Subcortical amplitude modulation encoding deficits suggest evidence of cochlear synaptopathy in normal-hearing 18–19 year olds with higher lifetime noise exposure

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Abstract: Noise exposure and aging can damage cochlear synapses required for suprathreshold listening, even when cochlear structures needed for hearing at threshold remain unaffected. To control for effects of aging, behavioral amplitude modulation (AM) detection and subcortical envelope following responses (EFRs) to AM tones in 25 age-restricted (18–19 years) participants with normal thresholds, but different self-reported noise exposure histories were studied. Participants with more noise exposure had smaller EFRs and tended to have poorer AM detection than less-exposed individuals. Simulations of the EFR using a well-established cochlear model were consistent with more synaptopathy in participants reporting greater noise exposure.
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1. Introduction

Animal studies have shown that mild noise exposure, which leaves no long-term effect on cochlear hair cells, can irreversibly damage auditory nerve fiber (ANF) synapses to which hair cells connect (see Kujawa and Liberman, 2015, for a review). The most susceptible synapses are those with high firing thresholds and low spontaneous firing rates (low-SR), while damage to low-threshold, high spontaneous rate (high-SR) fibers is comparatively less severe (Furman *et al.*, 2013). As a result, the proportionally greater loss of low-SR fibers is suggested to degrade suprathreshold listening ability (Bharadwaj *et al.,* 2014) such as hearing in noise or with competing signals. However, hearing thresholds commonly measured by clinical audiometry can remain normal, which require only some high-SR fibers and intact hair cells (Lobarinas *et al.*, 2013).

In humans, one approach suggested to reveal cochlear synaptopathy has been to measure amplitude modulation (AM) encoding in difficult listening circumstances (Bharadwaj *et al.*, 2014; Shaheen *et al.*, 2016; Paul *et al.*, 2017). Because the firing rate of high-SR fibers saturates near 40 dB sound pressure level (SPL) (Costalupes, 1985), low-SR fibers may contribute more to encoding envelope fluctuations above this level especially when AM is shallow or sounds are presented in background noise. An expected consequence of relatively greater low-SR loss is poor AM detection (AMD) thresholds and a degradation of the envelope following response (EFR), a subcortical potential evoked by an AM stimulus. The EFR is a composite of several auditory nuclei (including the auditory nerve) but when evoked by AM rates of 80 to 200 Hz, the strongest generators localize to the auditory midbrain (Shinn-Cunningham *et al.,* 2017). Bharadwaj *et al.* (2015) showed that inter-individual variability in AMD ability correlated with EFRs such that those with poorer AMD thresholds had weaker EFRs evoked by shallow AM, consistent with mostly low-SR synapse loss. These individuals also had more self-reported exposure to noise. Similarly, Paul *et al.* (2017) found that normal-hearing individuals with poorer AMD thresholds measured in 40 dB spectrum level background noise (designed to attenuate the contribution of high-SR fibers) had

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EFRs that were degraded more by the same background noise compared to individuals with better AMD thresholds. Simulations of the EFR using a well-established model of the auditory periphery (Zilany *et al.*, 2014) suggested mostly low-SR fiber loss in the former subjects.

Cochlear synaptopathy has also been observed with aging and precedes hair cell loss, even if the animal is never exposed to noise (Sergeyenko *et al.*, 2013). However synaptopathy induced by noise can accelerate synaptopathy associated with age (Fernandez *et al.*, 2015). These studies suggest that reports of cochlear synaptopathy in prior human studies could be the result of both aging and noise exposure. Although age differences in Bharadwaj *et al.* (2015) (age range of 21–39) and Paul *et al.* (2017) (range of 18–39) did not account for a significant portion of the AM encoding variability, no human synaptopathy study has controlled for age *a priori*, which would experimentally minimize age-related deficits. To this end, we restricted the participant sample to 18 and 19 year old adults in the current study to better control for age-related synaptic loss, and thereafter tested the hypothesis that suprathreshold AM encoding (EFRs and AMD thresholds) remains demonstrably poorer in individuals with greater history of noise exposure. We then used a computational model of the auditory periphery to determine if simulated synaptopathy matched observations of EFRs for participants with more noise exposure.

