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The association between hearing impairment and neural envelope encoding at different ages

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ABSTRACT

Hearing impairment goes with speech perception difficulties, presumably not only because of poor hearing sensitivity but also because of altered central auditory processing. Critical herein is temporal processing of the speech envelope, mediated by synchronization of neural activity to the envelope modulations. It has been suggested that hearing impairment is associated with enhanced sensitivity to envelope modulations which, in turn, relates to poorer speech perception. To verify this hypothesis, we performed a comparative electrophysiological study in hearing-impaired (HI) and normal-hearing (NH) human listeners of three age groups, investigating neural envelope encoding. HI young and middle-aged adults showed enhanced neural synchronization to envelope modulations relative to NH controls, particularly when stimulus audibility was corrected for. At an older age, the degree of neural synchronization was similar for HI and NH persons, yet HI persons showed a synchronization asymmetry toward the right hemisphere. This study demonstrates that hearing impairment is characterized by changes in the neural encoding of envelope modulations, the nature of which varies with age.

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1. Introduction

Good speech perception skills are vital for communication and social integration. Hearing impairment, however, greatly degrades speech perception (e.g., Peters et al., 1998; Souza and Turner, 1994). Worldwide, 360 million persons (5.3% of the world's population) suffer from moderate or greater degrees of hearing impairment and the prevalence of hearing impairment increases with advancing age (World Health Organization, 2012). According to the International Organization for Standardization (2017), 30% of persons aged 50 years or younger have hearing impairment, and at the age of 60 and 70 years, this prevalence increases up to 50% and 90%, respectively.

The poor hearing sensitivity (thresholds) of hearing-impaired (HI) persons explains only a part of the inferior speech perception: when correcting for differences in hearing sensitivity between normal-hearing (NH) and HI persons, speech understanding is still worse for HI individuals (Eisenberg et al., 1995; George et al., 2006; Peters et al., 1998; Summers and Molis, 2004). It has been suggested that altered central auditory processing (suprathreshold), and temporal processing in particular, also accounts for the poor speech

perception of HI individuals (Bernstein et al., 2013; Noordhoek et al., 2001). A central contribution to impaired speech perception is not unexpected, as numerous functional and structural changes emerge in the central auditory system throughout adult life, for example, changes in neural inhibition (e.g., Caspary et al., 2008) and in cortical thickness (e.g., Fjell et al., 2009). Moreover, evidence exists that such central changes are related to speech perception performance (Bilodeau-Mercure et al., 2015; Giroud et al., 2018).

Temporal processing plays a key role in speech perception. After all, speech sounds are characterized by a slowly varying amplitude and a rapidly varying temporal fine structure (TFS) (e.g., Moore, 2014). Such acoustic modulations are encoded in the central auditory system through synchronized activity of neural oscillations: in response to an auditory input, neural oscillations in the human brain, that is, delta ($<$4 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), and gamma ($>$30 Hz) oscillations, synchronize to acoustic modulations corresponding to their characteristic frequency (Lopes da Silva, 2013; Peelle and Davis, 2012; Wang et al., 2005). It has been demonstrated that the entire central auditory system is responsive to any modulation frequency, yet cortical and subcortical auditory neurons show to be most responsive to, respectively, low-frequency ($<$30 Hz) and higher-frequency modulations (Coffey et al., 2016; Giraud et al., 2000; Herdman et al., 2002; Joris et al., 2004). Another interesting feature of synchronized neural activity concerns a functional hemispheric asymmetry: neurons in the right hemisphere (RH) preferentially

synchronize to low-frequency acoustic modulations, while the left hemisphere (LH) mainly processes rapid acoustic modulations (Boemio et al., 2005; Poeppel, 2003).

Both behavioral and neuroimaging research have demonstrated that the speech envelope, that is, the slowly fluctuating overall amplitude of continuous speech, is a crucial temporal speech feature. Drullman et al. (1994) showed that speech intelligibility is greatly degraded when the low-frequency speech envelope modulations are removed. In addition, Shannon et al. (1995) observed nearly perfect intelligibility of speech when its spectral information was reduced, on the condition that the speech envelope was preserved. Likewise, electrophysiological studies showed that neural synchronization to the speech envelope is a prerequisite for speech understanding (Ahissar et al., 2001; Doelling et al., 2014; Peelle and Davis, 2012). Given the importance of the speech envelope, it seems likely that speech perception difficulties in HI persons can be attributed, at least in part, to changes in temporal envelope processing. Note that we use the term "HI" throughout this article to denote people who are diagnosed with peripheral hearing impairment as indicated by the audiogram, independent of altered central auditory processing.

Several behavioral studies have reported lower amplitude modulation detection thresholds, that is, better detection of envelope modulations, for HI compared to NH listeners (Ernst and Moore, 2012; Moore et al., 1996; Sek et al., 2015; Wallaert et al., 2017). Other studies, however, found amplitude modulation detection thresholds to be similar among NH and HI individuals (Grose et al., 2016; Moore and Glasberg, 2001). This behavioral discrepancy can be attributed to stimulus audibility. In fact, better detection of envelope modulations for HI relative to NH persons, is only observed when stimulus audibility is corrected for, that is, when the stimulus level is increased for HI participants (Bacon and Gleitman, 1992; Schlittenlacher and Moore, 2016). Interestingly, when envelope modulations are perceptually enhanced, NH listeners show worse speech perception, especially when the speech is masked by background noise (Moore et al., 1995; Moore and Glasberg, 1993). This indicates that enhanced envelope processing is related to poorer speech perception, which may be explained by a processing imbalance between envelope and TFS cues. In effect, processing of the TFS, next to the speech envelope is crucial for speech perception, especially when the speech is masked by background noise (Hopkins and Moore, 2009; Lorenzi et al., 2006). Moore and Glasberg (1993) and Moore et al. (1995) found envelope enhancement to be negatively correlated with the perception of masked speech for a NH population. Based on research demonstrating brain plasticity with hearing impairment (e.g., Neuman, 2005), caution should, however, be taken when generalizing these findings to HI people.

In agreement with behavioral research, electrophysiological studies in animals have shown that hearing impairment coincides with increased neural synchronization to acoustic envelope modulations in subcortical structures, that is, in the auditory nerve fibers (Henry et al., 2014; Kale and Heinz, 2010, 2012) and in the midbrain (Zhong et al., 2014). To date, only a few studies have investigated the association between hearing impairment and neural envelope encoding in the human brain. Millman et al. (2017) compared neural synchronization to envelope modulations in the auditory cortex between HI and NH similarly aged persons ($\sim$60 years). To control for stimulus audibility, the stimulus was amplified for the HI participants. Increased synchronized neural activity was detected in the auditory cortex of HI relative to NH adults. Anderson et al. (2013) looked into brainstem neural synchronization in NH and HI adults who were on average 64 years old. The HI participants exhibited higher-than-normal neural envelope encoding, whether or not amplification was applied. Ananthakrishnan et al. (2016) did not find neural envelope encoding in the brainstem to be enhanced in HI

persons between 21 and 71 years of age ($\sim$50 years). Importantly, Ananthakrishnan et al. (2016) detected a similar increase in neural synchronization with stimulus level among NH and HI adults, and they therefore concluded that stimulus audibility should be taken into account when comparing neural envelope encoding between persons with different hearing sensitivity. This notion fits with the observed interplay between stimulus audibility and behavioral sensitivity to envelope modulations (Bacon and Gleitman, 1992; Schlittenlacher and Moore, 2016).

