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Research Paper

Cortical potentials evoked by tone frequency changes compared to frequency discrimination and speech perception: Thresholds in normal-hearing and hearing-impaired subjects

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ABSTRACT

Frequency discrimination ability varies within the normal hearing population, partially explained by factors such as musical training and age, and it deteriorates with hearing loss. Frequency discrimination, while essential for several auditory tasks, is not routinely measured in clinical setting. This study investigates cortical auditory evoked potentials in response to frequency changes, known as acoustic change complexes (ACCs), and explores their value as a clinically applicable objective measurement of frequency discrimination. In 12 normal-hearing and 13 age-matched hearing-impaired subjects, ACC thresholds were recorded at 4 base frequencies (0.5, 1, 2, 4 kHz) and compared to psychophysically assessed frequency discrimination thresholds. ACC thresholds had a moderate to strong correlation to psychophysical frequency discrimination thresholds. In addition, ACC thresholds increased with hearing loss and higher ACC thresholds were associated with poorer speech perception in noise. The ACC threshold in response to a frequency change therefore holds promise as an objective clinical measurement in hearing impairment, indicative of frequency discrimination ability and related to speech perception. However, recordings as conducted in the current study are relatively time consuming. The current clinical application would be most relevant in cases where behavioral testing is unreliable.

1. Introduction

Our ability to discriminate small frequency changes, is essential for various auditory tasks in daily life. Among other aspects, frequency discrimination enables us to understand speech, distinguish relevant sounds from background noise and appreciate music. Previous research in a group of normal-hearing (NH) subjects, consisting of both musicians and non-musicians, found strong correlations between speech perception in noise and frequency discrimination (Parbery-Clark et al., 2009). Sensorineural hearing loss not only affects pure tone hearing thresholds but, due to outer hair cell damage, will also reduce cochlear frequency selectivity and thereby the ability to discriminate between (small) frequency differences (Moore, 2008; Oxenham, 2008; Halliday et al., 2019). Hearing loss management with hearing aids or cochlear implants improves auditory performance, although a considerable number of individuals still experience challenges with respect to speech perception in noise or appreciation of music (Kochkin, 2005; Takahashi et al., 2007; Gifford and Revit, 2010; Looi et al., 2012; Uys et al., 2012; Chasin and Hockley, 2013; Limb and Roy, 2014). Impaired frequency discrimination ability can contribute to their disturbed speech perception in noise or music appreciation (Zhang et al., 2019). Clinical frequency discrimination threshold tests can provide a better insight into why some hearing aid and cochlear implant (CI) users struggle in these difficult listening situations (Zhang et al., 2019). In CI users frequency

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

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discrimination ability has been shown to correlate to speech perception and level of satisfaction with CI use, which confirms the importance of frequency discrimination as a clinical factor (Zhang et al., 2019). Unfortunately, certain hearing-impaired patients are unable to reliably perform behavioral tasks. A frequency discrimination test, which does not require the subjects' attention, would therefore be more appropriate. The acoustic change complex (ACC), the cortical response evoked by change within an ongoing stimulus, might be a promising alternative.

