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Age-Related Changes in the Auditory Brainstem Response and Suprathreshold Processing of Temporal and Spectral Modulation

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Abstract

The purpose of this study was to determine whether cochlear synaptopathy can be shown to be a viable basis for age-related hearing difficulties in humans and whether it manifests as deficient suprathreshold processing of temporal and spectral modulation. Three experiments were undertaken evaluating the effects of age on (a) the auditory brainstem response as a function of level, (b) temporal modulation detection as a function of level and background noise, and (c) spectral modulation as a function of level. Across the three experiments, a total of 21 older listeners with near-normal audiograms and 29 young listeners with audiometrically normal hearing participated. The auditory brainstem response experiment demonstrated reduced Wave I amplitudes and concomitant reductions in the amplitude ratios of Wave I to Wave V in the older listener group. These findings were interpreted as consistent with an electrophysiological profile of cochlear synaptopathy. The temporal and spectral modulation detection experiments, however, provided no support for the hypothesis of compromised suprathreshold processing in these domains. This pattern of results suggests that even if cochlear synaptopathy can be shown to be a viable basis for age-related hearing difficulties, then temporal and spectral modulation detection paradigms are not sensitive to its presence.

Keywords

aging, cochlear synaptopathy, hidden hearing loss, auditory brainstem response, modulation detection

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Introduction

Sensorineural hearing loss is a common characteristic of advancing age, but some older listeners retain near-normal audiometric thresholds. Even these older listeners with good sensitivity, however, frequently report hearing difficulties in acoustically complex environments. This general profile of auditory deficiency belied by a normal audiogram has been recognized as a phenomenon for decades (e.g., King & Stephens, 1992; Saunders, Haggard, & Field, 1989; Stephens & Zhao, 2000). In recent years, a specific pathophysiological condition known as cochlear synaptopathy has gained attention as one possible basis for this general profile (e.g., Kujawa & Liberman, 2015; Kobel, Le Prell, Liu, Hawks, & Bao, 2017; Liberman & Kujawa, 2017). Cochlear synaptopathy refers to a permanent dysfunction at the junctions between inner hair cells and auditory nerve fibers caused by low-grade trauma to the inner ear, typically associated with noise exposure, that is insufficient to result in a permanent elevation of thresholds (Lin, Furman, Kujawa, & Liberman, 2011). The long-term sequela of cochlear synaptopathy is a depletion of auditory nerve fibers (Jensen, Lysaght, Liberman, Qvortrup, & Stankovic, 2015), with concomitant changes in more central stages of the auditory system (Muniak, Ayeni, & Ryugo, 2018). A reduction in the viable population of auditory nerve fibers,

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particularly of the subpopulation of low-spontaneous rate, high-threshold fibers (Furman, Kujawa, & Liberman, 2013), might be expected to lead to auditory deficits that emerge perceptually at suprathreshold levels and in challenging listening situations such as in background noise (Bharadwaj, Verhulst, Shaheen, Liberman, & Shinn-Cunningham, 2014; Parthasarathy & Kujawa, 2018; Ridley, Kopun, Neely, Gorga, & Rasetshwane, 2018). Although a wide range of studies have tested this expectation in humans, the results have been mixed (e.g., Bharadwaj, Masud, Mehraei, Verhulst, & Shinn-Cunningham, 2015; Grose, Buss, & Hall, 2017; Le Prell & Lobarinas, 2016; Liberman, Epstein, Cleveland, Wang, & Maison, 2016; Prendergast, Millman, et al., 2017; Yeend, Beach, Sharma, & Dillon, 2017). Many of these studies have also included electrophysiological measures as a means of demonstrating cochlear synaptopathy in humans, again with mixed success (e.g., Grinn, Wiseman, Baker, & Le Prell, 2017; Mehraei et al., 2016; Prendergast, Guest, et al., 2017; Stamper & Johnson, 2015; Valderrama et al., 2018).

The focus of this report is age-related cochlear synaptopathy. The notion that this pathophysiological condition contributes to hearing difficulties in senescence has gained traction in recent years. In terms of animal studies, Sergeyenko et al. (2013) demonstrated the presence of age-related cochlear synaptopathy by showing that the growth functions of Wave I of the auditory brainstem response (ABR) declined more rapidly with age than did otoacoustic emissions even when thresholds remained normal. This decline was associated with a marked loss of spiral ganglion cells. Building on this finding, Parthasarathy and Kujawa (2018) showed that age-related cochlear synaptopathy in mice affected suprathreshold temporal processing. In terms of human studies, the age-related loss of spiral ganglion cells has also been measured in temporal bone analyses. Makary, Shin, Kujawa, Liberman, and Merchant (2011) showed that the decline in spiral ganglion cell count occurred more rapidly than the associated decline in audiometric thresholds reconstructed from available clinical records, and both Viana et al. (2015) and Wu et al. (2018) demonstrated that the loss of spiral ganglion cells outpaced the loss of hair cells. In summary, both animal studies and human cadaver studies have supported the veracity of age-related cochlear synaptopathy.