The observed negative correlation between envelope processing and speech perception performance for NH adults (Moore et al., 1995; Moore and Glasberg, 1993) has raised the idea that speech perception difficulties may be associated with enhanced neural envelope encoding. Recent studies support this idea and, even more, indicate that such neural-behavioral association applies to both NH and HI people. Millman et al. (2017) found that enhanced neural synchronization to acoustic envelope modulations recorded from the left auditory cortex was predictive of worse speech perception for a middle-aged group ($\sim$60 years) consisting of both NH and HI listeners. Goossens et al. (2018) included young (20–30 years), middle-aged (50–60 years), and older (70–80 years) NH and HI adults and demonstrated that enhanced neural envelope encoding in the auditory cortex and in the brainstem, respectively, corresponded to poorer speech perception for NH and HI adults, irrespective of age.

As for the previously mentioned hemispheric asymmetry in neural envelope encoding, that is, the differential temporal sensitivity of the LH and RH, it has been documented that this is a prerequisite for good speech processing (for a review, see Specht, 2014). In addition, evidence exists that different hemispheric processing patterns relate to different speech perception abilities. Bellis et al. (2000) demonstrated that persons who performed well on a syllable discrimination task showed an LH processing asymmetry for the syllables, whereas a symmetrical processing pattern was observed for listeners who performed poorly on the discrimination task. Hämäläinen et al. (2012) compared the neural encoding of 2 Hz envelope modulations between typical readers and persons diagnosed with dyslexia, which is a reading and spelling disorder that has been related to inefficient speech processing. The first group exhibited an RH asymmetry, whereas no such hemispheric asymmetry was observed in the latter group. These studies—showing a correlation between speech processing and functional hemispheric asymmetry—raise the question whether hearing impairment interferes with functional hemispheric asymmetry. This has thus far not been explored.

Another unexplored aspect of neural envelope encoding concerns potential age-related variations. Neuroimaging studies in humans have been restricted to HI adults who are around 50–60 years of age. As aging is accompanied by changes in the degree and hemispheric asymmetry of neural envelope encoding (Anderson et al., 2012; Goossens et al., 2016), the association between hearing impairment and neural envelope encoding may very well vary with age. This remains to be investigated.

In sum, an important lack of knowledge exists on neural envelope encoding in the HI human brain. Yet, such is needed for developing advanced intervention strategies for remediating impaired speech perception. To address this need, we performed a comparative study in HI and NH adults belonging to three age groups (young, middle-aged, and older). While taking stimulus audibility into account, we investigated the degree as well as the hemispheric asymmetry of neural envelope encoding by measuring different neural responses of which the main sources are known to be located in different regions along the auditory pathway (i.e., from the brainstem up to the cortex).

In line with the electrophysiological research concerning HI subjects and reported correspondences between neural envelope encoding and speech perception discussed previously, we

hypothesized that HI human listeners would show enhanced neural envelope encoding compared to NH controls in both subcortical and cortical auditory regions. In the same vein, we presumed that HI and NH people would differ in functional hemispheric asymmetry. Moreover, hearing-related changes in neural envelope encoding were expected to be most evident when stimulus levels were adjusted for HI listeners, that is, when correcting for stimulus audibility. Finally, as neural envelope encoding changes with age, we postulated that hearing impairment would differentially affect neural envelope encoding at different ages throughout adult life.

2. Materials and methods

2.1. Participants

We recruited young (20—30 years), middle-aged (50—60 years), and older (70—80 years) adults who were either NH or HI (Table 1, Fig. 1). HI adults and their NH controls belonged to a narrow age cohort, spanning one decade.

Only persons who showed symmetrical hearing, consistent with the criteria of the audiogram classification system (Margolis and Saly, 2008), were eligible for participation. A person was classified as NH when he/she had audiometric thresholds within normal limits, that is, ≤25 dB HL (International Organization for Standardization, 1998), at all octave frequencies from 125 Hz up to 4 kHz. HI participants had audiometric thresholds ≥35 dB HL from 1 kHz onward. All hearing losses were sensorineural in nature (air-bone gaps ≤10 dB HL). The three age groups did differ in the etiology of their hearing impairment. Young participants suffered from congenital hearing loss or hearing impairment after severe/chronic otitis, middle-aged adults had a family history of hearing loss, manifesting either before or after the age of 40 years, and all older persons were diagnosed with age-related hearing loss, that is, presbycusis. Except for two HI young participants, all HI participants were hearing aid users (bilateral).

Because cognitive deficiencies are known to alter neural processing (Bidelman et al., 2017), only individuals who showed no indication of cognitive impairment were included: all participants scored at or above the cutoff score of 26/30 on the Montreal Cognitive Assessment (Nasreddine et al., 2005). All participants were Dutch native speakers, they were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and they had no medical history of brain injury, neurological disorders, or tinnitus.

The study was approved by the Medical Ethical Committee of the University Hospitals and University of Leuven (approval number B322201214866). All participants gave their written informed consent.

2.2. Auditory steady-state responses

We measured auditory steady-state responses (ASSRs) to acoustic amplitude modulations, reflecting the degree of neural envelope encoding: larger ASSRs reflect a higher degree of neural synchronization (for a review on ASSRs, see Rance, 2008). The stimuli and procedures for EEG recording, EEG processing, and ASSR evaluation were adopted from our previous study. An overview is given below. Detailed information can be retrieved from the study by Goossens et al. (2016).