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 or frequency 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; Presacco and Middlebrooks, 2018; Vonck et al., 2019). The ACC is an obligatory cortical evoked potential in response to change within a sound stimulus, and is thought to reflect neural detection of auditory changes in the auditory cortex (Martin et al., 2007; Kim, 2015). The ACC consists of 3 peaks, labeled as P1, N1 and P2 and can be recorded in a passive listening situation, comparable to the conventional cortical auditory evoked potential (CAEP) which is recorded in response to the onset of a stimulus. Other discriminative potentials have been used to assess sound discrimination, such as mismatch negativity (MMN) or the P300. The MMN uses an oddball paradigm and is also recorded in a passive listening situation. However, MMN has a small wave amplitude, imprecise latency calculations, a relatively poor reliability and is only valuable at group level (Martin and Boothroyd, 1999; Picton, 1995; Kim, 2015). The P300 occurs approximately after 300 ms and uses an oddball paradigm. This potential might be useful for clinical assessment of sound discrimination, although during the recording the subject is actively engaged in a discrimination task and the P300 is therefore not applicable in patients unable to reliably perform auditory tasks. The ACC has potential clinical value as an objective measurement, since correlations with psychophysical measures have been described in normal-hearing adults (Kim, 2015). For example, ACCs in response to frequency changes were correlated to frequency discrimination (He et al., 2012; Brown et al., 2017). In CI users, a 'spatial ACC' was recorded in response to changes in stimulated electrodes and a correlations was found with behavioral electrode discrimination (Mathew et al., 2017). Previous studies have demonstrated that ACC waveform amplitudes (of both the N1 and P2) depend on the magnitude and rate of frequency changes (McCandless and Rose, 1970; Martin and Boothroyd, 2000; Harris et al., 2008; Pratt et al., 2009; He et al., 2012; Vonck et al., 2019). The smallest frequency change magnitude, which generates an ACC, can be considered the 'ACC threshold'. ACC amplitudes, in response to frequency changes, reported in the literature vary considerably within the normal hearing population (McCandless and Rose, 1970; Martin and Boothroyd, 2000; Harris et al., 2008; Pratt et al., 2009; He et al., 2012; Vonck et al., 2019). ACC thresholds may be less variable and if so, would be more suitable for clinical application. ACCs in response to phoneme changes might be related to speech perception. However, these stimuli are less suitable for threshold determination and therefore less suitable for detection of subtle differences between subjects. Speech is complex and to fully understand the cue being used, simpler stimuli that form the perceptual building blocks for speech can be more informative (Chi et al., 1999). To date, ACC thresholds recorded to frequency changes in normal-hearing subjects were determined in three studies (Harris et al., 2008; He et al., 2012; Brown et al., 2017). In two of these studies, significant correlations were reported between ACC thresholds and psychophysically assessed frequency discrimination thresholds (FDTs) (He et al., 2012; Brown et al., 2017). However, it is unknown if this relation between ACC thresholds and frequency discrimination also holds true for patients with hearing impairment.

This study explores the value of the ACC threshold as an objective measurement of frequency discrimination in patients with sensorineural hearing loss and normal hearing. We chose basic auditory stimuli with well-defined parameters to evoke the ACC, therefore, we applied long-duration pure tones with a within-tone frequency change. Our primary objective was to investigate the correlation between ACC thresholds in response to frequency changes and FDTs. Our secondary objectives were to compare ACC thresholds between normal-hearing and hearing-impaired subjects, and to investigate the correlation between speech perception in noise and ACC thresholds. Therefore, we determined ACC thresholds and FDTs at four different base frequencies (0.5, 1, 2, and 4 kHz), and assessed speech perception in noise in normal-hearing and hearing-impaired subjects.

2. Methods

2.1. Subjects

Twelve normal-hearing (NH) subjects (5 males; age range 23–58; age median 47.5) and 13 subjects with sensorineural hearing loss (SNHL) (7 males; age range 21–66; age median 46) participated in the current study. Ages did not significantly differ between the two groups (unpaired *t*-test, $t_{(23)} = 0.18$, $p = 0.88$). 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. The sample size was assessed based on ACC threshold data in NH subjects (Harris et al., 2008) and frequency discrimination threshold data in hearing-impaired subjects relative to normal-hearing subjects (Tyler et al., 1983). The 12 NH subjects in the current study were different from the 12 younger subjects in our previous study, who were aged between 18 and 30 years (Vonck et al., 2019). Hearing loss was measured by conventional pure tone audiometry and defined as >15 dB hearing loss (HL) on pure tone average (PTA) at 500, 1000, 2000 and 4000 Hz, or >20 dB at one or more frequencies between 125 and 8000 Hz. SNHL subjects were hearing aid users who visited the UMC Utrecht for their audiometric follow-up. The SNHL group had a large variance in hearing thresholds, for example varying from 5 to 70 dB at 500 Hz and 40 to 90 dB at 4000 Hz. Fig. 1 illustrates the average hearing loss for both groups. For each subject both ears were tested. Their better ear was defined based on the PTA HL (averaged at 500, 1000, 2000 and 4000 Hz). In the NH group the better ear was left sided in 7 subjects, in the SNHL group the better ear was left sided in 6 subjects. All psychophysical and electrophysiological tests were performed using the participants' better ear. To be able to determine whether intelligence influenced ACC threshold, FDT or speech perception, subjects underwent a shortened WAIS IQ test in order to obtain an indicative IQ score (Silverstein, 1985). Furthermore, participants were asked if and how many hours a week they practiced music and for how many years. This provided us with an estimate of their musical experience. Their 'musical experience score' was calculated by multiplying the average amount of musical experience in hours per week by the years of active engagement.

