



Research paper

Evidence that hidden hearing loss underlies amplitude modulation encoding deficits in individuals with and without tinnitus

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ABSTRACT

Damage to auditory nerve fibers that expresses with suprathreshold sounds but is hidden from the audiogram has been proposed to underlie deficits in temporal coding ability observed among individuals with otherwise normal hearing, and to be present in individuals experiencing chronic tinnitus with clinically normal audiograms. We tested whether these individuals may have hidden synaptic losses on auditory nerve fibers with low spontaneous rates of firing (low-SR fibers) that are important for coding suprathreshold sounds in noise while high-SR fibers determining threshold responses in quiet remain relatively unaffected. Tinnitus and control subjects were required to detect the presence of amplitude modulation (AM) in a 5 kHz, suprathreshold tone (a frequency in the tinnitus frequency region of the tinnitus subjects, whose audiometric thresholds were normal to 12 kHz). The AM tone was embedded within background noise intended to degrade the contribution of high-SR fibers, such that AM coding was preferentially reliant on low-SR fibers. We also recorded by electroencephalography the “envelope following response” (EFR, generated in the auditory midbrain) to a 5 kHz, 85 Hz AM tone presented in the same background noise, and also in quiet (both low-SR and high-SR fibers contributing to AM coding in the latter condition). Control subjects with EFRs that were comparatively resistant to the addition of background noise had better AM detection thresholds than controls whose EFRs were more affected by noise. Simulated auditory nerve responses to our stimulus conditions using a well-established peripheral model suggested that low-SR fibers were better preserved in the former cases. Tinnitus subjects had worse AM detection thresholds and reduced EFRs overall compared to controls. Simulated auditory nerve responses found that in addition to severe low-SR fiber loss, a degree of high-SR fiber loss that would not be expected to affect audiometric thresholds was needed to explain the results in tinnitus subjects. The results indicate that hidden hearing loss could be sufficient to account for impaired temporal coding in individuals with normal audiograms as well as for cases of tinnitus without audiometric hearing loss.

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Text

1. Introduction

Animal studies have demonstrated that noise exposure that only temporarily raises auditory thresholds can permanently degrade auditory responses to suprathreshold sounds (Kujawa and Liberman, 2009). Diminished suprathreshold responses are associated predominantly with damage to synaptic terminals of inner hair cells (IHCs) innervated by auditory nerve fibers (ANFs) with low spontaneous rates of firing and high firing thresholds (low-SR

ANFs), while damage to ANFs with high spontaneous rates and low firing thresholds (high-SR ANFs) is relatively less severe (Furman et al., 2013; Kujawa and Liberman, 2009). Because low-SR fiber loss without accompanying severe high-SR fiber loss will not affect auditory thresholds in quiet (Lobarinas et al., 2013), this pattern of damage has been termed “hidden hearing loss” (Schaeffe and McAlpine, 2011; Plack et al., 2014). Synaptopathy affecting high-SR fibers can also be present and hidden from the audiogram with a potential effect on hearing, since it has been shown that hearing thresholds are not elevated as long as up to ~80% of inner hair cells remain intact (Lobarinas et al., 2013).

Hidden hearing loss involving low-SR fibers has been proposed to underlie inter-subject differences in temporal coding ability that have been observed in individuals with normal audiograms

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measured to the clinical standard of 8 kHz. Low-SR fibers typically respond at sound levels above 40 dB SPL (the level where the discharge rate of high-SR fibers is strongly saturated; Yates et al., 1990) and are robust to masking by background noise (Costalupes, 1985; Young and Barta, 1986). Low-SR fiber loss is thought to degrade auditory sensitivity to temporal modulations of sound that are important for listening in noisy environments, such that individual differences in listening under these conditions may reflect hidden low-SR fiber synaptopathy (Bharadwaj et al., 2014). To assess this hypothesis, Bharadwaj et al. (2015) measured the ability of subjects with normal audiograms (and without tinnitus) to detect the presence of amplitude modulation (AM) in a narrowband noise. Large individual differences were observed on this task that correlated with performance on other behavioral measures of temporal coding ability. Such differences were also correlated with the magnitude of the “envelope following response” (EFR) recorded by electroencephalography. EFRs are evoked from neural sources the auditory midbrain when sounds are AM at rates exceeding ~80 Hz (Herdman et al., 2002) and in animal studies have been shown to be sensitive to hidden synaptic losses induced in the cochlea by noise exposure (Shaheen et al., 2015). Poor AM sensitivity associated with reduced EFR magnitude was therefore consistent with the hypothesis of Bharadwaj et al. (2014) that individual differences in temporal coding ability found among subjects with audiometrically normal hearing may reflect varying degrees hidden low-SR fiber loss. Subjects exhibiting poor temporal coding abilities in their study were also more likely to report a history of noise exposure, which could have induced hidden low-SR fiber loss in these subjects (Bharadwaj et al., 2015).

Hidden hearing loss involving low-SR fibers has also been proposed to be a factor contributing to the development of chronic tinnitus (Schaette and McAlpine, 2011). Most cases of chronic tinnitus are believed to arise from neuroplastic changes that occur in central auditory pathways when these pathways are deaf-ferented by cochlear pathologies resulting from noise overexposure or the aging process (Eggermont and Roberts, 2004; Shore et al., 2016; Kaltenbach, 2011). Consistent with this view, up to 85% of adults with chronic tinnitus exhibit hearing loss detectable by the audiogram, a standard clinical test that measures thresholds of detection for tones in quiet (Axelsson and Ringdahl, 1989; Henry et al., 2005). In addition, the sound frequencies judged by tinnitus sufferers to resemble their tinnitus commence at the edge of their hearing loss and span the region of threshold shift typically peaking near or above 5 kHz (Roberts et al., 2008), showing that threshold shifts and tinnitus frequencies overlap. However, approximately 15% of adults with chronic tinnitus do not have audiometric threshold shifts (Henry et al., 2005; Roberts et al., 2008). While some studies have focused on hypothesized disorders of central auditory processing to explain these cases (Vanneste and De Ridder, 2016; Rauschecker et al., 2010), other evidence points to a role for hidden intracochlear pathology. Schaette and McAlpine (2011) and Gu et al. (2012) found that wave I of the auditory brainstem response (ABR) evoked by clicks exceeding ~70 dB SPL was reduced in tinnitus subjects with normal audiograms compared to controls, suggesting the presence of low-SR synaptopathy in the tinnitus group. Low-SR synapse loss induced by noise exposure is also known to reduce wave I evoked by suprathreshold sounds in guinea pigs in the absence of permanent threshold shift (Furman et al., 2013). However, Bourien et al. (2014) observed that the strongest contributors to ABR wave I were high- and medium-SR fibers, with the lowest SR fibers contributing the least. The amount of low- and high-SR synaptopathy potentially present in tinnitus sufferers therefore remains to be characterized.

Given this evidence for hidden hearing loss as a factor affecting

auditory processing, we investigated the extent to which low-SR fiber synaptopathy may account for individual differences in temporal coding ability among young adults with normal audiograms, and whether the presence of chronic tinnitus can be explained by a greater degree of synaptopathy in these cases. A control group and a tinnitus group with normal hearing thresholds completed two tasks. To assess the contribution of low-SR fibers to AM coding, we first measured the ability of the subjects to detect the presence of AM in a pure tone when the contribution of high-SR fibers was degraded by background noise. Next, we measured in the same session EFRs evoked by the same fully-modulated tone in quiet (where both high-SR and low-SR fibers were expected to contribute to the response) and at different AM depths in the same background noise (where AM coding was expected to depend preferentially on low-SR fibers). We subsequently used a model of the auditory periphery (Zilany et al., 2014) to simulate ANF responses to our stimuli with different mixtures of high- and low-SR fiber loss. We found that control subjects who exhibited EFRs that were comparatively resistant to the addition of background noise displayed better AM detection in background noise than did controls whose EFRs were more affected by noise. Simulated auditory nerve responses to our stimulus conditions suggested that low-SR fibers were better preserved in the former control subjects. We also found that tinnitus subjects exhibited significantly poorer AM detection than controls and had smaller EFRs than controls across all stimulus conditions. Cochlear modeling suggested that in addition to severe low-SR fiber loss, a further loss of high-SR fibers to an extent that would not affect the audiogram was needed to explain the EFRs of the tinnitus sufferers.