2.2.1. Stimuli

The acoustic stimulation setup was controlled by a laptop running a custom-made software platform. Octave bands of white noise centered at 1 kHz were presented with ER-3A insert phones. The noise, generated in MATLAB (the Mathworks Inc), was 100% sinusoidally amplitude modulated at 4, 20, 40, or 80 Hz, representing theta, beta, low gamma, and high gamma frequencies, respectively (Fig. 2). ASSRs are composite responses, reflecting both cortical and subcortical neural activity, yet ASSRs to specific modulation frequencies originate primarily from specific auditory regions. Various neuroimaging studies indicate that the 4, 20, 40, and 80 Hz ASSR included in the present study predominantly originate from the auditory cortex, thalamus, thalamus/upper brainstem, and brainstem, respectively (Herdman et al., 2002; Luke et al., 2017; Wang et al., 2012). Every modulation frequency was presented to the left ear (L), to the right ear (R), and to both ears simultaneously, that is, bilaterally (BI). We implemented different sides of stimulus presentation to verify whether functional hemispheric asymmetry depended on the side of stimulation, as indicated by previous research (Poelmans et al., 2012). It was also a way to evaluate the robustness of hearing-related differences: a difference that was found for all three sides of stimulation, was considered as highly robust. For NH participants, the stimulus level was set to 70 dB SPL, which they rated as comfortably loud (graphic rating scale). To control for differences in stimulus audibility among NH and HI listeners—no hearing aids were used during EEG recording—the presentation level of the modulated noises for HI participants was individually determined. Every HI participant was asked to adjust the level of the stimulus until he/she perceived it as comfortably loud, similar to the NH participants. In this way, the stimuli could be presented to all participants at equal loudness levels. The reason for using equal loudness levels to control for stimulus audibility instead of equal sensation levels is 2-fold. First, the sensation level of the 70 dB SPL stimulus equaled 65 dB SPL for the NH participants. This would have implied presenting the stimuli at ~108 dB SPL to the HI participants, thereby exceeding their uncomfortable loudness level (~103 dB SPL). Second, it has been demonstrated that the magnitude of the ASSR is highly correlated with the perceived loudness of the stimulus (Emara and Kolkaila, 2010; Ménard et al., 2008; Van Eeckhoutte et al., 2016). As such, using equal loudness levels is a way to prevent changes in ASSR magnitude between NH and HI listeners to result from the stimulus presentation level. In addition to equal loudness levels, the acoustic modulations were also presented to the HI adults at equal SPL, that is, 70 dB SPL. By using equal loudness levels as well as equal SPL, we could verify whether the relation between hearing impairment and neural envelope encoding depended on stimulus audibility. To reduce testing time, equal SPL conditions were restricted to L stimulus presentation.

Stimulus level calibrations were performed with a Brüel and Kjær type 2260 sound level meter, a 1-inch pressure-field microphone type 4144 and an artificial ear type 4152 (2 cc coupler).

2.2.2. EEG recording

EEG recordings were made in a double-walled soundproof booth with Faraday cage. Participants lay down on a bed and watched a muted, subtitled movie. Each recording, that is, for each stimulus condition (e.g., 4 Hz BI), lasted for 300 seconds. EEG signals were

Table 1
Number of people (women/men) and mean age ± standard deviation (SD), expressed in years, of the six participant groups

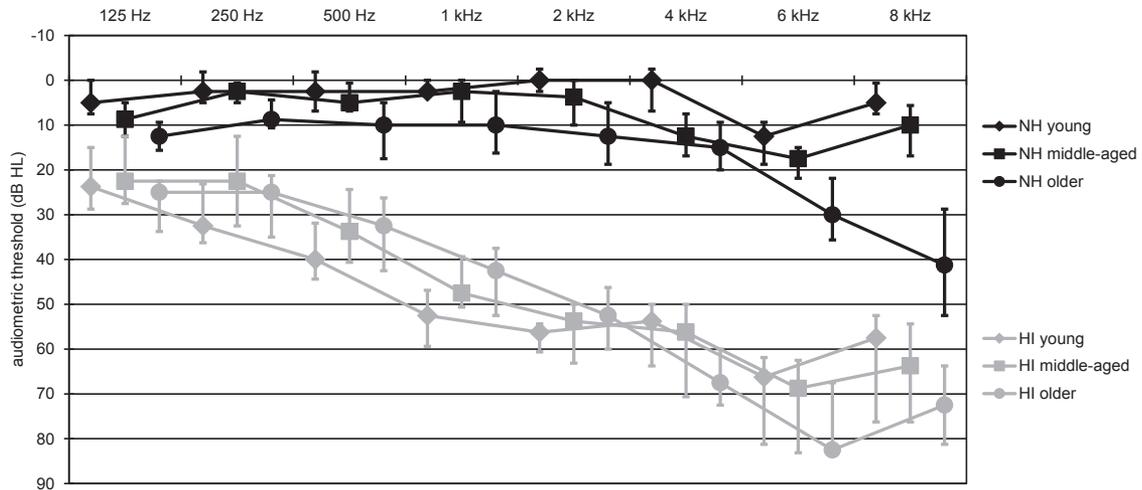|	Young		Middle-aged		Older	
	NH	HI	NH	HI	NH	HI
Number	20 (11/9)	10 (6/4)	20 (10/10)	14 (10/4)	14 (10/4)	13 (8/5)
Mean age ± SD	22 ± 1	27 ± 5	53 ± 2	57 ± 2	74 ± 3	78 ± 3

Fig. 1. Median audiometric thresholds (dB HL) of NH (black) and HI (gray) participants, averaged across both ears. Thresholds are illustrated by diamonds, squares, and circles for young, middle-aged, and older persons, respectively. Error bars indicate the interquartile range. Abbreviations: HI, hearing-impaired; NH, normal-hearing.

recorded with the ActiveTwo system (BioSemi B.V.) including 64 active pin-type electrodes that were mounted in a head cap (Fig. 2). ActiView software was used to display the EEG signal on screen and store it on hard disk.

2.2.3. EEG processing

Every EEG recording was segmented into epochs of 1.024 seconds, each including an integer number of 4, 20, 40, or 80 Hz modulation cycles (John and Picton, 2000). Artifact rejection was applied with BESA Research 5.3 software (BESA GmbH). The first 256 artifact-free epochs were imported into MATLAB, referenced to Cz and chunked into four sweeps of 64 epochs. The sweeps were averaged in the time domain, thereby reducing the noise in the EEG signal (John et al., 1998). The average EEG time signal was converted into the frequency domain through a Fast Fourier Transform. In the resulting spectrum, the ASSR was represented by a spectral peak in the frequency bin corresponding to the presented acoustic modulation frequency (Fig. 2).

2.2.4. ASSR evaluation

The neural responses recorded by eight posterior electrode pairs were retained for further analyses (Fig. 2). This electrode selection was adopted from our previous study showing that these electrodes were most sensitive to the neural responses under investigation (Goossens et al., 2016).

The magnitude of the ASSR, reflecting the degree of neural synchronization to the acoustic envelope modulations, can be investigated by the signal-to-noise ratio (SNR) (Eq. 1) or the amplitude (Eq. 2) of the neural response, calculated per hemisphere, that is, across the eight electrodes selected in each hemisphere.

$$SNR \ (dB) \ = \ 10 \times \log_{10} \frac{\sum_{i=1}^{8} \frac{P_{(S+N)_i}}{P_{N_i}}}{8} \tag{1}$$

$$amplitude \ (dB) \ = \ 20 \times \log_{10} \sqrt{\frac{\sum_{i=1}^{8} P_{(S+N)_i}}{8}} \tag{2}$$

P_{S+N} denotes the power of the Fourier component in the modulation frequency bin, including both the synchronized neural response (S) and the induced EEG noise (N). Induced EEG noise refers to random, non-synchronized neural activity during exposure to the acoustic modulations. We used the F test to compare P_{S+N} to P_N (Dobie and Wilson, 1996). A significant ASSR was detected when the power in the modulation frequency bin was ≥3.03 times higher than the power of the induced EEG noise, that is, SNR ≥4.8 dB ($10 \times \log_{10} 3.03$).