2. Methods

2.1 Participants

Twenty-seven 18 or 19 year old participants enrolled in undergraduate psychology courses at McMaster University volunteered for the study and provided written and informed consent. One participant did not complete the study, and another did not reach our statistical criterion for the presence of an EFR and was excluded (see below). The remaining 25 participants (eight males and ten 19-year olds) received course credit upon study completion. The Research Ethics Board at McMaster University approved all procedures.

2.2 Noise exposure questionnaire and audiogram

Participants were first given a list of 21 recreational and occupational activities associated with noise exposure taken from the Jokitulppo *et al.* (2006) questionnaire. Examples of activities include "playing in a band or orchestra," "listening to iPhone, iPod, or MP3 player (headphones)," "attending concerts, festivals, or musical events," and "using power tools indoors." For each item, participants (a) indicated how many hours per week (T_w) they participated in the activity, (b) rated the loudness of the activity on a 1 to 5 scale (1 = level of normal conversation; 5 = noise level where communication is impossible), and (c) indicated how many years (T_y) they participated in the activity. For each item we converted the five-point scale to 60, 70, 80, 90, or 100 dBA L_{Aeq} (following Jokitulppo *et al.*, 2006), and then calculated item-specific lifetime noise exposure (E_{cum}, measured in kPa^2 h) according to

$$E_{cum} = 4(T_w)10^{0.1(L_{Aeq}-100)}52(T_y). \qquad (1)$$

E_{cum} was then summed for all activities. Participants' lifetime noise exposure averaged 1.673 kPa^2 h and ranged from 0.005 to 10.236. Participants in the lower 50th percentile of noise exposure were assigned to the low noise exposure group ($N = 12$; exposure M = 0.104 kPa^2 h; SD = 0.970) and those in the upper 50th percentile to the high exposure group ($N = 13$; M = 3.122 kPa^2 h; SD = 3.289).

Participants' pure tone audiograms (PTAs) were measured from 125 Hz to 16 kHz on a GSI-61 clinical audiometer while they were seated in a sound-attenuated (ambient noise level 16 dBA) and electrically shielded booth. PTAs for each ear were measured in 5 dB steps using the pulsed-tone method. Grand average PTAs for each noise exposure group (averaged across ears), and PTAs for individual participants in both groups (separate ears), are depicted in Fig. 1(a). PTAs were ≤25 dB hearing level (HL) for all frequencies, with the exception of three ears reaching a maximum of 35 dB HL at 16 kHz, all belonging to two participants in the high-exposure group. PTAs did not significantly differ between the high and low noise exposure groups at any frequency (Bonferroni-Holm corrected *t* tests), suggesting the groups had well-matched hearing thresholds.

2.3 Amplitude modulation detection thresholds in quiet and noise

For all subsequent portions of the experiment, participants sat in a chair distanced 1.4 m from a computer monitor in the booth. Stimuli were generated by a Tucker-Davis

RP2.1 digital signal real-time processor and presented through EARtone 3 A transducers to both ears.

AMD thresholds were obtained in a forced choice procedure requiring participants to indicate which of three 5 kHz tones was amplitude modulated. Each tone was presented at 75 dB SPL, lasted 1 s in duration, and had an inter-stimulus interval of 1 s. The target tone was sinusoidally modulated at 19 Hz and was in a randomly chosen interval, while the two non-target tones were unmodulated. Modulation depth of the target, expressed herein in dB ($20\log10m$) with $m = 1$ corresponding to 100% depth, began at 0 dB (full modulation) and was adjusted adaptively by parameter estimation of sequential testing (PEST) (Taylor and Creelman, 1967) until a final step size of 0.45 dB was reached. Participants did not receive feedback during the task.

AMD thresholds were measured in conditions of quiet or in narrowband background noise (NBN) with a 1/3 octave bandwidth centered at 5 kHz. In each trial, NBN began 500 ms before the start of the first tone and ended 500 ms after the end of the last tone. NBN was presented at spectrum levels of either 25, 40, or 45 dB (four conditions total including quiet). Pilot experiments indicated that the 45 dB spectrum level NBN was the maximum level at which AM detection could be measured. NBN at 45 dB was observed to cover a majority of the spread of excitation across the range of auditory nerve fibers with characteristic frequencies (CFs) responding to the 5 kHz AM probe when simulated in the Zilany *et al.* (2014) auditory periphery model [Fig. 1(b)]. The contribution of most high-SR fibers within this region to the modeled neural response was attenuated with NBN at 45 dB, suggesting that low-SR fibers encoded most of the temporal modulations. However at this noise level weaker modulations were still observed within high-SR, high-CF fibers (>10 kHz) in model [Fig. 1(b), right panel], suggesting these fibers could contribute to an EFR recorded in 45 dB NBN.