2.2. Psychophysical and speech perception tests

Psychophysical and speech perception tests were conducted in a sound-attenuated booth. Frequency discrimination thresholds (FDTs) were determined using pure tone stimuli with reference frequencies of 500, 1000, 2000 and 4000 Hz in a 3-interval

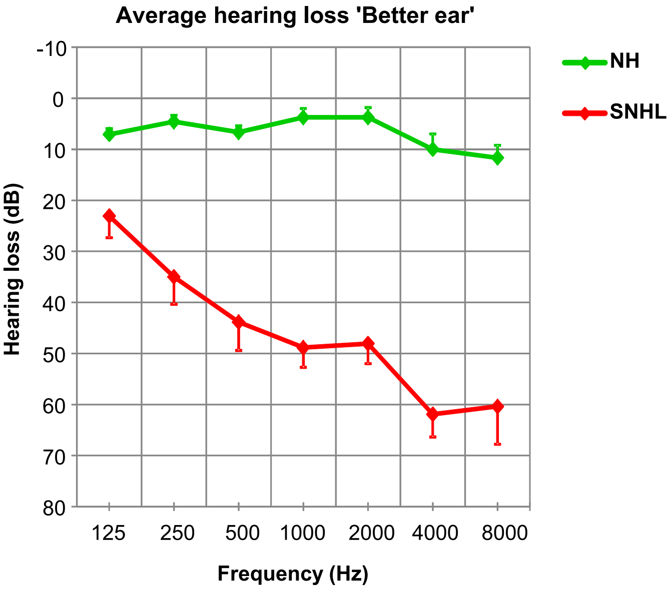

Fig. 1. Per subject the better ear was determined, this ear was tested during the study procedures. This figure shows the average better ear hearing level per group, 12 normal-hearing (NH) subjects and 13 hearing-impaired (SNHL) subjects. Error bars indicate standard error of the mean.

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. Duration of each tone pip was 400 ms with cosine-squared onset and offset ramps of 5 ms, followed by a silent interval of 300 ms. Subjects were asked whether the first or the last stimulus was different. A 3-down, 1-up adaptive staircase procedure was used to determine the frequency discrimination thresholds. After 12 reversals the definite frequency discrimination threshold was determined by averaging the frequency difference between higher tone and 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 headphones to the better ear at 75 dB SPL in NH subjects or at maximum comfortable loudness level in SNHL subjects. This resulted in presentation in SNHL subjects at 75 dB SPL or higher, resembling presentation levels of the ACC stimuli.

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. First, the reception threshold for speech in quiet was assessed. Then for the speech-in-noise test, stationary speech-shaped noise was applied that was set at a fixed level of 60 dB SPL for the NH subjects and at 15 dB above the threshold in quiet, with a minimum of 60 dB SPL for the SNHL subjects The test started with presentation of the speech level at 8 dB below the noise level. When the sentences could not be repeated by the subject the speech level was increased by 2 dB, when the sentence was repeated correctly the speech level was decreased by 2 dB. The SRT was defined as the speech-noise-ratio for which 50% of the materials were correctly repeated. During the whole procedure, the contralateral ear was plugged with an ear plug and covered by an ear cap.

2.3. ACC stimuli and recording procedure

ACCs were recorded using the procedure described by Vonck et al. (2019). The acoustic change stimuli consisted of three components (Fig. 2A): a) a reference tone at a base frequency, f_{base}, with a duration of 3000 ms, b) a fast logarithmic frequency modulation sweep with a frequency change (f_{base} $^{*}\Delta f$) and a duration of 3 ms, c) a target tone with a frequency of f_{base} $^{*}(1+\Delta f)$ with a duration of approximately 300 ms. We ensured that the second component started at the final phase of the first component and third component started at the final phase of the second component, in order to prevent transient signals. The silent interval between stimuli was 200 ms. Stimuli were presented at 4 base frequencies of 500, 1000, 2000 and 4000 Hz. With each base frequency the Δf was varied during several recordings, in order to determine the smallest frequency change which generated an ACC response. The rate of the frequency sweep varied depending on magnitude of the frequency change, e.g., it was 54 octaves/s for a 12% frequency change and 4.8 octaves/s for a 1% frequency change. For each base frequency, measurements started with a Δf increase with a magnitude of 12% (e.g. base frequency 1000 Hz gliding to a 1120 Hz target tone). Subsequently, Δf was decreased in several steps in order to determine the smallest Δf which generated an ACC response. Typically after 12%, we presented 3% and 1% (e.g., in case of base frequency of 1000 Hz, subsequent target tones of 1120 Hz, 1030 Hz and 1010 Hz); if a response was evoked, Δf was reduced, if not, Δf was increased. Near the ACC threshold the recordings were replicated to improve threshold accuracy. This procedure was performed for each base frequency. If the initial Δf of 12% did not evoke a response, Δf was increased to 24% followed by smaller Δf in order to determine the threshold.