In addition to the degree of neural synchronization, we examined functional hemispheric asymmetry, that is, the relative degree
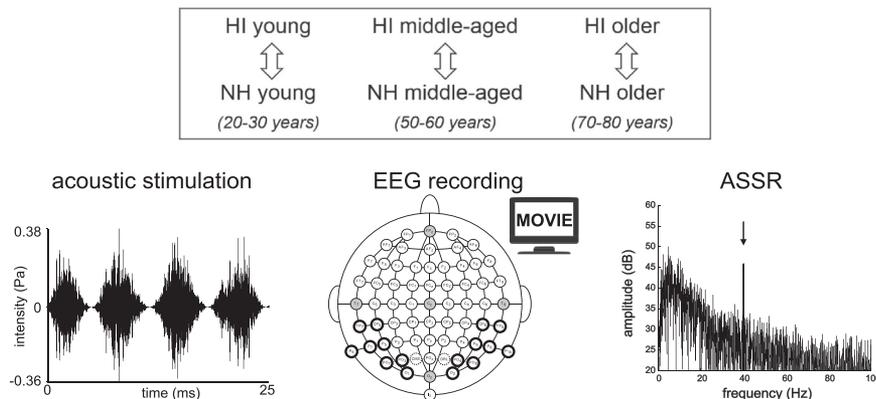

Fig. 2. Overview of the research design of the present study. Abbreviations: ASSR, auditory steady-state response; HI, hearing-impaired; NH, normal-hearing.

of neural synchronization across hemispheres. Hemispheric asymmetry was defined by three laterality categories: LH, RH, and SYM. For each modulation frequency (4, 20, 40, 80 Hz), per side of stimulus presentation (L, R, BI), every participant was classified into a laterality category. When a significant ASSR was only detected in the LH or RH, the participant was classified into the respective category. If the participant exhibited a significant ASSR in both hemispheres, a laterality index (LI) was calculated (Eq. 3).

$$LI = \frac{RMS\sqrt{P_{S+N_{RH}}} - RMS\sqrt{P_{S+N_{LH}}}}{RMS\sqrt{P_{S+N_{RH}}} + RMS\sqrt{P_{S+N_{LH}}}} \quad (3)$$

This LI represented the difference between the root mean square response amplitude of the electrode selection in the RH and the LH, normalized by the sum of the hemispheric response amplitudes. The LI could take on any value between −1 and +1: a negative and positive LI denoted lateralization to the LH and RH, respectively. If the absolute value of a person's LI exceeded the 25th percentile of the median LI among all participants, the hemispheric asymmetry was considered to be strong and the subject was assigned a LH (LI < 0) or RH (LI > 0) asymmetry. LIs below the 25th percentile were regarded as reflecting a negligible hemispheric asymmetry (SYM). This category assignment procedure was adopted from other studies on hemispheric asymmetry (Pujol et al., 1999).

2.2.5. Statistical analyses

All statistical analyses were performed with SPSS Statistics software (IBM Corp). The association between hearing impairment and the degree of neural synchronization was investigated by comparing SNRs and response amplitudes between HI young, middle-aged, and older adults and their NH controls (Fig. 2). Shapiro-Wilk testing was conducted to assess the distributions of the SNR and response amplitude. When deviations from the normal distribution were detected, nonparametric analyses were performed to verify the parametric statistics. Because parametric and nonparametric statistics yielded the same results, we only report parametric testing. For each modulation frequency (4, 20, 40, 80 Hz), we conducted a factorial mixed ANOVA with either the SNR (dB) or the response amplitude (dB) as the dependent variable, and hearing status (NH, HI) and age group (young, middle-aged, older) as the between-subject variables. For ASSRs to acoustic modulations presented at equal loudness levels, hemisphere (LH, RH) and side of stimulation (L, R, BI) were the within-subject variables. For ASSRs to the modulations presented at equal SPL, hemisphere (LH, RH) was the sole within-subject variable because only L stimulus presentation was applied. All analyses were 2-tailed ($\alpha = 0.05$). Mauchly's statistics determined whether or not a correction to the degrees of freedom had to be applied for examining within-subject effects. Post hoc comparisons were based on the conservative Bonferroni procedure.

As for the functional hemispheric asymmetry, we conducted binomial tests to identify significant hemispheric asymmetries, which, in turn, could be compared between HI and NH participants to examine the relationship between hearing impairment and hemispheric asymmetry. To correct for the multiple binomial testing, a corrected α level of 0.01 was applied. Per participant group, two binomial tests were performed for each stimulus condition (e.g., 4 Hz BI), yielding the exact probability of the observed number of participants in a certain laterality category under the null hypothesis that there was an equal number of participants in the two categories under investigation, for example, LH versus RH and LH versus SYM. A significant LH asymmetry was assigned to a participant group when significantly more subjects were classified into the category LH compared to both the categories RH and SYM (p of both binomial tests < 0.01). Similar criteria applied to the

assignment of a RH asymmetry or SYM processing. If no significant deviation from an equal distribution across laterality categories was detected, no significant hemispheric asymmetry (LH, RH) or SYM processing was assigned to the participant group.

3. Results

3.1. Degree of neural synchronization

When presenting the acoustic envelope modulations at equal loudness levels, thereby correcting for stimulus audibility (Fig. 3), the following effects were observed. First, we found a significant interaction between hearing status, age group, and hemisphere for the degree of theta synchronization, reflected by the magnitude of the 4 Hz SNR ($F(2,83) = 3.21$, $p = 0.045$). HI young adults showed higher 4 Hz SNRs than NH young listeners, particularly in the LH (4 Hz LH: mean difference [MD] = 3.6 dB, $p = 0.009$; 4 Hz RH: MD = 2.8 dB, $p = 0.051$). HI middle-aged participants also exhibited higher 4 Hz SNRs than their NH counterparts, and this was significant for both hemispheres (4 Hz LH: MD = 3.2 dB, $p = 0.012$; 4 Hz RH: MD = 3.0 dB, $p = 0.022$). HI older individuals, on the contrary, showed similar 4 Hz SNRs as NH older persons (4 Hz LH: MD = 0.9 dB, $p = 0.52$; 4 Hz RH: MD = 0.4 dB, $p = 0.79$). As for the 20 and 40 Hz SNRs, these did not differ significantly between HI and NH listeners for any of the three age groups (all $p > 0.05$). For the 40 Hz SNR, there was a significant interaction between hearing status, age group, hemisphere, and side of stimulation ($F(4,166) = 2.84$, $p = 0.026$). Post hoc comparisons demonstrated that HI and NH older participants differed in the relative degree of synchronization to 40 Hz modulations across hemispheres: HI older persons showed higher 40 Hz SNRs in the RH than in the LH for the three sides of stimulation (L, R, BI: MD = 2.2 dB, 1.6 dB, 1.6 dB, all $p < 0.005$), whereas NH older adults exhibited equally high 40 Hz SNRs in both hemispheres (L, R, BI: MD = 0 dB, 0.5 dB, 0.2 dB, all $p > 0.3$). Finally, for the degree of high gamma synchronization, reflected by the 80 Hz SNR, we found a significant interaction between hearing status and age group ($F(2,84) = 4.07$, $p = 0.021$). Young and middle-aged HI adults showed higher 80 Hz SNRs than their NH controls (young: MD = 5.6 dB, $p < 0.001$; middle-aged: MD = 5.1 dB, $p < 0.001$), whereas similar 80 Hz SNRs were observed for HI and NH older listeners (MD = 0.5 dB, $p = 0.72$).