The purpose of this report is to test hypotheses concerning age-related cochlear synaptopathy in humans. Three experiments were undertaken, evaluating the effects of age on (a) the ABR as a function of level, (b) temporal modulation detection as a function of level and background noise, and (c) spectral modulation as a function of level. Although the experiments were undertaken at different times and therefore incurred little overlap in subjects across the experiments,[1] the target participant populations were homogeneous. The two homogenous populations were young adults with normal audiometric hearing and older adults with near-normal audiometric hearing. Comparing performance for these two groups allows us to test for both the presence of and the perceptual consequences of cochlear synaptopathy in older adults. In summary, the purpose of this study was to determine whether cochlear synaptopathy can be shown, noninvasively, to be a viable senescent condition and whether it manifests as deficient suprathreshold processing of temporal and spectral modulation.

Experiment 1: ABRs

A signature of cochlear synaptopathy in animal studies is a reduced amplitude of Wave I of the ABR (Lin et al., 2011; Lobarinas, Spankovich, & Le Prell, 2017). Efforts to capitalize on this finding in the examination of cochlear synaptopathy in humans have had mixed results. Some studies show positive findings, with a reduced amplitude of Wave I in normal-hearing populations likely to include cochlear synaptopathy (e.g., Bramhall, Konrad-Martin, McMillan, & Griest, 2017; Schaette & McAlpine, 2011; Stamper & Johnson, 2015; Valderrama et al., 2018), while other studies find no effect (Guest, Munro, Prendergast, Howe, & Plack, 2017; Guest, Munro, Prendergast, Millman, & Plack, 2018; Prendergast, Guest, et al., 2017; Skoe & Tufts, 2018). In several cases, it is argued that absolute amplitude is not as informative as the ratio of the Wave I amplitude to either the amplitude of the summating potential (SP; Liberman et al., 2016) or to the amplitude of Wave V (Grose et al., 2017; Verhulst, Jagadeesh, Mauermann, & Ernst, 2016). As an aside, it should be noted that some ABR studies investigating cochlear synaptopathy in humans focus on wave latencies, particularly that of Wave V, in part because of the difficulty in recording Wave I (e.g., Mehraei et al., 2016; Skoe & Tufts, 2018). However, as described later, Wave I was successfully recorded in all participants here and so the focus remains on Wave I amplitude. Work by Burkard and Sims (2001) has shown that, for a single high click level, the amplitude of Wave I is markedly lower in older listeners with normal hearing or mild hearing loss compared with normal-hearing young adults. Similarly, McClaskey, Dias, Dubno, and Harris (2018) have shown that the amplitude of the compound action potential of the electrocochleographic response, which corresponds to Wave I of the ABR, is smaller in older adults with near-normal hearing than in young adults. The purpose of the present experiment was to extend this finding to measure the ABR in older listeners with near-normal audiometric hearing at two different levels to characterize growth functions, again with a particular focus on the amplitudes of Wave I and Wave V. In summary, the

hypothesis of this experiment is that older listeners with near-normal audiometric hearing have reduced Wave I amplitudes, and this is most evidenced by a reduced Wave I/Wave V amplitude ratio. Such a finding would be consistent with age-related cochlear synaptopathy.

Method

Subjects. Ten young normal-hearing (YNH) adults and 10 older adults with near-normal hearing (ONH) participated. The YNH group had a mean age of 20.6 years (range = 19.1–23.6 years) and comprised eight females and two males. The ONH group had a mean age of 68.9 years (range = 61.5–78.7 years) and comprised six females and four males. All of the YNH group had audiometric thresholds across the octave frequencies 250 to 8000 Hz of 15-dB HL or better. All of the ONH group had audiometric thresholds across the octave frequencies 250 to 4000 Hz of 20-dB HL or better except for three subjects with a 25-dB HL threshold at 4000 Hz. Thresholds at 8000 Hz ranged from 15- to 60-dB HL. Average audiograms for the test ear in both groups are shown in Figure 1, left panel. All participants in this and the subsequent two experiments provided written informed consent and were reimbursed for their participation. The study was approved by the institutional review board of the University of North Carolina at Chapel Hill (IRB# 92-0632).

It is evident from Figure 1 that, although the ONH group in this and both subsequent experiments had hearing within normal limits below about 4000 Hz, most of them exhibited a hearing loss at 8000 Hz. As such, these older listeners cannot be considered exemplars of audiometrically normal hearing in the truest sense of the term. Such measurable high-frequency hearing losses have been shown to be associated with poorer suprathreshold performance. For example, Bernstein and Trahiotis (2016) showed that subclinical hearing losses at high frequencies are associated with reduced binaural processing, and Yeend, Beach, and Sharma (2018) showed that elevated extended high-frequency thresholds are predictive of poorer speech-in-noise performance. Nevertheless, extensive regions of audiometrically normal hearing remain, consistent with an underpinning of cochlear synaptopathy. Indeed, cochlear synaptopathy can be viewed as an insidious precursor to overt sensorineural hearing loss (Liberman & Kujawa, 2017). From this perspective, the ONH population studied in these experiments supports an investigation of age-related cochlear synaptopathy.

