Effects of childhood hearing loss on the subcortical and cortical representation of speech

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Abstract

Little is known about the effects of childhood mild-to-moderate sensorineural hearing loss (MM HL) on the function of the auditory pathway. We aimed to examine the effect of childhood MM HL and the benefit of frequency-specific amplification on both subcortical and cortical auditory processing, and to relate it to speech-perceptual abilities. We recorded subcortical and cortical responses to speech syllables in nineteen children with congenital MM HL (unamplified and amplified), and sixteen children with normal hearing (unamplified sounds only). Speech perception was measured behaviourally. Congenital HL led to smaller subcortical and cortical responses to unamplified speech sounds. There was a significant benefit of amplification on subcortical and early, but not late, cortical responses, with some effects differing across age. No relationship was found between the neural and behavioural measures. Childhood MM HL affects both subcortical and cortical processing of speech. Amplification mostly benefits subcortical processing of speech in younger children. Childhood HL leads to functional changes in the processing of sounds, with amplification differentially affecting subcortical and cortical levels of the auditory pathway.

Introduction

Animal studies have shown biological and physiological changes in the properties of neurons in the cochlea, subcortex, and cortex following even a temporary, mild-to-moderate (MM) hearing loss (HL)[1,2]. Similar changes have been documented in humans with congenital deafness [3–5], or in older adults with age-related MM HL (for a review see [6]). Nowadays, most individuals with MM HL receive auditory stimuli via hearing aids, which amplify the incoming auditory signal. To date, the bulk of studies investigating the effects of MM HL (and the potential benefit of hearing aid amplification) on the functional integrity of auditory pathway has focused on older adults. However, congenital hearing loss affects up to 2 live births in 1000[7], milder degrees of loss being more prevalent yet more often overlooked. Here, we evaluate the effect of childhood MM HL and the benefit of amplification on simultaneously recorded subcortical and cortical responses to speech sounds.

In the auditory system, speech sounds travel from the cochleae to the auditory cortices, undergoing increasingly complex levels of processing. At the level of the cochleae, sounds undergo a frequency analysis. The output of each channel can be separated into their relatively slowly fluctuating modulated signals known as the envelope (ENV), imposed upon a rapidly varying carrier waveform, known as the temporal fine structure (TFS). Both ENV and TFS cues are thought to be important in decoding speech. ENV cues support the robust identification of speech in quiet[8], whereas TFS cues are thought to be especially useful in noisy backgrounds. Indeed, individuals with normal hearing (NH) typically benefit from the TFS when they glimpse into the "dips" (i.e., local improvements in SNR) of a fluctuating background noise[9]. Therefore, speech intelligibility is much better in the presence of fluctuating than steady background noise, a phenomenon termed "masking release". However, adults with HL show reduced ability to use TFS[10], a difficulty that limits the amount of masking release they experience[11]. Similarly to adults, children and adolescents with MM HL experience poorer

speech intelligibility in noise[12,13]. They show reduced sensitivity to TFS compared to children/adolescents with NH[14], which likely limits masking release of speech in the presence of a fluctuating background noise, even though they wear hearing aids[15].

At the subcortical level of the auditory pathway, the frequency following response (FFR) reflects the periodicity of speech sounds[16]. Adding the neural responses to speech sounds presented in alternating polarities is thought to enhance the ENV of the response (henceforth FFR_{ENV}, here used as an index of fundamental frequency encoding), whereas subtracting them is considered to enhance the TFS (henceforth FFR_{TFS}, an index of spectral harmonic encoding[17]. Although the primary generator of the FFR appears to vary according to the fundamental frequency (F0) of the input stimulus, the current view is that the FFR emerges from multiple generators, including the cochlear nucleus, inferior colliculus and thalamus[18,19]. In typical development, amplitude of both FFR_{ENV} and FFR_{TFS} appears to decrease from childhood to (late) adolescence [20].

At the cortical level, components of the late auditory event-related potentials (LAERs) arise which are thought to reflect the initial detection (P1, N1, and P2), classification and discrimination (P2 and N2) of stimuli, reflecting processes involved ranging from isolated sounds to complex auditory scenes[21]. LAERs are thought to be generated in the auditory cortex (for a review, see [22]). The mismatch negativity (MMN) is thought to reflect the discrimination of a deviant sound, and is typically evoked by a comparatively rare deviant in a stream of repeated standards (i.e. an oddball paradigm; for a review see [23]). The MMN is thought to have several additional generators, including bilateral temporal cortex, right inferior frontal gyrus, and bilateral frontal and centro-parietal regions (e.g., [24–26]). In addition to distinct topographies, both LAERs and MMNs show distinct developmental trajectories. In typical development, P1 and N2 responses are thought to decrease in amplitude as children grow older, while N1 and P2 progressively appear in childhood, growing in amplitude until adolescence[27,28]. MMN

amplitude is thought to increase throughout childhood[29], but to be stable from around 10 years of age to adulthood[30,31].

Both subcortical and cortical levels of the auditory pathway thus appear to follow a protracted trajectory, maturing until late adolescence. How MM HL affects the development of subcortical and cortical speech processing remains largely unknown. So far, studies have focused on *either* subcortical *or* cortical levels of processing, only providing fragmented information about the physiology of the auditory pathway in children/adolescents with MM HL. Yet using the right set of recording/analysis parameters, it is now possible to obtain subcortical and cortical responses at the same time[32,33]. Therefore, the first aim of this project was to evaluate the effect of childhood hearing loss on simultaneously recorded subcortical and cortical levels of processing. Noteworthily, the existing literature on this topic can be classified according to the strategy used to manage intensity levels across groups.

Neural processing of speech presented at fixed intensity levels across groups

When studying the effect of hearing loss on auditory processing, researchers often choose to investigate the unaided performance of individuals with HL. Stimuli are thus presented at a fixed intensity level for all individuals, with HL or not. Adult studies using this strategy to evaluate the effect of HL on subcortical processing have led to contradictory findings. While some authors reported smaller FFR_{ENV} and FFR_{TFS} in adults with HL than adults with NH[34,35], others failed to show such group differences[36,37]. Note that a possible explanation for this discrepancy lies in the age-matching across groups[38,39], or lack thereof[34,35]. To our knowledge, no study has focused on the effects of childhood MM HL on subcortical processing of speech, using fixed intensity stimuli across groups of children/adolescents.

At the cortical level, studies using fixed intensity levels across groups suggest that childhood MM HL leads to delayed and/or smaller LAERs evoked by speech[38] or pure

tones[38,39]. Developmental changes following MM HL were also apparent in the MMN: While children with MM HL showed age-appropriate MMN responses to sounds, this was no longer the case in adolescents with MM HL, as shown both cross-sectionally and longitudinally[38].

Neural processing of speech presented at similar sensation levels across groups

A common limitation of the above-mentioned studies using fixed intensity levels for all participants is that individuals with HL would have perceived the stimuli at reduced sensation levels (SL) relative to controls. To address this limitation, some researchers attempted to equate for effects of peripheral hearing loss. In this scenario, listeners with NH and those with SNHL are presented with sounds at different intensities – more intense for individuals with SNHL (either by simulating the frequency-specific gain provided by individuals' hearing aids, or by recording the neurophysiological response while listeners wear hearing aids). With such adjustments for HL, adults with acquired MM HL show larger FFR_{ENV} to an amplified syllable /da/ compared to unamplified speech[36, 40, 41] and in one study, than the FFR_{ENV} evoked by unamplified speech presented to NH listeners[36]. A similar benefit of amplification on the FFR_{ENV} evoked by the speech token /suʃi/ was recently reported in 18 children with HL aged 6 to 17 years, compared to the unamplified stimulus[42]. Note that older adults with acquired MM HL did not show a significant benefit of amplification on FFR_{TFS}[36]. To our knowledge, the effect of amplification and childhood HL on FFR_{TFS} has remained unexplored so far.