When using the response amplitude as a measure of the ASSR magnitude, statistical analyses identified the same hearing-related differences as outlined before. The one exception to this concerned the 40 Hz ASSR. In contrast to the SNR, the amplitude did reveal hearing-related differences in the degree of synchronization to 40 Hz modulations for the young and middle-aged groups (Fig. 3). For the amplitude of the 40 Hz ASSR, we found a significant interaction between hearing status, age group, hemisphere, and side of stimulation ($F(3.45,143.19) = 4.24$, $p = 0.005$). Compared to NH young adults, HI young participants showed higher 40 Hz amplitudes in the LH when the 40 Hz modulations were presented to the left ear (L) (MD = 3.1 dB, $p = 0.032$) and in the RH in the case of right ear (R) stimulus presentation (MD = 2.7 dB, $p = 0.038$). HI middle-aged adults showed higher 40 Hz amplitudes than NH middle-aged adults in both hemispheres for unilateral stimulus presentations (L LH, R LH, L RH, R RH: MD = 4.1 dB, 3.5 dB, 3.9 dB, 3.6 dB, all $p < 0.01$). For the older group, no significant differences in 40 Hz amplitudes were found between HI and NH listeners (all $p > 0.18$).

When presenting the acoustic modulations at equal SPL (70 dB SPL), that is, audibility was not corrected for, the SNR and amplitude analyses yielded the same results, without exception. We will therefore only report the outcomes of the SNR analysis. Note that, to reduce testing time, ASSR recordings at equal SPL were limited to L stimulus presentation. In contrast to the equal loudness level
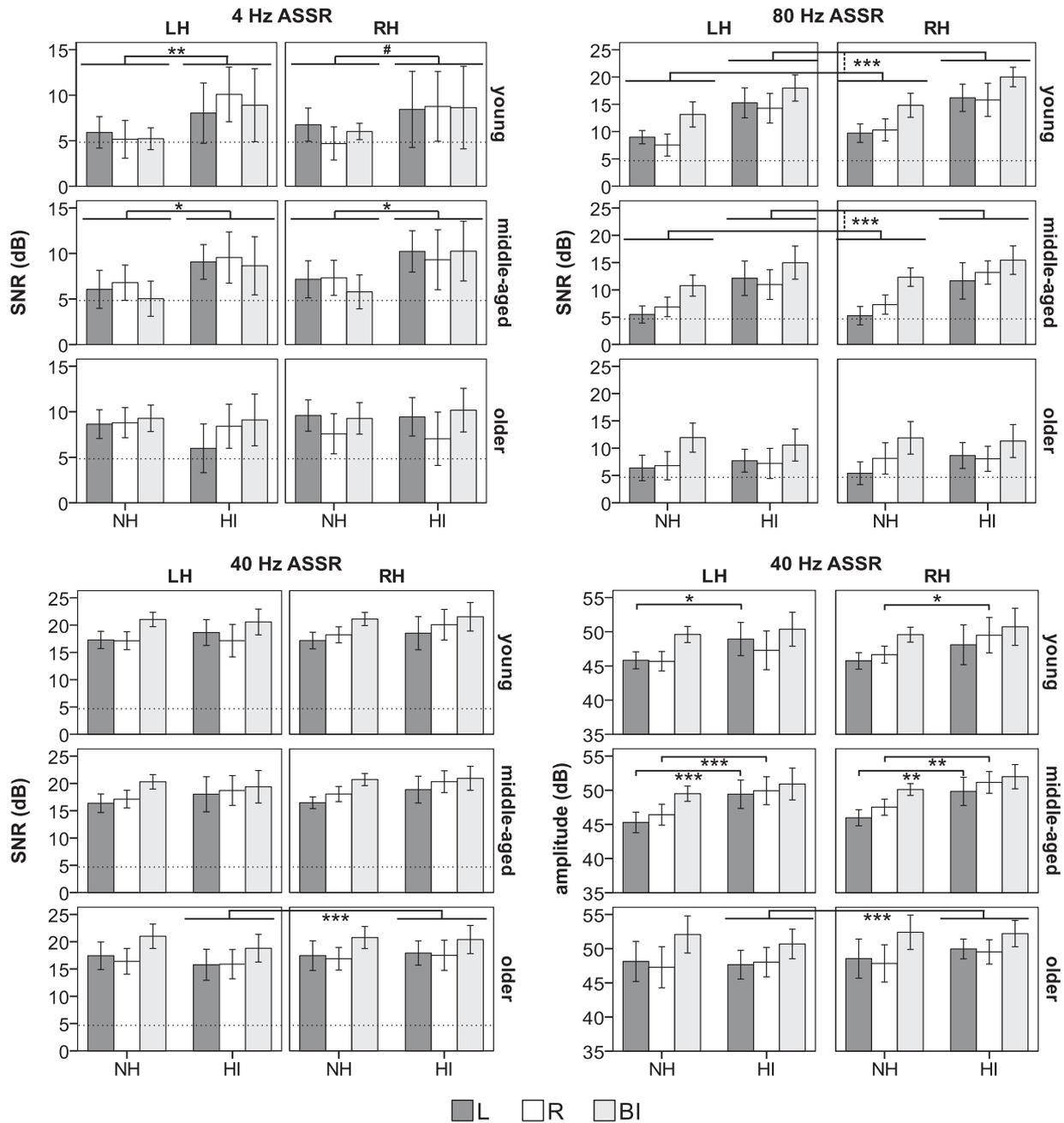
Fig. 3. Overview of the significant differences in degree of neural synchronization when presenting the acoustic modulations at equal loudness levels. The 4 and 80 Hz SNRs are shown in the top panels. The 40 Hz SNR and 40 Hz amplitude are displayed in the bottom panels. 20 Hz ASSRs are not displayed, as no significant effects were found for this frequency. The dotted line in the SNR figures indicates the significance cutoff, that is, 4.8 dB SNR. In each panel, age groups (young, middle-aged, older) are displayed per row and hemispheres per column (LH, RH). The bars are clustered per hearing status (NH, HI) and represent the mean ASSR magnitude per side of stimulation, that is, left ear (L) (dark fill), right ear (R) (no fill), and bilaterally (BI) (gray fill). Error bars indicate the 95% confidence interval. $0.05 < {}^{\#}p < 0.06$; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$. The explanation for the discrepant findings between the SNR and amplitude of the 40 Hz ASSR resides in the induced EEG noise. HI young and middle-aged persons exhibited more induced EEG noise at 40 Hz than NH controls (both $p < 0.05$) and more 40 Hz noise correlated with lower 40 Hz SNRs ($r_{\text{SNR noise}} = -0.40$, $p = 0.047$). When this correlation was controlled for, the 40 Hz SNR of young and middle-aged adults increased significantly with increasing PTA$_{125 \text{ Hz}-8 \text{ kHz}}$ ($r_{\text{PTA (SNR.noise)}} = 0.47$, $p = 0.013$), similarly to the hearing-related increase in the 40 Hz amplitude ($r_{\text{PTA ampl}} = 0.50$, $p = 0.016$). Abbreviations: ASSR, auditory steady-state response; LH, left hemisphere; RH, right hemisphere; HI, hearing-impaired; NH, normal-hearing; SNR, signal-to-noise ratio.