2. Materials and methods

2.1. Participants

The participants were students enrolled in undergraduate and graduate programs at McMaster University. Thirty subjects reporting no history of tinnitus were initially recruited, followed by fourteen individuals who reported chronic tinnitus in both ears. Because chronic tinnitus is less prevalent in young individuals than in older adults (Henry et al., 2005), it was expected that fewer subjects would be found for the tinnitus group. One control subject was excluded as a result of cerumen that occluded the right insert earphone. Three additional control subjects were excluded because of technical failure during measurement of the EFR. One tinnitus subject and two control subjects did not reach our statistical criterion for the presence of an EFR (see below). The remaining 24 control subjects (mean age 19.5 years, range 18–18 years) and 13 tinnitus subjects (mean age 23.2 years, range 18–39 years) completed all portions of the study. In addition to this cohort of 37 subjects, one additional subject was tested who reported hearing tinnitus at the time of each experimental session but stated that he experienced tinnitus only intermittently at other times. Because this subject did not meet our acceptance criterion of constant tinnitus, his data are reported separately from that of the 13 subjects all of whom reported chronic tinnitus (mean duration 10.7 years, SD = 9.9 years; see Table 1 below). No subjects reported a history of head trauma or use of medication during the time of the study. All procedures were approved by the Research Ethics board at McMaster University. Subjects provided informed consent and received monetary compensation (CAD 10.00/hour) or course credit for participation.

2.2. Initial session (tinnitus group only)

The initial session began with a questionnaire gathering a

Table 1
Participant characteristics. All tinnitus qualities except the THQ were taken with the Tinnitus Tester (Roberts et al., 2008). *M* refers to the average and *SD* refers to one standard deviation. dB HL is decibels hearing level (dB relative to the quietest sounds that a young healthy individual ought to be able to hear).

	Chronic tinnitus (N = 13)	Control (N = 24)
Age (years)	M = 23.2 (SD = 6.15; Range = 18–39)	M = 19.5 (SD = 2.82; Range = 18–28)
Sex	9 Females; 4 Males	20 Females; 5 Males
500 Hz pure-tone threshold (dB HL, diotic)	M = 0.23 (SD = 4.82; Range = –6–7.5)	M = 1.63 (SD = 3.55; Range = –4–10)
5 kHz pure-tone threshold (dB HL, diotic)	M = 1.65 (SD = 5.63; Range = –8–11)	M = 0.40 (SD = 3.46; Range = –5–8)
Indicated history of noise exposure	46% (6 of 13)	54% (13 of 24)
Tinnitus Qualities		
Tinnitus ear	Bilateral = 13	–
Tinnitus bandwidth	Tonal = 9; Ringing = 4; hissing = 0	–
Tinnitus duration (years)	M = 10.7 (SD = 9.9; Range: 25 to 0.25; 1 unsure)	–
THQ	M = 17.6 (SD = 9.9; Range = 4–40.4)	–
Borg CR100 loudness rating	M = 32.5 (SD = 20.8; Range = 10–65)	–
Loudness match averaged across 0.5, 1.0, and 5.0 kHz (dB SL)	M = 8.20 (SD = 8.55; Range = –4.1–15.5)	–
Likeness match at 5 kHz (1–100 scale)	M = 42.5 (SD = 17.1; Range = 13–79)	–

detailed history of each subject's tinnitus, including how long tinnitus had been experienced, perceived location of tinnitus (e.g., in ears, in head), how often during the day tinnitus was heard, how bothersome was, and other factors such as sensitivity to loud sounds, history of sound exposure, and daily hearing difficulties. Each subject then completed the Tinnitus Handicap Questionnaire (THQ, Kuk et al., 1990) to assess the impact of tinnitus on quality of life. After, we obtained hearing thresholds from 125 Hz to 16 kHz (125 Hz–6 kHz through Telephonics TD-39 296 D200 headphones; 8–16 kHz through Sennheiser HD250 headphones) in 5 dB steps using the pulsed-tone method for left and right ears separately. Subjects then used computerized tools (Tinnitus Tester; Roberts et al., 2008) to indicate the properties of their tinnitus. The ear of tinnitus (left, right, bilateral) and the bandwidth of the tinnitus percept (tonal, ringing, hissing) were determined followed by a rating of tinnitus loudness a Borg CR100 scale (Borg and Borg, 2001) which defined subjective loudness using semi-logarithmic verbal anchors. Thereafter, subjects adjusted the loudness of 11 pure tones (randomly ordered) ranging from 0.5 to 12 kHz to match the loudness of their tinnitus. Subjects then rated the likeness of each of the same 11 tones to their tinnitus on a 100 point scale where ratings above 40 indicate a sound in the tinnitus frequency region. The preliminary session concluded with a brief test for residual inhibition (Roberts et al., 2008).

2.3. Main session (tinnitus and control subjects)

In the main session, control subjects first completed the same questionnaire administered to the tinnitus group in their initial session, excluding questions related to tinnitus. Hearing thresholds were then measured at 500 Hz and 5 kHz in all subjects, diotically (left and right ears together) in 2 dB steps using the pulsed-tone method. The purpose of this procedure was to verify normal hearing thresholds at the two frequencies which were used for testing AM detection thresholds (see Section 2.3.1) in the tinnitus and control groups. Owing to time limitations in this session, a full audiogram was omitted for control subjects since our previous studies (Roberts et al., 2008) and those of others (Gu et al., 2012; Sanchez et al., 2016; Schaette and McAlpine, 2011) have shown that thresholds exceeding the clinical standard of 25 dB HL up to 8 kHz are rare in this young age group. Subsequently all participants were tested on AM detection and measurement of the EFR to AM sounds. During the experiment participants sat in a chair distanced 1.4 m from a computer monitor in a sound-attenuated (ambient noise level 16 dBA SPL) and electrically-shielded booth. All stimuli were generated by a Tucker-Davis RP2.1 digital signal real-time processor and presented through EARTone 3A transducers inserted in both ears.

2.3.1. Amplitude modulation detection task

AM sensitivity was first behaviorally assessed in each subject by obtaining their threshold for AM detection in the presence of a narrowband background noise (NBN). The stimuli were 5 kHz tones sinusoidally AM at 19 Hz and presented at 75 dB SPL. The 5 kHz carrier frequency was chosen because it was expected to be in the tinnitus frequency region of the tinnitus subjects (Roberts et al., 2008, 2015; Paul et al., 2014) and was known to evoke a recordable EFR in most subjects. Modulation depth (*m*, where *m* = 1 corresponds to 100% modulation) during the task was adaptively varied and herein will be expressed in dB (20 log₁₀ *m*) with respect to 100% AM depth (following Bharadwaj et al., 2015). The AM tone was embedded in NBN centered at 5 kHz with the spectrum level of the noise set to 40 dB, a level designed to attenuate the contribution of high-SR fibers (Costalupes, 1985) leaving temporal envelope encoding in the auditory nerve preferentially reliant on low-SR fibers (Bharadwaj et al., 2014). The bandwidth of the NBN was set at 1/3 of an octave. This bandwidth was determined by observing the spread of excitation across the range of auditory nerve fibers with characteristic frequencies (CFs) responding to the 75 dB SPL, 5 kHz AM probe in the Zilany et al. (2014) auditory periphery model, such that the 40 dB spectrum level NBN adequately covered this range.

In a 3-alternative forced choice task, subjects listened to three tones embedded in NBN. One tone was AM (target), while the other two were unmodulated. The position of the target tone was determined randomly on each trial. Each tone was presented for 1 s, with background NBN commencing 500 ms before the first tone and playing continuously until 500 ms after the third tone. The spacing between each tone was fixed at 1 s. After all three tones had been presented, subjects indicated by a keypress which tone was AM (target). AM depth of the target started at –6 dB (50% AM) and was adjusted adaptively by the method of parameter estimation through sequential testing (PEST; Taylor and Creelman, 1967) until a final modulation step size of 0.45 dB was achieved. The average AM depth of the two final steps was taken as the threshold. It should be noted that because AM detection thresholds are represented with respect to 100% AM depth in dB (20 log₁₀ *m*), large negative values in this metric signify low (good) AM detection thresholds.

Each subject also completed the same AM detection task for a 500 Hz tone AM at 19 Hz, to compare results at 5 kHz to a lower frequency region where hair cell damage or synaptopathy was unlikely to be present in these groups (Lieberman, 1978; Kujawa and Liberman, 2009). Tinnitus was also unlikely to be experienced at this frequency in the tinnitus cohort (Roberts et al., 2008; also confirmed by the tinnitus likeness ratings presented in Table 1 and Section 3.1). The 500 Hz tone was presented at 75 dB SPL against

40 dB spectrum level background NBN which was centered at 500 Hz with a 2/3 octave bandwidth.

