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Cortical potentials evoked by tone frequency changes can predict speech perception in noise

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ABSTRACT

Accurate and objective assessment of higher order auditory processing is challenging and mainly relies on evaluations that require a subjects' active participation in tests such as frequency discrimination or speech perception in noise. This study investigates the value of cortical auditory evoked potentials (CAEPs) evoked in response to auditory change stimuli, known as acoustic change complexes (ACCs), as an objective measurement of auditory performance in hearing impairment. Secondary objectives were to assess the effect of hearing loss and non-professional musical experience on the ACC, and compare the ACC to the 'conventional' CAEP evoked in response to stimulus onset. In 24 normal-hearing subjects, consisting of 12 musicians and 12 non-musicians, and 13 age-matched hearing-impaired subjects ACCs were recorded in response to 12% frequency increases at four base frequencies (0.5, 1, 2 and 4 kHz). ACC amplitudes and latencies were compared to frequency discrimination thresholds at each base frequency, and to speech perception in noise. Frequency discrimination and speech perception in noise were significantly better for larger ACC N1-P2 amplitudes and shorter N1 latencies, whereas both frequency discrimination and speech perception did not correlate with onset CAEP amplitude or latency. Multiple regression analysis for prediction of speech perception in noise revealed that the strongest model was obtained by averaging over three frequencies (1, 2 and 4 kHz) with two significant predictors: hearing loss ($R^2 = 0.52$) and ACC latency ($R^2 = 0.35$). Thus, explaining 87% of the variance, this model indicates that subjects with longer ACC latencies have worse speech perception in noise than subjects with comparable hearing thresholds and shorter ACC latencies. If hearing loss was removed from this model, the combination of ACC amplitude and latency over those three frequencies explained 74% of the total variance in speech perception in noise. There were no differences in frequency discrimination, speech perception, CAEP, or ACC between recreational musicians and non-musicians. We conclude that the objective ACC N1 latency is a good predictor of speech perception in noise. When confirmed in validation studies with larger numbers of subjects, it can aid clinicians in their evaluation of auditory performance and higher order processing, in particular when behavioral testing is unreliable.

1. Introduction

In management of the hearing-impaired patient, clinicians have a great variety of tests at their disposal to assess auditory performance. The great majority of these tests require the subjects' active participation, for example repeating words or sentences in speech perception tests. However, certain hearing-impaired patients are unable to perform auditory tasks reliably, such as (young) children

Abbreviations: ACC, acoustic change complex; FDT, frequency discrimination threshold; FM, frequency modulation; HL, hearing loss; NH, normal-hearing; PTA, pure tone average; SNHL, sensorineural hearing loss; SRT, speech reception threshold.

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and patients with cognitive impairment. Particularly troubled in speech perception tests are patients who are not native to the language of the test, and who represent a considerable group in modern multicultural society. In these different groups of patients, it is typically challenging for clinicians to accurately assess their hearing performance and fit their hearing aids and cochlear implants (CIs). To date, there is a limited availability of objective tests that do not require the subjects' active participation, and the most frequently used clinical evaluations, like auditory brainstem responses and otoacoustic emissions, provide information on peripheral auditory pathway function, but do not provide insight in higher order auditory processing. Therefore, an objective measurement of auditory performance, indicative of speech perception, would be valuable in subjects unable to perform auditory tasks reliably.

As recognized for several decades, cortical auditory evoked potentials (CAEPs) might be promising as objective measurements related to speech perception (Eggermont and Ponton, 2002). The conventional CAEP, which is evoked by the onset of a stimulus and can be recorded in a passive listening situation, reflects cortical detection of sound. The correlation between speech perception and the 'conventional' CAEP evoked in response to the onset of a pure tone is generally weak to absent (Billings et al., 2009; Brown et al., 2015; Lammers et al., 2015). However, with recordings of cortical potentials evoked in response to speech-in-noise stimuli, previous studies have found strong correlations with speech perception (Billings et al., 2013, 2015). A less applied variation of CAEP is the acoustic change complex (ACC), which is evoked by a change within an ongoing stimulus (Martin et al., 2007; Kim, 2015). The ACC has been recorded in response to changes within speech stimuli (Ostroff et al., 1998; Martin and Boothroyd, 2000; Tremblay et al., 2003; Friesen and Tremblay, 2006) and to intensity, frequency and/or location changes within continuous tones (McCandless and Rose, 1970; Arlinger and Jerlvall, 1979; Harris et al., 2007, 2008; Dimitrijevic et al., 2008; Pratt et al., 2009; He et al., 2012; Brown et al., 2017; Presacco and Middlebrooks, 2018; Vonck et al., 2019, 2021; Zhang et al., 2021). These studies indicate that ACCs can be reliably recorded showing similar P1-N1-P2 waveforms as the CAEP and that ACC variables such as threshold, amplitude or latency correlate with perceptual outcomes. ACCs to frequency changes correlate with frequency discrimination and speech perception (He et al., 2012; Brown et al., 2017; Vonck et al., 2021). Such correlations are expected considering that our ability to detect frequency changes is essential for various auditory tasks in daily life such as understanding speech, distinguishing relevant sounds from background noise and appreciating music (Parbery-Clark et al., 2009).

Recently our study group compared psychophysically assessed frequency discrimination thresholds (FDTs) to ACC thresholds, and found that frequency discrimination deteriorates with progression of hearing loss (Vonck et al., 2021). The NH group showed FDTs as known from the literature (0.5–1%; Sek and Moore, 1995; Amitay et al., 2006; Papakonstinou et al., 2011), whereas in the SNHL group FDT increased to a median of 2%. This previous study revealed a moderate to strong correlation between FDTs and ACC thresholds, which strengthens the potential value of the ACC as an objective tool in audiometry. However, both frequency discrimination and speech perception were mostly explained by hearing loss and the ACC threshold measurement is relatively time consuming, since ACCs to several frequency change magnitudes need to be recorded. The current study investigates the clinical applicability of the ACC evoked in response to a relatively large suprathreshold frequency change magnitude (12%) within a group of NH subjects and subjects with sensorineural hearing loss (SNHL). Additionally we address the effect of musical training, as recent studies have found that professional musical training in young adults is beneficial for frequency discrimination and frequency change detection and induces alterations in ACC amplitudes (Lee et al., 2020; Liang et al., 2016). However, it remains unknown if this effect of musical training also extends to recreational musical training. If this were the case, this may support the applicability of musical training in hearing-impaired patients, although evidence for efficacy as yet is weak (McKay, 2021). We hypothesized that musical training at a recreational level would also facilitate an increased frequency discrimination ability and induce alterations in ACC parameters. Therefore, the NH group in the current study is divided in subjects without musical training, and subjects with musical training at recreational level.

The primary objective of this study is to investigate whether the ACC in response to a large frequency change can predict frequency discrimination ability and speech perception in noise, in a population with a wide range of hearing loss. A secondary objective is to investigate the effect of musical experience at a recreational level on ACC and auditory performance in NH adults. Finally, literature suggests ACCs show higher correlations with perceptual measures than onset-CAEPs, but direct comparisons between ACCs and onset-CAEPs regarding such correlations in the same subjects are scarce. Therefore, in the present study, we compare ACC measures to onset-CAEP measures with respect to the correlations with perceptual measures in order to investigate the added value of ACCs relative to onset-CAEPs.

2. Methods

2.1. Subjects

Twenty-four NH subjects and 13 SNHL subjects participated in the study (Table 1). In order to investigate an effect of musical experience, we recruited 12 NH musicians and 12 NH non-musicians, as explained in detail below, and these were considered as two NH subgroups in our analyses. There was only one SNHL subject with musical training, therefore SNHL was treated as one group. SNHL subjects were hearing aid users who visited the UMC Utrecht for their audiometric follow-up. Subjects were actively recruited to match age among the three groups. The 13 SNHL subjects and 12 of the 24 NH subjects also participated in our previous study (Vonck et al., 2021). The study was approved by the Medical Research Ethics Committee of the UMC Utrecht (protocol number 11–359) and informed consent was obtained from all subjects. Sensorineural hearing loss was defined as an average pure tone threshold (PTA) of >15 dB at 0.5, 1, 2 and 4 kHz, or a threshold of >20 dB at one or more frequencies between 0.125 and 8 kHz. Subjects with a pure sensorineural hearing loss, without an additional conductive hearing loss at 0.5, 1, 2 or 4 kHz (thus air-bone gap <5 dB), were included. Thresholds in the SNHL group varied from 5 to 70 dB at 0.5 kHz and 40 to 90 dB at 4 kHz. All tests in SNHL subjects were conducted without their hearing aid. In all subjects both ears were tested with pure tone audiometry, their 'better ear' was defined as the ear with the lower PTA. All psychophysical and electrophysiological tests were performed using only the subjects' better ear. Prior to these tests, all participants answered a questionnaire on their musical background. In this questionnaire (see Supplementary material), participants were asked if they practiced music, how many hours a week and for how many years. Their 'musical experience score' was calculated by multiplying the average time of musical experience in hours per week by the years of active engagement. A musical experience score threshold of 15 was applied in recruiting twelve NH musicians (score ≥ 15) and twelve NH non-musicians (score <15; Table 1A). The threshold of 15 was based on data in 41 young adult subjects. In this psychophysical study (unpublished), 21 subjects who completed the questionnaire had a musical experience score between 0 and 6, whereas 20 subjects, who were recreational musicians, had a score of 20

Table 1
A. Subject characteristics.

