

Evaluation of peripheral compression and auditory nerve fiber intensity coding using auditory steady-state responses

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The compressive nonlinearity of the auditory system is assumed to be an epiphenomenon of a healthy cochlea and, particularly, of outer-hair cell function. Another ability of the healthy auditory system is to enable communication in acoustical environments with high-level background noises. Evaluation of these properties provides information about the health state of the system. It has been shown that a loss of outer hair cells leads to a reduction in peripheral compression. It has also recently been shown in animal studies that noise over-exposure, producing temporary threshold shifts, can cause auditory nerve fiber (ANF) deafferentation in predominantly low-spontaneous rate (SR) fibers. In the present study, auditory steady-state response (ASSR) level growth functions were measured to evaluate the applicability of ASSR to assess compression and the ability to code intensity fluctuations at high stimulus levels. Level growth functions were measured in normal-hearing adults at stimulus levels ranging from 20 to 90 dB SPL. To evaluate compression, ASSR were measured for multiple carrier frequencies simultaneously. To evaluate intensity coding at high intensities, ASSR were measured using a single carrier frequency at four modulation depths between 25 and 100%. The data showed that ASSR level growth functions exhibited compression of about 0.25 dB/dB. For levels above 60 dB SPL, the slope showed higher variability for the different modulation depths across subjects than for lower levels. The results indicate that the slope of the ASSR level growth function can be used to estimate peripheral compression simultaneously at four frequencies below 60 dB SPL, while the slope above 60 dB SPL may provide information about the integrity of intensity coding of low-SR fibers.

INTRODUCTION

The integrity of the hearing system has traditionally been assessed through audiometry, where the minimum sound level (hearing threshold) of pure tones presented at different frequencies is measured. Patients showing hearing thresholds comparable to standardized normal hearing thresholds are categorized as being normal-hearing (NH)

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listeners, whereas those patients with elevated hearing thresholds are categorized as being hearing-impaired (HI) listeners. Nevertheless, there is emerging evidence that the complexity of the hearing system cannot be fully characterized by just evaluating sensitivity by measuring thresholds. Several clinical studies showed that about 5 to 10% of patients self-reporting hearing difficulties, particularly in noisy background situations, show pure-tone audiograms better than 20 dB HL (Saunders and Haggard, 1989; Kumar *et al.*, 2007; Hind *et al.*, 2011). Furthermore, there is strong evidence from physiological studies in animal models that profoundly damaged hearing systems do not produce permanent threshold shifts. In Lobarinas *et al.* (2013) an anti-cancer drug was injected in chinchillas to produce a selective loss of inner hair cells (IHC) while keeping the total integrity of outer hair cells (OHC). The data show only minor effects on behaviorally measured audiometric thresholds, even with a loss of IHC that exceeds 80%. There exist also other examples of damaged systems that are not detectable by an audiogram. It was reported that noise over-exposure causing a temporal threshold shift with threshold recovery within two weeks after the exposure produced a rapid and permanent loss of about 40-50% of auditory nerve fiber (ANF) synapses in mice (Kujawa and Liberman, 2009) and guinea pigs (Lin *et al.*, 2011), leading to a slow loss of ANF spiral ganglion cells (ANF cell bodies). Furman *et al.* (2013) showed that the loss of ANF synapses (deafferentation) after noise over-exposure is more selective to low- spontaneous rate (SR) ANF. Since this damage does not hamper sensitivity, but rather supra-threshold coding, this new form of hearing loss is known as *hidden hearing loss* because it cannot be detected by the currently available diagnostic metrics. Therefore, the development of novel methods able to evaluate the integrity and functionality of the human hearing system assessing supra-threshold processing is required.

