz  
930 toneburst and then averaged across groups. Wave I and III amplitudes were measured as the  
931 difference in voltage between the wave peak and the following trough. Due to difficulty  
932 identifying the wave V trough in some participants, wave V amplitude was measured as the  
933 voltage difference between the wave V peak and the prestimulus baseline (average voltage  
934 measured for the 1-msec period of time before the stimulus presentation). Error bars indicate the  
935 standard error of the mean. ABR indicates auditory brainstem response. Reprinted with  
936 permission from Bramhall NF, Konrad-Martin D, McMillan GP, Griest SE. Auditory Brainstem  
937 Response Altered in Humans With Noise Exposure Despite Normal Outer Hair Cell Function.  
938 Ear Hear. 2017 Jan/Feb;38(1):e1-e12. <https://insights.ovid.com/pubmed?pmid=27992391>

939  
940 **Figure 3. Evidence of noise-exposure related increase in SP/AP ratio in humans.**  
941 Electrocochleography shows evidence for cochlear synaptopathy in the high-risk group. A:  
942 Averaged waveforms ( $\pm$ SEMs) from each group in response to clicks delivered at 9.1 Hz in  
943 alternating polarity at 94.5 dB nHL. SP and AP are measured from baseline to peak, as  
944 illustrated. B: Increasing click rate from 9.1 Hz to 40.1 Hz decreases AP without affecting SP:  
945 mean waveforms from 6 subjects are shown. C: Mean SP/AP ratio is nearly twice as high in the  
946 high-risk vs. the low-risk group. This difference remains when subjects are separated by sex. D:  
947 The difference in SP/AP ratios arises from both an increase in the SP and a decrease in the mean



948 AP, although only the SP differences are statistically significant. All data are means ( $\pm$ SEM).  
949 \*\*\* $p < 0.001$ ; \*\* $p < 0.01$ . From Liberman et al., 2016.

950  
951 **Figure 4. Evidence that self-reported noise exposure is not correlated with ABR wave I**  
952 **amplitude in humans.** The relationship between self-reported noise exposure (calculated as  
953  $L_{Aeq8760}$ ) and action potential (AP) amplitude is shown for male and female participants for  
954 stimuli including A: clicks, B: 2 kHz tone bursts, C: 3 kHz tone bursts, and D: 4 kHz tone bursts.  
955 All AP amplitude data were normally distributed. Pearson correlation analysis revealed no  
956 statistically significant relationships between self-reported noise history and AP amplitude within  
957 males or females. Lines of best fit are shown (Males: black symbols and regression lines;  
958 Females: red symbols and regression lines). From Grinn et al., 2017.

959  
960 **Figure 5. Evidence that ABR wave I amplitude is not decreased by noise exposure in**  
961 **humans.**  
962 Grand average ABR waveforms. Average waveforms are shown in microvolts for males and  
963 females separately and for the 15 lowest and 15 highest noise exposed individuals for each sex.  
964 Waves I, III and V can be seen at around 2, 4 and 6 ms respectively. Waveforms are plotted  
965 broadband in order to show the full morphology of the response. Reprinted with permission from  
966 Prendergast et al., 2017. Hearing Research.

967  
968 **Figure 6. Evidence that ABR wave I amplitude is not decreased among individuals with**  
969 **problems understanding speech in noise.**  
970 ABRs elicited by 102 dB peSPL clicks for verified-SPiN-impairment and control groups. A:  
971 Grand average waveforms (averaged across ears and across participants). Shaded areas represent  
972 the SEM. B: Wave I and wave V amplitudes, presented as mean  $\pm$  SEM. Reprinted with  
973 permission from Guest et al., 2018. Hearing Research.