	N	Gender		Best ear		Age			Indicative IQ score			Musicality score		
		Male	Female	Left	Right	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
NH music	12	8	4	4	8	40.7	14.6	23–60	108.8	15.6	84–130	50.4	49.4	15–186
NH non-music	12	6	6	8	4	42.5	13.1	23–58	98.3	16.8	76–129	1.8	1.7	0–5
SNHL* (*non-music*)	12	6	6	6	6	41.0	15.4	20–66	94.7	22.9	50–124	2.6*	3.5	0–9
(*music*)	1	–	1	–	1	46	–	–	103	–	–	56	–	–
Total population	**37**	**20**	**17**	**18**	**19**	**41.5**	**13.8**	**20–66**	**100.6**	**18.9**	**50–130**	**19.3**	**36.1**	**0–186**

B. Musical experience for subjects with score ≥ 15

Subject	Instrument 1	Instrument 2	Age	Age at start musical engagement	Age stopped	Years of musical engagement	Times per week	Musical experience score	Non-musical years before test
NH									
NH13	Trombone		58	49	n.a.	7	5	35	0
NH14	Cello		49	9	16	7	3	21	33
NH15	Vocal		43	22	n.a.	21	1.3	27	0
NH16	Piano		27	6	12	6	3	18	15
NH17	Vocal		23	15	n.a.	8	2.5	20	0
NH18	Piano		26	9	n.a.	17	5	85	0
NH19	Saxophone		28	8	18	10	3	30	10
NH20	Flute	Guitar	51	8	13	5	3	15	38
NH21	Piano	Guitar	24	10	n.a.	14	3	42	0
NH22	Vocal		59	16	n.a.	43	2.1	91	0
NH23	Drum	Vocal	60	53	n.a.	7	5	35	0
NH24	Saxophone	Clarinet	40	9	n.a.	31	6	186	0
SNHL									
SNHL13	Flute		46	8	22	14	4	56	24

* Table 1A presents values of the SNHL group divided in 12 SNHL non-music subjects, and 1 SNHL music subjects. Further analyses are conducted with SNHL combined as one group of 13 subjects: mean Age 41.4 (SD 14.8), mean IQ score 95.3 (SD 22.1), mean Music score 6.7 (SD 15.2).
Table 1B is based on the music questionnaire (Supplementary material). Additionally, subjects were instructed that instruments included the singing voice.

or higher. Out the 13 SNHL subjects only one subject had a musical experience score >15, therefore, we did not divide the SNHL group. To determine whether intelligence influenced our outcome measures, i.e. frequency discrimination, speech perception and ACC waveforms, a shortened WAIS IQ test was completed by all subjects to obtain an 'indicative IQ score' (Silverstein, 1985).

Subject characteristics are presented in Table 1A. Between the three groups, there were no significant differences in age (Kruskall-Wallis, 0.082, $p = 0.96$) or indicative IQ score (Kruskall-Wallis, 2.762, $p = 0.251$). Subjects were actively recruited to age match between groups. Although IQ scores appeared to be higher in the musician group, this trend was not significant and IQ was considered comparable between the three groups. Musical experience score did not significantly differ between the NH non-musicians and the SNHL subjects (Mann-Whitney U, 0.543, $p = 0.59$). Musical experience score varied within the NH musicians group, ranging from 15 to 186 (Table 1B). NH musicians played varying musical instruments or had musical experience as singers. Eight out of 12 NH musicians were active musicians while the other four musicians had stopped practicing music at least 10 years before they were enrolled in this study.

2.2. Psychophysical tests

Psychophysical tests were conducted in a sound-attenuated booth (Industrial Acoustics Company GmbH, Niederkrüchten, Germany). Frequency discrimination thresholds (FDTs) were determined using pure tone stimuli with base frequencies of 0.5, 1, 2 and 4 kHz in a 3-interval 2-alternative forced choice paradigm programmed in Matlab (version 7.11.0, Mathworks, Natick, MA, USA). Subjects were presented with sets of three subsequent tones of which either the first or the last was higher in pitch and were asked whether the first or the last stimulus was different. Duration of each tone pip was 400 ms with cosine-squared onset and offset ramps of 5 ms, and the duration of the silent interval was 300 ms. A 3-down, 1-up adaptive staircase procedure was used to determine the frequency discrimination thresholds. Before the actual test, a short practice round was performed so the participants were able to get familiar with the procedure and the sounds; this practice round was conducted at 1500 Hz, which differs from the test frequencies, and it started with Δf of 50% to make it easy for both NH and SNHL subjects. Subjects could practise several rounds to get familiar with the task (typically 1 to 4 rounds). For the actual test, the start size of Δf was 2% for both NH and SNHL subjects, and the step size was a factor 2 (decrease if correct, increase if incorrect), followed by a factor of 1.5. After 12 reversals, the frequency discrimination threshold was determined by averaging the frequency difference between the higher tone and the reference tone, Δf, for the last 6 reversals. Stimuli were presented, through a Creative® USB Sound Blaster HD sound card (Creative Technology Ltd., Jurong East, Singapore) and Decos Audiology Workstation (Decos systems BV, Noordwijk, the Netherlands) linked to a Sennheiser HD 200 headphone (Sennheiser electronic GmbH & Co., Wedemark, Germany). Stimuli were presented over the headphone to the better ear at 75 dB SPL in NH subjects or at maximum comfortable loudness level in SNHL subjects. We determined maximum comfortable loudness prior to the testing procedure by presenting the stimuli at 75 dB SPL and asking the SNHL subjects whether they were had a clear perception of the tones. Stimulus levels were increased with 5 dB until subjects had a clear perception at comfortable loudness. For the subjects with mild hearing impairment, the presentation level was 75 dB SPL, and for the subjects with more severe hearing impairment, levels were 80 to 90 dB SPL. Maximum comfortable loudness level was determined for each base frequency. Thereby, in a subject with sloping hearing loss this could result in stimuli at 0.5 kHz presented at 75 dB SPL while stimuli at 4 kHz were presented at 90 dB SPL.

Monaural (better ear only) and binaural speech reception thresholds (SRTs) in noise were measured using Dutch standardized sentences by Plomp and Mimpen (1979) presented from a Yamaha MSP5A speaker (Yamaha Music Europe GmbH, Rellingen, Germany) at the frontal central position at a distance of 1.0 m from the subject's head. When the better ear was tested, the contralateral ear was plugged with an earplug and covered by an ear cap (average noise reduction 32 dB; Howard Leight Viking V3, Honeywell, San Diego, CA, USA). SRTs were determined using lists of 13 sentences without stop criterion according a standardized protocol (Plomp and Mimpen, 1979) applied in the UMC Utrecht. For the SNHL subjects, first, SRT in quiet was assessed, which started with presentation of a sentence at 15 dB above the average pure tone thresholds for 0.5, 1 and 2 kHz. Levels were increased with 4 dB till the subject could repeat each word of the sentence correctly. Subsequently, the level was decreased by 2 dB, and when the subject could repeat the sentence correctly, the level was again decreased and when the subject could not repeat the sentence, the speech level was increased by 2 dB. The SRT was defined as the level for which 50% of the sentences were correctly repeated. For the SRT in noise test, stationary speech-shaped noise was applied at a fixed level of 60 dB SPL for the NH subjects, and at 15 dB above the SRT in quiet, with a minimum of 60 dB SPL for the SNHL subjects. The noise levels in the latter group varied from 60 to 92 dB SPL. The test started with presentation of the speech level at 8 dB below the noise level. When the subject could not repeat the full sentence, the speech level was increased by 4 dB till the sentence was repeated correctly. Subsequently, the procedure was followed as for the SRT in quiet using steps of 2 dB. The SRT was defined as the speech-to-noise ratio for which 50% of the sentences were correctly repeated.

2.3. ACC stimuli and recording procedure

The onset-CAEPs and ACCs were recorded using procedures as described in our previous studies (Vonck et al., 2019, 2021). The recording session started with baseline recordings of an onset-CAEP, evoked by a pure tone of 2 kHz with a duration of 300 ms and inter stimulus interval of 900 ms. This was followed by a baseline ACC recording in response to a 12% frequency increase from 2 to 2.24 kHz. The purpose of these baseline recordings was to reliably compare ACCs to onset-CAEPs at the same frequency. After the baseline recordings, the ACCs in response to 12% frequency increments were recorded at four different base frequencies (0.5, 1, 2 and 4 kHz), in a randomized order. Breaks of around one minute were introduced between each recording. These main ACC recordings were obtained in all 37 subjects, baseline recordings in 32 of 37 subjects (22/24 NH, 10/13 SNHL) as we decided to perform those recordings after the first 5 subjects in the study.

The acoustic change stimuli consisted of three components (Fig. 1A): a) a reference tone at a base frequency, f_{base}, with a duration of 2997 ms, b) an upward logarithmic frequency modulation (FM) sweep with a frequency change of 12% compared to f_{base} with a duration of 3 ms, c) a target tone with a frequency of $f_{base} + 12\%$ with a duration of 300 ms. We ensured that the second component started at the final phase of the first component and the third component started at the final phase of the second component, to prevent transient signals. The silent interval between stimuli was 200 ms. The 12% frequency increase corresponds to frequency increases from 0.5 to 0.56 kHz, 1 to 1.12 kHz, 2 to 2.24 kHz, and 4 to 4.48 kHz.

Sound stimuli were generated using Matlab (version 7.11.0, Mathworks, Natick, MA, USA) at a sample frequency of 50 kHz and presented monaurally to the better ear through a TDH-39 head-