2.3.2. EFR measurement

Following the AM detection task, we recorded by 32-channel electroencephalography (EEG) the EFR evoked by five stimulus conditions, shown in Fig. 1. In four conditions an EFR was evoked by presenting a 5 kHz tone (75 dB SPL) AM at 85 Hz, a modulation rate consistent with anatomical generators for the EFR in the auditory midbrain (Herdman et al., 2002). The first condition the AM tone was presented at a modulation depth of 0 dB (100% modulation) without background NBN, intended to evoke contributions from both low- and high-SR fibers to AM coding. The second through fourth conditions embedded the AM tones in continuous background NBN (identical to that used in the AM detection task) aimed at saturating high-SR fibers, leaving primarily low-SR fibers available to code AM. Low-SR fibers were further tested in these conditions by reducing AM depths from 0 dB (100% AM depth), to -2.5 dB (75% depth), and -6 dB (50% depth). Finally, a no-tone NBN-only condition was included as a control. For each condition the stimulus was presented continuously for 3 min. After each condition 3 s of silence lapsed before the next condition began. The condition order was randomly selected for each participant. During EFR recording participants were instructed to ignore sound stimuli and watch a subtitled silent film of their choice that was presented on the computer monitor.

2.3.3. EEG recording and analysis

The 32-channel EEG was sampled at 2048 Hz by a BioSemi ActiveTwo amplifier (Cortech Solutions, Wilmington, NC) from 0 to 417 Hz and stored as continuous data files. Using custom offline routines in MATLAB (The Mathworks, Natick, MA) the EEG was first re-referenced to the scalp average, high-pass filtered at 70 Hz, and downsampled to 850 Hz. For each condition data were segmented into 1000 ms epochs, creating 180 total trials per condition per person. Epochs that exceeded ± 50 μ V in any channel were considered to contain artifacts and were rejected. If a channel contributed to more than 1/3 of trials being rejected, the channel was removed. With these criteria an average of 156.2 trials were retained per subject per condition. To extract EFR power at 85 Hz, we used a multi-channel complex principal components analysis approach (Bharadwaj and Shinn-Cunningham, 2014) that was likewise used for EFR analysis in Bharadwaj et al. (2015). This technique adjusts for phase disparities of the EFR present in each channel and combines them across recording sites, providing a

more reliable EFR measurement and robustness to noise compared to single-channel recordings.

The presence of an EFR was assessed statistically for each subject and each condition by comparing the phase locking value (PLV) of the response at 85 Hz to 20 adjacent frequency bins (71–81 Hz; 89–99 Hz in 1 Hz steps). We subtracted the mean PLV of the adjacent bins from the 85 Hz PLV and divided this value by the standard deviation across the adjacent bins, creating a standardized score. Following Kuwada et al. (2002), if this score was greater than 3 (corresponding to the 99th percentile of the normal distribution of the noise in the frequency bins adjacent to 85 Hz) the EFR was deemed statistically present. Two control subjects and one tinnitus subject of the original recruited sample did not meet this criterion in one or more conditions, and were excluded. EFR power at 85 Hz herein is expressed in dB as a signal to noise ratio (SNR) relative to mean of the same 20 frequency bins used in the PLV analysis.

2.4. Peripheral auditory modeling

To determine if our EFR results could be explained by hidden ANF synaptopathy, we used a model of the auditory periphery (Zilany et al., 2014) to simulate levels of damage to ANF types that were expected to contribute to the EFR recorded in our stimulus conditions. Stimuli from each EFR condition were shortened to 400 ms and passed into the model. After the signal passes through a series of components simulating realistically the filtering and compression properties of the middle ear and cochlear structures, the model generates a neurogram depicting the spiking response of a set of ANFs to the stimulus. For our simulations we used 128 sets of ANFs with characteristic frequencies (CFs) ranging from 170 Hz to 7 kHz. For each CF there were 150 ANFs, reflecting the number of fibers covering this range in the human cochlea as determined by the Greenwood function (Greenwood, 1961). The fiber types were distributed in a 3:1:1 ratio for high-, medium-, and low-SR fiber types respectively, roughly consistent with the distribution found in the cochlea (Liberman, 1978). In modeling simulations that involved removal of ANFs, medium and low-SR fibers were always removed together. Herein loss of both fiber types is simply referred to as low-SR fiber loss.

In order to calculate the modulation response of the auditory nerve at 85 Hz, we collapsed the neurogram into an average of 4 AM periods and then passed this average through a spectro-temporal modulation filter bank (modified from Elhilali et al., 2003) to obtain a neural modulation power spectrum for modulation rates ranging from 0 to 105 Hz. We then averaged the response of CFs

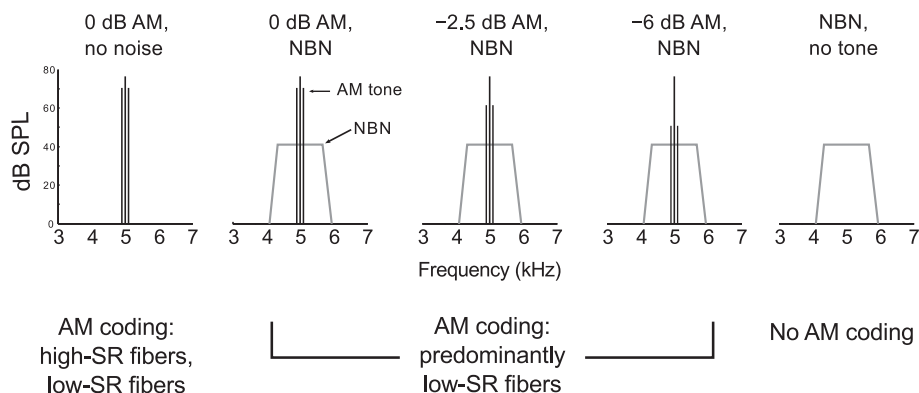


Fig. 1. Frequency spectrum representations of the four stimuli used to evoke the EFR plus a condition with no AM tone. Solid black lines represent the 5 kHz amplitude modulated (AM) tone. Gray lines depict the bandwidth and level of the background narrowband noise (NBN). Stimulus AM depth is expressed in dB relative to 100% modulation depth: 0 dB = 100% AM depth, -2.5 dB = 75% AM depth, and -6 dB = 50% AM depth.

from 2.8 to 7 kHz, which covered the range over which spiking was observed in the modeled neurograms to our stimuli, and averaged again over all spectral modulation rates and over time. The absolute value of the averaged modulation magnitude for the filters with best modulation frequencies neighboring 85 Hz was taken and referred to herein as the “modulation response magnitude.” Similar to EFR, the modulation response magnitude was expressed as dB SNR relative to the mean spontaneous activity of CFs averaged from 1 to 2.6 kHz where no signal-related responses were observed in the neurogram. All simulations reported below were repeated 8 times to obtain a mean and variance.

2.5. Statistics

Unless otherwise noted, statistical tests were two-tailed, and the alpha criterion for all tests was set at 0.05. Statistics were performed using the MATLAB statistics toolbox.

3. Results

3.1. Subject demographics and tinnitus measurements

Demographic information for the control and tinnitus subjects is provided in Table 1. Tinnitus subjects were on average 3.7 years older than controls, a difference that while small was statistically significant ($p = 0.03$, independent samples t -test) and driven by a wider range of ages in the tinnitus (18–39 years) than the control (18–28 years) group. Age did not correlate significantly with any audiometric threshold measurement or with any suprathreshold measurement (AM detection or EFR magnitude) reported below either within groups or when the control and tinnitus groups were combined into one sample (all $ps > 0.18$). Females predominated in both groups with no significant differences in gender between the groups ($p = 0.33$, χ^2 test). Diotic audiometric thresholds measured at 500 Hz and 5 kHz for tinnitus and control subjects averaged 0.99 dB HL overall and did not exceed 11 dB HL for any subject at either frequency. An analysis of variance (ANOVA) evaluating the factors group (tinnitus versus control) and frequency (5 kHz versus 500 Hz) found no main effects or interactions ($ps > 0.17$) on this measure, indicating that tinnitus and control subject groups were well-matched in hearing thresholds at the test frequencies where AM encoding and EFRs were measured. Approximately half of the individuals in each cohort reported a history of noise exposure, which did not differ between the groups ($p = 0.64$, χ^2 test).