2.4 Envelope following response recording and analysis

Following the AMD task, we recorded by 32-channel electroencephalography (EEG) the EFR evoked by a 75 dB SPL, 5 kHz tone sinusoidally amplitude modulated at 86 Hz (0 dB modulation depth). The EFR was measured in quiet and NBN with the same properties and levels used in the AM detection task. For all four conditions (order randomly chosen for each participant) the stimulus was presented for two continuous minutes. Three seconds of silence elapsed between each condition. During sound presentation and recording, participants were instructed to ignore the stimuli and watch a subtitled silent film of their choice that was presented on the computer monitor.

The EEG was sampled at 2048 Hz by a BioSemi ActiveTwo amplifier (Cortech Solutions, Wilmington, NC) and stored as continuous data files. Offline in MATLAB (The Mathworks, Natick, MA), the EEG was re-referenced to the scalp average, high-pass filtered at 70 Hz, and downsampled to 860 Hz. For each condition, data were segmented into 500 ms epochs, creating 240 total trials per condition per person. Epochs exceeding ± 50 μV in any channel were rejected as containing artifact. EFR power was computed using a multi-channel complex principal components analysis (Bharadwaj and Shinn-Cunningham, 2014). This technique combines EFR signals across the scalp montage and optimally adjusts for phase differences present in each channel, providing a more reliable EFR measurement and robustness to noise compared to single-channel recordings. Following Zhu *et al.* (2013), the presence of an
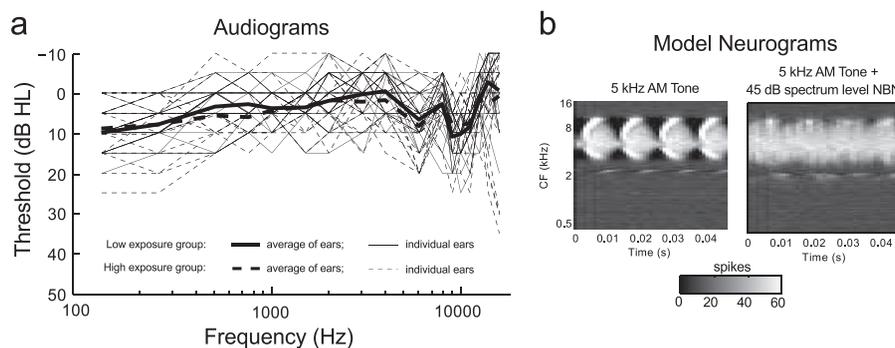

Fig. 1. (a) Audiograms from 125 Hz to 16 kHz showing the grand average audiogram (averaged between ears) of the high and low noise exposure groups (dashed and solid thick lines, respectively). Individual ears of the low and high exposure group are shown as thin solid and dashed lines, respectively. (b) Model neurograms for four pulses of the 5 kHz AM tone (left panel) and the AM tone within 45 dB spectrum level NBN (right panel) depicting the simulated spiking (shading) of model ANFs.

EFR was statistically determined by comparing bootstrapped distributions of the EFR phase locking value (PLV) at 86 Hz relative to the noise floor (five frequency bins above and below the 86 Hz bin) in parametric tests with an alpha criterion of 0.05 (Bonferroni corrected). One participant in the original recruitment sample did not meet this criterion in the 40 dB NBN condition and was excluded from further data analysis. EFR power at 86 Hz herein is referred to as "EFR strength" and is expressed in dB as a signal to noise ratio (SNR) relative to the mean of the same ten adjacent frequency bins used in the PLV analysis.