Stimulus. The ABR stimulus was a 100 -μs click calibrated in units of peak-to-peak equivalent sound pressure level (ppeSPL) re a continuous 1000-Hz tone. Two presentation levels were employed, 95- and 105-dB ppeSPL, which correspond nominally to 70- and 80-dB nHL. To optimize Wave I recording, the clicks were presented at a relatively slow rate of 7.7 clicks/s. The click trains were presented monaurally through 3A insert phones (Intelligent Hearing Systems, Glenvar Heights, FL). For the ONH group, the ear with the better audiometric thresholds was tested (four right ears and six left ears). To reflect this variation in test ear, the YNH group was evenly divided between right and left test ears.

ABR procedure. The participant relaxed comfortably in a recliner chair within an electromagnetically shielded, double-walled sound booth and was instructed to remain still and try to sleep. A single-channel electrode montage was used, with the noninverting electrode placed on the high forehead at the hairline and the ground electrode placed between the eyebrows. To optimize Wave I recording, an ear-canal placement was used for the

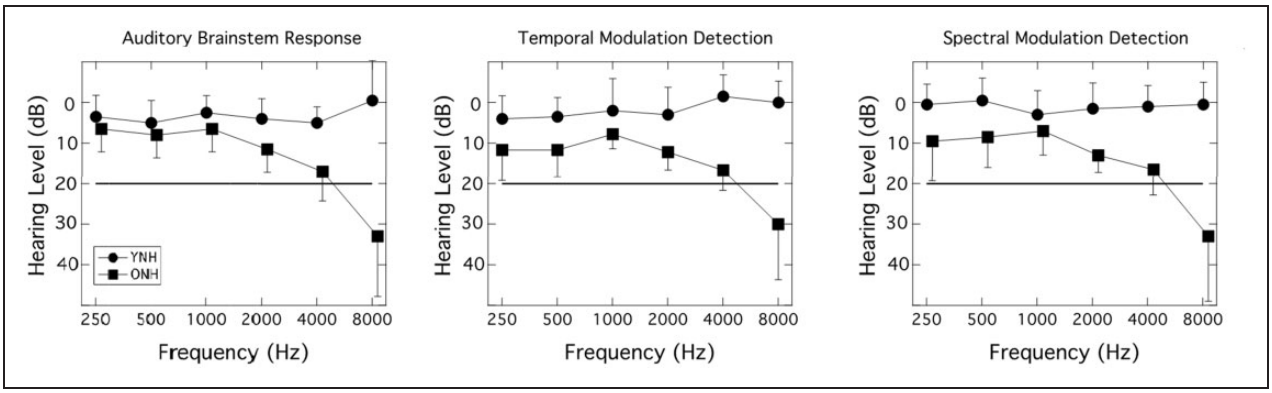

Figure 1. Group mean audiograms in the test ear for the young (YNH) and older (ONH) subjects. Panels, from left to right, are participants in Experiment 1 (ABR), Experiment 2 (temporal modulation detection), and Experiment 3 (spectral modulation detection). Error bars are 1 standard deviation. YNH = normal-hearing young; ONH = older with near-normal hearing.

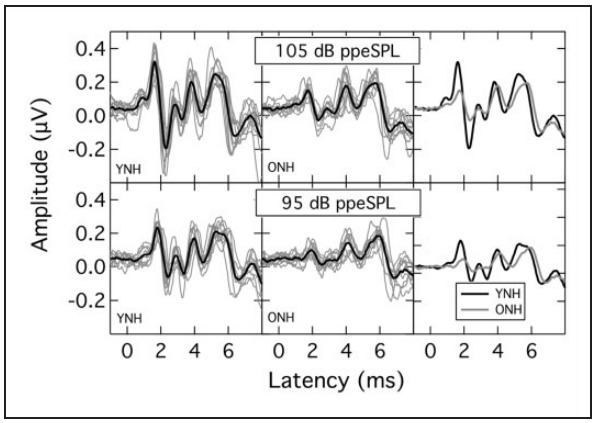

Figure 2. ABR waveforms for young (YNH, left column) and older (ONH, middle column) subjects. Lower and upper rows are for 95- and 105-dB ppeSPL presentation levels, respectively. In each panel, the gray waveforms are individual traces, and the heavy black line is the group mean. The group mean waveforms for the two levels are replotted overlaid in the right column.
YNH = normal-hearing young; ONH = older with near-normal hearing; ppeSPL = peak-to-peak equivalent sound pressure level.