Tinnitus qualities are reported in the lower half of Table 1. All tinnitus subjects had bilateral tinnitus with an average duration of 10.7 years ($SD = 9.9$). Tinnitus Handicap Questionnaire (THQ) scores averaged 17.6 ($SD = 9.9$) indicating a tinnitus that for most subjects was not highly disturbing. Tinnitus loudness assessed by sound level matching averaged 8.20 dB SL ($SD = 8.55$ dB) collapsed over the frequencies 500 Hz, 1 kHz, and 5 kHz, while ratings of tinnitus loudness on the Borg CR 100 scale averaged 32.5 ($SD = 20.8$) corresponding to a tinnitus of “moderate” loudness on this scale. Each of these measurements taken in our young subjects (mean age 23.2 years) with normal audiometric hearing was lower than corresponding averages reported by Roberts et al. (2008) for a sample of older tinnitus subjects ($n = 74$, mean age 58.6 years) where high-frequency audiometric hearing loss was typically present (mean loudness match 16.3 dB SL, Borg CR 100 rating 42.9, and THQ 32.0 in the group of older subjects). Audiometric thresholds for our subjects measured to 16 kHz are shown in Fig. 2a where it can be seen that thresholds were <25 dB HL up to 12 kHz in all tinnitus subjects, except for two ears where thresholds were 30 dB HL at 8 kHz only. Individual tinnitus likeness spectra and the group average are shown in Fig. 2b. The group averaged spectrum

increased with increasing tone frequency in agreement with tinnitus spectra reported by young subjects with normal audiometric thresholds (Schaette and McAlpine, 2011), exceeding the boundary of the tinnitus frequency region (likeness rating ≥ 40 on a scale of 0–100) at 4 kHz (broken line, Fig. 2b). Consistent with previous findings (Roberts et al., 2008), likeness ratings at 5 kHz averaged 42.5 (black square, Fig. 2b) which was in the tinnitus frequency region, although the mean peak rating (76.0) in our younger subjects occurred on average at 9.9 kHz (black circle, Fig. 2b). Tinnitus likeness ratings at 500 Hz averaged 7.64 (black diamond, Fig. 2b) which was well below the tinnitus frequency region, also consistent with previous research (Roberts et al., 2008; Paul et al., 2014).

3.2. Group differences in suprathreshold measures of amplitude modulation encoding

3.2.1. Amplitude modulation detection thresholds in background noise

Amplitude modulation (AM) detection thresholds were measured for a 19 Hz AM tone using either a 5 kHz carrier frequency or a 500 Hz carrier frequency, both presented within narrowband background noise (NBN) designed to suppress the contribution of high-SR fibers. The firing rate of high-SR fibers is known to saturate near 40 dB SPL (Yates et al., 1990), which was the spectrum level of the NBN. AM detection thresholds are shown for both groups and carrier frequencies in Fig. 3a. A main effect of frequency ($F(1,70) = 376.78$, $p < 0.0001$) indicated that AM detection thresholds in NBN were higher (i.e., worse) for the 5 kHz stimulus than for the 500 Hz stimulus. The main effect of group was not significant in this analysis ($p = 0.177$), but an interaction was found between group and frequency ($F(1,70) = 6.44$, $p = 0.013$). Post-hoc Least Significant Difference (LSD) tests indicated that tinnitus subjects had worse AM detection thresholds than control subjects for the 5 kHz probe ($p = 0.016$), but AM detection thresholds for 500 Hz did not differ significantly between the groups ($p = 0.48$). These results indicate that the tinnitus group had poorer suprathreshold AM sensitivity in background noise for the 5 kHz tone which was in the tinnitus frequency region, but had normal AM sensitivity at 500 Hz which was well below the tinnitus frequency region (Fig. 2b). These findings were obtained even though the sound thresholds measured for the test stimuli were normal and near identical at the two carrier frequencies in the tinnitus and control groups (Table 1).

3.2.2. Envelope following responses

We studied envelope following responses (EFRs) in the five conditions shown in Fig. 1, which are reprised below the abscissa in Fig. 3b. The first condition was a 0 dB (100%) AM tone in quiet where both low-SR and high-SR fibers were available to support AM encoding. In the second condition the 0 dB AM tone was presented within NBN intended to diminish the contribution of high-SR fibers to AM coding relative to that of low-SR fibers. In subsequent conditions AM depth was further reduced to -2.5 dB and -6 dB, yielding a progressively smaller AM signal for coding by low-SR fibers while the contribution of high-SR fibers remained suppressed by NBN. A final condition (NBN alone) contrasted 85 Hz power to a condition where no AM tone was present.

EFR power recorded as dB SNR in each of these conditions is plotted in Fig. 3b for the control and tinnitus groups separately. Comparison of the no noise, 0 dB AM depth condition to the three NBN conditions where the 5 kHz tone was modulated at varying AM depths shows that for both groups, EFR power decreased when NBN was added to the AM tone. Over the latter three conditions in NBN, EFR power declined further as AM depth was reduced. These

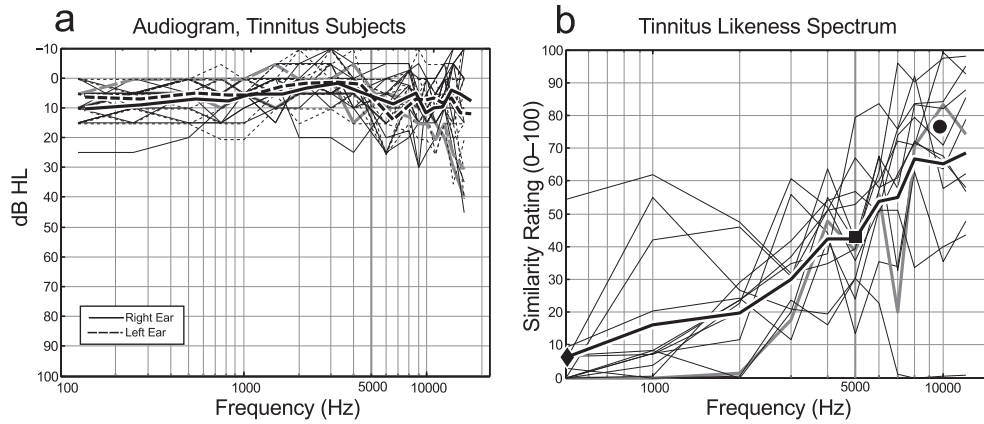


Fig. 2. Characteristics of the tinnitus group. a) Audiometric thresholds for all individuals (thin lines) from 125 Hz to 16 kHz. Group means for left (dashed line) and right (solid line) ears are plotted as thick black lines. A vertical line is 5 kHz, the frequency of the AM tone used for EFR measurement (see later). Audiometric thresholds for the intermittent tinnitus case are represented by thick grey lines. b) The tinnitus likeness spectrum in which tinnitus subjects rate the similarity of their tinnitus to pure tone frequencies. Thin lines represent individual spectra which were measured three times. The thick line is the group mean. The frequency rated highest per individual on average is represented by the black dot, and the average 500 Hz and 5 kHz likeness ratings are represented respectively by the black diamond and black square. The intermittent tinnitus subject is represented by the thick grey line.

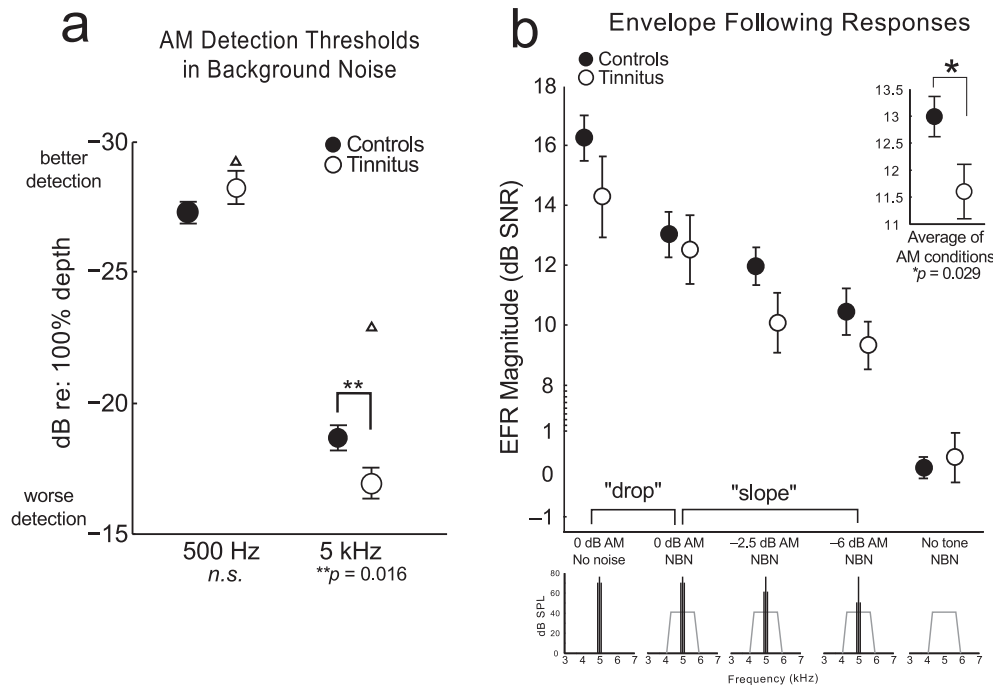


Fig. 3. Behavioral and electrophysiological measurements of AM coding for the tinnitus and control groups. a) Amplitude modulation detection thresholds for 500 Hz and 5 kHz AM tones embedded in background narrowband noise. AM thresholds for the intermittent tinnitus case are depicted as open triangles. *n.s.* = group difference not significant. b) EFR magnitudes (dB SNR) for tinnitus and control groups for the five stimulus conditions of Fig. 1. The inset shows the main effect of group based on the four conditions that included the AM tone. Error bars for all panels are 1 standard error of the mean (SEM).