The compressive nonlinearity of the peripheral auditory system is commonly assumed to be a result of healthy OHC function, and to be a good indicator of the system's integrity. Ruggero *et al.* (1997) showed that basilar membrane (BM) velocity grows linearly (slope of 1 dB/dB) when recorded as a function of sound level (dB SPL) in a dead cochlea. The BM input/output function grows compressively in an alive and healthy cochlea, where the healthy function of OHC generates a gain mechanism. In impaired systems, like listeners with a sensorineural hearing loss, a reduction of OHC leads to a reduction in compression and a loss of sensitivity. Since a reduction of sensitivity could also be caused by other mechanisms, like severe loss of IHC, the reduction in sensitivity does not necessarily imply a loss of OHC. Therefore, a method able to provide an estimate of peripheral compression in humans would be an excellent complement to the audiogram to characterize better the hearing system function at supra-threshold levels.

Intensity coding in the auditory nerve is done by different types of auditory nerve fibers (ANF). Typically, the types of afferent fibers that innervate an IHC have been divided according to their firing rate (number of spikes per second) in quiet (without sound stimulation). The fibers that produce more than 18 spikes/second are referred

to as high-SR fibers, while the fibers producing less than 18 spikes per second are named low-SR fibers (Lieberman, 1978). The high- and low-SR fibers show different rate-intensity functions (spike rate as a function of sound level). High-SR fibers have lower thresholds, their discharge rate increases with level at the lower stimulation levels range and it saturates at medium and high sound levels. On the contrary, low-SR fibers show higher thresholds and their discharge rate function grows with sound intensity (Winter *et al.*, 1990). Each of these types of fibers has a limited dynamic range of around 30 dB, such that high-SR fibers are already completely saturated at levels of 60 dB SPL. Since ANF are connected to a narrow region in the cochlea, noninvasive assessment of intensity coding would provide a good method to assess intensity coding in narrow frequency regions.

Auditory steady-state responses (ASSR) represent a well-studied objective measure of auditory function (see Picton *et al.*, 2003, for a review). ASSR are gross electroencephalography (EEG) potentials that follow the envelope of periodic acoustic stimuli. The most common acoustic stimulus used to record ASSR are sinusoidally amplitude modulated (SAM) tones. The use of SAM tones is very convenient because its envelope is a sinusoid defined by the modulation frequency (f_m). When the recorded ASSR is analyzed in the frequency domain, the energy at frequency f_m is a measure of the encoded stimulus envelope. Thus, increasing the amplitude of the SAM stimulus leads to a larger ASSR magnitude, and a reduction in the modulation depth (m) of the stimulus results in a smaller ASSR magnitude. One common clinical application of ASSR is the estimate of thresholds in non-responding listeners. It has been shown that ASSRs can be measured for multiple SAM tones simultaneously over a broad frequency range (Picton *et al.*, 2003). Since ASSRs encode the stimulus envelope at various intensities after peripheral processing, the measurement of ASSR at supra-threshold levels is a promising method to assess peripheral processing, including compression and high-intensity coding.

In this study, the applicability of ASSR to assess peripheral compression and to evaluate the integrity of ANF is investigated. Processing an SAM tone by a compressive system, such as the cochlea, will reduce the modulation depth of the processed signal. Since ASSR codes the envelope of the stimulus after cochlea processing, the ASSR must be also affected by the cochlear compressive nonlinearity. We hypothesize that ASSR recorded as a function of stimulation level reflects peripheral compression in NH listeners and a loss of compression at the impaired frequencies in listeners with a mild HI. For SAM tones at high intensities, different groups of ANF are required to encode the intensity fluctuations of the envelope. For shallow modulation depths and high carrier levels, especially low-SR fibers are required to encode the temporal fluctuations. Hence, ASSR recorded at higher stimulus intensities using shallow modulated SAM tones must rely mostly on the accurate temporal coding of low-SR fibers. Assuming that deafferentation is more predominant in low-SR fibers (Furman *et al.*, 2013), we hypothesize that ASSR magnitudes get reduced at higher stimulation levels and shallow modulation depths.