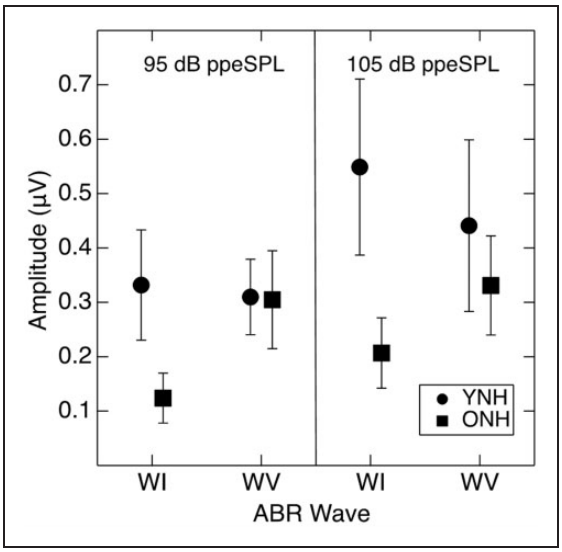

Figure 3. Group mean ABR amplitudes for WI and WV for the younger (YNH, circles) and older (ONH, squares) groups. Left panel: 95-dB ppeSPL; right panel: 105-dB ppeSPL level. Error bars are ± 1 standard deviation. YNH = normal-hearing young; ONH = older with near-normal hearing; ppeSPL = peak-to-peak equivalent sound pressure level; WI = Wave I; WV = Wave V.

inverting electrode (Tiptrode, Etymotic Research Inc., Elk Grove Village, IL). Electrode impedances were maintained below 3 kΩ. The ABR was recorded with an Intelligent Hearing System SmartEP platform using a recording bandwidth of 100 to 3000 Hz, and an artifact rejection setting of ±15 μV. For each stimulus level, three replications of 2,048-sweep averages were collected, which were subsequently averaged to give a single waveform representing 6,144 artifact-free sweeps.

Results

Individual and group mean ABR waveforms are displayed in Figure 2 for the YNH and ONH groups (left and middle panels, respectively; group mean data are replotted overlaid for the two age groups in the right panels). Responses appeared to be larger for the YNH group than for the ONH group at each level, and the amplitude of Wave I appeared to be larger relative to Wave V for the YNH group than the ONH group.

To assess these observations, the amplitudes of Wave I and Wave V for each participant were measured as the voltage difference between the respective positive peak and the succeeding negative peak. The mean amplitudes of these waves are plotted in Figure 3, with age-group and level as the parameters. The wave amplitudes were submitted to a repeated-measures analysis of variance (RMANOVA) with two within-subject factors of *Wave* (I, V) and *Level* (95-, 105-dB ppeSPL), and one between-subject factor of *Age-Group* (YNH, ONH). The analysis indicated a significant effect of *Level*, $F(1, 18) = 42.97$; $p < .001$, but no effect of *Wave*, $F(1, 18) = 1.98$; $p = .176$. The interaction between these two within-subject factors was significant, $F(1, 18) = 4.65$; $p = .045$. The between-subject effect of *Age-Group* was significant, $F(1, 18) = 40.64$; $p < .001$, as was its interaction with both the within-subject factor of *Level*, $F(1, 18) = 11.75$; $p = .003$, and *Wave*, $F(1, 18) = 12.26$; $p = .003$. The three-way interaction was not significant, $F(1, 18) = 0.19$; $p = .667$. Post hoc analysis of simple main effects indicated that the *Level–Wave* interaction was due to the amplitude of Wave I increasing more with level than the amplitude of Wave V. The *Age-Group–Level* interaction was due to the increase in wave amplitudes with level being more pronounced for the YNH group than the ONH group. The *Age-Group–Wave* interaction was due to the Wave I amplitude being significantly lower than the Wave V amplitude for the ONH group but not for the YNH group. This result indicates that the ratio of Wave I amplitude to Wave V amplitude is larger in the YNH group.

Discussion

Wave I was successfully recorded in all subjects and was found to be reduced in amplitude in the ONH group relative to the YNH group, consistent with the findings of Burkard and Sims (2001) and McClaskey et al. (2018). The age-related reduction in Wave I amplitude, and in particular its reduced amplitude relative to Wave V, is consistent with an interpretation of age-related cochlear

synaptopathy (e.g., Verhulst et al., 2016). As a caveat, however, it should be noted that the amplitudes of Waves I and V of the ABR have been shown to be weakly, but significantly, correlated with sex (Trune, Mitchell, & Phillips, 1988), with females having larger amplitudes. The relevance here is that the YNH group contained more females than did the ONH group, which may have accentuated the age-group difference. The more modest change in Wave I amplitude with increasing level in the ONH group, although only measured as a two-step function here, suggests a shallower growth function in the older listeners which is also consistent with animal models of cochlear synaptopathy (e.g., Lin et al., 2011). However, this interpretation must be qualified by the observation that Wave V also grew more modestly with level in the ONH group than the YNH group, a result that is not a direct expectation of cochlear synaptopathy. In summary, the results of the ABR experiment are consistent, at least in part, with an interpretation of synaptopathy. The question then arises of whether this pathophysiology might underlie suprathreshold processing deficiencies. Two domains in which a depleted population of auditory nerve fibers might be expected to give rise to suprathreshold deficits are in the processing of amplitude modulation (AM; e.g., Paul, Waheed, Bruce, & Roberts, 2017) and spectral modulation (e.g., Ozmeral, Eddins, & Eddins, 2018). The following pair of experiments test the effects of age on detection of amplitude and spectral modulation.