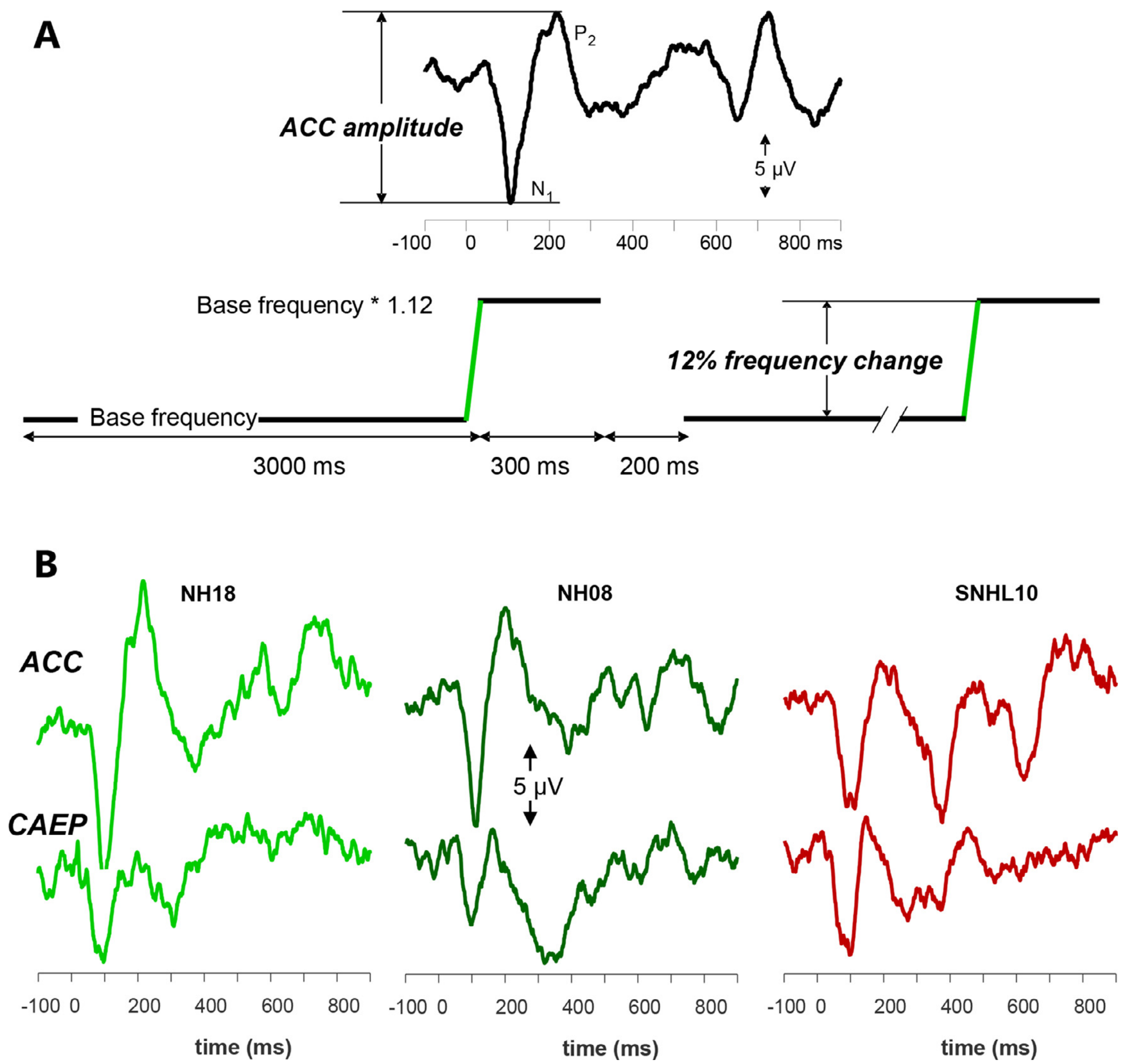

Fig. 1. A schematic representation of the frequency change stimulus. The stimulus consists of 3 components: a) a reference tone at a base frequency with a duration of 3000 ms, b) a fast logarithmic frequency modulation (FM) sweep with a 12% frequency change from base frequency a duration of 3 ms, c) a target tone with a frequency of 'base frequency * 1.12' and a duration of approximately 300 ms. The silent interval between subsequent stimuli is 200 ms. The ACC waveform occurs in response to the frequency change, with the N1 peak at approximately 100 ms after the stimulus onset followed by the P2 peak at approximately 200 ms. ACC N1 latency in ms and ACC N1-P2 amplitude in µV are determined for analysis. B Baseline CAEP and ACC waveform examples in 3 subjects evoked in response to an onset CAEP stimulus of a 2 kHz pure tone, and a 12% frequency increase ACC stimulus at a base frequency of 2 kHz. The lower waveforms indicate the CAEP, the upper waveforms indicate the ACC. Both the onset of the CAEP stimulus, and the onset of the frequency change in the ACC stimulus occurred at 0 ms. In both the CAEP and the ACC the N1 peak occurred at approximately 100 ms. Waveforms on the left were evoked in a NH recreational musician, waveforms in the middle column evoked in a NH non-musician and waveforms on the right in an SNHL subject with 35 dB HL at 2 kHz.

phone (Telephonics, Farmingdale, NY, USA). In order to reduce an effect of loudness variation among subjects, we aimed at similar loudness by presenting the stimuli at 75 dB SPL in NH subjects, and at maximum comfortable level in the SNHL subjects. This resulted in stimulus presentation levels in SNHL subjects of 75 dB SPL or higher (up to 90 dB SPL), similar to levels used for the frequency discrimination tests including levels varying with frequency within subject (see 2.2).

Recordings were performed inside an electrically shielded, sound-attenuated booth. Participants were seated in a comfortable reclining chair and were allowed to watch a silent, captioned movie. They were carefully instructed prior to each recording to minimize movements and to fixate on the center of the video screen to minimize muscle and eye movement artefacts. Electrophysiological responses were recorded by Ag/AgCl electrodes placed according to the 10–20 system using a Medelec Synergy T-10 Evoked Potential system. The active electrode, Cz, was placed at the vertex of the skull. The contralateral mastoid was used as site for the reference electrode and the ground electrode was placed on the forehead. Eye movements and blinks were monitored using electrodes above and below the eye, contralateral of the stimulated ear, and blink artefact rejection was applied while recording.

Electrode impedance was kept below 4 kΩ for each electrode, with a between-electrode difference of less than 2 kΩ and was regularly checked during the test session. The electrode signals were recorded with a sampling rate of 50 kHz and filtered from 0.01 to 100 Hz while recording. Responses were acquired in a 1000 ms time window, including a pre-stimulus period of 100 ms. Responses containing amplitudes of >100 µV at any electrode were rejected and excluded from the averaged response. For the baseline CAEP and ACC recordings at 2 kHz, 100 accepted sweeps were averaged. For the following randomized ACC recordings at the four base frequencies, 50 accepted sweeps were averaged for each condition. The recording of 50 accepted sweeps was performed twice, and amplitudes and latencies of both recordings were averaged. Duration of the total recording procedure was approximately one hour. We did not encounter displacement of recording electrodes or subjects' discomfort because of the headphone.

2.4. Data analyses

The N1 was defined as the most negative peak between 70 and 180 ms after the onset of the frequency change in case of ACC or onset of tone in case of CAEP. P2 was defined as the first pronounced positive peak occurring after N1 between 150 and 250 ms after the change. The N1-P2 amplitudes and N1 latencies were determined. Peaks were manually identified by two investigators (BV, JvH) independently, using a custom-made Matlab script. Disagreements, for example in case of bifid peaks, were resolved by discussion and examination of the waveforms obtained during the previous recordings. ACCs were defined by an isoresponse frequency change using a cut-off value for the N1-P2 amplitude of 4 µV. This cut-off value was applied because ACCs of that amplitude were still clearly distinguishable from the noise in all recordings and this value was also applied in our previous study on ACC threshold determination (Vonck et al., 2021).

If N1-P2 amplitudes were below 4 µV and therefore less distinguishable from the noise, which was only the case in two SNHL subjects, larger frequency increments (24%) were used to evoke reliable and robust ACC waveforms with a clear N1 to confirm the presence of the smaller N1 peak in the waveforms at 12% around the same latency (Vonck et al., 2021). For ACC waveforms with N1-P2 amplitudes below 4 µV (at 12% frequency change), only the N1-P2 amplitudes were included in the analyses; ACC latencies for these small waveforms were considered less reliable and therefore not used in analyses.

Statistical analyses were completed using SPSS software (version 25, IBM Corp., Armonk, NY, USA). Psychophysical FDTs were obtained as Δf in% of base frequency. One-way ANOVA and *t*-tests, or in case of non-parametric distribution, the Kruskal-Wallis *H* and Mann-Whitney *U* tests were used to examine differences between the independent groups. Wilcoxon signed-rank test was used to compare non-parametric distributed related variables (CAEP versus ACC variables). Spearman's rank correlation analysis was performed to determine if hearing loss (in dB at 0.5, 1, 2, and 4 kHz), indicative IQ score (explained above), or musical experience score (explained above) were correlated to FDT (Δf%), SRT (dB), or ACC variables (N1-P2 amplitudes, N1 latencies), and whether ACC variables were correlated to FDT or SRT. Correlation analyses were performed in the total study population, except for musical experience score which was only performed in the 24 NH subjects, since the SNHL group were mostly non-musicians (12/13). The significance threshold was set at $p < 0.05$, with the notion of careful interpretation of data with p values just below 0.05 considering multiple testing. For each of the conducted tests, the strength (R) and significance (p) of the effects are presented. Correlation coefficients of $R<0.30$ were considered weak, R between 0.30 and 0.50 moderately strong, and $R>0.50$ strong (Cohen, 2003). In case of several significant correlations between ACC variables and other measures, additional multiple linear regression was conducted. We checked for collinearity between independent variables (defined as Tolerance<0.1 and variance inflation factor (VIF)>10).

3. Results

3.1. Psychophysical outcomes

3.1.1. Frequency discrimination thresholds

FDTs for four base frequencies were determined in all 37 subjects. FDTs are depicted in Fig. 2 for the three groups separately, for each of the four base frequencies. NH musicians had median FDTs of 0.4% to 0.9%, NH non-musicians median FDTs of 0.5% to 1.0%, and SNHL subjects median FDTs of 1.1% to 2.0%.

The FDTs differed significantly between the three groups for each base frequency (H = 6.2–15.9, $p < 0.001$ to 0.045). Post-hoc analysis revealed that the SNHL subjects had poorer FDTs than both the NH musicians for all four frequencies ($Z = 2.42$ to 3.59, $p < 0.001$ to 0.015) and the NH non-musicians at 1, 2 and 4 kHz ($Z = 2.4$ to 3.16, $p = 0.002$ to 0.017; 0.5 kHz: $Z = 1.77$, $p = 0.077$). Frequency discrimination thresholds did not differ between NH musicians and non-musicians ($Z = 0.6$ to $Z = 1.62$, $p = 0.10$ to $p = 0.95$) for any of the four frequencies. Additional subgroup analysis on the eight active musicians did not reveal FDT differences between these eight active NH musicians and the 12 NH non-musicians ($Z = 1.36$ to 1.53, $p = 0.13$ to 0.17)

Correlations between FDT and subject characteristics were analyzed across the total study population (Table 2A), with the exception of musical experience, which was analyzed only in the NH groups. FDT was significantly correlated to hearing loss for all four frequencies ($R>0.49$, $p < 0.01$), and average FDT was correlated to PTA ($R = 0.63$, $p < 0.001$). FDT was not associated with musical experience (Table 2A, $p>0.23$). The FDT had no relation to indicative IQ score at 1, 2 or 4 kHz, but was solely correlated to indicative IQ score at 0.5 kHz and this correlation was only borderline significant ($R=-0.36$, $p = 0.027$).

3.1.2. Speech reception thresholds in noise

In all 37 subjects, SRTs were determined for two conditions: monaural (better ear) and binaural. As shown in Fig. 3, there was a significant difference between the three groups in SRT for both the monaural ($H = 22.99$) and binaural ($H = 21.47$) conditions ($p < 0.001$). Post-hoc analyses confirmed significantly worse SRTs for SNHL subjects compared to both NH musicians and NH non-musicians for both the monaural and binaural conditions (SNHL vs NH musicians: $Z = 3.86$ to 4.06, $p < 0.001$; SNHL vs NH non-musicians: $Z = 4.01$ to 4.09, $p < 0.001$). There were no significant differences in SRT between NH musicians and NH non-musicians (monaural: $Z = 0.65$, $p = 0.519$; binaural: $Z = 0.79$, $p = 0.433$). The NH musicians had a monaural median SRT of −5.0 dB (range −6.2 to −3.0 dB) and a binaural median SRT of −5.8 dB (range −7.0 to −4.2 dB). For the NH non-musicians, the median SRT was −5.3 dB (range −6.2 to −3.4 dB) for the monaural condition and −5.9 dB (range −6.8 to −5.0 dB) for the binaural condition. For the SNHL subjects, the monaural median SRT was −1.6 dB (range −4.2 to 4.4 dB) and the binaural median SRT was −2.2 dB (range −5.8 to 5.2 dB).