At the cortical level, studies looking at the effect of childhood HL on LAERs by accounting for the effects of peripheral HL have led to contradictory findings. Pilot data from a small sample of 5 children aged 2 to 6 years show age-appropriate P1 and N2 evoked by speech stimuli when the children wore their hearing aids[43]. Another study focused on older, unaided children (9-12 years) with MM HL, to whom speech stimuli were presented on average 18 dB greater than in children with NH[44]. Note that here, the amplification provided to the

group with HL was not frequency-specific – unlike hearing aids. Results indicate age-appropriate P1 and MMN responses in children with MM HL, but smaller (but not later) N2 responses compared to children with NH. However, 5 to 8 year-old children who wore their hearing aids (n = 7) showed significantly smaller LAERs evoked by complex tones than age-matched children with NH[45] . Interestingly, when re-tested three years later, the same children with HL showed age-appropriate LAERs. At both time-points, MMN amplitudes were age-appropriate in children with MM HL. To our knowledge, no study has directly investigated the intra-individual benefit of amplification on the cortical processing of speech in children/adolescents with MM HL.

Study objectives

In summary, studies comparing the effect of MM HL on the processing of speech presented at fixed intensity levels across age-matched groups seem to indicate appropriate subcortical responses (in older adults) but smaller/later cortical responses (in children/adolescents). Results of studies investigating the effects of amplification on subcortical and cortical processing of speech in individuals with MM HL have led to mixed results. At the subcortical level, amplified speech stimuli seem to entail larger FFR_{ENV} (but not FFR_{TFS}) than unamplified stimuli. At the cortical level, amplification seems to result in age-appropriate LAERs and MMN – yet the magnitude of the amplification benefit for children/adolescents with MM HL has remained unexplored. Therefore, the main goal of this study was twofold, to evaluate (i) the effect of childhood HL and (ii) the benefit of amplification on both subcortical and cortical auditory processing. Given that subcortical and cortical processing have both been related to speech perception[46,47], especially in noise[46,48], a third objective was (iii) to investigate how these neurophysiological responses to sounds relate to speech intelligibility in quiet and in noise.

Methods

Participants

Thirty-five children aged 8 to 16 years were included in the study. Nineteen (8 female) had a diagnosis of mild-to-moderate SNHL (HL group) and sixteen (8 female) were age-matched children with normal hearing (NH group). All participants were monolingual British English natives and obtained a nonverbal IQ (NVIQ) score of at least 85 (Block Design subtest of the Weschler Abbreviated Scale of Intelligence[49]). No child had any known medical, psychological, neurological or developmental disorders other than SNHL. Individual air-conduction audiometric thresholds were measured bilaterally in all children at octave frequencies from 0.125 to 8 kHz using an Interacoustics AC33 audiometer. Group comparisons are presented in Table 1. Some children did not perform all behavioural and electrophysiological tasks (see Supplementary Material). The study was conducted with the verbal assent of the participants, the written consent of their parents, and was approved by the UCL Research Ethics Committee (2109/004). It was performed in accordance with the Declaration of Helsinki.

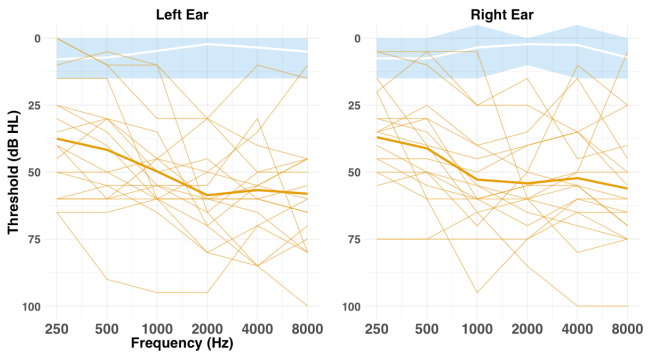


Figure 1: Pure-tone air-conduction audiometric thresholds for children with HL (orange) and children with NH (blue and white). Audiometric thresholds are shown across octave frequencies from 0.25 to 8 kHz in the left and right ears. Individual thresholds for the HL group are shown as lines, and the group mean is shown as a bold line. Mean thresholds for the NH group are marked in white, with the shaded blue area representing the range for the NH group.

Participants in the HL group had better-ear pure tone average (BEPTA) thresholds of 21-70 dB HL across 0.25-8 kHz (see Figure 1). All children in the HL group were spoken language users (i.e., non-signers), and sixteen had prescription hearing aids, but these were not used in this study. Children in the HL group were individually matched in age (± 6 months) to those in the NH group, and mean age did not differ significantly between the two groups (see Table 1). Note however that there was a significant age effect on BEPTA in children with HL (p = 0.008). In our sample, older children had better (i.e., approximately 5 dB lower) BEPTA. None of the children in the NH group had a known history of hearing loss (including otitis media with effusion), educational difficulties, or speech and language problems (based on parent/guardian report). All had mean PTA thresholds ≤ 20 dB HL across octave frequencies 0.25-8 kHz in both ears and obtained thresholds no higher than 25 dB HL at any given frequency.

Table 1 : Mean (SD) participant characteristics for the HL and NH groups. Comparisons are independent-samples *t*-tests. Effect sizes are Cohen's *d*. Significant effects are shown in boldface.

Variable	NH (n = 15)	HL (n = 19)	*t*(df)	*p*-val	Effect size	95 % CI
Age (years)	12.6 (2.43)	12.4 (2.44)	0.26 (32.1)	.795	0.08	[-1.46, 1.89]
Nonverbal IQ	119.1 (12.6)	102.5 (12.5)	3.83 (31.44)	**<.001**	1.32	[-25.4, -7.7]
Maternal education	20.9 (2.59)	18.3 (2.78)	2.76 (30.99)	**.009**	0.96	[-4.49, -0.67]
BEPTA threshold (dB HL)	3.7 (2.87)	45.0 (13.30)	-13.18 (19.97)	**<.001**	4.12	[-47.86, -34.78]
Age of HL detection (years)	-	3.6 (3.03)				

Data acquisition and pre-processing

Stimuli were digitised /bɑ/ (standard) and /dɑ/ (deviant) syllables (see Figure 2) originally spoken by a native British female speaker, and identical to those used in[14, 38, 50]. The

phonetic contrast was primarily cued by differences in the properties of the initial release burst (more intense for the /dɑ/, especially at higher frequencies) and on the formant transitions into the vowel (with a falling F2 for /dɑ/ and no transition for /bɑ/). The intonation contours were made monotone at 220 Hz using Praat[51] and the final stimuli were RMS equalised with GoldWave[52].

Each condition consisted of 1320, 175-ms stimuli, presented in a passive oddball paradigm (deviant probability: 10%). Half of all stimuli were presented in positive polarity and the other half in negative polarity. The order of presentation of each polarity was randomized. The inter-stimulus interval was jittered randomly between 275 and 375 ms to limit neural adaptation[53].