METHOD

ASSR were recorded using a Biosemi ActiveTwo system. The electrode placement followed the 10-10 system. The results in this study were obtained from the Cz-P10 vertical montage potential in response to right-ear stimulation and the Cz-P9 potential in response to left-ear stimulation. The acoustic stimuli were generated in MATLAB and presented to the subject through a pair of ER-2 insert earphones (Etymotic Research Inc.) mounted on an ER-10B+ low noise distortion product oto-acoustic emissions (DPOAE) microphone probe connected to a RME Fireface UCX 24-bit audio interface at a sampling rate of 48 kHz. Subjects were lying on a bed in a double-walled soundproof and electrically shielded booth.

Subjects

A total of 23 adult subjects (12 females) participated in this study. Sixteen (10 females, 26 ± 3 years old) had normal hearing at octave frequencies between 125 and 8000 Hz (threshold ≤ 15 dB HL). Seven mild HI subjects (2 females, 53 ± 14 years old) showed hearing thresholds above 20 dB HL and not higher than 45 dB HL at 4 kHz but normal thresholds at lower audiometric frequencies.

Stimuli and recordings

For the evaluation of peripheral compression, stimuli were presented at sound pressure levels (SPL) ranging from 20 to 80 dB in steps of 5 dB, using a multi-frequency stimulation paradigm. For the HI listeners, the input levels ranged from 30 to 80 dB SPL in 5 dB steps. The multi-frequency stimulus was composed by the addition of four SAM tones, each having a different carrier frequency ($f_c = 498, 1000, 2005, \text{ and } 4011$ Hz) to excite four different regions on the BM, and modulated at a different modulation frequency ($f_m = 81, 87, 93, \text{ and } 98$ Hz), respectively. For the evaluation of high-intensity level fluctuations, a single SAM tone with $f_c = 2005$ Hz and $f_m = 93$ Hz was used as stimulus. ASSR growth functions were recorded using four modulation depths ($m = 100, 85, 50, \text{ and } 25\%$) and input levels of 34, 40, 54, 60, 63, 66, 71, 74, 77, 81, and 87 dB SPL. All stimuli were generated in epochs, each lasting 1 second.

Data analysis

The recorded epochs were band-pass filtered between 60 to 400 Hz using a zero-phase fourth-order Butterworth filter and rejected if a voltage amplitude of $\pm 80 \mu\text{V}$ was reached. Weighted averaging was used to improve the signal-to-noise ratio (Picton *et al.*, 2003). Trials of 16 epochs were concatenated prior to analysis in the frequency domain. A fast Fourier Transform was applied to each trial, and an F -test statistic was used to determine the presence of a signal (Picton *et al.*, 2003). A significant level of 1% was used as criterion for statistical significance of the ASSR. To estimate compression, a two-slopes model similar to the one suggested by Neely *et al.* (2003) was used to estimate the slopes of the level growth function. The model was fitted exclusively to the statistically significant data points.

RESULTS

Estimates of peripheral compression

Figure 1 shows ASSR level growth functions in a representative NH subject. ASSR magnitudes (circles) were well above the background noise (crosses and grey areas), showing smooth and clear functions at all carrier frequencies (panels A-D). Significant ASSR magnitudes (solid circles) were recorded at stimulation levels as low as 20-30 dB SPL and above. ASSR level growth functions showed a compressive growth with level (slopes < 1) up to about 60 dB SPL. Above 60 dB SPL, ASSR growth functions were found to saturate. A compressive growth was found at all frequencies for all subjects, with averaged slope estimates of about 0.25 dB/dB, ranging from 0.1 to 0.5 dB/dB.