conditions (Fig. 3), no differences in degree of neural synchronization to 4 and 40 Hz modulations were detected between HI and NH adults for any of the three age groups (all $p > 0.05$) (Fig. 4). For the 80 Hz synchronization, we found a significant interaction between hearing status and age group ($F(2,83) = 3.08$, $p = 0.05$). Enhanced synchronization to 80 Hz modulations, reflected by higher 80 Hz SNRs, was detected for HI young and middle-aged

adults, but not for HI older participants (young: MD = 3.6 dB, $p = 0.016$; middle-aged: MD = 4.6 dB, $p < 0.001$; older: MD = 0 dB, $p = 1.00$).

It is to be noted that the effects of hearing status, except for the 40 Hz amplitude, showed no interaction with side of stimulation. Hence, the observed hearing-related differences in the degree of neural synchronization were considered to be robust.

3.2. Hemispheric asymmetry

When a significant majority of participants of a certain group were classified into the laterality category LH, RH, or symmetrical (SYM) (see Section 2.2.5), this group was considered to show a significant hemispheric asymmetry (Table 2). For a specific modulation frequency, the observed hemispheric asymmetry was not overall significant for the three sides of stimulation, which agrees with previous research (Poelmans et al., 2012). A number of differences in hemispheric asymmetry were found between HI adults and NH controls, but the RH asymmetry for 40 Hz modulations for HI older adults compared to NH older persons who showed no significant asymmetry, was most striking because of two reasons. First, the difference in hemispheric asymmetry for 40 Hz modulations in the older cohort was the only one apparent for the three sides of stimulation. Second, the analysis on the degree of neural synchronization only revealed a significant hearing-hemisphere interaction for the 40 Hz ASSR in the older cohort: HI older persons exhibited larger 40 Hz ASSRs in the RH compared to the LH, while NH older adults showed equivalent ASSRs in both hemispheres (Fig. 3).

When presenting the stimuli at equal SPL (70 dB SPL), the difference in 40 Hz hemispheric asymmetry between HI and NH older adults remained (Table 2).

4. Discussion

The aim of the present study was to characterize changes in neural envelope encoding related to hearing impairment in persons of different ages. By recording ASSRs to different modulation frequencies, that is, 4, 20, 40, and 80 Hz, we indirectly measured neural envelope encoding from the brainstem up to the cortex. We investigated the degree as well as the hemispheric asymmetry of neural envelope encoding. Adults belonging to three age groups
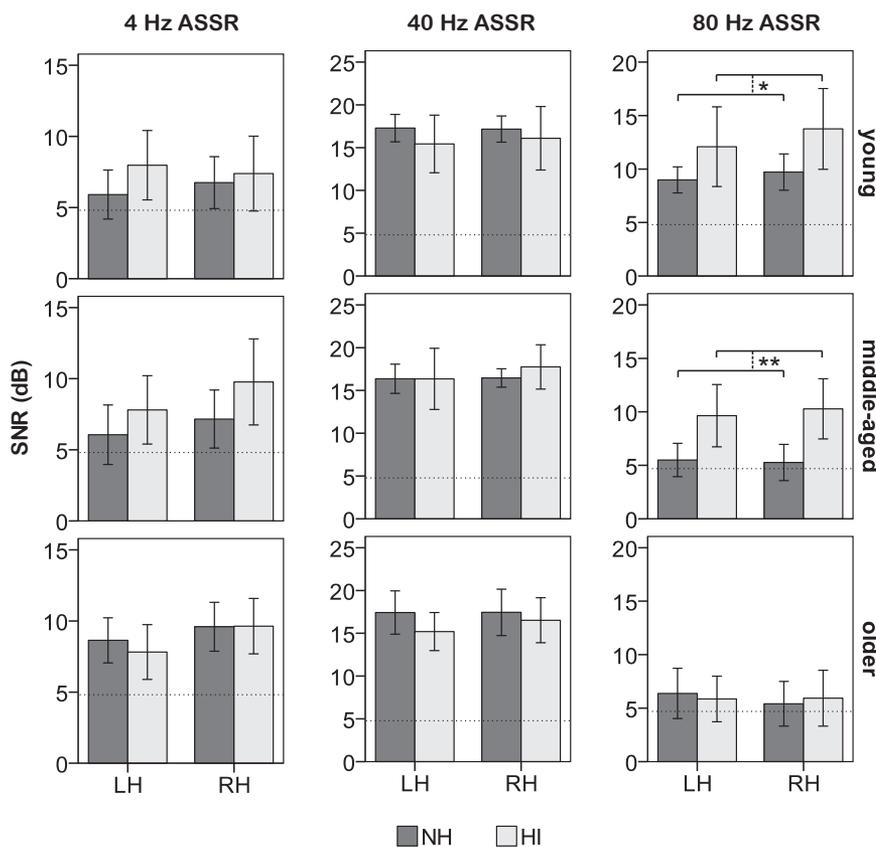
Table 2
Overview of the laterality categories (LH, RH, and SYM) into which a significant majority of participants of a particular group (NH/HI young, middle-aged, older) were classified for each acoustic envelope modulation (4, 20, 40, 80 Hz) per side of stimulus presentation (L, R, BI) when presenting the stimuli at equal loudness levels

Modulation frequency	Side of stimulation	Young		Middle-aged		Older	
		NH	HI	NH	HI	NH	HI
4 Hz	L			RH*			RH
	R	LH					
	BI				RH		
20 Hz	L						
	R						
	BI						
40 Hz	L						RH*
	R	RH	RH				RH
	BI						RH
80 Hz	L						
	R	RH			RH	RH	
	BI	RH			RH		

If no category is reported, the distribution among the three categories was similar. An asterisk indicates that the hemispheric asymmetry was observed in the equal loudness level as well as in the equal SPL (L only) condition.