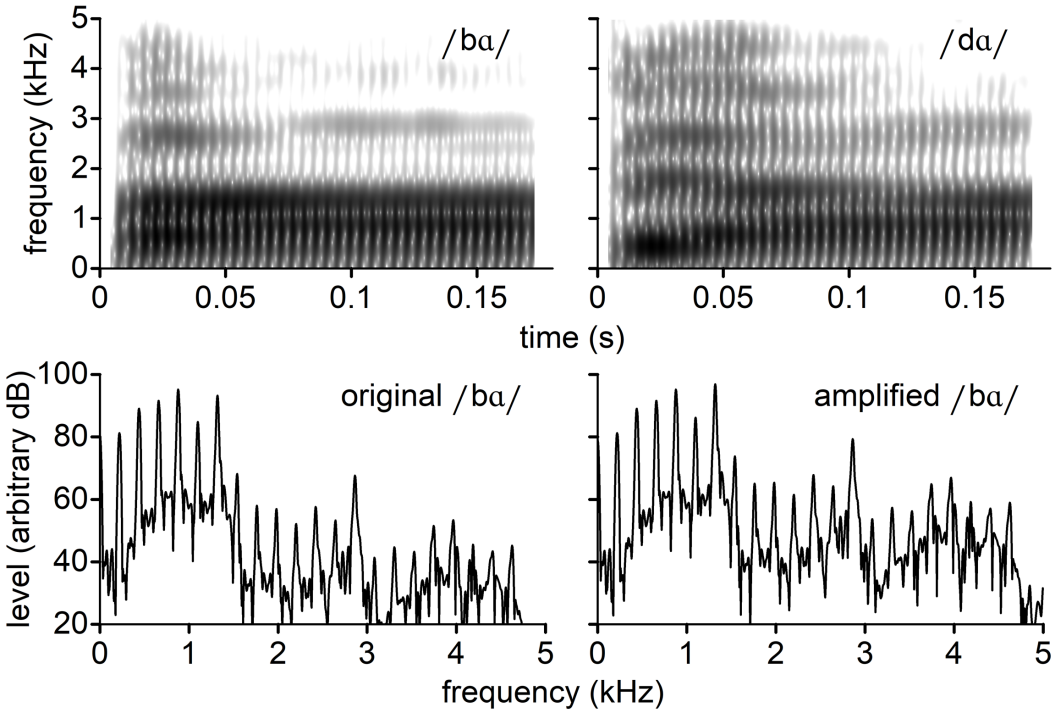


Figure 2: Top row: Spectrograms of the standard and deviant speech syllables in their unamplified form. Bottom row: Spectra of the vocalic portion (20 to 170 ms) of the standard syllable /bɑ/ in both unamplified and NAL-R amplified versions. Children with NH were only presented with unamplified versions of the stimuli. Children with HL were presented with both versions of the stimuli, with the amplification being dependent upon each individual's audiogram. For visualisation purposes, the amplified stimulus here was generated based on the average audiogram of the HL group. It can clearly be seen that, as expected, the level of the harmonics below ~2 kHz is unchanged because there is minimal hearing loss at those frequencies, with amplification of the higher harmonics in the frequency region in which there is substantial hearing loss.

Children with NH were presented with only one condition, consisting of unamplified stimuli that were presented binaurally at 70 dB SPL through shielded insert earphones (ER-2, Etymotic Research). Children with HL undertook two conditions - unamplified and amplified – presented in counter-balanced order. Amplification used the National Acoustic Laboratory-Revised algorithm (NAL-R[54]) to provide a frequency-specific gain (without compression), based on each individual child's audiogram. This strategy minimizes the risk of potential confounds related to sound-field testing as well as potential inter-individual variability in the hearing aid processors of individual children (see [55]). Stimuli in the amplified condition were limited in intensity such that they did not exceed 85 dB SPL. Each condition lasted approximately 20 minutes, with three short breaks offered every 5 minutes. During the recording, participants were seated comfortably in a shielded, sound-attenuated booth, and watched a silent movie.

EEG was recorded using a BioSemi ActiveTwo system at a sampling rate of 8192 Hz, from 32 scalp electrodes in the standard 10/20 configuration[56]. Additional electrodes were placed on each mastoid and recordings were re-referenced offline to the average of activity at the mastoid electrodes. Electrode offsets were consistently < 50 mV.

Subcortical response analysis

Epochs used for analysis of subcortical responses were obtained by applying a band-pass filter (90-1600 Hz) to the EEG data evoked by the standard syllables (/bɑ/) at Cz, and extracting data 20-170 ms relative to stimulus onset. Trials exceeding ± 100 µV were rejected before averaging. The averaged responses to positive and negative polarities were then added together to enhance the envelope of the response (FFR_{ENV}), and subtracted from each other (i.e. positive minus negative polarity) to enhance the TFS of the response (FFR_{TFS}). Spectral amplitudes were calculated using a fast Fourier transform (FFT), after applying zero-padding to the sampling rate to obtain an FFT with a resolution of 1 Hz. Spectral peaks at F0 (220 Hz)

and harmonics (H2: 440 Hz; H3: 660 Hz; H4: 880 Hz; H5: 1120 Hz; and H6: 1320 Hz) were computed as the maximum amplitude within an 8-Hz bin centred on F0 and subsequent harmonics. Neural background noise amplitudes were calculated by taking the mean amplitude of the fast Fourier transform across 100-Hz windows surrounding each spectral peak (50 Hz on each side, excluding the ±70 Hz adjacent bins).

Cortical response analysis

Evoked potentials considered to be cortical in origin were obtained by band-pass filtering the EEG recorded at electrode Fz between 0.5 Hz and 35 Hz and creating epochs from -100 ms to 500 ms relative to each stimulus onset time. Epochs were baseline corrected using the mean value from -100 to 0 ms. Trials exceeding ± 100 μV were rejected before averaging. There was no significant difference in the proportion of trials that were rejected across groups [NH-U: 12.7%; HL-U: 13.4%; HL-A: 15.75%; $F(2, 50) = 0.43$, $p = 0.654$, $\eta^2 = 0.01$].

P1 and N2 amplitudes were computed for each participant and condition as the mean amplitude within a 40-ms window centred around the grand averaged peak evoked by standards, as observed in children with NH (P1: 81.6 ms post-stimulus onset; N2: 294.4 ms post-stimulus onset). P1 and N2 latencies were computed for each participant and condition as the latency for the local peak to appear, within the 40-ms window centred around the NH grand average evoked by standards. The MMN was computed as the differential wave obtained by subtracting the neural response evoked by the standard to that evoked by the deviant, for each participant for each condition. The MMN was then statistically assessed in two ways. First, to determine whether there was evidence for neural discrimination of speech deviants, the presence of an MMN was evaluated for the three combinations of group and amplification conditions. Point-to-point comparison of the differential wave amplitudes was performed to determine the latency period over which the waveforms were significantly smaller than zero, if any. One-sided *t*-tests were computed within the 100-500 ms post-stimulus-onset time window

which was identified as the region most likely to contain the MMN by visual inspection of the grand average waveforms. Because adjacent points in the waveform are highly correlated, potentially leading to spurious significant values in short intervals, an MMN was considered present when $p < .01$ (one-tailed) for more than 20 ms at adjacent time-points. MMN amplitudes for each participant and condition were then computed as the mean differential waveform amplitude in a 40-ms window centred around the grand averaged MMN peak observed in children with NH (at 454 ms post-stimulus onset). MMN latencies were computed for each participant and condition as the latency for the local peak to appear, within the 40-ms window centred around the NH grand average differential waveform amplitude.

Speech discrimination in quiet

The speech discrimination in quiet task was the same as that used in previous studies from our laboratory[14,57]. The two endpoints of the continuum were based on the same digitised /bɑ/ (the standard) and /dɑ/ (the deviant) used in the electrophysiological recordings. A continuum of 100 stimuli was then constructed (including the endpoints), using the morphing capabilities of the programme STRAIGHT[58]. The task was delivered via a child-friendly computer game, incorporating an adaptive, three-interval, three-alternative, forced-choice paradigm. Stimuli were presented via headphones (Sennheiser 25 HD) at a fixed intensity (70 dB SPL), on a tablet, meaning identical levels presented in the two groups. Children were required to detect the odd-one-out, where two of the intervals corresponded to the /bɑ/ end of the continuum, and the third, target stimulus fell somewhere along the rest of the continuum. Participants received visual feedback regarding the accuracy of their responses. A three-down, one-up procedure was used to select, on each trial, the appropriate target sound from a continuum, tracking a performance level of 79.4% correct[59]. This was preceded by an initial one-down, one-up procedure until the first reversal[60]. The initial step size was 15 stimulus places along the continuum, which reduced to five after the first reversal. The threshold was

the arithmetic mean of the last four reversals in response direction, expressed as the stimulus number (0-99) of the target stimulus along the continuum. Therefore, smaller numbers indicate better performance.