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 headphone at a level of 75 dB SPL in NH subjects or at maximum comfortable loudness level in SNHL subjects in order to attempt to correct for differences in loudness. This resulted in stimulus presentation in SNHL subjects at 75 dB SPL or higher, with the mild hearing impaired subjects at 75 dB SPL and the more severe hearing-impaired subjects generally at 80–90 dB SPL, 2 severe SNHL subjects were tested at 110 dB SPL at 4 kHz. Maximum comfortable loudness level was determined for each base frequency, for example in sloping hearing losses this could indicate that stimuli at 0.5 kHz were presented at 75 dB SPL while stimuli at 4 kHz were presented at 90 dB SPL in the same SNHL subject.

Participants were seated in a comfortable reclining chair in an electrically shielded, sound attenuated booth 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 was placed at the vertex of the skull, Cz, the contralateral mastoid was used as 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 impedances were kept below 4 kΩ. The electrode signals were recorded with a sampling rate of 50 kHz and they were 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

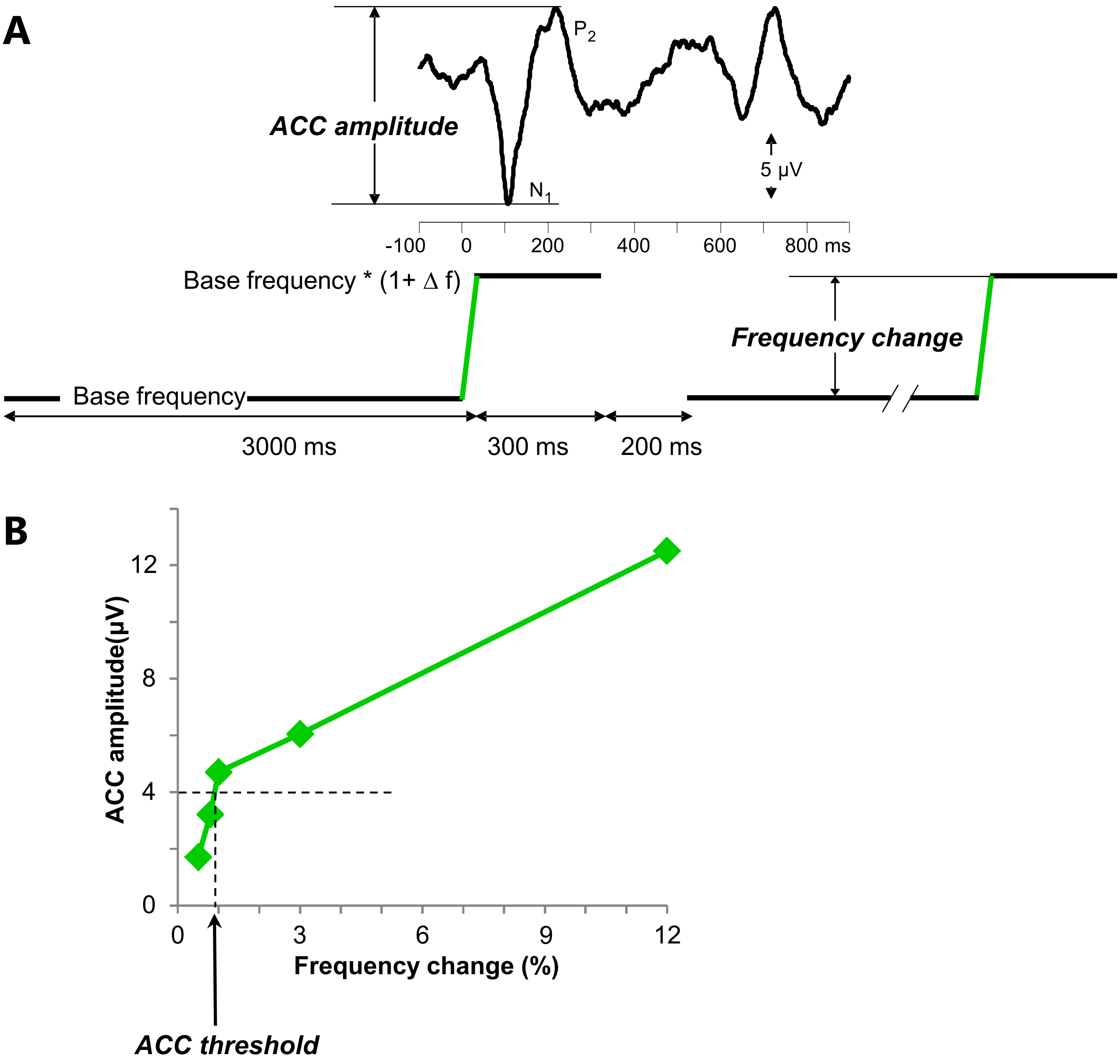

Fig. 2. **A** A schematic representation of the frequency change stimulus. The stimulus consists of 3 components: a) a reference tone at a base frequency, f_{base}, with a duration of 3000 ms, b) a fast logarithmic frequency modulation (FM) sweep with a frequency change f_{base} $*\Delta f$ and a duration of 3 ms, c) a target tone with a frequency of $f_{base}*(1+\Delta f)$ with a duration of approximately 300 ms. The silent interval between subsequent stimuli is 200 ms. The green vertical line represents the fast FM sweep, where the stimulus frequency increases and glides from the base frequency towards base frequency + Δf. 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. **B** Example of the assessment of ACC threshold. The X-axis presents magnitude of the frequency change stimulus. On the Y-axis the ACC amplitudes in response to the varying frequency changes are presented. ACC recordings in this NH subject started with a 12% frequency change stimulus, followed by 3% and 1% frequency change. The next frequency change stimulus of 0.5% did not generate an ACC response, therefore a 0.8% frequency change was presented in order to approach the threshold at which an ACC was generated. With these values and the ACC amplitude cut-off value of 4 µV the ACC threshold was interpolated.

response. For each condition 50 accepted sweeps were averaged. The first 12% Δf recording of 50 accepted sweeps was performed twice, and amplitudes of both recordings were averaged, in order to obtain reliable values of the largest frequency change at the start of the threshold determination procedure. For the smaller Δf recordings only the 50 accepted sweeps were used with the aim of progressing efficiently towards the ACC threshold. For the smallest Δf which generated an ACC response, recordings were again repeated twice in order to obtain reliable values of this smallest suprathreshold ACC. Duration of the total ACC recording procedure for the 4 base frequencies was approximately 2 h. We did not encounter displacement of recording electrodes or subject discomfort during this time due to the TDH-39 headphones for any participant.