Fig. 4. Overview of the degree of neural synchronization to the 4, 40, and 80 Hz acoustic envelope modulations presented at equal SPL (70 dB SPL), expressed in SNR (dB). Because equal SPL conditions were restricted to L stimulus presentation, no distinction is made between side of stimulation. Similarly to the equal loudness conditions (Fig. 3), no significant effects were observed for the 20 Hz ASSR, hence this ASSR is not shown. Amplitudes are not shown either, because they yielded the same results as the SNRs. The dotted line indicates the significance cutoff, that is, 4.8 dB SNR. Age groups (young, middle-aged, older) are displayed per row. The bars are clustered per hemisphere (LH, RH) and represent the mean ASSR magnitude per hearing status, that is, NH (dark fill) and HI (gray fill). Error bars indicate the 95% confidence interval. $*p \leq 0.05$; $**p \leq 0.01$. Abbreviations: ASSR, auditory steady-state response; LH, left hemisphere; RH, right hemisphere; HI, hearing-impaired; NH, normal-hearing; SNR, signal-to-noise ratio.

were tested to examine whether associations between hearing impairment and neural envelope differed between different age groups. In addition, the acoustic modulations were presented at equal loudness levels and at equal SPL to look into the effect of stimulus audibility.

Our data show that, when stimulus audibility is corrected for, neural synchronization in both subcortical and cortical auditory regions is significantly enhanced in young and middle-aged HI adults. When audibility is not corrected for, the enhancement is only observed in the brainstem. Interestingly, older HI adults do not show changes in the degree of neural synchronization relative to NH controls; however, they present with a significant synchronization asymmetry toward the RH.

The enhanced neural synchronization in the brainstem of HI young and middle-aged adults is in agreement with observations in animal models (Henry et al., 2014; Kale and Heinz, 2010, 2012; Zhong et al., 2014) and with the study on middle-aged human listeners of Anderson et al. (2013). In addition to confirming that the degree of neural envelope encoding in the brainstem is independent of stimulus audibility, we extend the findings of Anderson et al. (2013) by showing that increased subcortical neural synchronization is also present in HI young adults, although not in HI older individuals.

Our observation of enhanced neural synchronization in the auditory cortex is in accordance with the study of Millman et al. (2017). They tested NH and HI persons who were ~60 years of age and amplified the stimuli for the HI participants. Note that this setup did not allow them to investigate variations related to age or stimulus audibility, whereas our setup did allow for this detailed examination. In fact, we demonstrate that, similar to middle-aged HI adults, young HI adults exhibit enhanced neural synchronization in the auditory cortex, and that no such enhancement is found for older HI persons. In addition, our data show an interplay between stimulus audibility and cortical neural synchronization. When correcting for stimulus audibility, HI young and middle-aged listeners show more neural synchronization in the auditory cortex, relative to NH controls. Yet, when the stimulus is presented at equal SPL, HI young and middle-aged individuals show a similar degree of cortical neural synchronization as NH controls. This interplay between stimulus audibility and cortical neural synchronization is in line with behavioral research documenting that, compared to NH persons, HI listeners show better detection of envelope modulations (lower amplitude modulation detection thresholds) when the modulations are presented at equal sensation levels, but not when they are presented at equal SPL (Bacon and Gleitman, 1992; Schlittenlacher and Moore, 2016).

A notable discrepancy in the present study concerns the unaffected processing of 20 Hz modulations as opposed to the enhanced neural synchronization to 4, 40, and 80 Hz modulations. Because both 20 and 40 Hz modulations are primarily processed near the thalamus (Giraud et al., 2000; Luke et al., 2017), the difference cannot be attributed to a distinct anatomical location for processing of 20 Hz modulations that would remain unaffected in HI individuals. The reason for the discrepancy remains unclear.

The enhanced neural synchronization for HI listeners can be explained by homeostatic mechanisms. It has been demonstrated that the reduced cochlear output in HI individuals because of hair cell loss and/or synaptopathy, triggers various mechanisms that induce central gain to sustain an operative degree of neural excitability (Kujawa and Liberman, 2015; Salvi et al., 2017). For instance, HI auditory nerve fibers show steeper-than-normal response growths with acoustic input level (Heinz and Young, 2003; Kale and Heinz, 2010), enhanced onset responses (Crumling and Saunders, 2007), and slower recovery from neural adaptation (Scheidt et al., 2010). Moreover, from the HI brainstem up to the cortex, the influx of inhibitory neurotransmitters into excitatory neurons is reduced, while it is preserved for inhibitory neurons (Sanes and Kotak, 2011; Sarro et al., 2008; Vale and Sanes, 2002).

Despite a compensatory increase in neural synchronization, higher sensitivity to envelope modulations in HI persons is thought to be negatively correlated with speech perception. This theory is supported by behavioral research showing poorer masked speech perception performance when perceptually enhancing the envelope modulations of the target speech (Moore et al., 1995; Moore and Glasberg, 1993). Likewise, electrophysiological research has indicated that a higher degree of neural envelope encoding in the auditory cortex correlates with poorer speech understanding in the presence of a masking noise (Millman et al., 2017). The correspondence between enhanced sensitivity to envelope modulations and degraded speech perception might be attributed to an envelope-to-TFS processing imbalance. Adequate processing of the speech envelope is required yet not sufficient for the perception of masked speech: the TFS needs to be adequately processed as well (Lorenzi et al., 2006; Peelle and Davis, 2012). Neuroimaging studies have found neural TFS encoding to be reduced for HI adults relative to NH controls (Ananthakrishnan et al., 2016; Vercammen et al., 2018) and behavioral research has demonstrated that HI listeners show poor sensitivity to TFS information (Buss et al., 2004). Taken together with the observations of enhanced neural encoding and behavioral detection of envelope modulations for HI listeners, hearing impairment appears to be accompanied by a marked imbalance between processing of envelope and TFS cues, which is assumed to be detrimental for speech perception. In this framework, further research is warranted to clarify whether the poorer speech perception with enhanced envelope encoding concerns either a one-to-one relationship or an indirect relationship mediated by TFS deficits, that is, envelope enhancement acting as a compensatory strategy.

Altogether, young and middle-aged HI adults show enhanced neural synchronization to envelope modulations, especially when stimulus audibility is corrected for. Importantly, audibility correction by hearing aids currently constitutes the basis of rehabilitation strategies to improve speech perception. As it is presumed that enhanced neural envelope encoding is related to worse speech perception, one could argue that the amplification provided by hearing aids may not always be beneficial for HI listeners, especially not in noisy listening situations. Further research is required to explore this idea.

In contrast to young and middle-aged HI persons, older HI adults do not show enhanced neural synchronization to envelope modulations. The reason for this age-related variation remains to be determined. According to the study by Kale and Heinz (2010), the increase in neural synchronization correlates with the degree of hearing impairment. In effect, these authors demonstrated that higher threshold shifts correspond to more enhanced envelope encoding in auditory nerve fibers. In the present study, however, the degree of hearing impairment does not yield an adequate explanation for the observed age-related disparity. The threshold shift, calculated as $PTA_{125-8000\ Hz}$ HI $-$ $PTA_{125-8000\ Hz}$ NH, was significantly smaller in the older group (33 dB HL) than in the young group (47 dB HL), yet it was similar to the threshold shift in the middle-aged group (39 dB HL). Another possible explanation for the age-related variation could lie in neural plasticity, which is a key feature of the human brain. Auditory plasticity refers to morphological and physiological alterations in the central nervous system because of changes in the auditory environment. There is a large body of evidence showing altered neural behavior (e.g., neural synchronization) in the auditory brain due to hearing impairment or hearing aid use, causing auditory deprivation and amplification, respectively (Munro, 2008; Neuman, 2005). Nonetheless, we do not

find our older HI participants to differ significantly from both the young and middle-aged HI participants with respect to three important environmental factors related to auditory plasticity, which are the duration of having hearing impairment, using hearing aids, and being auditory deprived (Table 3).