Speech perception in noise

Speech reception thresholds (SRTs) were measured adaptively for 13 consonants presented in vowel-consonant-vowel (VCV) logatomes. Vowels were /i/, /ɑ/, and /u/, and consonants were /p/, /k/, /b/, /d/, /g/, /f/, /m/, /n/, /l/, /v/, /w/, /y/, and /z/. Both the vowels and consonants varied from trial to trial, but only the response for the consonant was scored. Stimuli were recorded by a native British English female speaker in an anechoic chamber and were digitized via a 16-bit analogue-to-digital converter at a 44.1-kHz sampling frequency. The logatomes were presented together with two types of background noise: steady (i.e., unmodulated, but see[61]) or fluctuating in amplitude sinusoidally at 8 Hz (with the modulator fixed in depth at 1.0 and with a starting phase randomized between 0° and 360° on each trial). The noise was shaped on-and-off using a raised-cosine with 50-ms rise-fall times.

Children were seated in a quiet room and the stimuli were presented binaurally over Etymotics ER-2 earphones at an overall level of 75 dB SPL, again meaning identical levels presented in the two groups. They were asked to repeat the logatomes as best as they could. The experimenter scored the participants' responses using a graphical interface which showed the 13 possible consonants. No feedback was provided.

The expected wide variability in intelligibility across consonants at a given SNR would not allow their reliable use in a simple adaptive procedure. Therefore, SRTs for each combination of consonant and vowel were estimated from a prior study, allowing the calculation of adjustment factors in SNR to give all stimuli the same nominal SRT. These factors were then used during the adaptive procedure to adjust the presented SNR. The signal-to-noise ratio (SNR) was varied adaptively by varying the level of the target and fixing the level

of the noise at 70 dB SPL. The first logatome was presented at a nominal SNR of -10 dB (taking into account that token's adjustment factor). Depending on the participant's response (correct/incorrect), the SNR of the second logatome was decreased/increased by 10 dB. Again, depending on the participant's response (correct/incorrect), the SNR of the third logatome was decreased/increased by 6 dB. For each subsequent logatome, the SNR increased/decreased by 2 dB for incorrect/correct responses, respectively. Measurement stopped after either 12 reversals or 78 trials, whichever occurred first. The SRT was computed by taking the mean SNR (dB) across all track reversals.

Speech perception in quiet

As a baseline for the speech perception in noise task, we also included a speech perception in quiet task. Percentage correct responses were measured for 78 consonants presented at a fixed intensity of 75 dB SPL, using the same VCV logatomes and procedure for recording the participants' responses as those used in the speech perception in noise task.

Statistical analyses

Regarding the subcortical data, we first ran an outlier detection algorithm. Data points that fell outside the mean ± 3 *SD* (within each combination of group, amplification, FFR component and harmonic) were considered outliers and excluded from the analyses reported below. In total, 2.7% of data points were excluded from the analyses, most of them from the HL group. After excluding outliers, the subcortical data were normally distributed (Kolmogorov-Smirnov test: all ps < .05). Note that for both FFR_{ENV} and FFR_{TFS}, there were significant differences in variance between groups as evidenced by Levene's test for equality of variance (both ps < 0.001).

Second, paired two-tailed *t*-tests with Bonferroni-Holm correction were conducted separately for each group (NH_U, HL_U, HL_A), FFR component (FFR_{ENV} and FFR_{TFS}) and harmonic (F0 to H6) to determine whether the FFR responses were significantly above the

neural noise floor. FFR responses are considered present if at least one of the three groups showed a significant difference between target frequency peak and spectral noise floor in each component, at each harmonic. For FFR_{ENV}, peaks were significantly larger than the noise floor only at F0 and H2 (all *p*s < 0.001). For FFR_{TFS}, peaks were significantly larger than the noise floor at H3, H4, H5 and H6 (all *p*s < 0.05).

Third, a linear mixed model was used to determine whether amplitude of the spectral noise floor differed across groups (NH_U, HL_U, HL_A), FFR component (FFR_{ENV} and FFR_{TFS}) or harmonic (F0 to H6). As expected, the only significant predictor was harmonic ($p < 0.001$). In the absence of a significant group effect on the baseline ($p > 0.10$), subsequent analyses were performed on the target frequency peak amplitude.

Regarding the cortical data, we found no outliers (± 3 *SD* from the mean) in the amplitude of either P1 or MMN. The cortical data were normally distributed (Kolmogorov-Smirnov test: all *p*s < .05). For both P1 and MMN amplitudes, there were no significant differences in variances between groups (Levene's test for equality of variance: both *p*s > .05).

Linear mixed models (lme4 package of R[62]) were used to evaluate group differences in both cortical (P1 and MMN) and subcortical (FFR_{ENV} and FFR_{TFS}) measures. Backward stepwise reduction was used to optimize the models based on AIC. In all models, the factor listener was used as a random intercept. Only significant results are reported below. Analyses of group differences aimed to answer three main questions. First, is there a significant group difference in electrophysiological responses to unamplified speech stimuli? Here, the predictors were group (NH_U vs. HL_U), age (continuous variable) and their two-way interaction. In addition, harmonic (FFR_{ENV}: F0 and H2; FFR_{TFS}: H3 to H6) and its two- and three-way interactions with group and age were used as predictors to model the subcortical data. Second, for children with HL only, is there a benefit of amplification on the neural encoding of sounds? Here, the predictors were amplification (HL_U vs. HL_A), BEPTA and age. In the case of

subcortical data, harmonic and its two- and three-way interactions with group and age were also included in the model. Third, does sound amplification in children with HL lead to electrophysiological responses that are similar to the control group (NH_U vs. HL_A)? Again, the predictors were group (NH_U vs. HL_U), age (continuous variable) and their two-way interaction. In addition, harmonic (FFR_{ENV}: F0 and H2; FFR_{TFS}: H3 to H6) and its two- and three-way interactions with group and age were used as predictors to model the subcortical data. When significant, interactions were decomposed using Bonferroni-corrected post-hoc comparisons.

With respect to the speech intelligibility measure in quiet, whose outcome variables was binomial, generalized linear mixed models (logistic regressions) were fitted to the data. Group (NH, HL) and age, as well as their two-way interaction were included in the model as between-subjects factors, and both listener and consonant were included as random effects. For speech perception in noise, a linear mixed model was computed with group (NH, HL), noise type (steady, fluctuating), age, and their 2- and 3-way interactions as fixed factors, and listener as a random effect.

Finally, the relationship between subcortical and cortical measures, as well as that between electrophysiological and behavioural measures were investigated using correlations, conducted separately on the NH and HL groups, and separately for unamplified and amplified conditions in the latter group.