Correlations between monaural SRT and subject characteristics are presented in Table 2B. SRT was significantly correlated to HL for each of the four base frequencies ($R>0.70$, $p < 0.001$), and for PTA ($R = 0.75$, $p < 0.001$). SRT did not vary with either musical experience score or indicative IQ score (Table 2B, $p>0.60$). Monaural SRT was significantly correlated to FDT for each of the four base frequencies (Table 2C, $R>0.53$, $p < 0.002$), and for the averaged FDT (Table 2C, $R = 0.69$, $p < 0.001$).

3.2. Auditory evoked potentials

3.2.1. ACC recordings

Fig. 1B displays examples of onset-CAEP and ACC waveforms at 2 kHz in three different subjects: one NH musician (NH18), one NH non-musician (NH08) and one SNHL subject (SNHL10). Baseline CAEP and ACC recordings were conducted in 32 subjects, and present in all these 32 subjects. Main ACC recordings, with ACCs in response to 12% frequency increases at the four base frequencies, were performed in all 37 subjects. Almost all recorded waveforms clearly showed the N1-P2 complex with an amplitude > 4 µV and a N1 around 100–120 ms. In three of the 148 recordings, ACCs

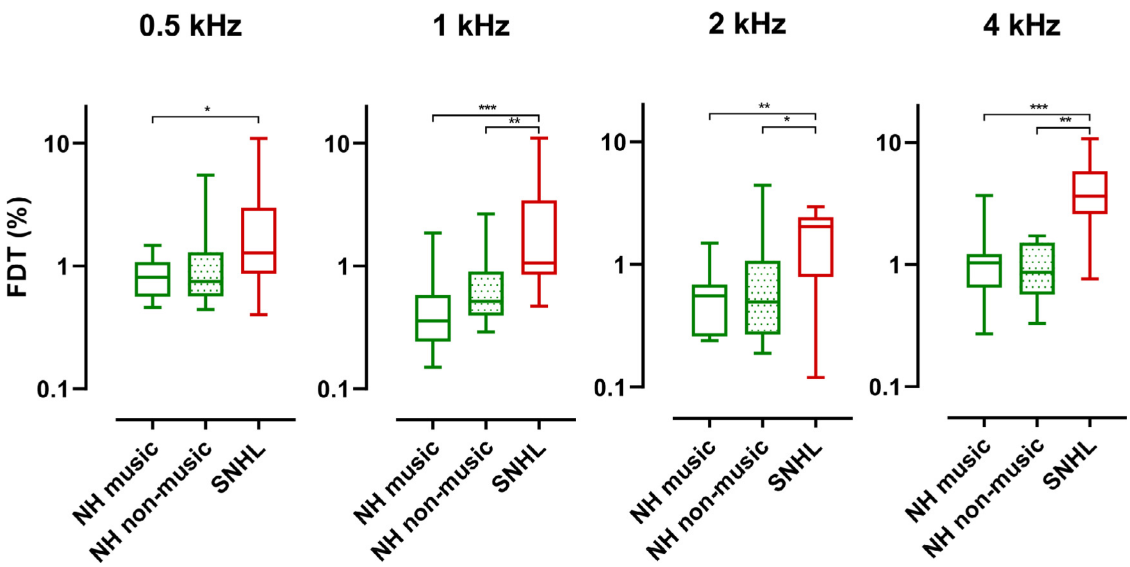

Fig. 2. Frequency discrimination thresholds for the 3 groups separately, for each of the 4 base frequencies. The boxplots represent the four quartiles of the data. Significant differences between groups are indicated with asterisks (*<0.05, **<0.01, ***<0.001).

Table 2
A. Correlations of FDT with subject characteristics.

	0.5 kHz		1 kHz		2 kHz		4 kHz		Average**	
	R	*p*	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*
HL	0.49	**0.002**	0.59	**<0.001**	0.57	**<0.001**	0.59	**<0.001**	0.63	**<0.001**
Music*	−0.02	0.922	−0.25	0.233	0.07	0.730	0.11	0.623	−0.02	0.927
IQ	−0.36	**0.027**	−0.25	0.136	−0.15	0.373	−0.22	0.180	−0.27	0.113

B. Correlations of monaural SRT with subject characteristics

	frequency	*R*	*p*
HL	0.5 kHz	0.76	**<0.001**
	1 kHz	0.79	**<0.001**
	2 kHz	0.73	**<0.001**
	4 kHz	0.70	**<0.001**
	Average	0.75	**<0.001**
Music*		0.06	0.792
IQ		−0.09	0.604

C. Correlations of monaural SRT with FDT

	R	*p*
0.5 kHz	0.53	**0.001**
1 kHz	0.62	**<0.001**
2 kHz	0.65	**<0.001**
4 kHz	0.57	**<0.001**
Average	0.69	**<0.001**

* for NH subjects, $N = 24$.
** FDT averaged over 0.5, 1, 2 and 4 kHz, HL averaged over 0.5, 1, 2 and 4 kHz.

were below 4 µV and could be less reliably distinguished from the noise. This was the case in one SNHL subject at 0.5 and 1 kHz, and in another SNHL subject at 4 kHz. As described in the Methods section, in these three cases ACC waveforms in response to larger frequencies increments (24%) were used to determine the presence of the ACC waveforms at 12% and assess amplitudes. CAEP and ACC amplitudes and latencies per group are presented in Table 3.

3.2.2. ACC vs CAEP

To compare ACC to CAEP, we recorded baseline recordings with CAEPs in response to onset stimuli of 2 kHz and compared these to ACCs in response to 12% frequency increases from 2 kHz (target frequency 2.24 kHz). Amplitudes and latencies per group are presented in Fig. 4 and values are shown in Table 3.

In NH subjects, ACC amplitudes were about two-fold larger than their CAEP amplitudes (Fig. 4A; NH musicians 1.7 fold, $Z = 2.85$, $p = 0.004$; NH non-musicians 2.0 fold, $Z = 2.93$, $p = 0.003$). In SNHL subjects ACC amplitudes did not significantly differ from their CAEP amplitudes ($Z = 1.682$, $p = 0.093$). Between-group comparisons demonstrated significant differences in ACC amplitude between the three groups (Fig. 4A; $H = 13.71$, $p = 0.001$). Post-hoc analyses revealed that SNHL subjects had smaller ACC amplitudes compared to both NH musicians (factor 1.6, $Z = 3.273$, $p = 0.001$) and NH non-musicians (factor 1.6, $Z = 2.937$, $p = 0.002$). There was no difference in ACC amplitude between NH musicians and NH non-musicians ($Z = 0.831$, $p = 0.406$). In contrast to the ACC amplitude, in between group comparisons revealed that CAEP amplitudes did not differ between the three groups (Fig 4A; $H = 1.8$, $p = 0.401$).

The ACC latency was longer than the CAEP latency for all three groups (Fig. 4C: NH musicians: 2 ms median latency difference, $Z = 2.85$, $p = 0.004$; NH non-musicians: 9 ms difference, $Z = 2.7$,

Table 3
A. N1-P2 amplitudes in µV.

	Baseline recordings		Main ACC recordings			
	CAEP	ACC	0.5 kHz	1 kHz	2 kHz	4 kHz
NH music	6.9 (2.5–12.6)	11.4 (7.3–18.3)	12.1 (7.7–18.2)	12.3 (7.4–18.2)	12.3 (7.4–18.2)	9.0 (3.1–14.9)
NH non-music	5.8 (4.3–12.4)	11.6 (6.6–15.8)	11.7 (5.7–18.0)	12.1 (5.2–15.0)	11.1 (8.7–18.0)	9.4 (7.0–13.0)
SNHL	5.8 (4.1–11.2)	7.3 (2.2–11.6)	8.0 (2.2–13.9)	8.3 (2.2–12.6)	7.2 (4.7–12.6)	7.2 (2.3–9.1)

B. N1 latencies in ms

	Baseline recordings		Main ACC recordings			
	CAEP	ACC	0.5 kHz	1 kHz	2 kHz	4 kHz
NH music	102 (86–114)	104 (97–131)	112 (105–129)	110 (101–132)	105 (95–119)	114 (102–152)
NH non-music	101 (81–110)	110 (102–123)	120 (104–135)	112 (100–141)	112 (91–123)	117 (94–139)
SNHL	96 (78–138)	116 (88–158)	123 (103–161)	126 (107–163)	126 (98–176)	131 (93–166)

Medians (ranges) are presented.

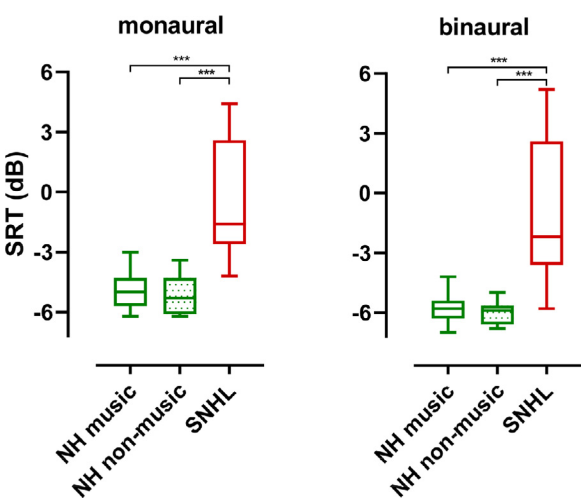

Fig. 3. SRTs for the monaural (better ear) and the binaural condition for the 3 groups separately. Significant differences between groups are indicated with asterisks (*<0.05,**<0.01, ***<0.001).

p = 0.007; SNHL subjects: 20 ms difference, Z = 2.09, p = 0.037). ACC latency did not differ between the three groups (Fig. 4C, H = 5.178, p = 0.075), and neither did the CAEP latency differ between the three groups (Fig. 4C, H = 0.743, p = 0.69).