Although the older HI adults had been HI and had been using hearing aids for a shorter period of time than the young HI adults, no such differences were apparent between older and middle-aged HI participants. Moreover, HI older participants had been auditory deprived for the same amount of time as HI young and middle-aged participants.

Rather than the degree of hearing impairment or factors related to neural plasticity, the etiology of hearing impairment and/or altered neural envelope encoding at an older age could account for the divergent outcomes for the older compared to the young and middle-aged adults. Recall that, although all participants had hearing loss that was sensorineural in nature, the etiology of hearing impairment was different for the three age groups. Hearing loss at birth or after severe/chronic otitis was the case for the young adults, familial hearing loss was indicated in the HI middle-aged participants, and all older persons were diagnosed with presbycusis. Given that the hearing impairment of older adults was not associated with enhanced neural envelope encoding, as opposed to the hearing impairment of young and middle-aged adults, the present study suggests that presbycusis, in contrast to hearing losses of other origins, is not associated with enhanced neural envelope encoding. An important note to make is that different mechanisms are associated with presbycusis, including metabolic changes, loss of outer hair cells, and loss of afferent nerve fibers (for a review, see Gordon-Salant et al., 2010). It would be interesting to implement diagnostic measurements to differentiate between different types of presbycusis among HI older participants (e.g., Verhulst et al., 2016) to investigate whether there is an interplay between neural envelope encoding and type of presbycusis. Altered neural envelope encoding at an older age may also explain the absence of increased cortical neural synchronization for older adults, and particularly with regard to 4 Hz envelope modulations. In a previous study (Goossens et al., 2016), we observed a higher degree of neural synchronization to 4-Hz envelope modulations for older NH persons compared to young and middle-aged NH individuals. This observation is in line with other studies indicating enhanced cortical envelope encoding at an older age, independent of hearing impairment (Bidelman et al., 2014; Presacco et al., 2016;

Sörös et al., 2009). This age-related enhancement can be attributed to the previously described homeostatic mechanisms, because, similarly to hearing impairment, aging goes with a decrease in cochlear output (Sergeyenko et al., 2013). Hence, at an older age, homeostatic mechanisms are activated, independent of hearing sensitivity. Taken together with the current observation that hearing impairment at an older age does not relate to increased cortical synchronization, we presume that the homeostatic potential is maximally exploited at an older age. As a consequence, no (further) increase in cortical envelope encoding is detected for hearing impairment at an older age, in contrast to hearing impairment at a young and middle age. In sum, presbycusis and altered neural envelope encoding at an older age are the most plausible explanations for the discrepant observations for older versus young and middle-aged adults. Disentangling their differential contribution is, however, not possible because presbycusis and older age are intrinsically related to each other.

Interestingly, the older group shows another striking difference with the young and middle-aged group. While no substantial differences in hemispheric asymmetry are detected between HI and NH young and middle-aged individuals, HI and NH older adults show a marked difference in hemispheric asymmetry. For 40 Hz modulations, HI older persons show a significant synchronization asymmetry toward the RH, whereas no such hemispheric asymmetry is present in NH older persons. To our knowledge, this study is the first to look into the association between hearing impairment and functional hemispheric asymmetry. Previously, Bellis et al. (2000) documented that young NH adults show greater neural synchronization to speech syllables in the LH compared to the RH, whereas older NH adults show a similar degree of neural synchronization in both hemispheres. This altered hemispheric asymmetry with age is in agreement with the evidence-based HAROLD model (Cabeza, 2002), which states that neural processing is less asymmetrical in older than in young adults. Although aging is thus thought to be characterized by less asymmetrical neural processing, our HI older participants exhibit a clear asymmetrical processing pattern. This novel observation indicates that presbycusis interferes with age-related variations in functional hemispheric asymmetry, which may be explained by the reduced integrity of white matter tracts related to presbycusis (Mudar and Husain, 2016). The corpus callosum, which plays a predominant role in interhemispheric interactions (Hoptman and Davidson, 1994), is a large bundle of white matter tracts. As such, white matter deficits in the presbycusic brain can impact the hemispheric asymmetry in neural synchronization. Intriguingly, research on functional hemispheric asymmetry and speech intelligibility suggests that persons who show an asymmetrical processing pattern have better speech perception than persons who show a symmetrical pattern (Bellis et al., 2000; Hämäläinen et al., 2012). Because of the significant speech perception difficulties of HI older persons, it seems, however, unlikely that their RH asymmetry would have a beneficial effect on speech perception. Further research is needed to clarify the contribution of this RH asymmetry to speech perception.

5. Conclusions

In conclusion, this study demonstrates that hearing impairment is characterized by changes in neural envelope encoding, the nature of which is different for young and middle-aged compared to older persons. Hearing impairment in young and middle-aged adults is associated with enhanced neural envelope encoding from the brainstem up to the cortex, which is most pronounced when stimulus audibility is corrected for. Importantly, such enhanced envelope encoding is thought to underlie impaired speech perception. In older adults, hearing impairment (presbycusis) is not

Table 3
The upper part of the table shows the mean duration ± SD (expressed in years) of three factors related to auditory plasticity - having hearing impairment, using hearing aids, and being auditory deprived - for the HI young, middle-aged, and older participants. The duration of auditory deprivation was calculated by subtracting the duration of hearing aid use from the duration of having hearing impairment

	Hearing impairment	Hearing aid use	Auditory deprivation
	Mean ± SD	Mean ± SD	Mean ± SD
Young	24 ± 4	21 ± 5	3 ± 3
Middle-aged	18 ± 8	10 ± 8	8 ± 8
Older	12 ± 8	7 ± 7	5 ± 5

	Hearing impairment		Hearing aid use		Auditory deprivation	
	MD	p^a	MD	p^a	MD	p^b
Older vs. young	12	0.002	14	<0.001	2	0.467
Older vs. middle-aged	6	0.132	3	0.815	3	0.514

For each factor, a one-way ANOVA and post hoc testing were performed for comparing older to young and to middle-aged listeners: the MDs (expressed in years) and p values are outlined in the lower part of the table.
[a] Bonferroni corrected.
[b] Games-Howell corrected.

associated with enhanced neural envelope encoding, yet it co-incides with a clear hemispheric asymmetry in neural synchronization, which might act on speech perception.

These are important insights into a key neural mechanism underlying speech perception for HI people that can contribute to the development of advanced intervention strategies to remediate impaired speech perception.

Disclosure

The authors have no actual or potential conflicts of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2018.10.008.

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