974  
975  
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977

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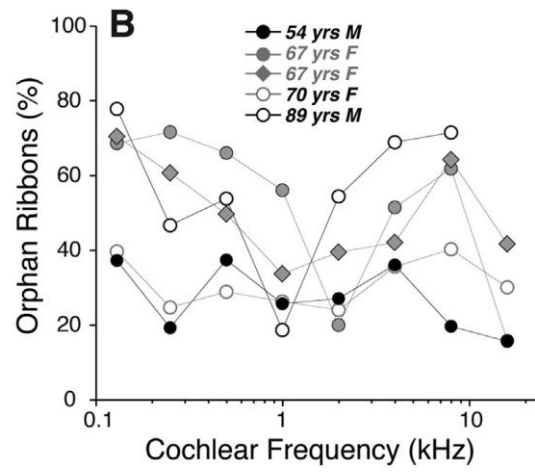
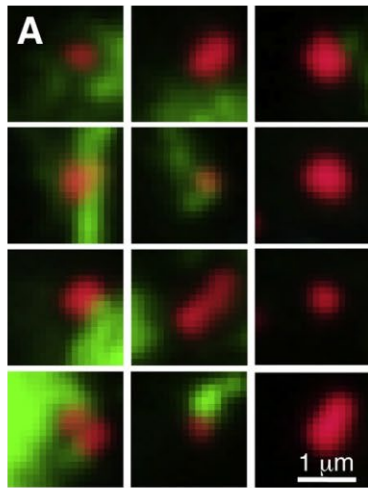
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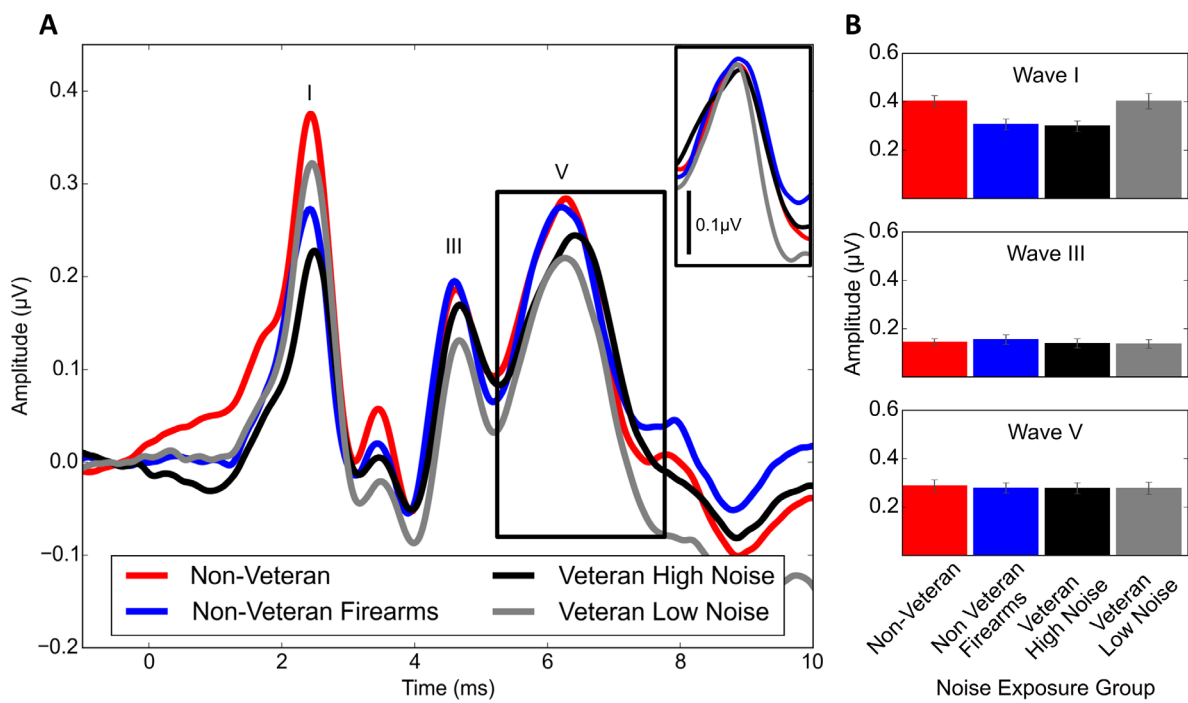
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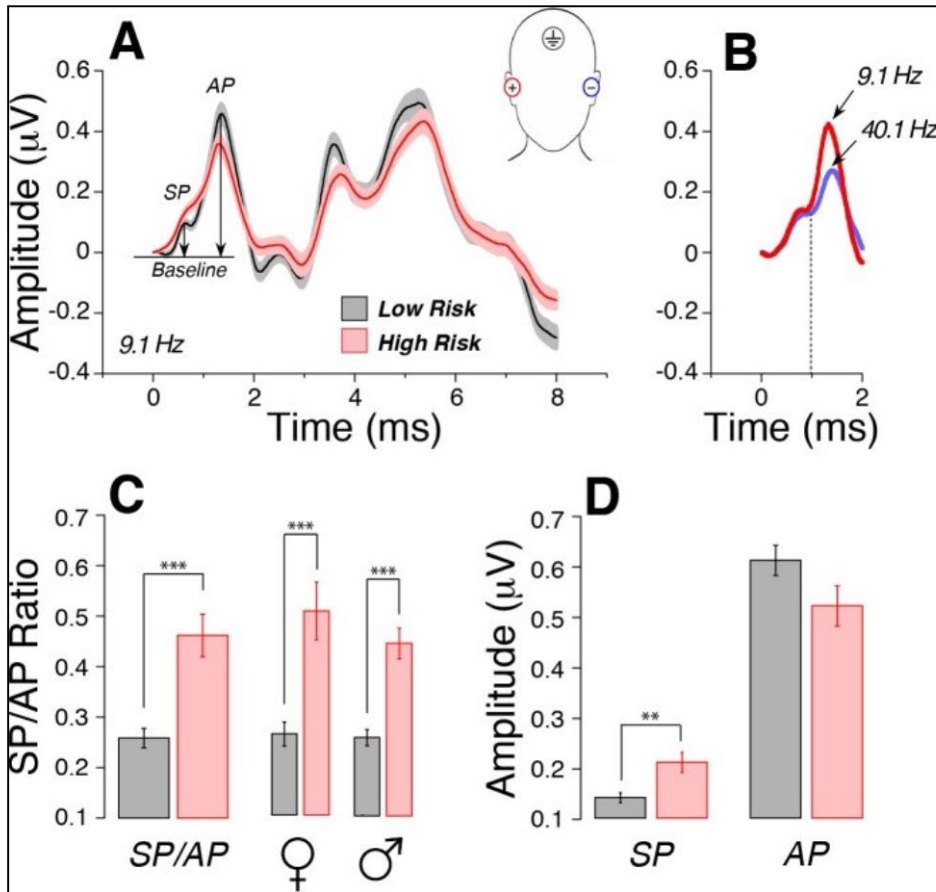