Fig. 4B and 4D display the relation between ACC and CAEP for amplitude and latency. ACC is correlated with CAEP for both amplitude (Fig. 4B, R = 0.49, p = 0.005) and latency (Fig. 4D, R = 0.36, p = 0.041). These scatter plots suggest that with smaller CAEP amplitudes and shorter CAEP latencies there is a larger variation in ACC amplitudes and latencies, respectively.

3.2.3. CAEP vs subject characteristics

Correlations of CAEP amplitude and latency with subject characteristics and psychophysical outcomes are presented in Table 4. CAEP amplitude had a moderate correlation with age (R = 0.35, p = 0.049) although the direction of this effect, CAEP amplitude increased with older age, is in contrast with findings in the literature. CAEP latency had no correlation with age. Neither CAEP amplitude nor latency were correlated with HL, IQ, or musicality, and

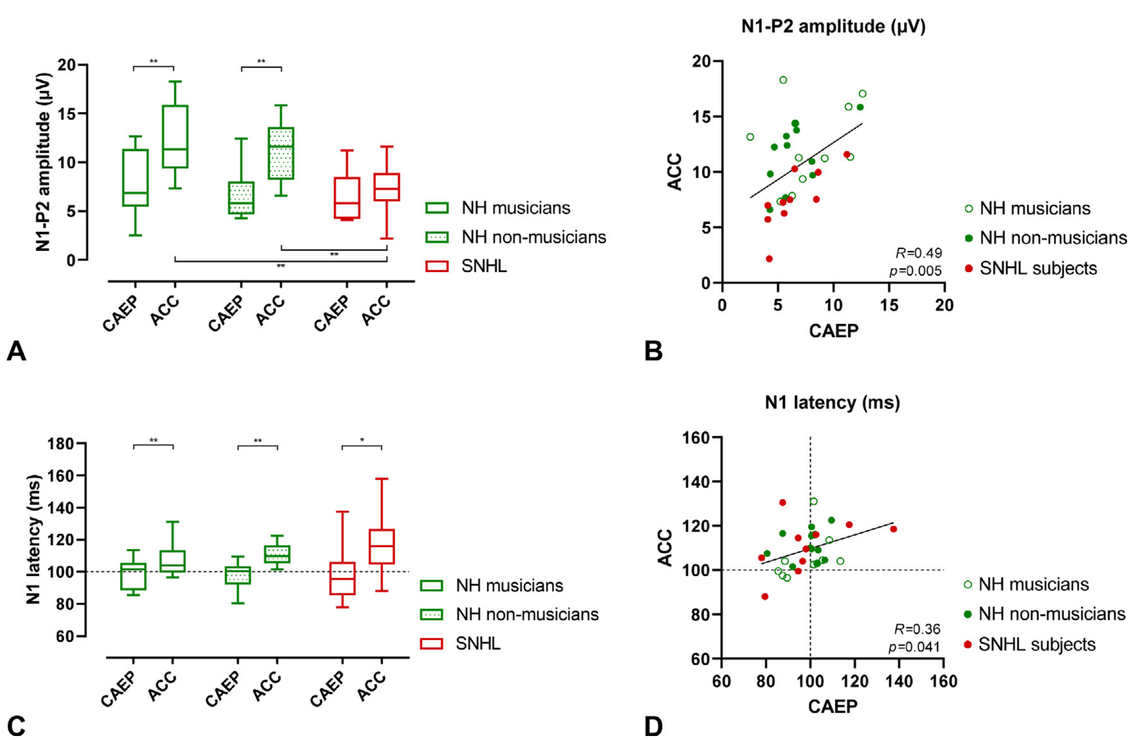

Fig. 4. CAEP compared to ACC for the 3 groups separately with boxplots and scatter plots representing N1-P2 amplitudes (A and B) and N1 latencies (C and D). Differences between recordings or between groups are indicated with asterisks (*<0.05, **<0.01). The horizontal dashed line in C and D represent 100 ms, where the N1 latency of the CAEP response is expected in NH subjects. Group medians and ranges are presented in Table 3.

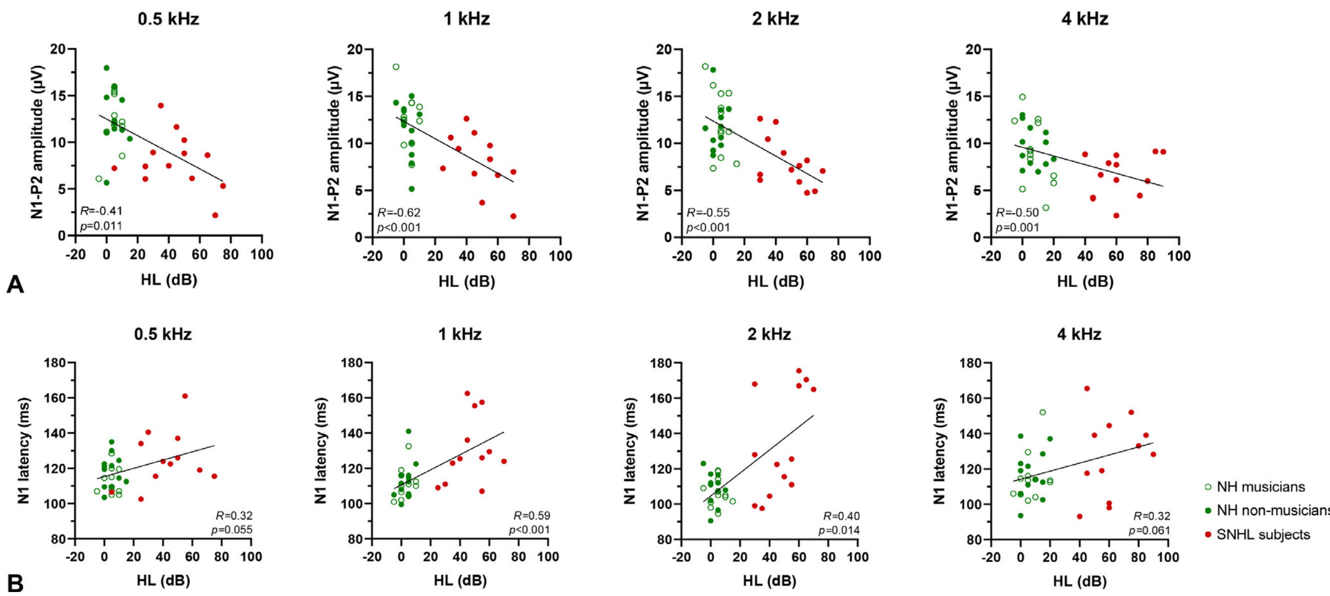

Fig. 5. ACC N1-P2 amplitudes (A) and N1 latencies (B) plotted as a function of HL for the four base frequencies for all 37 subjects. Open green dots indicate NH musicians, closed green dots NH non-musicians and closed red dots SNHL. Spearman's correlation coefficient *R* is noted at the bottom in each plot. The group medians and ranges of the amplitudes and latencies are presented in Table 3.

Table 4
Correlations of CAEP amplitude and latency with subject characteristics, FDT and SRT.

CAEP	N1-P2 amplitude		N1 latency	
	R	*P*	*R*	*p*
HL (2 kHz)	0.14	0.453	0.04	0.828
Music*	0.11	0.638	−0.02	0.913
IQ	−0.15	0.422	−0.03	0.857
Age	0.35	**0.049**	0.04	0.842
FDT (2 kHz)	−0.34	0.059	−0.00	0.991
SRT	−0.29	0.106	−0.07	0.711

* for NH subjects, $N = 22$.

there was no relation with FDT or SRT (Table 4, amplitude $p>0.05$, latency $p>0.7$).

3.2.4. ACC vs subject characteristics

Correlations between ACC amplitudes and latencies and subject characteristics are presented in Table 5. ACC amplitude was significantly correlated with HL for four base frequencies (Fig. 5A, $R<-0.41$, $p < 0.02$) with ACC amplitudes decreasing with higher hearing thresholds. In Fig. 5B longer N1 latencies are observed with poorer hearing thresholds, being significant at 1 kHz ($R = 0.32$, $p < 0.001$) and 2 kHz ($R = 0.40$, $p = 0.014$). Both ACC amplitude and latency had no relation with musical experience score or age (Table 5). ACC amplitude was not significantly correlated with indicative IQ score while the relation between ACC latency and IQ was borderline significant only at 0.5 kHz ($R=-0.34$, $p = 0.045$, therefore we conclude that there was no consistent relationship between ACC latency and IQ (Table 5).

3.2.5. Psychophysical outcomes vs ACC

Better frequency discrimination was associated with larger ACC N1-P2 amplitudes and shorter N1 latencies. FDT had a moderate correlation with both ACC amplitude and latency at 1, 2 and 4 kHz (Table 6; amplitude: $R<-0.34$, $p < 0.05$; latency: $R>0.41$, $p < 0.02$), but not at 0.5 kHz ($p>0.07$). Averaged over four frequencies, FDT had a moderate correlation with ACC amplitude ($R=-0.48$, $p = 0.002$) and a strong correlation with ACC latency ($R = 0.66$, $p < 0.001$).

Subjects with better speech perception in noise were found to have larger N1-P2 amplitudes and shorter N1 latencies (Fig. 6, Table 6). There was a moderate to strong correlation between SRT and ACC amplitude at each base frequency (Fig. 6A; R-0.46 to −0.67, $p < 0.005$). SRT was significantly correlated to ACC latency at 1, 2 and 4 kHz (Fig. 6B, $R>0.48$, $p < 0.004$), but not at 0.5 kHz ($p = 0.24$).

3.3. Multiple regression analysis for speech reception thresholds in noise

3.3.1. Multiple regression analysis with four independent variables

Multiple regression analysis was performed with SRT as dependent variable. Correlations between SRT and independent variables were generally stronger for averaged values over the four frequencies than for separate frequencies. Based on the strength of correlations (Tables 2 and 6), four variables were included as independent predictors of SRT, each presented in Fig. 7: average HL or PTA ($R = 0.75$, $p < 0.001$), average FDT ($R = 0.69$, $p < 0.001$), average ACC amplitude ($R=-0.67$, $p < 0.001$) and average ACC latency ($R = 0.65$, $p < 0.001$). Multiple regression analysis with stepwise backward elimination was performed and revealed a final multiple linear regression model with two independent predictors – average HL (R^2=0.46) and average ACC latency (R^2=0.36) – explaining 81% of the total variance in SRT (Table 7A, R^2=0.81, $p < 0.001$).