Experiment 2: AM Detection

The purpose of this experiment was to test the hypothesis that age-related cochlear synaptopathy results in deficient temporal modulation processing, particularly at higher levels and in the presence of background noise. The question of whether age itself, as a factor, affects the processing of AM remains unresolved. Some studies have found that older listeners with near-normal audiograms are poorer at detecting AM than their young counterparts at both low and high carrier frequency regions (Fullgrabe, Moore, & Stone, 2014; He, Mills, Ahlstrom, & Dubno, 2008; Wallaert, Moore, & Lorenzi, 2016). However, other studies have not found an age effect for AM detection for either a tonal carrier (Paraouty, Ewert, Wallaert, & Lorenzi, 2016) or a noise-band carrier (Schoof & Rosen, 2014). Although these studies employed older listeners with near-normal audiometric hearing, they were not specifically focused on cochlear synaptopathy. Other studies have tested AM detection with the expectation that the fidelity of temporal modulation processing should reflect cochlear synaptopathy. This expectation arises from the notion that because low-spontaneous rate, high-threshold auditory nerve fibers are better able to maintain synchrony at high sound levels and exhibit greater resilience to background noise, their depletion in cochlear synaptopathy should be evidenced as a loss in fidelity of suprathreshold sound processing. Bharadwaj et al. (2015) found that measures of AM processing were unrelated to audiometric thresholds and interpreted this as a manifestation of cochlear synaptopathy. Paul et al. (2017) tested the hypothesis that audiometrically normal (young) listeners likely to have an etiology of cochlear synaptopathy have compromised AM detection thresholds, especially in background noise. Although they observed a trend for this to occur, it was not a significant effect. In contrast to this trend, Yeend et al. (2017) found no effect on AM detection as a function of the likelihood of cochlear synaptopathy in their subjects. In summary, although there are theoretical reasons to expect that cochlear synaptopathy might detrimentally affect the processing of AM, particularly at high levels and in background noise, the findings to date are inconclusive. The purpose of this study, therefore, was to determine whether AM detection as a function of level and background noise provided evidence of age-related cochlear synaptopathy. The hypothesis was that older listeners with near-normal hearing are poorer at detecting AM, especially at high levels and in noise.

Method

Subjects. Ten YNH adults and nine ONH adults participated. The YNH group had a mean age of 23.2 years (range = 19.4–28.4 years) and comprised six females and four males. The ONH group had a mean age of 69.4 years (range = 61.3–74.6 years) and comprised two females and seven males. All of the YNH group had audiometric thresholds $\leqslant$15-dB HL across the octave frequencies 250 to 8000 Hz. All of the ONH group had audiometric thresholds across the octave frequencies 250 to 4000 Hz of 20-dB HL or better except for one subject with a 25-dB HL threshold at 250 Hz. Thresholds at 8000 Hz ranged from 10 - to 50-dB HL. Average audiograms for the test ear in both groups are shown in Figure 1, middle panel.

Stimuli. The signal was a sinusoidally amplitude modulated tone having a carrier frequency of 2000 Hz and a modulator frequency of 80 Hz. Each stimulus was 400 ms in duration, including 50-ms raised cosine rise/fall ramps. A new stimulus sample was generated for each presentation at a sampling rate of 24414 Hz, with the starting phase of the carrier selected randomly and the starting phase of the modulator fixed at $3\pi/2$. The signal was presented at two levels, 70 - and 85-dB sound pressure level (SPL), in quiet and in background noise. The noise was a one-octave band centered at 2000 Hz (i.e., bandwidth = 1414 Hz), and presented at a

level such that the signal-to-noise ratio within a nominal equivalent rectangular bandwidth centered at 2000 Hz was 15 dB. The nominal equivalent rectangular bandwidth at 2000 Hz was taken to be 255 Hz (Moore & Glasberg, 1983) which mandated a noise level within this band of 70-dB SPL for the 85-dB SPL signal and 55-dB SPL for the 70-dB SPL signal. In turn, this resulted in an overall level of the one-octave band noise of 77.5-dB SPL for the 85-dB SPL signal and 62.5-dB SPL for the 70-dB SPL signal. The stimuli were presented monaurally to the left ear through a Sennheiser HD380 Pro headphone (Wedemark, Germany), except for two ONH subjects who received right-ear stimulation because of better audiometric thresholds in that ear.

Procedure. Modulation detection thresholds were measured with a three-alternative, forced-choice (3AFC) procedure that incorporated a three-down, one-up stepping rule that converged on the 79.4% correct point. The initial step size of modulation depth adjustment was 4 dB in units of 20log$m$, where m is the modulation index (0–1); this was halved after the second and fourth reversals, to result in a final step size of 1 dB. A threshold estimation track was terminated after 10 reversals, and the mean of the modulation depths at the final 6 reversal points was taken as the threshold estimate. At least three threshold estimates were collected per condition, with a fourth collected if the range of the first three exceeded 3 dB. Where more than three estimates were collected, the final threshold value was taken as the mean of the three estimates that yielded the smallest standard deviation.