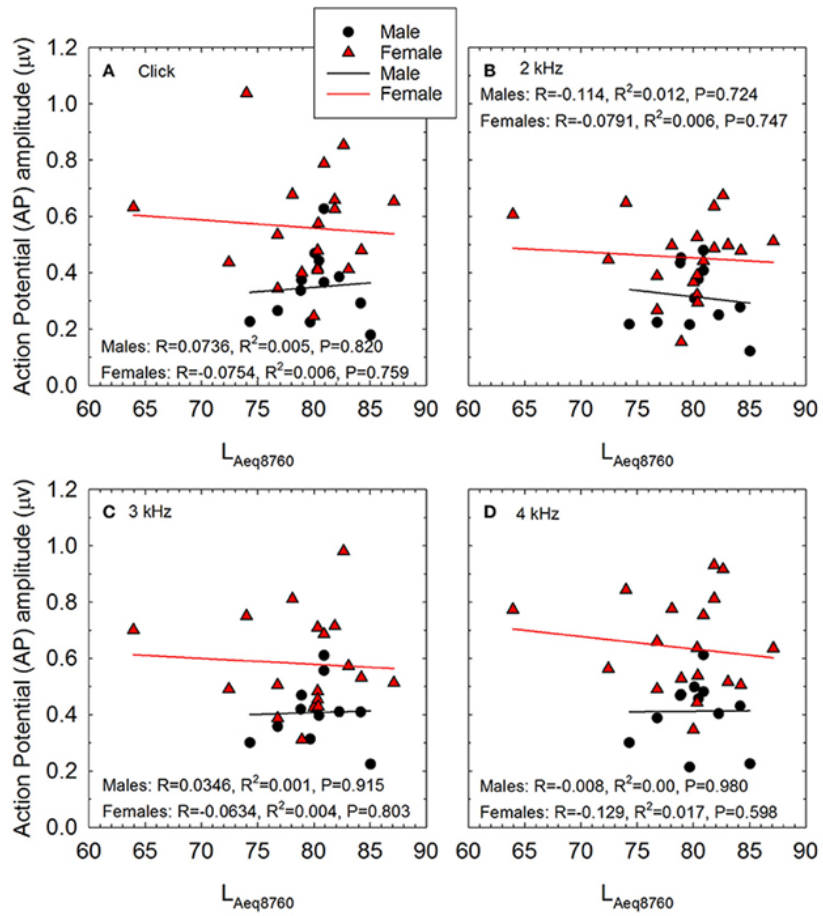
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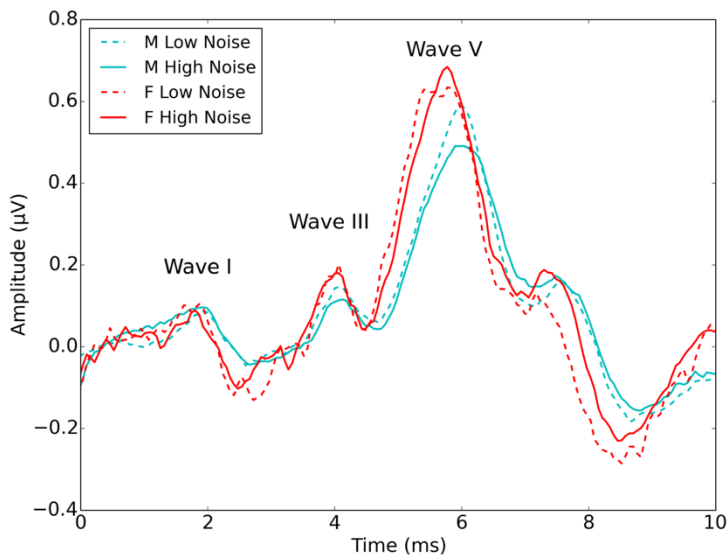