results were evaluated by ANOVA including the factors group (tinnitus versus control) and condition (all conditions AM tone conditions excluding the last NBN-only condition). A main effect of group was found ($F(1,140) = 4.9, p = 0.029$) indicating that individuals with tinnitus had overall smaller EFRs than controls (see inset, Fig. 3b). Post-hoc contrasts of the main effect were not significant for any individual stimulus condition, although the 0 dB condition ($p = 0.16$) and the -2.5 dB AM, NBN condition ($p = 0.10$, LSD tests) appeared to have contributed most to the overall group effect. A main effect of stimulus condition was also found ($F(3,140) = 14.55, p < 0.0001$). Post-hoc LSD tests showed

that in controls, the no-noise, 0 dB AM (fully modulated) condition in quiet was larger than each of the remaining conditions ($ps < 0.0001$), while in the tinnitus subjects the EFR in the 0 dB AM condition in quiet was larger than in the -2.5 and -6 dB AM conditions in NBN ($ps < 0.016$). The results are consistent with the known response properties of high-SR fibers, in which their contribution to AM coding saturates when background sound is presented at near 40 dB spectrum level. The interaction of group and condition was not significant in this analysis. Thus AM encoding was poorer overall in tinnitus subjects than in controls, suggesting greater synaptic loss in the tinnitus group.

3.3. Individual differences in AM detection and subcortical encoding in background noise

In order to characterize the nature of that synaptic loss, we investigated simulating our EFR results with different mixtures of high-SR and low-SR fiber loss using the peripheral model of Zilany et al. (2014). The aim was to understand which patterns of fiber loss could best explain individual differences in AM coding and EFR magnitude that were observed within our control and tinnitus groups. It was instructive to consider the control subjects first.

3.3.1. Individual differences in control subjects

Although the average EFR power of control subjects dropped significantly with the addition of background NBN (“drop” referring herein to the decrease of EFR power from the no-noise, 0 dB fully modulated AM tone to the 0 dB AM tone in NBN; see Fig. 3b), some control subjects showed large drops whereas others showed small drops. These individual differences correlated significantly with AM detection thresholds in NBN (Fig. 4a; $r = 0.45$, $p = 0.027$). Thus control subjects with EFRs that were strongly diminished by NBN had worse AM detection thresholds in NBN compared to subjects whose EFR power dropped little in NBN.

One explanation of these results could be that subjects with large EFR drops and worse AM detection in NBN had fewer low-SR fibers available to support AM coding once high-SR fibers were saturated by NBN. To assess this interpretation we used the peripheral auditory model (Zilany et al., 2014) to simulate ANF responses to our stimulus conditions. We computed first a set of simulations in which all ANFs were intact (0% loss), and then in subsequent simulations removed low-SR fibers progressively until

all low-SR fibers were absent. Similar to EFR power, the addition of NBN to the AM tone reduced ANF modulation response magnitude for all conditions, and the size of the ANF response drop increased as more low-SR fibers were removed (see Fig. 4b). This result is qualitatively consistent with the suggestion that control subjects with large EFR drops had more low-SR fiber loss.

With high-SR fibers predominantly saturated by NBN, we aimed to further assess low-SR fiber function by reducing the AM depth of the stimulus during the EFR recordings. We fit a straight line to each subject's EFR power values for the 0 dB, -2.5 dB, and -6 dB AM depth conditions (Fig. 2, the three middle stimuli) and calculated the slope of this line (“slope” referring herein to changes in response magnitude across these three conditions; see abscissa of Fig. 3b). For control subjects, slope did not correlate with AM detection thresholds ($r = -0.01$, $p = 0.96$). To understand if EFR slope related to the effect of adding NBN, we correlated EFR slope with the EFR drop observed when NBN was added to the AM tone. A relationship was found indicating that individuals with smaller EFR drops had steeper EFR slopes ($r = 0.47$, $p = 0.019$, see Fig. 4c; it should be noted that negative slope values denote steeper slopes across the three NBN conditions). In other words, those individuals whose EFR was not strongly reduced when NBN was added showed a sensitivity to decreasing AM depths in NBN, suggesting that (in contrast to the remaining individuals) they had sufficient low-SR fibers available to code variations in AM depth. Peripheral model simulations (not shown) supported this interpretation, revealing that when low-SR fiber loss was greater the slope of the ANF response magnitude across the three NBN conditions was shallower. These results suggest that the EFR recorded at varying AM depths in NBN can reveal information about the status of low-SR

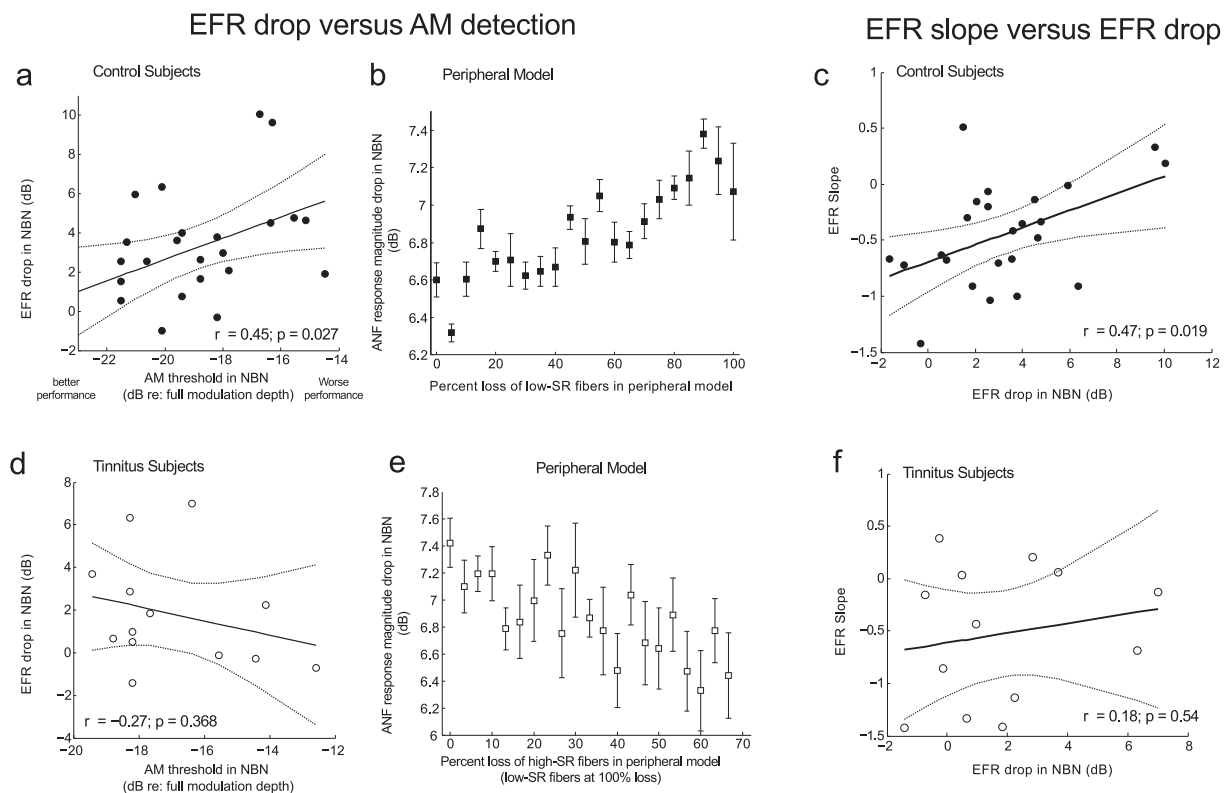


Fig. 4. Individual differences in EFR drops, AM detection, and auditory peripheral model simulations of the EFR. a,d) Relationship of individual differences in EFR drops to AM detection in the control and tinnitus groups, respectively. Dotted lines are 95% confidence intervals around the solid regression line. b,e) Auditory peripheral model simulations showing the calculated ANF response magnitude drop when NBN was added to the AM tone (ordinate). Percent loss of either low (b) or high (e) spontaneous rate fibers is plotted along the abscissa. c,f) The observed EFR drop (abscissa) is plotted as a function of the observed EFR slope (Ordinate) for control subjects (c) and tinnitus subjects (f).

fibers in normal hearing individuals without tinnitus, but only when sufficient numbers of low-SR fibers are available to encode suprathreshold sound.