2.5 Peripheral auditory modeling

ANF responses to EFR stimuli were simulated in the Zilany *et al.* (2014) auditory periphery model under different degrees of ANF loss (herein as a proxy to synapse loss) that could descriptively match EFR differences between high and low noise exposure groups. The model takes 400 ms stimuli from each EFR condition and simulates the filtering and compression properties of the middle ear and cochlear structures, producing a neurogram depicting the spiking response of 128 sets of ANFs with characteristic frequencies (CF) logarithmically spaced between 440 Hz and 17 kHz. Each CF set contained 150 ANFs, with high-, medium-, and low-SR types distributed in a 3:1:1 ratio for each CF (herein, low-SR fibers encompass medium- and low-SR fibers). The 86 Hz modulation response of the fibers (in dB SNR) was calculated following Paul *et al.* (2017).

In a previous study we applied synaptopathy uniformly across all CFs to 8 kHz (Paul *et al.*, 2017). However, predictions of the EFR data in the present study were poor using this approach when we considered an extended range of CFs up to 17 kHz. Furthermore, animal studies suggest that higher CFs are more susceptible to synaptopathy (Liberman, 2017). Therefore, in this study synaptopathy was simulated as an exponential loss of both high and low-SR ANFs as a function of cochlear position only beyond edge CFs, with the spatial decay constant λ having units of octaves. In healthy sections of the cochlea the number of ANFs at each CF was set at 90 for high-SR fibers and 60 for low-SR fibers. The ratio of low- to high-SR ANF loss in the region with synaptopathy was held constant at a ratio of 3:1, following the estimated proportion of synapse loss to these fiber types estimated by Marmel *et al.* (2015) for animals reported in Furman *et al.* (2013). Model simulations were computed over a range of decay constants (λ) and edge CFs at which the exponential loss commenced. For purposes of visualization, we report decay constants of 0.1 (steep synaptopathy) and 1.0 (shallow synaptopathy), which qualitatively covered the range of observed EFR data. The simulated asymptotic low-SR loss was 100%, and thus the asymptotic high-SR loss was 22%. Although it is difficult to predict the frequency where noise-induced synaptopathy begins in humans, here we chose a 4 kHz edge CF where noise induced hearing loss often first appears in young, noise-exposed adults before spreading to higher frequencies (Seixas *et al.*, 2004). Simulations were repeated eight times to obtain a mean and variance.

3. Results

3.1 Differences between high and low noise-exposure groups

AMD thresholds and EFRs were assessed separately in 2 × 4 factorial analysis of variance (ANOVA) models including the between subjects factor of group (high vs low noise exposure) and the within-subjects factors of condition (quiet and three NBN levels). AMD thresholds for all conditions in both exposure groups are shown in Fig. 2(a). The ANOVA returned a main effect of condition [$F(3,92) = 214.46$, $p < 0.001$] indicating that thresholds increased with increasing NBN level. Although detection thresholds tended on average to be poorer in the high-exposure group, the main effect of group did not reach significance ($p = 0.067$). The interaction of group across the four NBN conditions was also not significant ($p = 0.76$). Two-tailed *post hoc* tests comparing the groups for AMD threshold differences were not significant for any individual condition.