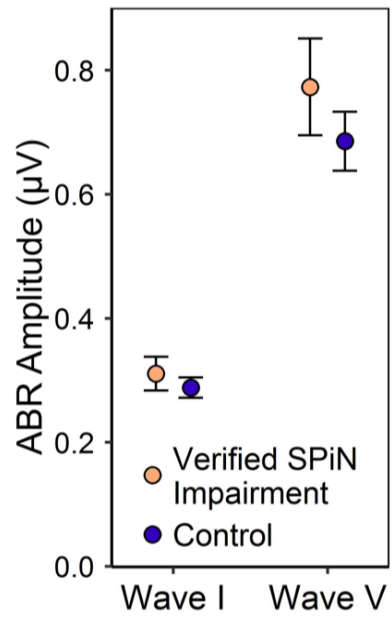
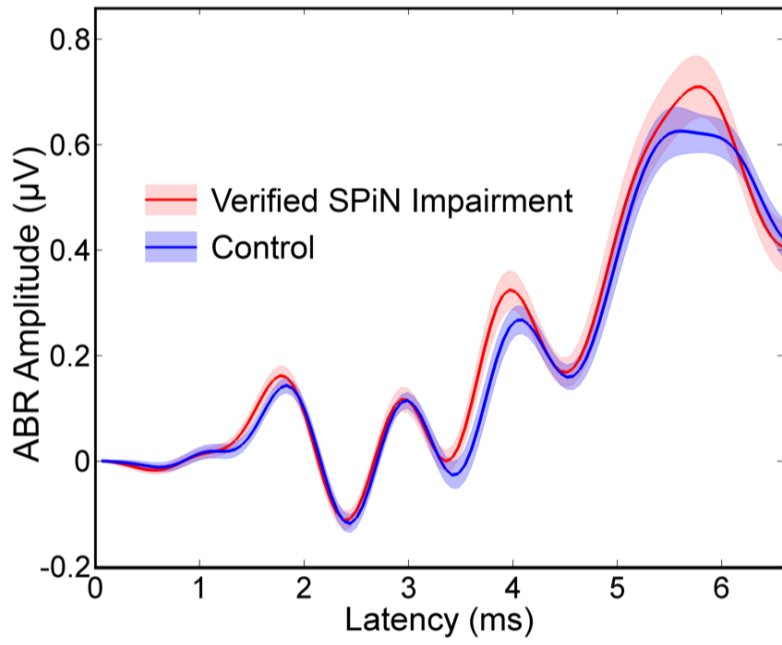




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