2.4. Data analyses

Averaged evoked potential data were used for determining peak amplitudes and latencies for each subject. The first peak, P1, was considerably smaller compared to the following N1 and P2 peak. The low signal-to-noise ratio of this peak makes it difficult to reliably determine amplitude and latency of P1. Therefore, only the N1-P2 amplitudes were analyzed (Fig 2A). Offline baseline correction was not applied, since we did not analyze the amplitudes of the N1 and P2 peaks separately. The N1 of the ACC was defined as the most negative peak at 70 to 170 ms after the onset of the frequency change (the second segment of the stimulus). P2 was defined as the first pronounced positive peak occurring after N1 at 150 to 250 ms after the change. The N1-P2 amplitudes were computed. Peaks were manually identified, using a custom made Matlab script, by two investigators (BV, WS) independently. Disagreements, for example in case of bifid peaks, were resolved by discussion and examination of the waveforms obtained during the previous recordings with larger frequency changes. The N1-P2 amplitudes were averaged in case of repeated recordings (see previous subsection). ACC thresholds 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 distinguishable from the noise in virtually all recordings. As illustrated in Fig. 2B, the Δf with the N1-P2 amplitude of 4 µV was interpolated based on two recordings with amplitudes above and below 4 µV. In order to visualize the effect of Δf and N1-P2 amplitude with hearing loss in the figures, the SNHL group was divided in minor SNHL (<50 dB) and major SNHL (≥50 dB). This cut-off value of 50 dB was applied based on the distribution of HL within the SNHL group, in order to obtain similar numbers of minor vs major SNHL subjects. The separation between minor and major SNHL was determined per base frequency, resulting in varying groups per base frequency. Statistical analyses were completed using SPSS version 22.0 software (IBM, Armonk, NY, USA). ACC thresholds and psychophysical FDTs were obtained as Δf in % of base frequency. Since their distributions are positively skewed, logarithm transformation of ACC thresholds and psychophysical FDTs was performed in order to obtain normal distributions. To compare the means of ACC thresholds and FDT the paired samples *t*-test was used on the logarithmic values. Linear regression was performed to determine whether hearing loss (dB at 0.5, 1, 2 and 4 kHz), indicative IQ score (continuous variable, explained above), musical experience score (continuous variable indicative of musical engagement, calculated by multiplying hours per week by the years of active engagement) or age (in years) could predict ACC thresholds (Δf %), and whether ACC thresholds were related to FDTs (Δf %) or SRTs (dB). The significance threshold was set at $p<0.05$. Correlation coefficients of $R<0.3$ were considered were considered weak, R between 0.3 and 0.5 moderately strong, and $R>0.5$ strong (Cohen, 2003). In case of several significant correlations between ACC thresholds and other measures, additional multiple 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. ACC waveforms