3.3.2. Individual differences in tinnitus subjects

As just noted, control subjects with EFRs strongly degraded by NBN (large drops) had poorer AM detection thresholds in the NBN (Fig. 4a), consistent with low-SR fiber loss in the model (Fig. 4b). If low-SR fiber loss were to explain worse AM detection thresholds in tinnitus subjects, we would expect larger EFR drops in this group. However, although the range of drops observed in tinnitus subjects was similar to the range observed in controls (contrast the ordinates, Fig. 4a and 4c), the correlation relating EFR drop to AM detection was in the opposite direction compared to that seen in control subjects. Although this correlation did not reach significance in the tinnitus subjects ($r = -0.27$, $p = 0.37$, see Fig. 4c), it was significantly different from that of controls shown in Fig. 4a ($p = 0.047$, Fisher's r -to- z transformation). A possible explanation for these results could be that undetected high-SR fiber loss in the tinnitus subjects may have reduced their EFRs in the no-noise condition, such that smaller EFR drops occurred in tinnitus subjects with poorer AM detection thresholds when NBN was added. To assess this possibility, we progressively removed high-SR fibers in the peripheral model with low-SR fiber loss set at 100%. As shown in Fig. 4d, the size of ANF response magnitude drop caused by NBN decreased as high-SR fibers were removed. If a pattern of undetected high-SR fiber loss (reducing EFR drops) and significant low-SR fiber loss (reducing EFR slope) were to approximate the conditions present in our tinnitus subjects, relationships of EFR drops to AM detection and of EFR drops to slope would be expected to differ from those of control subjects where ANF function is likely better preserved for both fiber types. While EFR drops were significantly correlated with AM detection in background noise and EFR drops with slope in controls ($r = 0.45$, $p = 0.027$ and $r = 0.47$, $p = 0.019$, show in Fig. 4a and 4c, respectively), Fig. 4d and 4f shows that neither correlation reached significance in the tinnitus subjects.

3.4. Comparison of simulated and observed EFR responses in control and tinnitus subjects

In a further qualitative analysis we compared the EFRs simulated by the auditory nerve model with the EFRs observed in our tinnitus and control subjects at the group level. Fig. 5a shows EFR modulation response magnitude simulated for no ANF loss (black squares), 100% low-SR fiber loss with high-SR fibers intact (grey squares), and 100% low-SR fiber loss plus high-SR fiber loss simulated from 0 to 70% of these fibers (open rectangles). The latter condition represents a range of high-SR fiber loss that would not be expected to affect audiometric thresholds based on reported animal data (Schuknecht and Woellner, 1953; Lobarinas et al., 2013). For comparison with these simulations, Fig. 5b reports the EFRs observed for the tinnitus group, and for control subjects divided into two subgroups with comparatively good and poor AM detection, respectively, based on a median split of their AM detection thresholds.

Examination of the 0 dB AM stimulus in the quiet (no noise) condition in Fig. 5a shows that the modeled EFR diminished little when all low-SR fibers were lost (grey square) compared to when all fibers were present (black square). This suggests that high-SR fibers contribute more to the EFR than do low-SR fibers in the no-noise condition. Consistent with this conclusion, the measured EFR responses shown in Fig. 5b for the same 0 dB AM tone in quiet showed little difference between controls with good and poor AM detection (compare the grey and black circles). Fig. 5a shows

further that an additional loss of up to 70% of high-SR fibers (open rectangle) strongly diminished the modeled EFR for the 0 dB AM tone in quiet. Correspondingly, the measured EFR response observed in Fig. 5b for the tinnitus subjects (open circle), for whom additional high-SR fiber loss is expected on the basis of results discussed above, was lower in quiet than the EFRs observed in both control subgroups. The modeling results of Fig. 5a further show that modulation response magnitudes were reduced across all NBN conditions with 100% low-SR fiber loss (grey squares) compared to all fibers intact (black squares), and were reduced still further when high-SR fiber loss approached 70% (open rectangles). These results correspond with the lower EFRs seen in NBN in control subjects with poor compared to good AM detection in Fig. 5b, and with the finding that across all conditions tinnitus subjects had significantly smaller observed EFRs compared to controls. It should be noted, however, that 70% loss of high-SR fibers may overstate the extent of such losses in tinnitus subjects owing to scaling considerations in the model that would affect all three modeling simulations, but equally (see Section 4.4 below). In sum, high-SR fiber loss combined with low-SR fiber loss aligns more closely with EFRs observed for our tinnitus subjects compared to low-SR fiber loss alone.

3.5. Relationship of AM detection and EFRs to audiometric thresholds

Audiometric threshold shifts are known to affect both suprathreshold EFRs (Vander Werff and Brown, 2005) and AM detection (Stone and Moore, 2014). Therefore, although all subjects in the tinnitus and control groups had normal thresholds <11 dB HL at the test frequencies, we assessed whether individual differences in audiometric thresholds could account for variability in suprathreshold AM encoding performance. Diotic audiometric thresholds at 5 kHz did not correlate significantly with 5 kHz AM detection thresholds in NBN, with EFR drop, or with EFR slope in control subjects ($r_s = -0.27$, -0.07 , and -0.07 , respectively, all p 's > 0.21) or in tinnitus subjects ($r_s = -0.24$, 0.17 , and -0.05 respectively, all p 's > 0.42). Scatterplots of these correlations are presented in the on-line [Supplementary material](#) for this article. AM detection thresholds in NBN at 500 Hz also did not correlate with diotic thresholds at 500 Hz (Control: $r = 0.14$, $p = 0.522$; Tinnitus: $r = -0.342$, $p = 0.253$) or with EFR measurements taken at 5 kHz in either group (all p 's > 0.712, not shown). These results indicate that suprathreshold measurements of AM detection and EFR encoding did not relate to audiometric thresholds in either subject group. Hence the synaptic losses suggested by our simulations for controls with poor AM coding and in the tinnitus group appear to have been hidden from the audiogram. This is consistent with animal data showing that destruction of up to 80% of IHCs (Lobarinas et al., 2013) or auditory nerve fibers (Schuknecht and Woellner, 1953) does not affect audiometric thresholds.

3.6. Intermittent tinnitus case

The individual who reported episodes of tinnitus (intermittent tinnitus, IT) was an 18 year old male who experienced a bilateral tonal tinnitus intermittently over 16 months. His THQ score was 14.4 indicating a low level of tinnitus disturbance. The audiogram for left and right ears of this subject is plotted in Fig. 2a as thick grey lines, showing normal thresholds (<25 dB HL) in both ears to 12.5 kHz. His diotic auditory thresholds were -6 dB HL and 1 dB HL for 500 and 5 kHz respectively, which were lower (better) than the group mean for subjects with chronic tinnitus. The tinnitus likeness spectrum of the IT subject is produced in Fig. 2b as a thick grey line showing with one exception increasing likeness with increasing frequency. Notably, his tinnitus loudness matches at the time he

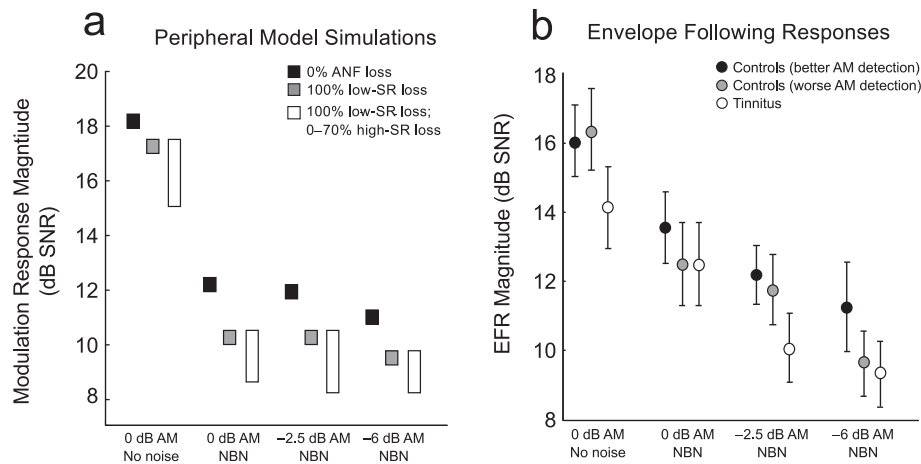


Fig. 5. Summary of simulated and observed EFR responses in the tinnitus and control groups. a) Modulation response magnitude in dB SNR simulated by the peripheral auditory model for the four stimulus conditions in which an AM tone was present (see Fig. 1). No fiber loss and 100% low-SR fiber loss are shown by blackened squares and shaded squares, respectively. The white rectangles represent EFRs simulated for 0–70% high-SR loss combined with 100% low-SR fiber loss. b) Observed EFR magnitudes for tinnitus and control subjects. Control subjects are broken out into two subgroups exhibiting good (blackened circles) and poor (grey circles) AM detection based upon a median split of their AM detection thresholds ($n = 12$ subjects per group). The EFRs of the tinnitus subjects (open circles) are repeated from Fig. 3c for purposes of comparison. Error bars are 1 SEM calculated for each condition separately.

experienced his tinnitus in the laboratory averaged 55 dB SL across the frequencies of 500 Hz, 1 kHz, and 5 kHz, which was 5.51 SDs higher than the chronic tinnitus group mean. AM detection thresholds in NBN for the IT subject (Fig. 3a, open triangles) were -23.6 dB for 500 Hz, close to the chronic tinnitus group mean for this frequency, and surprisingly -23.2 dB for the 5 kHz condition, which was 3.4 SDs better than the chronic tinnitus group mean. This individual also had an EFR that was 2.54 SDs greater than the mean of the chronic tinnitus subjects. A good AM detection threshold and large EFR at 5 kHz are consistent with each other but inconsistent with tinnitus-associated low/high-SR fiber loss in the tinnitus frequency region. Episodic tinnitus would not be expected to follow from synaptic losses on ANFs, which do not recover and precede a delayed degeneration of the auditory nerve (Kujawa and Liberman, 2009). Given other reported aetiologies for tinnitus (Henry et al., 2005), it is possible that this individual's intermittent tinnitus may have been caused by inflammatory (Yüksel and Karataş, 2016), neuromodulatory (Simoens and Hebert, 2012), or unknown transient factors and not by cochlear injuries.