Results

The results of the experiment are shown in Figure 4, which plots AM detection thresholds for the four conditions for each age-group. The data were subjected to a RMANOVA with two within-subject factors of *Level* (70-dB SPL, 85-dB SPL) and *Background* (Quiet, Noise), and one between-subject factor of *Age-Group* (YNH, ONH). The analysis indicated a significant effect of *Level*, $F(1, 17) = 26.13$; $p < .001$, and *Background*, $F(1, 17) = 418.72$; $p < .001$. The interaction between these two factors was also significant, $F(1, 17) = 17.52$; $p = .001$. The effect of *Age-Group* was not significant, nor were any of its interactions with the within-subject factors. The significant interaction between *Level* and *Background* was due to an improvement in threshold with increased stimulus level in quiet but not in noise.

Discussion

The presence of background noise severely compromises the ability to detect AM, as also found by Paul et al. (2017). However, the key result of this experiment is that, for our relatively small sample, there were no age-related differences in temporal modulation detection either in quiet or in background noise, irrespective of presentation level. Whereas the lack of an age effect in AM detection contrasts with some findings (Fullgrabe et al., 2014; He et al., 2008; Wallaert et al., 2016), it is in line with others (Paraouty et al., 2016; Schoof & Rosen, 2014). The absence of deficient AM processing in the older subjects tested here does not support the hypothesis that age-related cochlear synaptopathy compromises temporal modulation processing, particularly in the presence of background noise. However, it is worth pointing out two caveats. First, AM detection by definition restricts the processing task to minimally salient modulation and does not test the processing of perceptually pronounced envelope fluctuations. For example, the study of Paul et al. (2017) examined both psychophysical AM detection and envelope following responses (EFRs) in young subjects grouped according to likelihood of exhibiting cochlear synaptopathy. Although they found no effects in psychophysical AM detection, they did find trends in EFR strength (Paul, Bruce, & Roberts, 2018). It is possible, therefore, that effects of age-related cochlear synaptopathy on suprathreshold temporal modulation processing might emerge in AM processing tasks other than detection. Second, whereas the older listeners in this study had audiometric thresholds at the carrier frequency of 2000 Hz that were within normal limits, it is the case that their thresholds were nevertheless about 10 dB poorer than the younger listeners. If this reflects subclinical cochlear impairment, and if loss of basilar membrane compression accompanies such cochlear impairment, then it is

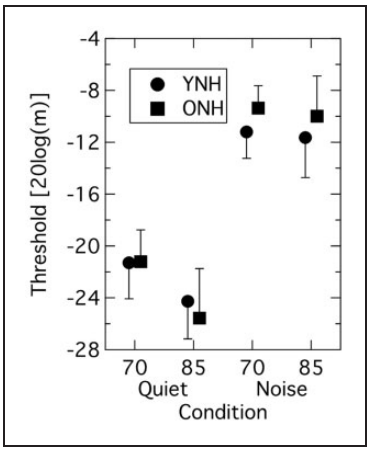

Figure 4. Group mean temporal modulation detection thresholds for the young (YNH) and older (ONH) subjects as a function of presentation level and background noise condition. Error bars are 1 standard deviation. YNH = normal-hearing young; ONH = older with near-normal hearing.

possible that the AM cues were more salient for the older listeners, thus bolstering their performance. However, consensus is lacking as to whether cochlear hearing loss affects AM detection (for further discussion of this issue, see Grose, Porter, Buss, & Hall, 2016).

Experiment 3: Spectral Modulation Detection

In the normally functioning ear, spectral modulation detection likely depends on several factors including spectral resolution, intensity discrimination, and the ability to compare intensities across frequency (Eddins & Bero, 2007; Ozmeral et al., 2018). The relative balance of these factors depends on the spectral modulation rate. The purpose of this experiment was to test the hypothesis that age-related cochlear synaptopathy results in deficient spectral modulation processing, particularly at higher presentation levels. As in previous experiments, this expectation is based on the assumption that depletion of auditory nerve fibers, particularly those of the low-spontaneous-rate, high-threshold subpopulation which retain some dynamic range for high-level input, reduces the information-bearing capacity of the auditory nerve and the richness of spectral representation. Given that spectral resolution is level dependent, with auditory filters broadening with increased level (e.g.,Oxenham & Simonson, 2006), it might be expected that sensitivity to spectral modulation should depend on presentation level.

The effect of age on spectral modulation detection has received attention in a recent report that tested at a single level (Ozmeral et al., 2018). In that study, older listeners were grouped according to degree of hearing loss, and one group had near-normal audiometric thresholds. The study found that age, per se, had very little effect on sensitivity to spectral modulation. This would suggest that spectral modulation processing is not sensitive to an underlying cochlear synaptopathy. The purpose of this study was to test this further by measuring spectral modulation detection at both a nominal conversation level (65-dB SPL) and at a higher level (85-dB SPL).