Reproducible and clear ACC responses, exhibiting the typical N1-P2 waveform morphology, could be evoked in almost all 25 subjects for each of the four base frequencies. In one SNHL subject the first stimulus with a 12% frequency change did not evoke a response at the base frequencies 0.5 and 1 kHz, while in another SNHL subject this 12% frequency change did not evoke a response at 4 kHz. In these 2 subjects the Δf was increased in order to determine the threshold. In only one SNHL subject the ACC threshold could not be determined at one base frequency (1 kHz) because the largest 24% Δf did not generate an ACC response with a reproducible amplitude of > 4 µV.

Fig. 3 shows examples of ACC waveforms evoked at a base frequency of 1 kHz for a NH subject, a subject with minor and a subject with major SNHL. In the NH subject the smallest frequency change that generated an ACC amplitude > 4 µV was identified at a 1% frequency change (Fig. 3, left column). In an SNHL subject with minor hearing loss at 1 kHz (pure tone threshold of 40 dB at 1 kHz) the smallest ACC amplitude above 4 µV was identified at 2% frequency change (Fig. 3, middle column). In a SNHL subject with major hearing loss at 1 kHz (60 dB) the ACC threshold was found at 6% frequency change (Fig. 3, right column).

The ACC examples of these three subjects correspond with the findings on group level. In all subjects, N1-P2 amplitudes decreased with decreasing frequency change, and accordingly, thresholds could be determined. Fig. 4 depicts ACC N1-P2 amplitude as a function of the magnitude of the frequency change for all subjects at 1000 Hz. Amplitudes varied considerably among subjects, even within the NH group there was a considerable variance in ACC amplitudes, ranging from 7.7 to 15 µV at the frequency change of 12%. The slopes of the amplitude curves were steeper around the small frequency changes (Fig. 4). The SNHL group was divided in a minor SNHL group (6 subjects with thresholds of <50 dB HL at 1 kHz) and a major SNHL group (7 subjects with thresholds ≥50 dB HL at 1 kHz). At the 12% frequency change, the NH subjects appeared to have the largest ACC amplitudes, compared to the amplitudes of the SNHL subjects. The major SNHL subjects showed generally smaller ACC amplitudes than the minor SNHL subjects. For the other base frequencies of 0.5, 2 and 4 kHz, amplitude vs frequency change curves displayed a pattern similar to the 1 kHz curves displayed in Fig. 4: subjects with more severe hearing loss revealed smaller ACC amplitudes. This observation was confirmed by a significant correlation between ACC amplitude at 12%, averaged for all 4 base frequencies ($R = 0.71$, $p = 0.005$) and PTA HL.

3.2. Correlation of ACC thresholds to subject characteristics and psychophysical outcomes

3.2.1. Correlation of FDT and ACC thresholds to hearing loss

ACC thresholds were significantly correlated with hearing loss for all base frequencies (Table 1A, $R = 0.51$–0.63, $p<0.01$). Fig. 5A illustrates the strong correlation between the averaged, across the four frequencies, ACC threshold and PTA HL ($R = 0.70$, $p<0.001$). As expected, FDTs were significantly correlated to hearing loss for all base frequencies (Table 1B, $R = 0.55$–0.72, $p<0.01$). Fig. 5B depicts the correlation between the averaged, four frequency, FDT and PTA ($R = 0.67$, $p<0.001$).

3.2.2. Correlation of ACC thresholds to non-hearing subject characteristics

The total study population of 25 subjects had a median musical experience score of 3 (range 0–56), only 5 NH and 1 SNHL subject had a musical experience score above 15, which indicated active musical engagement through several years. The scores did not significantly differ between the two groups (Mann-Whitney test, $U = 55$, $p = 0.21$). The mean indicative IQ score was 97.5, NH mean was 99.8 and SNHL mean was 95.3, which did not differ (unpaired *t*-test, $t_{(23)} = 0.62$, $p = 0.13$). Additional regression analysis revealed that ACC threshold was not related to musical experience score (Table 1C, $|R|<0.36$, $p>$ 0.07), indicative IQ score (Table 1D, $|R|<0.39$, $p>$ 0.06) or age (Table 1E, $|R|<0.15$, $p>$ 0.4) in our study population.