Table 2: Summary of the main effects of hearing loss (HL_U versus NH_U) and amplification (HL_A versus HL_U) for subcortical, cortical and behavioural measures. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

		Effect of hearing loss (HL_U versus NH_U)	**Benefit of amplification** (HL_A versus HL_U)	**Benefit of amplification** (HL_A versus NH_U)
Subcortical measures				
FFR_{ENV}	Amplitude	$HL_U < NH_U$ ***	Amplification × Age *	
FFR_{TFS}	Amplitude	$HL_U < NH_U$ *	Amplification × Harmonic ***	Amplification × Harmonic ***
Cortical measures				
P1	Amplitude	$HL_U < NH_U$ ***	Amplification × BEPTA *	
	Latency	$HL_U < NH_U$ ***		
N2	Amplitude	$HL_U < NH_U$ ***		$HL_U < NH_U$ **
	Latency			
MMN	Amplitude	$HL_U < NH_U$ **		Group × Age
	Latency			Group × Age *

Results

A summary of the main effects of hearing loss (HL_U versus NH_U) and of amplification (HL_A versus HL_U) is provided in Table 2, for subcortical, cortical and behavioural measures.

1. Subcortical responses

Figure 3 shows the grand-average spectra of the subcortical responses evoked at electrode Cz by unamplified speech for children with NH (left panel), and unamplified and amplified speech for children with HL (middle and right panels, respectively). Scatterplots of the amplitude of the various components are shown as a function of age in Figure 4.

First, group differences in the subcortical processing of unamplified speech were examined (NH_U vs. HL_U; see Supplementary Table 1). FFR_{ENV} were significantly smaller (by 0.082 µV) in children with HL_U than in children with NH_U ($p = .001$) for both harmonics, with no effect of age. Similarly, FFR_{TFS} were significantly smaller (by 0.028 µV) in children with HL_U than in children with NH_U ($p = .015$). Note that in neither analysis was there a significant group x harmonic interaction.

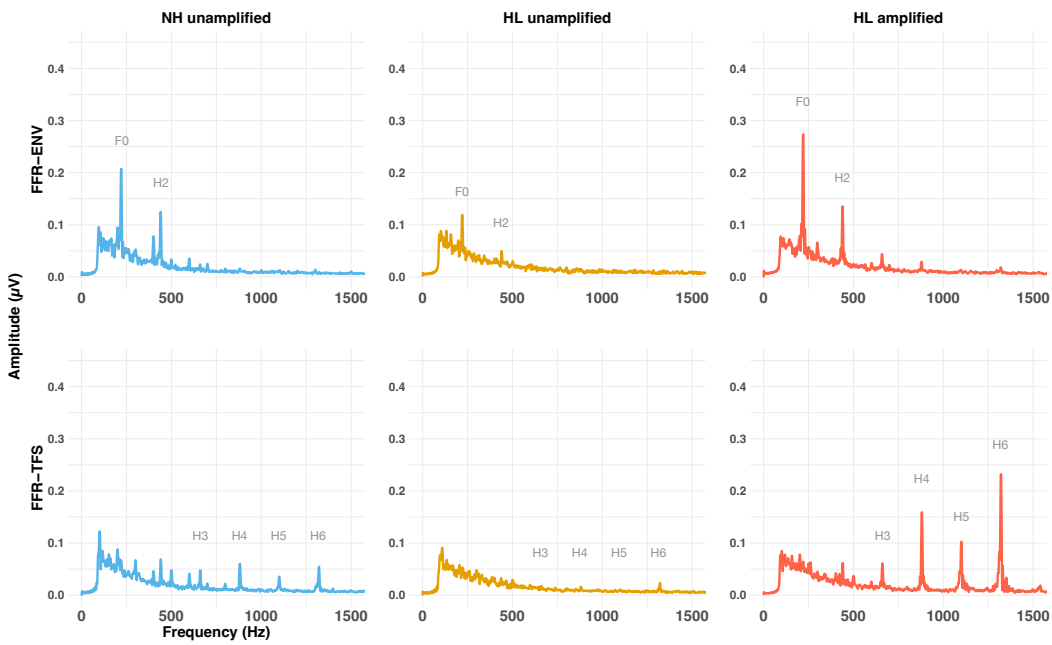


Figure 3: Fast Fourier transforms of the subcortical grand average responses at Cz to the envelope (upper row) and the TFS (lower row) evoked by the standard sound /bɑ/, presented either unamplified to the children with NH (left panel), unamplified to the children with HL (middle column), or amplified to the children with HL (right panel).

Next, the effects of amplification were examined by comparing the subcortical responses of children with HL presented with unamplified versus amplified speech stimuli (HL_U vs. HL_A; see Supplementary Table 2). Overall, FFR_{ENV} were significantly larger (by 0.118 μV) in response to amplified compared to unamplified speech sounds ($p = 0.003$). However, this has to be considered in light of the significant amplification × age interaction ($p = 0.028$). Indeed, we observed a nearly significant decreasing benefit of amplification with age on FFR_{ENV} amplitude, but not of unamplified sounds. With respect to the FFR_{TFS}, we observed a significant amplification × harmonic interaction ($p = 0.001$). FFR_{TFS} were significantly larger in response to amplified than unamplified speech sounds at H4, H5 and H6, but not at H3.

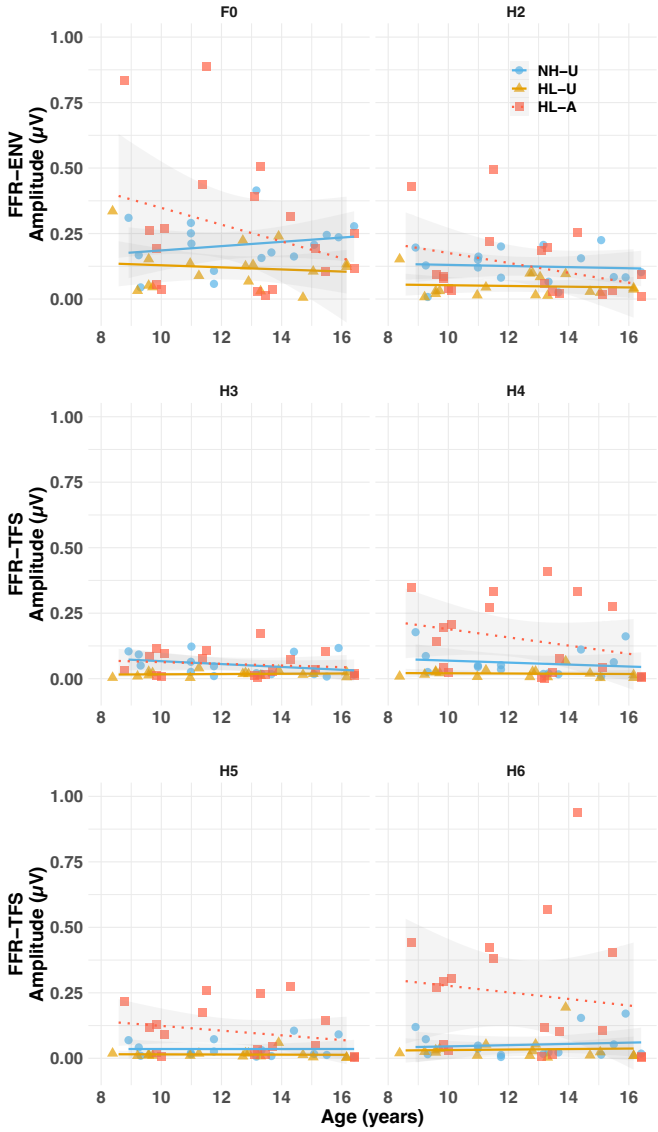


Figure 4: Scatterplots of the amplitude (μV) of the FFR_{ENV} (F0 and H2) and FFR_{TFS} (H3 to H6) over age, for each group (NH_U, HL_U and HL_A).

Last, we compared the amplitude of the responses obtained when amplified sounds were presented to children with HL versus unamplified sounds presented to children with NH (HL_A vs. NH_U; see Supplementary Table 3). The amplitude of the FFR_{ENV} did not significantly differ between HL_A and NH_U ($p = 0.168$). With respect to the FFR_{TFS}, we observed a group × harmonic interaction ($p < 0.001$). FFR_{TFS} were significantly larger in the HL_A than NH_U groups at both H4 and H6, but not at H3 and H5.