Method

Subjects. Ten YNH adults and 10 ONH adults participated. The YNH group had a mean age of 23.8 years (range = 19.8–32.3 years) and comprised eight females and two males. The ONH group had a mean age of 70.7 years (range = 66.5–80.1 years) and comprised six females and four males. All subjects in the YNH group had audiometric thresholds across the octave frequencies 250 to 8000 Hz of 10-dB HL or better. All subjects in the ONH group had audiometric thresholds across the octave frequencies 250 to 4000 Hz of 20-dB HL or better, except for one subject with a 25-dB HL threshold at 250 Hz and two subjects with 4000-Hz thresholds of 25-dB HL. Thresholds at 8000 Hz ranged from 10 - to 55-dB HL. Average audiograms for the test ear in both groups are shown in Figure 1, right panel.

Stimulus. The stimulus was a two-octave band of noise extending from 800 to 3200 Hz. It was 400 ms in duration, including 20-ms raised cosine rise/fall ramps. When presented as a signal, this band of noise was shaped with a spectral ripple that was sinusoidal when expressed on a dB by log-frequency axis. The frequency of this spectral modulation was 0.5, 1, or 2 cycles per octave (cyc/oct). A new stimulus sample was generated for each presentation at a sampling rate of 24414 Hz, with the starting phase of the sinusoidal modulator for the signal selected randomly. Two nominal presentation levels were employed: 65 - and 85-dB SPL. However, the actual level was roved below these levels over a 3-dB range on a presentation-by-presentation basis in order to render cues based on level changes at any particular spectral region to be less reliable. The stimuli were presented through a Sennheiser HD380 Pro headphone to the left ear of the YNH subjects and four of the ONH subjects; the remainder of the ONH subjects received right-ear stimulation.

Procedure. Spectral modulation detection thresholds were measured using a 3AFC procedure that incorporated a three-down, one-up stepping rule. In two of the listening intervals of a 3AFC trial, at random, a spectrally flat band of noise was presented, with independent samples of noise computed for each standard interval. In the remaining target interval, the spectrally modulated band was presented. The initial modulation depth step size for the adaptive procedure was 4 dB, and this was reduced to 1 dB after two reversals and then to a final step size of 0.4 dB after a further two reversals. A threshold estimation track was terminated after 10 reversals, and the mean of the final 6 reversal depths was taken as the threshold estimate for that track. Any track where the standard deviation of the final six reversal depths exceeded 1.0 dB was excluded and replaced. For the ONH group, four valid threshold estimates were collected per condition, with the exception of one subject at the 85-dB SPL level where three valid threshold estimates were collected per condition, and where those three ranged by less than 1.5 dB. For the YNH group, three valid threshold estimates were collected per condition unless the range of those three exceeded about 3.5 dB in which case a fourth estimate was collected. Final threshold value for a condition was taken as the mean of all estimates collected.

Results

The results of the experiment are shown in Figure 5, which plots spectral modulation detection threshold as

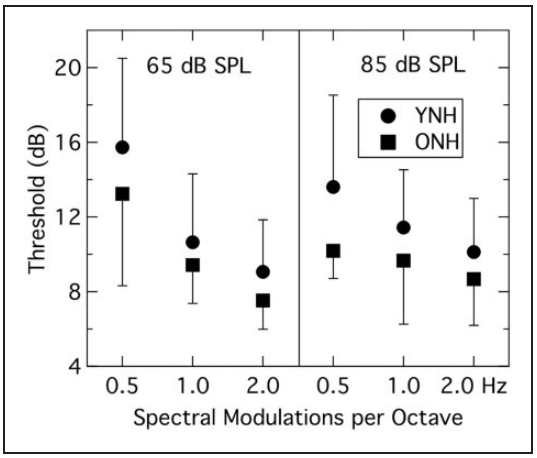

Figure 5. Group mean spectral modulation detection thresholds as a function of modulation rate for the young (YNH) and older (ONH) subjects. The left and right panels depict presentation levels of 65- and 85-dB SPL, respectively. Error bars are 1 standard deviation. YNH = normal-hearing young; ONH = older with near-normal hearing; SPL = sound pressure level.

a function of spectral ripple rate at each of the two presentation levels. The data were submitted to a RMANOVA with two within-subject factors of *Level* (65-dB SPL, 85-dB SPL) and *Ripple* (0.5, 1.0, 2.0 cyc/oct) and one between-subject factor of *Age-Group* (YNH, ONH). The analysis showed a significant effect of *Ripple*, $F(1, 18) = 38.63$; $p < .001$ but no main effect of *Level*. However, the interaction between *Ripple* and *Level* was significant, $F(2, 36) = 8.00$; $p = .001$. The effect of *Age-Group* was not significant, $F(1, 18) = 2.66$; $p = .121$, nor were its two-way interactions with either *Level*, $F(1, 18) = 0.42$; $p = .526$, or *Ripple*, $F(1, 18) = 1.41$; $p = .258$, or its three-way interaction with *Level* and *Ripple*, $F(2, 36) = 0.13$; $p = .877$. This pattern of results indicates that thresholds improved with increasing frequency of spectral ripples, at least over the range tested here, and that this improvement was more pronounced at the lower presentation level than at the higher presentation level. However, this pattern did not depend on listener age.