EFR strength for both exposure groups is depicted in Fig. 2(b). An ANOVA on this measure revealed a main effect of condition [$F(3,92) = 4.71$, $p = 0.004$] indicating that higher NBN levels significantly diminished EFR strength. A main effect of group was also found [$F(1,92)$, $p = 0.0198$] indicating that EFR strength in the high noise exposure group was lower overall than the low noise exposure group. No interaction was present between group and condition ($p = 0.87$) and *post hoc* tests did not find significant differences between groups in any single EFR condition, although EFR strength within the 40 dB spectrum level NBN tended to be lower in the high exposure group ($p = 0.07$, LSD test).
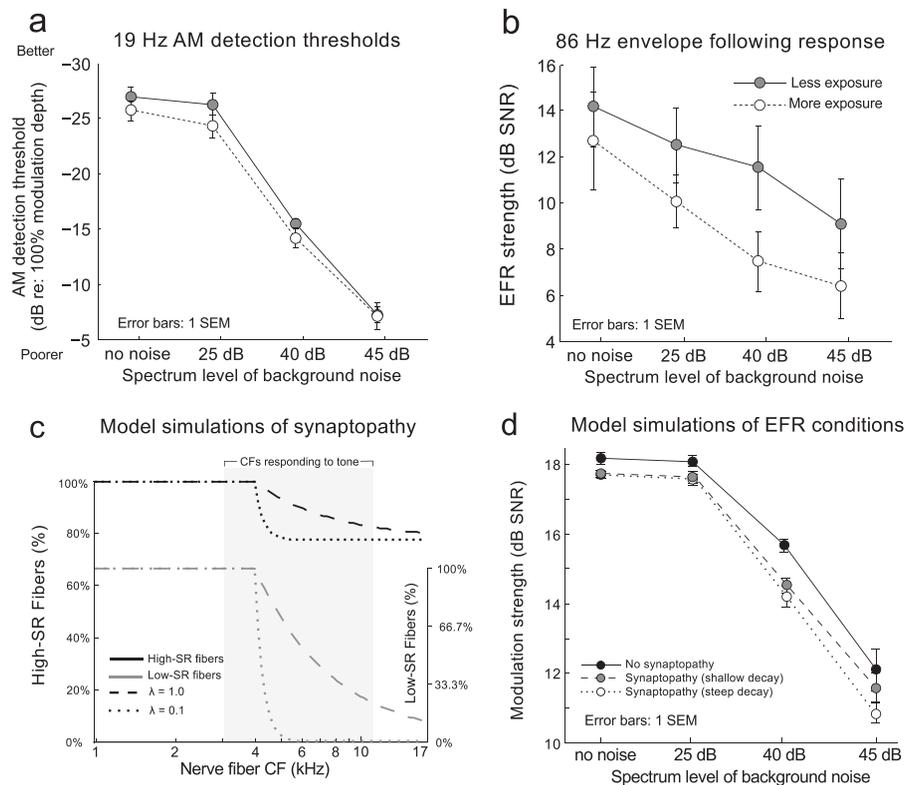
Fig. 2. (a) Amplitude modulation detection thresholds in each condition averaged for the high (dashed line) and low (solid line) noise exposure groups. Smaller numbers indicate low (better) thresholds. (b) EFRs evoked for all NBN conditions averaged for the high (dashed line) and low (solid line) noise exposure groups. (c) Exponential loss of high- and low-SR ANFs of different CFs simulated in the model. The ratio of low- to high-SR loss was maintained at 3:1, and the spatial decay constant lambda describes either shallow (1.0) or steep (0.01) exponential synaptopathic loss in units of octaves. The shaded region represents ANFs observed to respond to the AM tone, which are expressed as a SNR in (d). (d) Auditory periphery model simulations of EFR conditions with levels of synaptopathy described by (c). Error bars in panels (a), (b), and (d) are 1 standard error of the mean (SEM).

Degrees of synaptopathy applied to ANFs of different CFs in the Zilany *et al.* (2014) model are shown in Fig. 2(c), and simulations of ANF 86 Hz modulation strength to EFR stimuli under these conditions are shown in Fig. 2(d). With no synaptopathy [Fig. 2(d), solid line], ANF modulation responses were smallest at NBN of 40 and 45 dB spectrum level where high-SR fibers reach saturation and contribute less to AM encoding. A shallow gradient of synaptopathy [Fig. 2(d), dashed line] produced a smaller overall modulation response compared to no synaptopathy, with the largest difference at 40 dB NBN but less so at 45 dB NBN. With steeper synaptopathy (dotted line), ANF modulation responses differences were smaller than shallow and no synaptopathy. Because EFRs in the high-noise exposure group tended to differ most from the low-exposure group at 40 dB NBN and less so at 45 dB, the model suggests that a shallow or mild degree of synaptopathy best described the EFRs of these subjects.

3.2 Individual differences in noise exposure and amplitude modulation encoding deficits

Past reports have found that inter-individual differences in EFR strength correlate with AMD such that those with relatively weaker EFRs evoked by shallow envelope modulations or in noise have poorer AM detection thresholds (Bharadwaj *et al.*, 2015; Paul *et al.*, 2017). In the current data we explored similar individual differences by computing the slope of a straight line fit over each individual's four EFR and AMD values with the expectation that those with steeper EFR slopes (degradation of the EFR in noise) would have steeper AMD threshold slopes (higher elevation of thresholds in noise). The relationship of EFR slope to AMD slope was in the expected direction but did not reach significance ($r = 0.24$, $p = 0.25$). Noise exposure history did not correlate with EFR slope ($r = -0.13$, $p = 0.52$) or AMD slope ($r = 0.10$, $p = 0.63$) or with EFRs or AMD thresholds in any single condition ($p > 0.36$, uncorrected for multiple comparisons), with the exception of a tendency for noise exposure history and AMD thresholds at 40 dB NBN to positively correlate ($r = 0.37$, $p = 0.072$, uncorrected).