Two more multiple regression analyses were performed with the same four independent predictors but averaging limited to three (1, 2 and 4 kHz) or two (1 and 2 kHz) frequencies, thereby simplifying the clinical test methodology. The weakest correlations of 0.5 kHz followed by 4 kHz (see Tables 2 and 6) were excluded from the analysis. As presented in Table 7A, the analyses revealed final models with the same two independent variables (average HL and ACC latency) and there was no collinearity between these predictors (Tolerance>0.42, VIF<2.11). The multiple linear regression model averaged over two frequencies (1 and 2 kHz) explained 82% of the total variance in SRT (R^2=0.82, $p < 0.001$). The strongest multiple linear regression model was obtained by averaging over three frequencies (1, 2 and 4 kHz) and explained 87% of the total variance in SRT (R^2=0.87, $p < 0.001$).

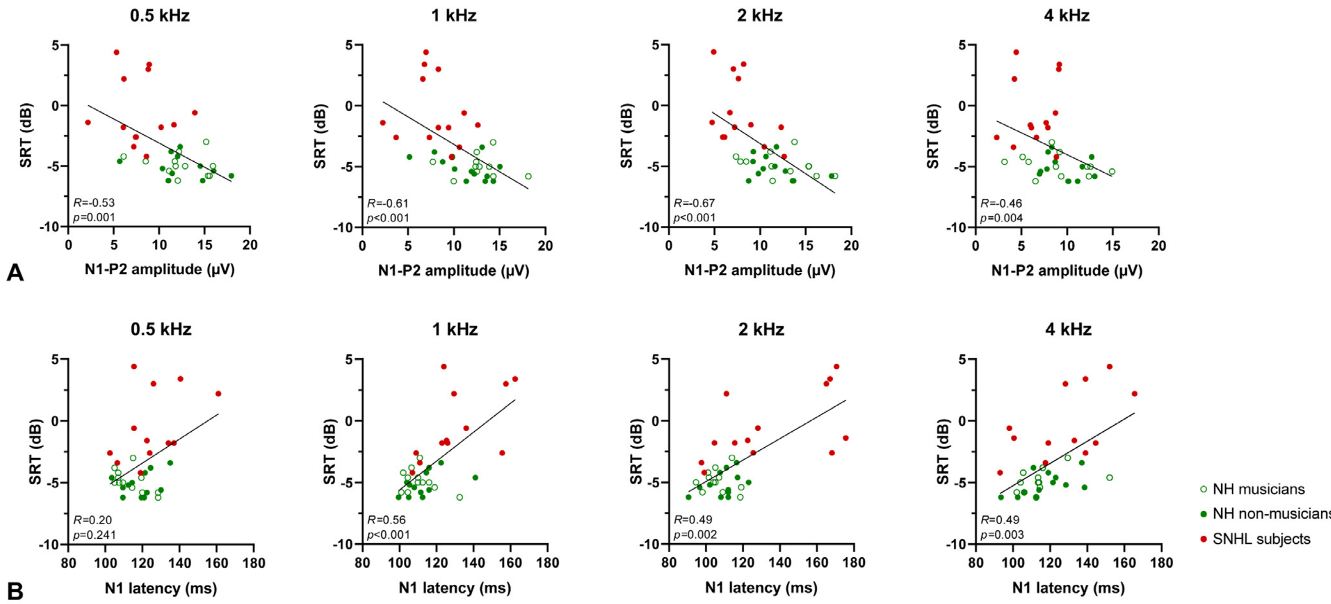

Fig. 6. SRT plotted as a function of ACC amplitude (A) and latency (B) for the four base frequencies for all 37 subjects. Open green dots indicate NH musicians, closed green dots NH non-musicians and closed red dots SNHL. Spearman's correlation coefficient *R* is noted at the bottom in each plot.

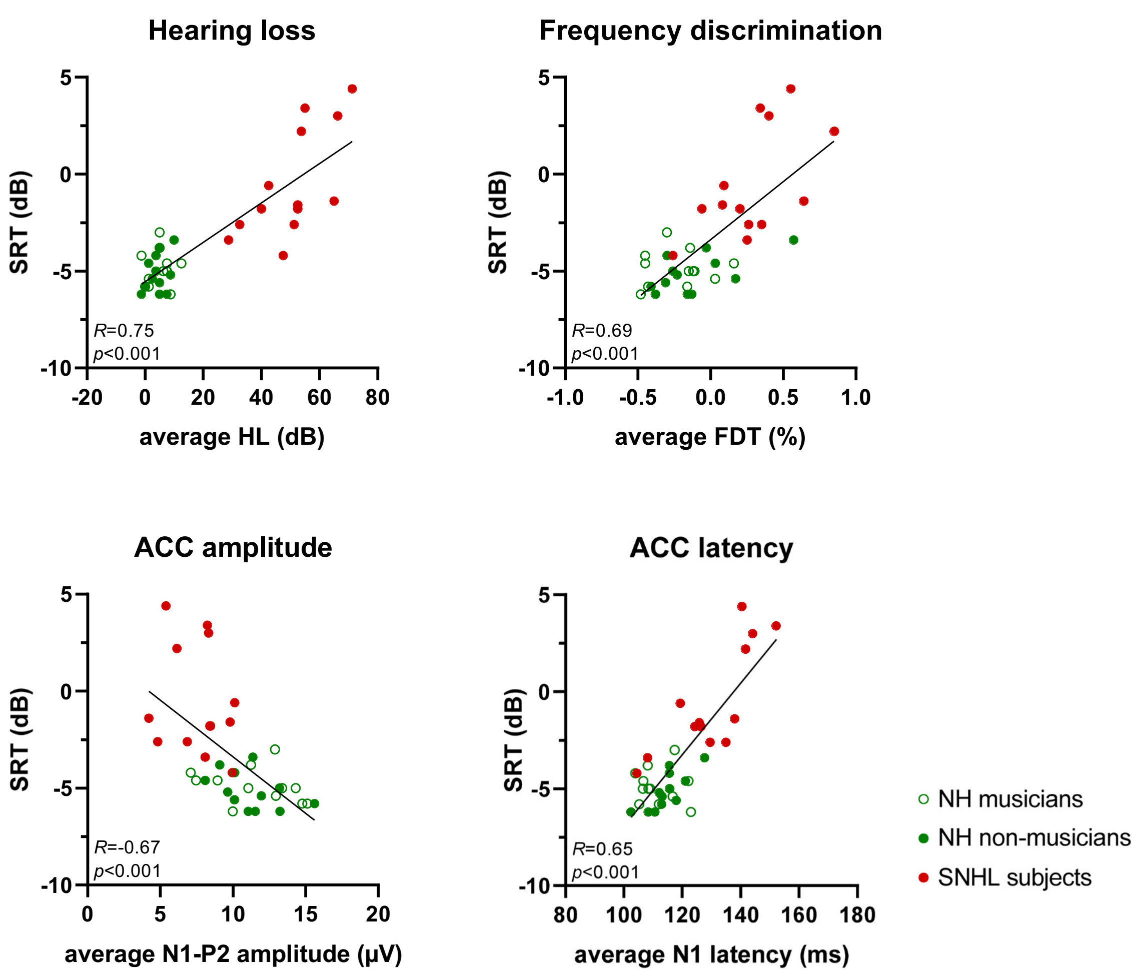

Fig. 7. Correlations of SRT with four independent variables across all 37 subjects: average HL, average FDT, average ACC amplitude and average ACC latency. The values are averaged over the four base frequencies (0.5, 1, 2 and 4 kHz). Open green dots indicate NH musicians, closed green dots NH non-musicians and closed red dots SNHL. Spearman's correlation coefficient *R* is noted at the bottom left side in each plot. The four independent variables were included in the final multiple regression analysis.

Table 5
Correlations of ACC amplitudes and latencies with subject characteristics.

ACC N1-P2 amplitude								
	0.5 kHz		1 kHz		2 kHz		4 kHz	
	R	*p*	*R*	*p*	*R*	*p*	*R*	*p*
HL	−0.41	**0.011**	−0.62	**<0.001**	−0.55	**<0.001**	−0.50	**0.001**
Music*	0.11	0.595	0.22	0.298	0.06	0.773	−0.12	0.571
IQ	0.05	0.755	0.16	0.347	0.28	0.096	0.21	0.220
Age	0.15	0.372	−0.09	0.590	−0.12	0.498	−0.07	0.672

ACC N1 latency								
	0.5 kHz		1 kHz		2 kHz		4 kHz	
	R	*p*	*R*	*p*	*R*	*p*	*R*	*p*
HL	0.32	0.055	0.59	**<0.001**	0.40	**0.014**	0.32	0.061
Music*	−0.37	0.079	−0.21	0.333	−0.26	0.218	−0.10	0.631
IQ	−0.34	**0.045**	−0.09	0.610	−0.16	0.340	−0.20	0.253
Age	0.04	0.798	0.14	0.426	0.09	0.581	0.11	0.519

* for NH subjects, $N = 24$.

Table 6
Correlations of FDT and SRT with ACC N1-P2 amplitude and N1 latency.

	Frequency	FDT		SRT	
		R	*p*	*R*	*p*
ACC amplitude	0.5 kHz	−0.30	0.071	−0.53	0.001
	1 kHz	−0.40	0.012	−0.61	<0.001
	2 kHz	−0.46	0.004	−0.67	<0.001
	4 kHz	−0.34	0.040	−0.46	0.004
	Average	−0.48	0.002	−0.67	<0.001
ACC latency	0.5 kHz	0.15	0.387	0.20	0.241
	1 kHz	0.42	0.012	0.56	<0.001
	2 kHz	0.42	0.009	0.49	0.002
	4 kHz	0.41	0.012	0.48	0.003
	Average	0.66	<0.001	0.65	<0.001

Based on this model, averaged over three frequencies, SRT in an individual patient is estimated as follows:

*SRT = −6.4 + 0.071*HL + 0.083*(ACClatency - 100)* with *SRT* and *HL* in dB, and *ACClatency* in ms. These findings indicate that patients with longer ACC latencies have worse speech perception in noise than patients with comparable hearing thresholds and shorter ACC latencies.