Discussion

The improvement of spectral modulation detection over the range of spectral ripple frequency measured here replicates the finding of Ozmeral et al. (2018). However, that study demonstrated that thresholds deteriorate as spectral modulation rates are increased above 2 cyc/oct, the highest rate tested here; that is, the 2 cyc/oct rate proves to be a minimum in a bowl-shaped function. Also in line with Ozmeral et al., the present data set showed no effect of age. This lack of an age effect was evident at both presentation levels even though degree of spectral resolution might be expected to vary across these levels. The results of this experiment, therefore, do not support the hypothesis that age-related cochlear synaptopathy results in deficient spectral modulation processing, particularly at higher levels.

General Discussion and Conclusion

There is increasing interest in whether cochlear synaptopathy constitutes a viable basis for age-related hearing difficulties (e.g., Wu et al., 2018). The purpose of this report was to determine whether noninvasive ABR measures support the hypothetical presence of cochlear synaptopathy in older listeners with near-normal hearing and, if so, whether a consequence of this condition is compromised suprathreshold processing of temporal and spectral modulation. The ABR experiment demonstrated reduced Wave I amplitudes and concomitant reductions in the amplitude ratios of Wave I to Wave V in the ONH group. These findings were interpreted as consistent with an electrophysiological profile of cochlear synaptopathy. However, the temporal and spectral modulation detection experiments provided no support for the hypothesis of compromised suprathreshold processing in these domains. That is, the ONH groups in both of these latter experiments did not perform significantly differently from the YNH groups. This overall pattern of results could mean that either the ABR results were not indicative of cochlear synaptopathy or that the temporal and spectral modulation detection paradigms are not sensitive to this etiology.

There are at least two alternative explanations for the pattern of ABR results observed here. First, there is some evidence that the generators of Wave I are dominated by more basal regions of the cochlea in comparison to the generators of Wave V (Don & Eggermont, 1978; Verhulst, Bharadwaj, Mehraei, Shera, & Shinn-Cunningham, 2015). This might suggest that differences in high-frequency audiometric thresholds across the ONH and YNH groups would affect Wave I amplitude more than Wave V amplitude. That is, the high-frequency hearing losses exhibited by the ONH subjects might reduce their Wave I amplitudes but not their Wave V amplitude. In theory, this could generate the same pattern of relative Wave I and Wave V amplitudes as observed in here. Differences in high-frequency audiometric thresholds could also have influenced the ABR growth functions. As the insert phones used for stimulation had an effective cutoff of about 4000 Hz, upward spread of cochlear excitation associated with increased stimulation level would have been less pronounced in the case of high-frequency hearing loss. A second alternative explanation for the ABR results is that aging changes the auditory nerve response for reasons other than a depletion of nerve fibers associated with cochlear synaptopathy. Specifically, increased neural jitter in the

aging auditory nerve might also be expected to reduce Wave I amplitude (cf. Mamo, Grose, & Buss, 2016), although this would also likely affect the amplitude of later waves as well. In summary, the pattern of ABR results observed here, although consistent with an interpretation in terms of age-related cochlear synaptopathy, is not conclusive.

The possibility that temporal and spectral modulation detection paradigms are not sensitive to cochlear synaptopathy must also be considered. As intimated in the preamble to Experiment 2, there are strong theoretical grounds for the expectation of reduced temporal modulation processing associated with cochlear synaptopathy. Animal work has shown EFRs to be a reliable indicator of this etiology (Parthasarathy & Kujawa, 2018; Shaheen, Valero, & Liberman, 2015), and human work shows EFR patterns that trend toward consistency with cochlear synaptopathy (Paul et al., 2017; Roberts, Paul, & Bruce, 2018), although this is not universally found (e.g., Guest et al., 2016; Prendergast, Guest, et al., 2017). Because EFR testing tends to use stimuli with perceptually pronounced levels of modulation, it is possible that detection tasks that focus on minimally salient modulation are less sensitive to potential effects of cochlear synaptopathy. In any case, the present results are more in line with those studies that have failed to find, in humans, an association between a likely substrate of cochlear synaptopathy and deficits in the detection of modulation (Grose et al., 2017; Prendergast, Millman, et al., 2017; Yeend et al., 2017).

In conclusion, this study found a profile of ABR results that is consistent with age-related cochlear synaptopathy. However, measures of modulation detection at levels well above audibility threshold did not reveal any age-related effects. This pattern of results suggests that cochlear synaptopathy—even if it is a valid contributor to age-related hearing difficulties—cannot be reliably detected using temporal and spectral modulation detection paradigms as implemented here. The question of the association, if any, between cochlear synaptopathy and age-related hearing difficulties in the presence of normal audiometric thresholds remains open. A comprehensive approach that combines electrophysiological measures and behavioral measures is likely to remain a viable strategy in the pursuit of this question (cf. Barbee et al., 2018; Plack et al., 2016; Ridley et al., 2018).

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Note

1. Separate subject groups participated across the three experiments with the following exceptions: two older subjects participated in all three experiments and two additional older subjects and one young subject participated in two of the experiments. The combined total subject count was 29 young subjects and 21 older subjects.

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