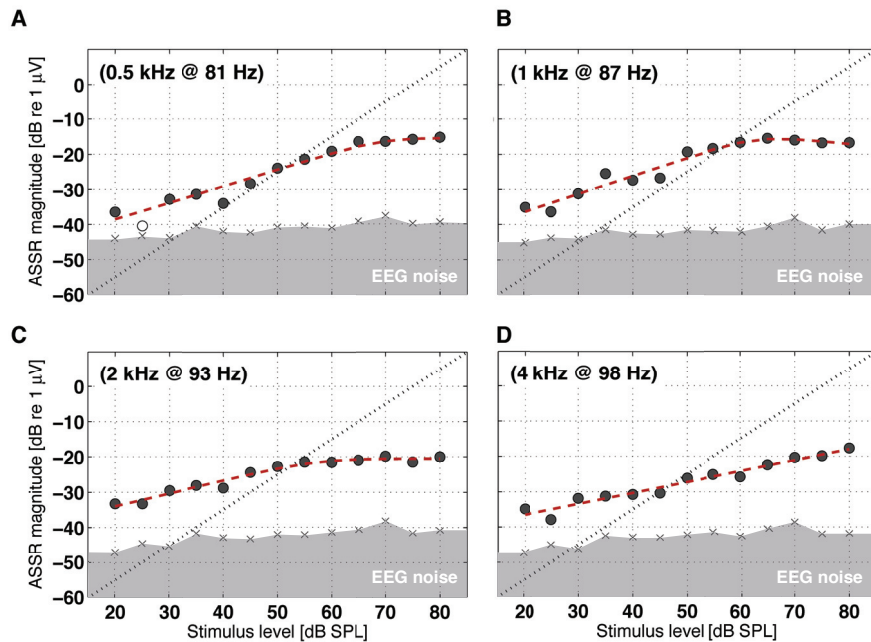


Fig. 1: ASSR growth functions in a representative NH subject. Panels A-D show frequencies at 0.5, 1, 2, and 4 kHz. Filled circles represent statistically significant ASSR magnitudes. Open circles represent non-significant ASSR. Crosses and grey areas show EEG background noise. A linear reference with slope of 1 is represented by the dashed line. The dotted line show a two-slopes fitting curve.

Figure 2 shows ASSR level growth functions in a representative HI subject. For simplicity, panels A and B show results for the 2 and 4 kHz carrier frequencies only. The results at 0.5 and 1 kHz were similar to panel A (not shown). In general, the ASSR level growth functions at the non-impaired audiometric frequencies (panel A) were similar to those in the NH subjects. Panel B shows results at the impaired frequency

for this specific subject (with a 30 dB HL threshold). Open circles at the lower input levels represent statistically non-significant ASSR magnitudes.

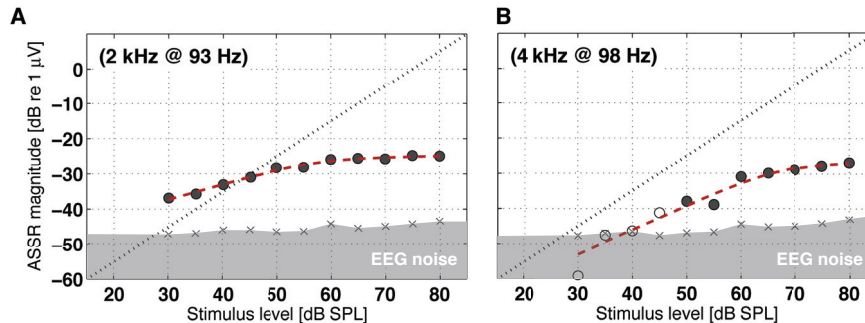


Fig. 2: Same as Fig. 1 but for a representative HI subject. Only frequencies 2 and 4 kHz (panels A and B) are shown (same as panels C and D in Fig. 1)

ASSR growth functions at different modulation depths

Figure 3 shows results from ASSR level growth functions recorded using four modulation depths for three individual NH subjects. Only the upper input level range is shown. Modulation depths ranged from fully modulated ($m = 100\%$, circles) to shallow modulation ($m = 25\%$, squares). Modulations at $m = 85\%$ are indicated by downwards triangles and $m = 50\%$ are shown as upwards triangles. The results from subjects NH2 and NH5 (panels A and B) were similar, with ASSR magnitudes growing monotonically with level at all modulation depths. The ASSR level growth functions in subjects NH2 and NH5 showed constant compressive slopes comparable to the slopes shown in Fig. 1. The ASSR level growth functions for 100% and 25% modulation depths were parallel, with larger magnitudes for 100% modulation results than for 25% modulation depth. The results from subject NH4 (panel C) showed similar ASSR growth functions only at the larger modulations, whereas ASSR magnitudes at 25% modulation depth (squares) were reduced.