2. Cortical responses

Figure 5 shows the grand-average cortical waveforms evoked by standard and deviant stimuli at electrode Fz for both groups. In children with NH, the response to the standard sound was dominated by a large positivity occurring around 80 ms post-stimulus onset (the P1), followed by a large and prolonged negativity peaking around 300 ms (the N2). As we and others have reported previously, this pattern of results is typical of children with NH in this age range [28,39]. For children with HL, the overall pattern of responses to the standard and deviant sounds was similar, albeit reduced in amplitude compared to children with NH. Note that there is no reliable evidence of an MMN in children with HL in either unamplified or amplified conditions, but strong evidence for one in children with NH (illustrated by a horizontal line covering the range from 330 to 500 ms in the left panel of Figure 5).

First, we assessed group differences in the cortical processing of unamplified speech (NH_U vs. HL_U; see Supplementary Table 4). As shown in Figure 6, P1 was smaller (by 2.50 μV) and later (by 9.76 ms) in the HL_U than the NH_U group (both ps < 0.001). N2 was also smaller (by 4.07 μV) but not later in the HL_U than the NH_U group ($p < 0.001$). Additionally, children with HL_U had significantly smaller MMN responses (by 3.67 μV) than children with NH_U ($p = 0.002$).

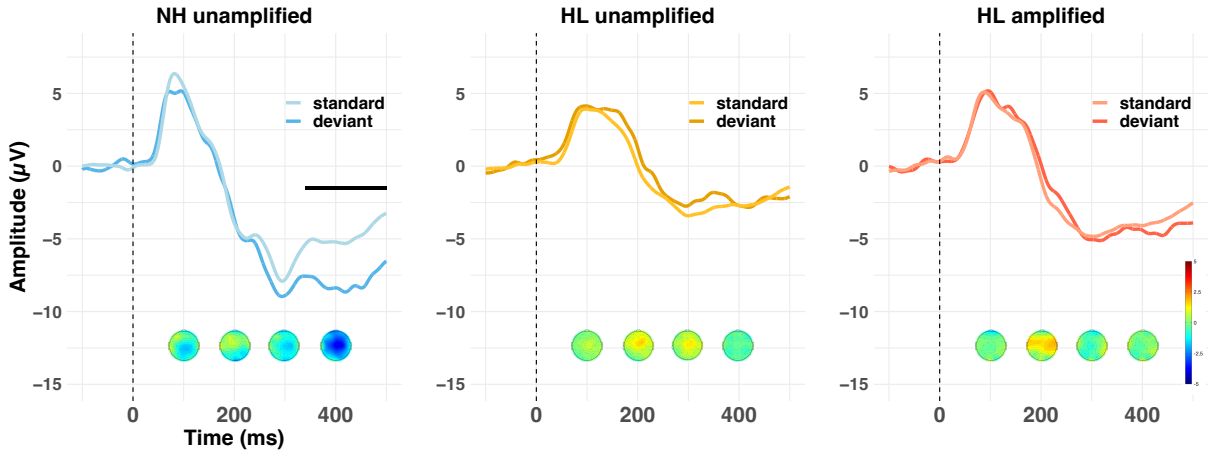
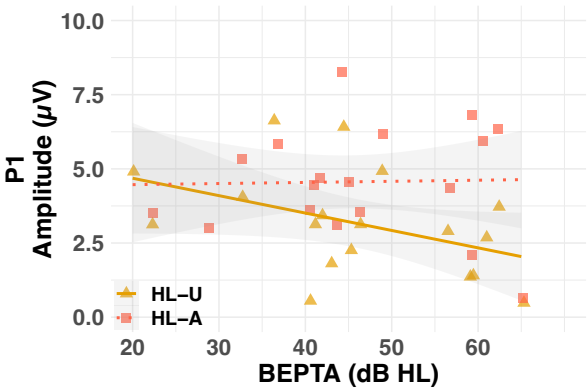


Figure 5: Grand average waveforms at Fz, evoked by the standard (lighter line) and deviant (darker line) presented either unamplified to both children with NH_U (left column) and children with HL_U (middle column) or amplified to children with HL_A (right column). Voltage maps show the mean MMN activity during the 100-500 ms post-stimulus time window. Negative values of the MMN are shown in blue, and positive values in red. The horizontal line represents the duration of a significant MMN in the period of the 100-500 ms post-stimulus-onset epoch evoked in children with NH. No significant MMNs were observed in either the unamplified or amplified conditions for the children with HL as a group.

Next, we sought to determine whether amplification benefited the cortical processing of speech sounds in children with HL (HL_U vs. HL_A; see Supplementary Table 5). For P1 amplitude, there was no significant main effect of amplification ($p = 0.425$). However, we found a just significant amplification × BEPTA interaction ($p = 0.048$; see Supplementary Figure 1). Specifically, in the unamplified condition, children with higher (i.e., poorer) BEPTA thresholds tended to have a smaller P1, with no such effect of BEPTA in the amplified condition. P1 latency was also longer for individuals with higher BEPTA thresholds ($p = 0.044$), irrespective of the condition. There was no significant benefit of amplification on N2 or MMN amplitude or latency (all ps > 0.05). Yet there was a main effect of age on MMN amplitude ($p = 0.016$): irrespective of the condition, MMN amplitude decreased with age in children with HL (see Figure 6).

Last, we evaluated the potential benefit of amplification for cortical processing of speech in children with HL to that of children with NH (HL_A vs. NH_U; see Supplementary Table 6). There was no significant effect of group on P1 amplitude or latency (both *p*s > 0.05). Yet there remained a group difference when looking at N2 ($p = 0.005$): despite amplification, N2 amplitude was smaller (by 2.66 µV), but not later, in the group with HL_A than the group with NH_U. With respect to the MMN, we observed a nearly significant group × age interaction ($p = 0.057$). In children with HL_A, the amplitude of the MMN decreased with age ($p < 0.05$). This was not the case in children with NH_U ($p = 0.883$; see Figure 6).



Supplementary Figure 1: Amplitude (µV) of the P1 for the HL group as a function of BEPTA. Individual (shapes) and group (lines) data are shown for both unamplified (HL_U, plain lines) and amplified (HL_A, dotted lines) raw. Shaded lines represent the 95% confidence intervals.