3.2.3. Correlation of ACC thresholds to psychophysical measures

Fig. 6 shows the FDTs as a function of the ACC thresholds for each of the four frequencies. ACC thresholds in the NH subjects at 0.5, 1 and 2 kHz varied between 0.3% and 3%. At 4 kHz NH ACC thresholds varied between 0.5% and 5%. ACC thresholds in SNHL subjects varied between 0.9% and 18%. Significant correlations were found for all four base frequencies, which were strong at 1 and 2 kHz ($R = 0.67$, $p<0.001$; $R = 0.54$, $p = 0.006$) and moderate at 0.5 and 4 kHz ($R = 0.41$, $p = 0.038$; $R = 0.46$, $p = 0.021$). ACC thresholds were significantly higher than FDTs for 3 out of 4 base frequencies: by a factor 1.6 at 0.5 kHz ($t_{(24)}$=2.4, $p = 0.03$), a factor of 1.7 at 1 kHz ($t_{(24)}$=3.4, $p = 0.002$) and by a factor of 1.8 at

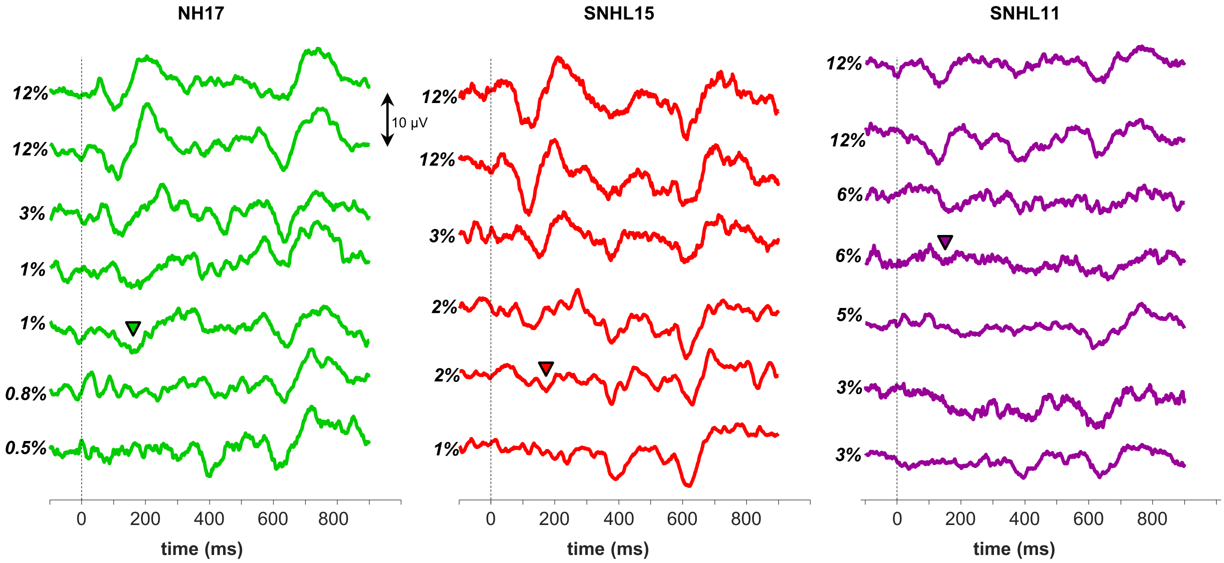

Fig. 3. ACC Waveform examples in 3 subjects evoked in response to varying stimuli with a base frequency of 1 kHz. Onset of the frequency changes (stimulus component b, Fig. 2A) within the stimuli occurred at 0 ms. The ACCs in the upper waveforms are evoked in response to 12% frequency changes which generate ACCs with the N1 peak at approximately 100 ms and amplitudes > 10 μV. On the left column a NH subject's waveforms are presented. With smaller frequency changes the ACC amplitude diminishes, with the smallest ACC amplitude > 4 μV in this NH subject at 1% frequency change. The waveforms in the middle column were evoked in a SNHL subject with minor hearing loss, the smallest ACC amplitude was determined at 2% frequency change. In the SNHL subject with major hearing loss in the right column the smallest ACC was identified at 6% frequency change.

Table 1
Simple linear regression analysis.