DISCUSSION AND CONCLUSION

The results in Fig 1 showed that ASSR level functions grow compressively for stimulation levels up to 60 dB SPL. Compression could be estimated from all NH subjects and at all frequencies simultaneously using a multi-frequency paradigm. Estimates of compression were on average about 0.25 dB/dB (compression ratio of 4), which is in good agreement with behavioral estimates of cochlear compression (Plack *et al.*, 2004) and compression estimates using DPOAEs (Neely *et al.*, 2003). Above 60 dB SPL, ASSR growth functions recorded from multi-frequency stimulation saturate, probably due to the interaction between the different SAM components at the level of the cochlea and suppression mechanisms in the BM (Picton *et al.*, 2007). This may also explain why ASSR growth functions saturate less at 4 kHz (Panel D in Fig. 1), as there is not a higher frequency tone that suppresses the 4 kHz response.

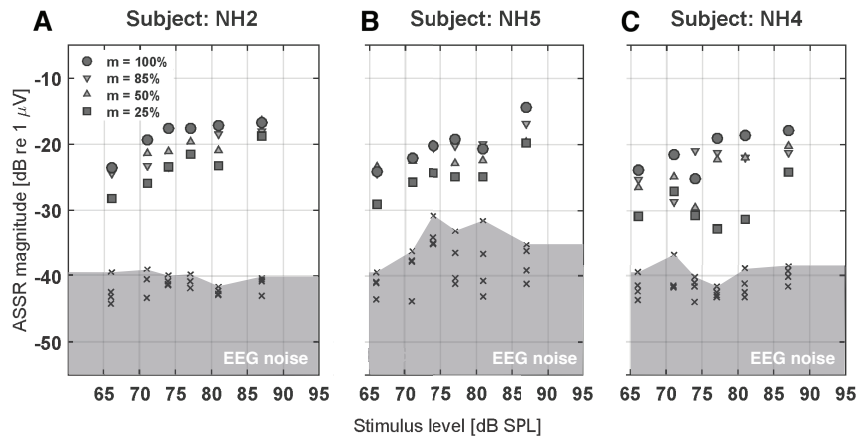


Fig. 3: ASSR growth functions for three NH subjects at four modulation depths. Circles show 100% modulation depth, downward triangles show $m = 85\%$, upward triangles show $m = 50\%$ and squares show $m = 25\%$. Crosses and grey areas show EEG background noise.

For the HI subjects, the ASSR growth functions at the non-impaired frequencies (panel A in Fig. 2) showed the same behavior as the results for the NH subjects (Fig. 1). However, at the mildly impaired frequency (panel B in Fig. 2), the ASSR magnitudes at lower input levels were statistically non-significant, which represents the loss of sensitivity or threshold elevation at this frequency. The non-significant ASSR magnitudes at low stimulus levels did not allow a proper fit of the two-slope model. The data indicate, however, a loss of compression at the impaired frequencies.

ASSR growth functions at higher supra-threshold levels and shallow modulations showed a large variability across young subjects with normal audiograms. Figure 3 showed that, in some NH subjects, ASSR growth functions at shallower modulations are reduced, in line with the initial hypothesis. At higher input levels, the rate-intensity function of high-SR fibers saturate, whereas it increases with level for the low-SR fibers (Liberman, 1978). Considering that deafferentation is more predominant in low-SR fibers (Furman *et al.*, 2013), the reduction in ASSR magnitude at these higher levels might be connected to the inability of the ANF to code the intensity fluctuations.

In addition to the use of ASSR to estimate thresholds, it is suggested here that the slope of ASSR level growth functions at low supra-threshold levels can be used to estimate peripheral compression at different frequencies simultaneously both in NH and HI listeners. It is also hypothesized that ASSR growth functions at higher stimulation levels, using shallow modulations, reflect the integrity of ANFs in special low-SR fibers, which can lead to a potential tool to evaluate individuals suffering from deafferentation.

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