4. Discussion

4.1. Summary

Low-SR fiber loss has been hypothesized to underlie between-subject differences in temporal coding ability in individuals with clinically normal audiograms (Bharadwaj et al., 2014, 2015) and to be present in individuals experiencing chronic tinnitus with audiometrically normal hearing (Schäette and McAlpine, 2011; Plack et al., 2014; Roberts et al., 2013). To evaluate these hypotheses, we measured detection thresholds for the presence of AM in 500 Hz and 5 kHz pure tones presented singly in 40 dB spectrum level narrow-band noise (NBN), which is known to preferentially saturate high-SR ANFs leaving temporal processing reliant on low-SR fibers (Yates et al., 1990). In the same session we subsequently recorded EFRs evoked by 5 kHz tones at 75 dB SPL in quiet, and again when the contribution of high-SR fibers was suppressed by NBN. We found that the EFRs of control subjects with poor AM detection in noise were more strongly reduced by the addition of NBN than was the case for control subjects with good AM detection. The results were consistent with hidden low-SR fiber loss in the

poor-performing control subjects estimated by a computational model of the auditory nerve. Tinnitus subjects had overall worse AM detection in noise and smaller EFRs across the noise and no-noise conditions, suggesting hidden hearing impairment in this group. Computational modeling indicated that in addition to low-SR fiber loss, a further loss affecting high-SR fibers (losses up to 70% were simulated) was needed to approximate the EFR results observed in tinnitus subjects across all stimulus conditions. High-SR fiber losses over this range would not be expected to elevate audiometric thresholds which remain unaffected with up to $\sim 80\%$ IHC loss (Lobarinas et al., 2013). In agreement, EFRs and AM sensitivity did not correlate with audiometric thresholds in either subject group.

4.2. AM sensitivity in control subjects

Our control subjects with normal audiometric thresholds at the test frequencies varied widely in their AM detection thresholds and in the magnitude of their EFRs measured in background noise. Comparatively poor performance on these tasks may signify difficulties in coding temporal modulations in sound that can impact spatial listening and speech comprehension in multi-talker environments (Ruggles et al., 2011; Mehraei et al., 2016). Consistent with this supposition, individual differences in the extent to which temporal modulations are coded by the EFR have been shown to correlate positively with the ability of subjects to detect shifting interaural time delays (a skill needed to detect a change in the spatial location of a sound source) and with their ability to direct attention to one of two speech streams presented simultaneously (Bharadwaj et al., 2015). These same investigators also found that EFR slope measured at different modulation depths in notched background noise correlated inversely with behavioral AM detection thresholds, such that subjects with steep slopes were comparatively poorer at AM detection. Although this correlation was not significant in our data ($r = -0.01$, $p = 0.96$, see Section 3.3.1), it should be noted that Bharadwaj et al. (2015) measured the EFR in background noise containing a notch around the AM tone. This feature of their stimulus procedure was intended to prevent off-frequency contributions to performance, but in so doing it allowed both high- and low-SR fibers to contribute to AM coding. With this procedure it is possible that slope was shallower across

the noise conditions in subjects with good AM detection because both types of fibers were available to these subjects for AM coding as AM depth declined, consistent with predictions made in their cochlear modeling (Bharadwaj et al., 2014). In contrast to the procedure of Bharadwaj et al. (2015), we suppressed the contribution of high-SR fibers to AM coding with unnotched background noise, and reduced AM depth thereafter to test predominantly low-SR fibers. We found that the slope was significantly steeper in controls for subjects whose EFR drop was smaller when NBN was added to 100% AM depth (Fig. 4c). Cochlear modeling suggested that low-SR fibers were comparatively well preserved in these subjects such that the EFR now decreased in noise as AM depth diminished, but not in controls with poorer AM detection in NBN where modeling suggested that low-SR fiber synaptopathy was present. Differences in the relationship of EFR slope steepness to behavioural AM detection between Bharadwaj et al. (2015) and the current study are thus attributable to the notched-noise versus on-band NBN stimulus, and both studies point to low-SR synaptopathy as a factor contributing to deficits in AM coding observed among otherwise normal hearing subjects.

4.3. Role of high-SR and low-SR fiber loss in tinnitus

Our findings suggesting hidden hearing loss in the tinnitus subjects invite a re-evaluation of earlier results revealing differences in audiometric thresholds between individuals with and without tinnitus. Roberts et al. (2008) compared audiometric thresholds to 16 kHz between human tinnitus sufferers and controls that were explicitly matched in age while thresholds were allowed to vary. Audiometric thresholds were normal (≤ 20 dB HL) to 10 kHz in controls and tinnitus subjects aged less than fifty years (mean age 34.4 yrs), whereas subjects over age fifty (mean age 65.6 yrs) showed expected high-frequency audiometric hearing losses above 2 kHz. However, audiometric thresholds above 2 kHz were on average 11 dB higher in tinnitus than control subjects in both age cohorts. Similar results are found in studies by Roberts et al. (2015) and Wienbruch et al. (2006). If age matching is assumed to control for OHC losses caused by aging (Sergeyenko et al., 2013), the audiometric difference observed by Roberts et al. (2008) between young tinnitus and control subjects with normal thresholds to 10 kHz could reflect a degree of hair cell damage and/or synaptic losses in the young tinnitus group that resulted from prior noise exposure or other factors, although these cochlear changes were insufficient to elevate audiometric thresholds into the clinically abnormal range. Similar cochlear changes may have distinguished the older subjects expressing tinnitus from their age matched controls, while age-related OHC loss contributed principally to the threshold shifts seen in both groups. It is noteworthy that in contrast to the findings just discussed, auditory thresholds measured for our test stimuli did not differ between the tinnitus and control groups of the present study (Table 1). Our tinnitus subjects were younger (mean age 23.2 yrs) than the cohorts of Roberts et al. (2008; overall mean age 58.6 yrs), the loudness and disturbance of their tinnitus was lower (see section 3.1), and the extent of their synaptic losses suggested by cochlear modeling was insufficient, at least at this time point in the development of tinnitus (Roberts, 2016; Sanchez et al., 2016), to affect threshold measurements.

Other findings point to undetected cochlear pathology as a factor distinguishing tinnitus and control subjects, when (unlike above) subjects are explicitly matched for audiometric thresholds. Tan et al. (2013) found that tinnitus subjects with high-frequency hearing loss had better frequency selectivity and compression measured psychophysically compared to non-tinnitus subjects matched closely in thresholds. The results suggested that tinnitus

was not strongly associated with OHC impairment estimated by the psychophysical tests, and that by inference IHC cell dysfunction and ANF loss may instead have accounted for the threshold shifts and presence of tinnitus in their subjects. Our modeling results are consistent with this view and add the hypothesis that a degree of high-SR fiber loss insufficient to affect threshold measurements may be present in individuals with chronic tinnitus and hearing thresholds in the clinically normal range. Weisz et al. (2006) studied a group of young adults with tinnitus and age-matched controls both with normal hearing thresholds, comparing the groups for evidence of off-frequency listening expected at frequencies where hidden cochlear dead regions may have been present. Compared to controls, tinnitus subjects showed steeper slopes for functions relating perceived pitch to frequency, reflecting a shift of pitch judgments for sounds in the tinnitus frequency region toward lower frequencies and implying off-frequency listening in the tinnitus group. Auditory thresholds measured in threshold-equalizing noise (TEN test, Moore et al., 2000) after pitch scaling were also higher for sounds in the tinnitus region in 8 of the 11 tinnitus subjects studied (Weisz et al., 2006), giving added confirmation that hidden cochlear injury was present. A subsequent study by Gilles et al. (2013) using the TEN test did not find evidence for off-frequency listening in tinnitus subjects with differing degrees of audiometric hearing loss, which suggested to the authors that this test may have limited reliability for detecting cochlear dead regions in a tinnitus population (pitch scaling was not tested).