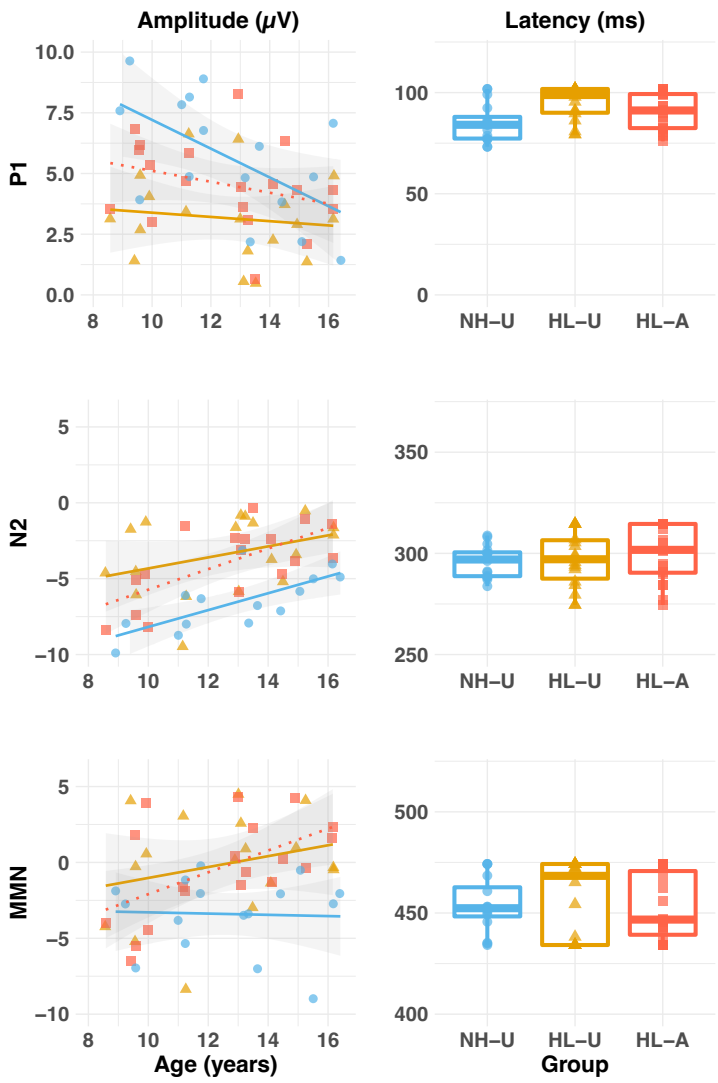


Figure 6: Amplitude (μV; left column) and latency (ms; right column) of the P1, N2 and MMN for each group (NH vs. HL). Individual (shapes) and group (colour) data are shown for both unamplified (HL_U, orange) and amplified (HL_A, red) data. Shaded lines represent the 95% confidence intervals. Latencies (right column) are illustrated as group boxplots because there was no effect of age.

3. *Behavioural data*

3. 1. Speech discrimination in quiet

Figure 7 shows the behavioural performance of the two groups on the speech perception tasks. For speech discrimination of the speech sounds /bɑ/ vs /dɑ/ in quiet (Figure 7A), there was no significant effect of group, age, or their two-way interaction on response thresholds (all *p*s > .10; see Supplementary Table 7A).

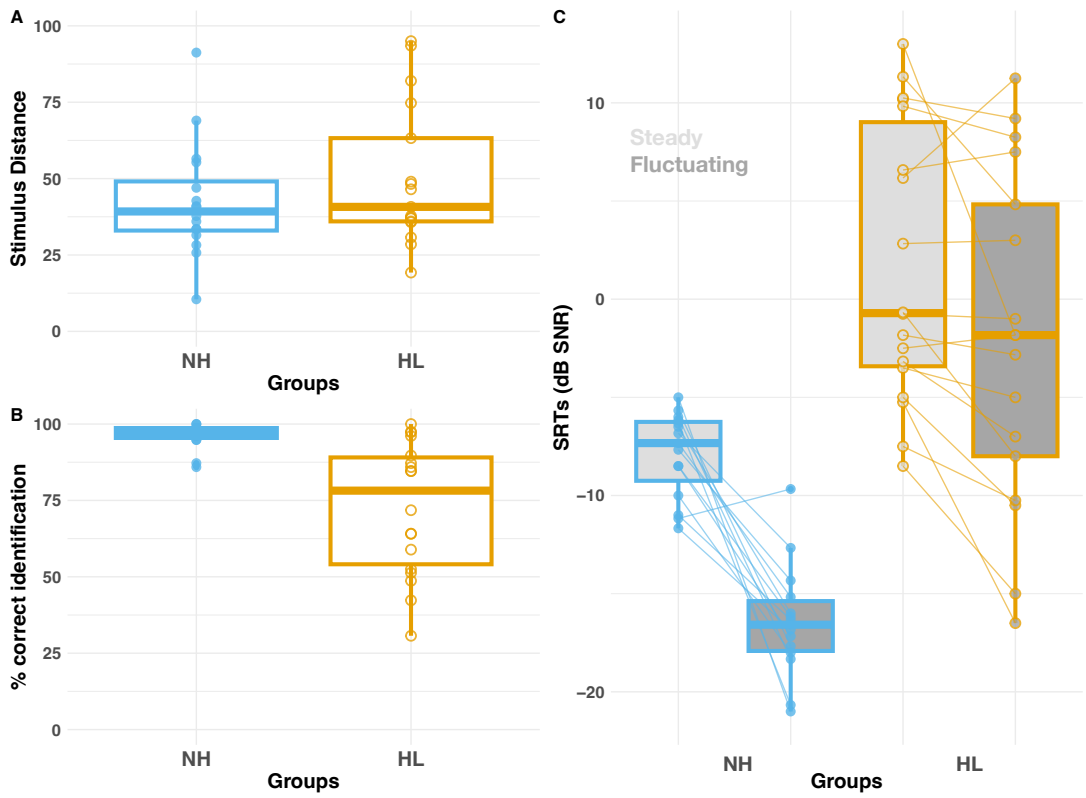


Figure 7: Boxplots of (A) stimulus distance (B) percentage correct consonant identification in quiet and (C) SRTs for consonant identification in steady (light grey) and fluctuating (dark grey) background noises. Children with NH are shown in blue, HL children are shown in orange. The boxes show the interquartile range (25th-75th percentile) of the data with horizontal line indicating the median. The whiskers indicate values that fall within 1.5 times the interquartile range.

3. 2. Speech identification in quiet and noise

Figure 7B presents the percentage correct consonant identification in quiet for the children with NH and those with HL (also see Supplementary Table 7B). Children with HL were significantly poorer than children with NH ($p < 0.001$). Note that for both groups, performance significantly improved with age ($p = .003$), although ceiling effects meant only a very small increase in percentage correct for the NH group.

Finally, Figure 7C presents the SRTs in steady and fluctuating background noise for the NH and HL groups (also see Supplementary Table 7C). The significant main effects of group and noise type (both *p*s < .001) need to be considered in light of the significant group × noise type interaction ($p = .006$). As expected, both groups experienced masking release when they

were presented with fluctuating noise (both *p*s < 0.001). However, the magnitude of this effect was larger in children with NH (8.5 dB SNR) than in children with HL (3.9 dB SNR).

4. Relationship between the neural and behavioural responses

The relationship between electrophysiological activity and behavioural responses was investigated by means of a set of correlations. Holm-Bonferroni correction was applied to correct for multiple comparisons where appropriate.

Given the evidence that perception of speech in quiet is dominated by the encoding of the envelope of the signal, we investigated the relationship between the amplitude of the FFR_{ENV} at both F0 and H2 and behavioural performance of speech identification in quiet, separately for children with NH_U and children with HL_U. None of the correlations were significant (all *p*s > 0.05).

Adequate perception of speech in noise requires precise spectro-temporal processing of speech, particularly in the dips of a fluctuating background noise. Therefore, we investigated the relationship between amplitude of the FFR_{TFS} at H4 and H6 and behavioural speech perception in steady and fluctuating noise, as well as masking release, separately for children with NH and children with HL (in both unamplified and amplified conditions). None of the correlations were significant (all *p*s > 0.05).

The speech stimuli used for the electrophysiological recordings were the endpoints /bɑ/ and /dɑ/ of the continuum used for the speech discrimination in quiet behavioural task. As such, we hypothesised that a relationship might be observed between the amplitude of the MMN and the stimulus distance threshold measured in the speech discrimination in quiet behavioural task. However, there was no significant correlation between speech discrimination in quiet and MMN amplitude, as evaluated separately for both groups, and separately for the amplified and unamplified conditions in children with HL (all *p*s > 0.05).

Last, we investigated the relationship between subcortical and cortical responses, separately for both groups (and separately for HL_A and HL_U). There was no significant correlation between FFR_{ENV} at F0 and either P1 or MMN amplitude (all *p*s > 0.05).