3.3.2. Multiple regression analysis with solely ACC parameters as independent predictors

Additional multiple regression analyses were performed with SRT as dependent variable, but with solely ACC amplitude and latency as independent variables. Similar to the previous multiple regression analyses with all independent predictors, separate analyses were performed with values averaged over four frequencies, three frequencies (1, 2 and 4 kHz) and two frequencies (1 and 2 kHz). Table 7B shows that the regression models with values averaged over two and four frequencies revealed only ACC latency as the significant independent predictor. However, the multiple linear regression model averaged over three frequencies (1, 2 and 4 kHz) revealed both ACC amplitude (R^2=0.14, p = 0.045) and latency (R^2=0.60, $p < 0.001$) as independent predictors and explained 74% of the total variance in SRT (R^2=0.74, $p < 0.001$). Based on this model, averaged over three frequencies, SRT in an individual patient is calculated as follows:

$SRT = -3.4 + 0.143*(ACClatency-100) - 2.88*ACCamplitude_{Norm}$ with *SRT* in dB, *ACClatency* in ms and $ACCamplitude_{Norm}$ the normalized ACC amplitude. We normalized by dividing by the average amplitude for ACCs for 1, 2 and 4 kHz, obtained in 14 subjects who each had an average HL over 1, 2 and 4 kHz ≤ 5 dB. This average amplitude was 11.4 µV. The regression model indicates that speech perception in noise is better in patients with larger ACC amplitudes and shorter ACC latencies with the latter as the stronger predictor.

Table 7
A. Multiple regression analysis of SRT with HL + ACC latency.

Average 0.5, 1, 2 and 4 kHz		R^2	p
Total		0.81	**<0.001**
Partial	HL	0.46	**<0.001**
	ACC latency	0.36	**0.001**
Average 1, 2 and 4 kHz			
Total		0.87	**<0.001**
Partial	HL	0.52	**<0.001**
	ACC latency	0.35	**<0.001**
Average 1 and 2 kHz			
Total		0.82	**<0.001**
Partial	HL	0.56	**<0.001**
	ACC latency	0.26	**0.003**

B. Multiple regression analysis of SRT with ACC amplitude + latency

Average 0.5, 1, 2 and 4 kHz		R^2	*p*
Total		0.71	**<0.001**
Partial	amplitude	0.10	0.134
	latency	0.61	**<0.001**
Average 1, 2 and 4 kHz			
Total		0.74	**<0.001**
Partial	amplitude	0.14	**0.045**
	latency	0.60	**<0.001**
Average 1 and 2 kHz			
Total		0.65	**<0.001**
Partial	amplitude	0.16	0.053
	latency	0.49	**<0.001**

4. Discussion

This study investigated the clinical value of the ACC, evoked in response to large frequency increases, as an objective measurement of auditory performance in normal hearing and hearing-impaired subjects. Our results demonstrate that frequency discrimination has a moderate to strong correlation to both ACC N1-P2 amplitude and N1 latency, and speech perception in noise has a strong correlation to ACC amplitude and latency. Multiple regression analysis for prediction of SRT revealed that in addition to HL, ACC latency is a significant predictor of SRT. The multiple regression model combining HL (52%) and ACC latency (35%) as independent predictors explained 87% of the total variance in SRT: higher (i.e., worse) SRTs were seen with progression of HL and prolonged latencies. With the proposed models, good estimates of SRT can be made without the requirement of performing the more difficult speech in noise tests. Even if pure tone audiometry is not possible, a strong estimate of SRT can still be obtained using both N1-P2 amplitude and N1 latency averaged across 1, 2 and 4 kHz.

The ACC differs from the onset CAEP, as CAEP parameters do not correlate to FDT or SRT. In both recordings stimulus loudness was adjusted to maximum comfortable level in hearing-impaired subjects in order to minimize effect of loudness.

4.1. ACC in NH subjects

Our study found in NH subjects ACC N1-P2 amplitude medians of 11–12 μV in response to 12% frequency increases at 0.5, 1 and 2 kHz, and amplitude medians around 9 μV at 4 kHz (Table 3). These results are in line with findings in our previous study in 12 younger subjects aged 18–30 years (Vonck et al., 2019). In that study, we found N1-P2 amplitudes around 14 μV in response to frequency increases by 0.26 octave (approximately 20%) from 1 kHz. This is in line with other studies revealing larger ACC amplitudes with larger frequency increases and younger age (Vonck et al., 2019; Harris et al., 2008). However, other studies reported considerably smaller N1-P2 amplitudes varying between 2.5 to 9 μV in response to frequency increases from 5% to 50% (Dimitrijevic et al., 2008; Harris et al., 2008; He et al., 2012; Liang et al., 2016). Amplitudes vary among subjects and among studies and have a strong dependence on subject factors such as thickness of skin or skull, recording equipment, or stimulus factors such as frequency change magnitude or rate (Martin et al., 2007; Vonck et al., 2019). The larger amplitudes in our previous and current study can be attributed to the relatively long duration of the first stimulus component before the change, which was 3 s. This duration was based on our pilot data obtained in three subjects (Vonck et al., 2019), which indicated that prolonging this component from 1 s to 3 s generates approximately 30%−50% larger amplitudes. The longer duration of the first stimulus component facilitates neural adaptation with less neuronal activity after 3 s compared to 1 s, which allows more neurons to respond to the frequency change. Another explanation for the larger amplitudes might be that the current study used a limited number of electrodes, carefully placed to ensure low impedances opposed to multi-electrode configurations with advantage of source localization but disadvantage of suboptimal electrode tissue contact.

The current study found median ACC N1 latencies of 105–120 ms corresponding with findings in our previous study and in literature (Dimitrijevic et al., 2008; Harris et al., 2008; He et al., 2012; Liang et al., 2016; Vonck et al., 2019). ACC N1 latencies in our previous study in younger subjects in response to 0.26 octave (~20%) frequency increases from 1 kHz varied between 102 and 130 ms. Harris et al. (2008) reported a latency of approximately 132 ms in response to an 8% frequency increase, He et al. (2012) reported a N1 latency of 110 ms in response to 20% frequency changes, and Dimitrijevic et al. (2008) reported latencies of 105 ms and Liang et al. (2016) 114 ms in response to a 50% frequency increase. Taking together, these studies reveal that latency decreases with frequency change magnitude, which is confirmed by Vonck et al. (2019).

As discussed above, ACC N1-P2 amplitudes in NH display a strong variation among subjects and studies. For development of the ACC into a clinically applicable tool, determination of normative values for amplitudes might pose a challenge. Even with similar recording settings and stimuli, a certain variation in ACC amplitudes would still remain. On the other hand, ACC N1 latency appears to be less variable among studies, since the latency, like the amplitude, varies with acoustic change parameters (Vonck et al., 2019) but, unlike the amplitude, not with recording electrode configurations. ACC latency is therefore more suitable to determine normative values and would be a valuable parameter based on the limited variability.

In the current study, we applied ACC stimuli with a frequency change magnitude of 12%, which corresponds with approximately 0.16 octave (or two semitones). Our main study objective was to investigate the clinical value in hearing impairment. Therefore, we needed a relatively large suprathreshold ACC considering that in SNHL, ACC thresholds increase with hearing loss (Vonck et al., 2021). In severe SNHL > 60 dB HL, ACC thresholds may even increase beyond 12% (Vonck et al., 2021). For clinical application in profound hearing-impaired subjects, ACCs in response to larger frequency increases might be indicated. Therefore, for application in NH and moderate to severe SNHL, magnitudes of 12% are sufficient and clinically valuable as demonstrated in the current study.

4.2. ACC vs CAEP

In NH subjects, ACC amplitudes were nearly two-fold larger than onset CAEP amplitudes, in SNHL subjects on the other hand, with sound levels set to obtain similar loudness as in NH subjects, ACC amplitudes were similar to CAEP amplitudes. ACC latency was longer than CAEP latency in both NH and SNHL subjects. Literature on the comparison of ACC to CAEP is limited. Liang et al. (2016) recorded ACCs in response to frequency increases in NH subjects at base frequencies 160 Hz and 1200 Hz and in line with our results, these authors reported larger amplitudes and longer latencies for the ACC in comparison to the onset CAEP. This might be due to differences in neural generators between the ACC and CAEP: ACC depends on magnitude, rate, and direction of change (Vonck et al., 2019) whereas CAEP depends on sound level (Adler and Adler, 1991; Martin et al., 2007). Therefore, the ACC/CAEP amplitude ratio depends on all these factors. The notably larger ACC than CAEP (by a factor of nearly two) suggests that a substantial population of neurons rather respond to changes than to onsets, the change being comprised of the FM component and the target tone. However, Liang et al. (2016) found that subjects with larger ACCs tend to have larger CAEPs and therefore these authors stated that both responses may also have shared neural populations. In line with these findings, our results show that ACC was correlated to CAEP for both amplitude and latency (Fig. 4C,D).

Hearing loss will affect the CAEP and could lead to increase of amplitude and shorter latency as a result of broadening of frequency tuning, with neurons over a larger cortical area responding to the tone. Although an opposite effect might generate decrease of amplitude and longer latency because of degraded peripheral input (with less neurons per cortical area), both effects more or less may cancel resulting in similar amplitude and same latency in SNHL and NH, exactly as we found.

The finding that the CAEP amplitudes and latencies did not differ between NH and SNHL subjects supports our assumption that all subjects indeed perceived similar loudness. As discussed in our previous study, it is not feasible to loudness balance the stimuli for the development of the ACC into a clinically applicable tool due to time constraints and this would defeat the usefulness of a measure that is intended most for hearing-impaired patients who are unable to reliably perform auditory tasks (Vonck et al., 2021).

Regarding the ACC, hearing loss might lead to decrease of amplitude and increase of latency because of broadening of frequency tuning (Rajan, 2001; Seki and Eggermont, 2002) and hence more overlap of neuronal populations responding both to target tone and reference tone. Hearing loss due to aging leads to loss of cortical responsiveness to fast FM rates (Mendelson and Ricketts, 2001; Trujillo and Razak, 2013), thus considering the rate of 55 octaves/s in the FM component of the applied change stimulus is fast, responses to the FM component will have faded in several of our subjects. Increase of ACC latency generally corresponds with decrease of amplitude (e.g. Vonck et al., 2019). The cortical response to a frequency change stimulus consists of the sum of the responses to the FM sweep and to the target tone. Individual cortical neurons may be sensitive to both components or to either of the two (Heil et al., 1992; Shamma et al., 1993; Kowalski et al., 1995; Nelken and Versnel, 2000). In primary areas, the response to a pure tone is relatively strong; whereas in nonprimary areas, the response to the FM sweep is relatively strong as further discussed in literature among which our previous study on ACC thresholds (Tian and Rauschecker, 2004; Vonck et al., 2021).

Based on the neuronal physiology, we may state that the ACC provides information on advanced auditory processing in comparison to the onset CAEP and could therefore be more valuable for clinical application as an indicator of auditory performance such as frequency discrimination or speech perception. This is supported by the findings in Table 4, which show that CAEP measures were not related to frequency discrimination or speech perception.