The pure tone audiogram at 5 kHz (averaged across ears) did not correlate with any suprathreshold measure, expressed either as slope or within individual NBN conditions ($p > 0.11$, uncorrected) with the single exception that the EFR evoked in 40 dB NBN tended to be smaller with higher thresholds ($r = -0.40$, $p = 0.05$, uncorrected). Similarly, the high-frequency audiogram (averaged from 9 to 16 kHz and across ears), reported to be an early sign of noise-induced damage to the cochlea (Liberman *et al.*, 2016), did not correlate to suprathreshold AM encoding measures ($p > 0.10$, uncorrected) or to noise exposure history ($p > 0.51$).

4. Discussion

Our goal was to test for evidence of cochlear synaptopathy in an age-restricted sample of young adults with normal hearing thresholds who had higher reported lifetime noise exposure compared to a group with lower lifetime noise exposure. Consistent with our hypothesis we found that those in the former group had on average smaller EFRs (suggesting poorer subcortical AM encoding) compared to individuals in the latter group. Simulated ANF responses to our EFR stimuli using the auditory periphery model of Zilany *et al.* (2014) suggested that degraded EFRs in the high noise exposure group could result from a mild degree of synaptopathy. Similarly, behavioral AMD thresholds were on average poorer in the high-exposure group, but this difference did not reach statistical significance. Thus in the present data the EFR was more sensitive to the group difference in noise exposure history than was the threshold of AMD.

A question to be considered is why this may have been so. One possibility is that random modulations within the NBN may have added to the difficulty of the behavioral task, in which the stimuli were only 1 s long, whereas the effects of random modulation in the NBN may be averaged out substantially more in the EFR signal, which is averaged over 2 min of stimulation. It may also be relevant that AMD thresholds are necessarily measured at shallow modulation depths while EFRs can be recorded over a wider dynamic range. In our study, EFRs were evoked by a fully modulated tone (0 dB AM depth). Thus, the two measures likely depended on different contributions of low-SR and high-SR ANFs. High-SR fibers saturate ~40 dB SPL (Costalupes, 1985) and may not contribute to AMD thresholds if envelope fluctuations are too shallow to enter their dynamic range. In contrast, the fully modulated tones used to evoke the EFR here would have been sufficient to engage these fibers fully at low levels of NBN and at high CFs not covered by NBN > 40 dB spectrum level, as seen in the model. Thus, assuming the mild synaptopathy case suggested by the model, AMD thresholds may have been affected only by low-SR loss while the EFR would have been sensitive to both this loss and to any off-frequency high-SR loss occurring with noise-induced synaptopathy. The fully modulated tone may also have engaged a larger population of low-SR fibers overall than the shallower modulations used for AM detection. This would have rendered the EFR more sensitive to synaptopathy than AMD thresholds, as was found here.

Looking ahead, these considerations suggest that EFRs evoked by fully modulated tones may be more sensitive to synaptic loss than is the measurement of AM detection thresholds. The losses implied by our findings also appeared to have been largely hidden from audiometric thresholds, which correlated poorly or not at all with the EFR in agreement with previous reports (Bharadwaj *et al.*, 2015; Paul *et al.*, 2017) and did not differ between the high and low noise exposure groups.

Notwithstanding that EFRs and AMD thresholds may reflect overlapping synaptic populations, a further factor to consider is the range of low-SR and high-SR synapse losses that may be present among the participants studied. We restricted the age of our participants to remove potential confounds related to the age factor, thereby setting noise exposure history into relief. However, in doing so, our subjects may have been too young to have experienced the range of noise exposures that could have produced synaptic losses large enough to be detected by AMD as well as the EFR. Previous reports of evidence for synaptopathy in both measures (Bharadwaj *et al.*, 2015; Paul *et al.*, 2017) employed subjects aged 18–39 years, where a wider range of synaptic losses owing to cumulative noise exposure or to intrinsic age-related changes may have been present. In additional studies it would be desirable to compare the present data to an older, age-restricted cohort who presumably have more variable noise exposure history and thus more variable synaptopathy.

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