In addition to revealing the presence of synaptic loss, some animal studies have examined the specific pattern of low-SR and high-SR fiber synaptopathy observed in subjects expressing behavioral evidence of tinnitus. After noise exposure, animals with tinnitus typically exhibit increased spontaneous activity throughout the auditory pathway including in the auditory cortex (Basura et al., 2015), the dorsal cochlear nucleus (DCN; Kaltenbach et al., 2004; Dehmel et al., 2012; Wu et al., 2016), and the inferior colliculus (IC; Bauer et al., 2008). Increased neural synchrony accompanies these changes in the auditory cortex (Engineer et al., 2011), IC (Bauer et al., 2008), DCN (Wu et al., 2016) and possibly other brain regions (Eggermont and Roberts, 2014). These changes are believed to reflect diminished inhibition and increased gain in central auditory pathways after deafferentation (Berger and Coomber, 2015; Noreña and Farley, 2013), with altered spike-timing dependent plasticity playing a role in altering the response properties of neurons in these structures (Dehmel et al., 2012). In two animal studies in which the pattern of low-SR and high-SR fiber loss associated with tinnitus-related neural changes was examined, Bauer et al. (2007) and Rüttiger et al. (2013) found evidence that high-SR fiber loss was more strongly associated with tinnitus behaviour than was low-SR fiber loss. To explain these findings, Knipper et al. (2015) suggested that protein expression needed to compensate for deafferentation of central auditory structures could not be achieved once high-SR fibers sustained a significant loss, which triggered tinnitus-generating hyperactivity and hypersynchrony in auditory pathways (Rüttiger et al., 2013; Singer et al., 2013; Wu et al., 2016). An alternative (and not incompatible) hypothesis may be that in normal hearing individuals feed-forward inhibition driven by the high rates of spontaneous activity of high-SR fibers may act to preserve the sensitivity of the targeted neurons in central auditory structures to their cochlear inputs, even in quiet environments. When inhibition driven by the high-SR fibers is lost, other inputs including those from somatosensory and visual domains may be upregulated in the DCN and other multimodal auditory structures (Zeng et al., 2009), fostering tinnitus related neural activity in these structures and enabling cross modal modulation of tinnitus which is often

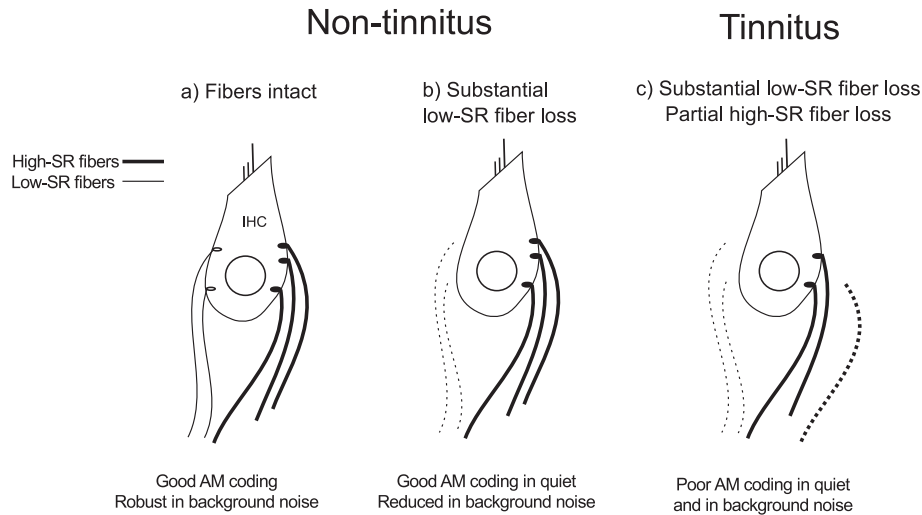


Fig. 6. Conceptual model of peripheral synaptic loss (broken lines) in tinnitus and non-tinnitus individuals. Noise exposure or other auditory insults damage vulnerable low-SR auditory nerve fibers (thin lines) that tend to locate on the modiolar surface of the IHC and less vulnerable high-SR nerve fibers (thick lines) that tend to locate on the pillar side. (a) Subjects with normal AM coding, normal audiometric thresholds, and no tinnitus. All synapses are intact. (b) Subjects have low-SR loss that degrades AM coding, but because hair cell mechanical function and high-SR fibers remain intact, tinnitus is not present and auditory thresholds are normal. (c) Tinnitus subjects have additional synaptic loss to high-SR fibers sufficient to trigger aberrant hyperactivity in higher auditory structures, but the extent of high-SR fiber loss is not sufficient to affect auditory thresholds.

observed in tinnitus sufferers (Levine et al., 2003; Lockwood et al., 2001; Sanchez and Rocha, 2011). Mechanisms dependent on a loss of high SR fibers may also explain why some individuals with suprathreshold temporal processing deficits and EFR evidence for low-SR fiber synaptopathy do not develop tinnitus (Bharadwaj et al., 2015; Mehraei et al., 2016; control subjects with poor AM detection in the present data). In our simulations using a well-established model of the auditory periphery, a degree of high-SR fiber loss was required in addition to low-fiber loss to explain the EFRs observed in our tinnitus subjects relative to control subjects.

A summary model based on our findings and the evidence discussed above is depicted in Fig. 6. IHCs and ANFs tuned to high frequencies covering the tinnitus spectrum are depicted for three cases. Tinnitus is absent in cases (a) and (b) since high-SR fibers are preserved; however, temporal coding dependent on intact low-SR fibers is impaired in case (b) in the presence of background noise. Tinnitus is present in case (c) owing to added partial loss of high-SR fibers but not enough to elevate audiometric thresholds. AM coding in quiet is also reduced in this case, since high-SR fibers would be expected to contribute to temporal processing in this condition. Although the subjects we studied did not have high frequency hearing loss, the model can be extended to account for audiometric threshold shifts with and without tinnitus. Here tinnitus with threshold shift would correspond to case (c), and threshold shift without tinnitus to case (b), adding OHC loss and/or hair cell stereociliar damage in both cases to elevate audiometric thresholds.

4.4. Role of central mechanisms in AM coding

The EFR reflects a composite of phase-locked activity from the auditory nerve and subcortical structures (Kuwada et al., 2002; Shaheen et al., 2015) and when evoked at 85 Hz has sources consistent with generators in the auditory midbrain (Herdman et al., 2002; Kiren et al., 1994). Any of the tinnitus-related central neural changes discussed above could disrupt subcortical AM processing in midbrain (Burger and Pollak, 1998) in addition to the degradations caused by ANF loss and thereby further alter EFR amplitude in tinnitus. In mice, EFRs recorded at AM rates of <600 Hz appear to be less sensitive to verified synaptic losses on

IHCs compared to EFRs recorded at higher AM rates, possibly because EFRs recorded at lower rates reflect activity in the later-occurring ABR waves IV and V which localize to midbrain nuclei and are subject to increased gain after deafferentation (Shaheen et al., 2015) while EFRs recorded at higher AM rates are more closely related to the activity of the cochlear nerve. To the extent that increased central gain increases the EFR, the difference we observed between tinnitus and control subjects could understate what might be observed at higher modulation frequencies, particularly for carrier frequencies close to the peak of individual tinnitus spectra. Our findings do not preclude a role for central structures in modulating EFR amplitude in tinnitus and control subjects, in addition to altered input to these structures dependent on possible synaptic losses in the cochlea. However, they do suggest that hidden synaptopathy could by itself be sufficient to account for impaired temporal coding in subjects with normal audiograms, and for cases of tinnitus unrelated to audiometric hearing loss.

While the auditory periphery model was able to qualitatively describe the patterns of EFR responses in the different stimulus conditions for our control and tinnitus groups, the range of EFR drops observed in our control subjects exceeded the comparatively narrower range estimated by the model (cf. ordinates, Fig. 4a and 4b). Central AM processing is known to enhance strong but not weak modulations (Joris et al., 2004), which could partly explain the quantitative differences between the obtained and simulated EFR data. In addition, not evaluated in the peripheral model was the function of the medial olivocochlear reflex (MOCR), an efferent gain control mechanism that suppresses ANF firing rates under continuous stimulation and may assist listening in noise (Guinan, 2006). There are known individual differences in MOCR strength (De Ceulaer et al., 2001), which may additionally contribute to the EFR drops seen in control and tinnitus subjects. Hyper-responsivity of medial olivocochlear neurons in tinnitus sufferers (Knudson et al., 2014) may also lead to stronger reductions in cochlear gain during long-duration stimuli as used in this study. However this might be expected to bring high-SR ANFs out of saturation and lead to an increased EFR in our tinnitus subjects compared to controls, rather than the decreased EFR that we observed in our tinnitus subjects.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.heares.2016.11.010>.

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