4.3. ACC in hearing loss

We found that with progression of hearing loss, ACC amplitude decreased and ACC latency increased (Fig 5). This effect of hearing impairment was strong for ACC amplitude, and moderate for ACC latency. Although previous studies have aimed at the clinical value of the ACC as an objective measurement in hearing impairment, literature on ACCs in SNHL patients is surprisingly scarce. Martinez et al. (2013) recorded ACCs in young children (two to six years old) and compared ACCs in response to vowel stimuli in five NH children and five SNHL children. These authors did not observe consistent ACC changes in hearing impairment; however, waveforms in children differ greatly from adults with respect to P1-N1-P2 complexes due to their ongoing maturation of the auditory pathway (e.g., Eggermont and Ponton, 2003) which impedes comparisons. To our knowledge, there are no previous studies comparing ACCs in adult patients with moderate to severe hearing loss to NH subjects nor studies investigating the relation between ACC measures and extent of hearing loss. Tremblay et al. (2006) conducted a feasibility study in seven adult SNHL subjects, and concluded that ACCs can be measured in hearing aid users. In CI users however, the ACC has been recorded in several studies (Han and Dimitrijevic, 2020; He et al., 2014; Liang et al., 2018; Mathew et al., 2017; Scheperle and Abbas, 2015). Waveforms are generally comparable in CI users to those in NH subjects. These studies on ACC in CI users show smaller ACC N1 amplitudes and longer N1 latencies in CI users compared to NH subjects, which is consistent with our findings. Assuming electric hearing in CI users is comparable to hearing in subjects with severe SNHL (our cases with HL>60 dB), these studies confirm our findings that hearing impairment affects advanced auditory processing, reflected by the changes in ACC amplitude and latency. The underlying physiology on the effect of hearing impairment on the ACC waveform is discussed in 4.2.

4.4. Relation between ACC and psychophysical outcome measures

The relation between ACC and psychophysical measures has been investigated by previous studies (Brown et al., 2017; He et al., 2012; Kim, 2015; Vonck et al., 2021), but these studies mainly focused on the ACC threshold and correlation thereof with subject characteristics or psychophysically assessed frequency or intensity discrimination. The smallest frequency change stimulus that generated an ACC response is referred to as the ACC threshold (Vonck et al., 2021). He et al. (2012) recorded ACC thresholds in young NH subjects and found a correlation with FDT ($R = 0.7$, $p < 0.05$). Brown et al. (2017) determined ACC thresholds by visual inspection and also reported a correlation with FDT ($R = 0.49$, $p = 0.03$). In the current study, we investigated ACC amplitudes and latencies and their correlation to both FDT and SRT, and to our knowledge correlations with FDT and SRT have not been investigated by preceding studies in NH nor in SNHL subjects.

In the current study, the relation between FDT and ACC amplitude or latency was generally moderate to strong (Table 6). These correlations are comparable to the relation with ACC threshold investigated in our previous study ($R = 0.41$–0.67, $p < 0.05$), which partially includes the same subjects (12 NH, 13 SNHL). Our study found a strong correlation between SRT and ACC amplitude or latency (Table 6). These correlations are stronger than the relation with ACC threshold in our previous study ($R = 0.54$, $p = 0.005$).

Although there are no previous studies on ACC in relation with SRT, CAEPs to stimulus onsets have been compared to SRT (Billings et al., 2013, 2015; Billings and Madsen, 2018). Applying several vowel-in-noise stimuli for CAEP recordings and using a 64-channel electrode cap in a study in young NH subjects, Billings et al. (2013) found the strongest correlations for N1 amplitude ($R = 0.72$, $p < 0.01$) and N1 latency ($R = 0.62$, $p = 0.012$). This contrasts to our CAEP outcomes which did not show correlations with SRT, probably because of the differences in stimulus between the studies (pure tone vs speech stimulus). Billings et al. (2015, 2018) also found strong correlations (R values between 0.53 and 0.8) between syllable-in-noise evoked CAEPs and SRT in older subjects (60–84 years of age). However, SRTs were better predicted in NH than in SNHL subjects. Speech onset evoked CAEPs (Billings and colleagues) or speech change evoked ACCs (e.g., Cheek and Cone, 2020) may thus be similarly valuable as tone change evoked ACCs to predict SRT. The advantage of the frequency change is that the stimulus parameters can be systematically varied (Vonck et al., 2019): reference frequency (in Hz), frequency change (in%), rate of change (in octaves/s), direction (up or down). The possibility to perform frequency specific ACC recordings offers a clinical benefit as it enables comparisons between unaffected and severely affected frequency regions. In addition, by substantially separating the onset of the base frequency stimulus and target stimulus (at least 500 ms), one avoids overlap of the response waveforms seen using short speech signals (Billings et al., 2017). With frequently used speech stimuli, the P2 peak of the first speech token can affect the N1 amplitude of the target speech token, and reduce signal-to-noise ratios which are especially important in severe sensorineural hearing loss and for the applicability of the ACC prediction model.

While the correlation between ACC and SRT has not been investigated in NH and SNHL subjects, it has been examined in CI users (Han and Dimitrijevic, 2020; Liang et al., 2018). Han and Dimitrijevic (2020) recorded ACCs in response to frequency increases in 10 CI users and found correlations between N1 latencies and various speech perception tests including vowel ($R = -0.84$, $p < 0.05$) and word ($R = -0.72$, $p < 0.05$) perception in noise. A study by Liang et al. (2018) recorded ACCs in response to frequency increases in 12 CI users and found N1 latencies correlated to both FDT ($R = 0.48$, $p < 0.05$) and SRT ($R = -0.6$, $p < 0.05$). These relatively strong correlations in CI users are comparable to our current findings in which SRT correlated more strongly to ACC latency than to ACC amplitude. In agreement with our data, better SRTs in CI users were also observed with larger ACC amplitudes and shorter latencies.

4.5. Effect of recreational musical experience

We compared 12 NH musicians at recreational level to 12 NH non-musicians. There were no differences in frequency discrimination, SRT, ACC or CAEP between musicians and non-musicians. These findings are in contrast to previous literature on the musician effect on auditory performance (Başkent et al., 2018; Bianchi et al., 2016; Brown et al., 2017; Lee et al., 2020; Liang et al., 2016; Parbery-Clark et al., 2009). Liang et al. (2016) determined FDTs in quiet and in noise and recorded ACCs at two base frequencies (160 Hz and 1200 Hz) in 12 young NH musicians and 12 young NH non-musicians. These authors found better FDTs in musicians for all stimulus conditions. Interestingly, P2 amplitudes, but not N1-P2 amplitudes, were larger in musicians only at 160 Hz but not at 1200 Hz. The neural changes induced by musical training can be measured as enhanced ACC P2 amplitudes, as the P2 is thought to be a more cognitive component reflecting attention-modulated process required for the performance of auditory discrimination tasks (Crowley and Colrain, 2004; Liang et al., 2016). Lee et al. (2020) compared FDTs in quiet and in noise to ACCs in 13 young musicians to 11 young non-musicians. ACCs were evoked in response to frequency increases of 10%, 25% and 50% at base frequencies of 250 and 4000 Hz. These authors found that musicians had better FDTs in quiet and larger ACC P2 amplitudes than non-musicians. The summed N1 and P2 amplitude reported by Lee et al. (2020) was also larger for musicians, which opposes our findings. The contrast in perceptual and ACC outcomes between these two studies and our current study might be due to the level of and age at musical training. Both Liang et al. (2016) and Lee et al. (2020) included young musicians who received professional musical training whereas in the current study musicians of varying ages at recreational level were included. This suggests that if musical training induces an effect in auditory processing which provides better frequency discrimination ability, it has to be at a (quasi) professional level, i.e., extensive, and preferably at relatively young age.

4.6. Clinical implications

An objective measurement of auditory performance is valuable in case behavioral tests are unreliable or unexpected. Reliable behavioral test results, regarding speech perception, can be difficult to obtain in patients with cognitive impairment or language barriers, or in young children. A specific group among these patients are those with a language barrier for whom tone audiometry is possible while speech perception tests are unreliable. In patients unable to reliably perform behavioral tests, it is challenging not only to accurately assess their hearing performance, but also to properly fit their hearing aids or to determine cochlear implant candidacy. An objective and simple predictor of speech perception might offer a solution. Extensive research has focused on prediction of SRT in hearing impairment, by calculation of several models including patients with and without hearing aids, and among others, it appears that prediction solely based on hearing levels remains suboptimal (Plomp, 1978, 1986; Rhebergen et al., 2010, 2014; Smoorenburg, 1992). Smoorenburg (1992) found that averaging HL at 2 and 4 kHz provides a fairly strong predictor of SRT (R^2=0.52), which corresponds with our findings that averaging HL over 0.5, 1, 2 and 4 kHz provides a comparable predictor (R^2=0.56, Table 2B).

The current study demonstrates that SRT can be better predicted using ACC measures even in patients who are unable to reliably perform tone audiometry (total R^2=0.74, Table 7B). Moreover, in patients who are able to perform tone audiometry but unable to perform speech perception tests (such as those with language barriers), the N1 latency provides a strong predictor in addition to hearing loss, both averaged across 1, 2 and 4 kHz (total R^2=0.87, Table 7A).

The ACC recorded in response to three base frequencies can be recorded in a passive listening situation with a procedure duration of 45–60 min. Equipment applied for auditory brainstem recordings can be modified for ACC recordings as conducted in the current study without requirement for multichannel testing or advanced analysis. For further development of the ACC into a clinical tool, the accuracy and clinical applicability of this model should be investigated in a larger population. As described earlier, ACC amplitude varies between studies due to its strong dependence on stimulus factors and factors such as electrode impedance and number of electrodes. Our proposed model, in particular the factor ACC amplitude, should therefore be validated and normalized in another clinic and patient population.

We conclude that the ACC evoked in response to a large suprathreshold frequency change can be developed into an audiological tool, with potential added value to measurements such as auditory brainstem responses.

CRediT authorship contribution statement

Bernard M.D. Vonck: Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Jan A.A. van Heteren:** Investigation, Visualization, Writing – review & editing. **Marc J.W. Lammers:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Dominique V.C. de Jel:** Investigation, Formal analysis. **Wouter A.A. Schaake:** Investigation, Formal analysis. **Gijsbert A. van Zanten:** Conceptualization, Resources, Writing – review & editing. **Robert J. Stokroos:** Writing – review & editing, Supervision. **Huib Versnel:** Conceptualization, Methodology, Software, Formal analysis, Writing – review & editing, Supervision, Project administration.

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The authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.heares.2022.108508.

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