Discussion

This study aimed at investigating the effect of childhood MM HL and the benefit of amplification on both subcortical and cortical processing of speech sounds. When sounds are presented at the same intensity across groups, both subcortical and cortical responses are smaller in children with HL than in children with NH. When sounds are amplified, the subcortical responses increase in children with HL_A compared to HL_U, although this effect is modulated by age with respect to the FFR_{ENV}. In fact, the subcortical response even appears to be larger in children with HL when sounds are amplified, in comparison to children with NH when unamplified (although this effect was only significant for the FFR_{TFS}). At the cortical level, an amplification benefit was also observed on P1 amplitude, but not on any other measure (P1 latency, N2 amplitude and latency, MMN amplitude and latency). In fact, at the group level, children with HL did not show a significant MMN (unlike children with NH), whether the sounds were amplified or not. When looking at individual responses, the amplitude of the MMN decreased with age in children with HL but not in those with NH. Behaviourally, children with HL had poorer speech intelligibility than those with NH both in quiet and in noise, and they showed less benefit from background noise fluctuations.

Our main finding suggests that amplification leads to larger subcortical (FFR_{ENV} and FFR_{TFS}) responses, but it does not seem to be beneficial for cortical processing of speech, except for larger P1 amplitudes in children/adolescents with MM HL and high BEPTA. This is in line with a recent study conducted in older adults with mild to severe HL who were fitted with hearing aids for the first time. Speech evoked subcortical and cortical responses were recorded

successively in the participants, with and without hearing aids[63]. When sounds were presented at 65 dB SPL, the authors reported a significant benefit of amplification on the amplitude of the subcortical, but not cortical response. (Note that the opposite pattern of results was observed when sounds were presented at 80 dB SPL: there was no significant benefit of amplification on the subcortical response, only on the P1 amplitude and latency[63]). This is in line with the results we observed, as we presented the unamplified sounds at 70 dB SPL. These observations are also consistent with data collected in gerbils with developmental conductive HL, which have shown age-appropriate subcortical, but not cortical responses to amplitude modulated sounds presented at a similar sensation level in the group with HL and that with NH[64]. Together, these results suggest that HA amplification differentially affects successive levels of processing along the auditory pathway.

Importantly, this benefit of amplification seems to be dependent on the age of the participants. Indeed, in two instances, we observed a decrease in the amplification benefit from childhood to late adolescence. At the subcortical level, amplitude of the FFR_{ENV} was larger in response to amplified stimuli (HL_A) than unamplified stimuli (both HL_U and NH_U). Yet this benefit marginally decreased from childhood to adolescence in HL_A. This seems to indicate a developmental decrease in the benefit of FFR_{ENV} amplification in the group with MM HL. At the cortical level, individual MMN amplitude decreased with age in the group of children/adolescents with HL, in both amplification conditions – yet there was no age effect on the MMN amplitude of the children/adolescents with NH_U. This finding replicates our previous finding of a "disappearing" MMN: whereas 8-12 year-old children with MM HL showed age-appropriate MMNs, 12-16 year-old adolescents with MM HL did not[38].

Unfortunately, in the current study, we experienced a sample bias that limits the interpretation of this developmental effect. Indeed, in our sample, older children had better BEPTA (by approximately 5 dB HL), putting them at an advantage in terms of audibility,

compared to younger children. A 5 dB HL difference is very small, and within the error limits of any measured threshold, so therefore unlikely to explain some of the group by age interactions we have observed. However, given this potential sample bias, BEPTA was included as a predictor in the models comparing HL_U to HL_A neurophysiological responses. With the exception of P1 amplitude, BEPTA did not interact with amplification, indicating that our results cannot simply be explained by changes in the audibility of the stimuli. On the contrary, our data suggests developmental changes in the function and/or structure of the auditory cortex that occur throughout late childhood/adolescence following a period of permanent MM HL, despite amplification. The timing and the exact nature of this developmental change remains largely unknown, but could operate as follows:

Regarding timing, the onset of puberty could act as a biological trigger to the neurophysiological changes in the auditory pathway following childhood HL. Adolescence is characterized by the onset of puberty, and accompanied by unique changes in social, biological and cognitive traits[65]. Sex steroids are elevated during puberty[66], which fuels a cascade of biological changes. In animals, hormonal changes observed at adolescence seem to play a role in regulating the mechanisms of plasticity (for a review, see [67]). In humans, changes in pubertal hormones could thus modulate plasticity in higher-order cognition during adolescence. Strikingly, brain development at adolescence seems to follow a puberty-dependent trajectory[68-70]. Synaptic pruning accelerates around puberty onset in frontal, temporal and parietal brain areas, which host executive functions, auditory and multimodal processing, respectively[69]. How congenital MM HL modulates the outcome of these functional changes remains an open question.

Regarding the underlying cause of the developmental effect of MM HL on the function and/or structure of the auditory pathway, an overlooked, but not unlikely candidate is cross-modal plasticity. Cross-modal plasticity is defined as a physiological change in the properties

of neurons following sensory deprivation, which leads to stronger responsiveness to stimuli presented in the preserved sensory modalities (for a review on cross-modal plasticity in hearing loss, see[71]). Brain responses to tactile and visual stimuli are thought to be larger in deaf adults and adolescents than age-matched individuals with NH[72-74]. In line with these results, electrophysiological data collected in adults with age-related HL indicate that even moderate degrees of sensory deprivation can induce cross-modal plasticity (for a review, see[75]). For example, older adults with early-onset, high-frequency HL showed larger visual event-related potentials than age-matched individuals with NH[76]. Therefore, the smaller and sometimes later cortical responses we observed in response to speech syllables could reflect the effect of cross-modal plasticity in children with mild or moderate congenital HL, even when provided with amplification. This could also explain why we observed a benefit of amplification at the subcortical, but not cortical level of the auditory pathway. Indeed, whereas the inferior colliculus is a major locus of integration of auditory inputs (for a review, see[77]), the auditory cortex integrates the auditory input with input received from other sensory modalities[78]. If there is indeed cross-modal reorganisation following childhood MM HL, we would expect young individuals with HL to exhibit larger neural responses to non-auditory (e.g., visual) stimuli. In fact, should puberty really trigger cross-modal reorganization following HL, we would expect *adolescents* with HL to exhibit larger neurophysiological responses to visual stimuli than *children* with HL. More studies are warranted to further of understanding of the mechanisms underlying the developmental changes associated with HL, and their exact timing.

In addition to changes in the neurophysiological responses to speech sounds, children with HL also showed poorer speech identification in quiet and in noise than children with NH (all children tested without amplification in the behavioural tasks). This is in line with previous results showing that even mild degrees of sensorineural HL impact speech perception in children[79]. In particular, children/adolescents with HL showed significantly less masking

release than those with NH in fluctuating compared to steady background noise. This is in line with previous studies indicating that childhood HL affects the perception of TFS[14,15,80]. Surprisingly, we did not observe significant relationships between any neurophysiological response and behavioural performance, in either children with HL_U or NH_U.

In conclusion, children/adolescents with MM HL show poorer simultaneously recorded subcortical and cortical activity evoked by speech syllables presented without any amplification. When provided with amplification, subcortical responses significantly increased, which was not the case for late cortical responses. Both at the subcortical (FFR_{ENV}) and cortical (MMN) levels, the amplification benefit seemed to decrease as children grew older. Puberty might act as a biological trigger for cross-modal reorganization of the auditory pathway following even a mild/moderate childhood HL.

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Author contributions

A.C. and S.R. conceived the idea, A.C. collected data, A.C. and S.R. analysed the data, A.C. and S.R. interpreted the data, A.C. and S.R. wrote the manuscript.

Data availability

Unidentifiable data, stimuli and statistical analyses scripts are publicly available on: https://github.com/acalcus/MMHL_amplification

Competing interests

The authors declare no competing interests

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