A. ACC threshold vs *Hearing loss*				*B. FDT* vs *Hearing loss*			
Freq (kHz)	R	R^2	p	Freq (kHz)	R	R^2	p
0.5	0.634	0.402	**0.001**	0.5	0.549	0.301	**0.004**
1	0.566	0.320	**0.004**	1	0.720	0.518	**0.00005**
2	0.569	0.324	**0.003**	2	0.629	0.396	**0.001**
4	0.513	0.263	**0.009**	4	0.656	0.430	**0.0004**
Average	0.695	0.483	**0.0001**	Average	0.669	0.448	**0.0003**

C. ACC threshold* vs *Musical experience*				*D. ACC threshold* vs *IQ*			
Freq (kHz)	R	R^2	p	Freq (kHz)	R	R^2	p
0.5	−0.357	0.127	0.080	0.5	−0.145	0.021	0.489
1	−0.244	0.060	0.251	1	−0.384	0.148	0.064
2	0.086	0.007	0.682	2	−0.113	0.013	0.590
4	−0.172	0.030	0.411	4	−0.053	0.003	0.800
Average	−0.209	0.044	0.317	Average	−0.200	0.040	0.338

E. ACC threshold vs *Age*			
Freq (kHz)	R	R^2	p
0.5	0.101	0.010	0.631
1	−0.143	0.021	0.504
2	−0.149	0.022	0.477
4	0.045	0.002	0.840
Average	−0.014	0.000	0.949

F. SRT vs *ACC threshold*				*G. SRT* vs *FDT*			
Freq (kHz)	R	R^2	p	Freq (kHz)	R	R^2	p
0.5	0.590	0.349	**0.002**	0.5	0.585	0.342	**0.002**
1	0.481	0.232	**0.017**	1	0.609	0.371	**0.001**
2	0.405	0.164	**0.045**	2	0.664	0.441	**0.0003**
4	0.268	0.072	0.195	4	0.659	0.434	**0.0003**
Average	0.544	0.296	**0.005**	Average	0.737	0.543	**0.00003**

A significant p value is indicated in bold. * Table C: Spearman correlation has been applied.

2 kHz ($t_{(24)}$=3.4, p = 0.003). ACC thresholds were a factor of 1.4 higher for the base frequency of 4 kHz, which was not significant ($t_{(24)}$=1.7, p = 0.10).

With respect to speech reception in noise, SRT increased with increasing ACC thresholds as shown in Fig. 7A (SRT vs averaged ACC thresholds: R = 0.54, p = 0.005). As shown in Table 1F, we found a strong correlation between SRT and ACC thresholds for 0.5 kHz (R = 0.59, p = 0.002), and a moderate correlation at 1 and 2 kHz (R = 0.48, p = 0.017; R = 0.40, p = 0.045). SRTs did not correlate with the ACC threshold at 4 kHz (p = 0.195). Fig. 7B presents the relation between SRT and average FDT (R = 0.74, p<0.001). Correlations between SRT and psychophysical thresholds were strong for all 4 base frequencies (Table 1G, R = 0.59–0.66, p<0.01).

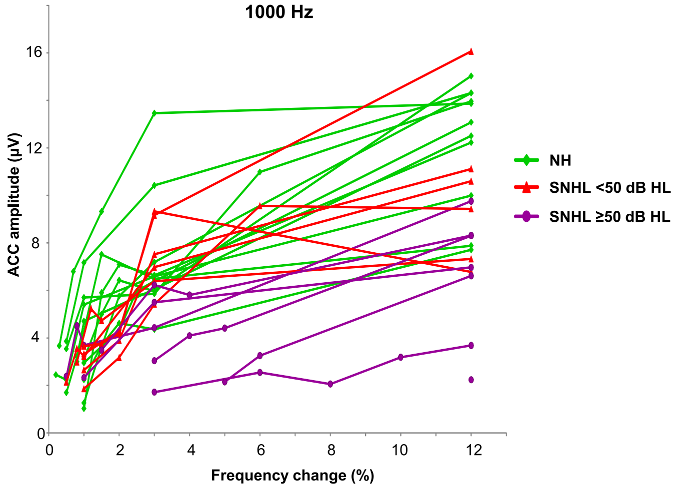

Fig. 4. ACC N1-P2 amplitude depicted as a function of the magnitude of the frequency change for all subjects at 1000 Hz. There is a considerable variation in ACC amplitude, even within the NH group with amplitudes at 12% frequency change ranging from 7.7 to 15 µV. The SNHL subjects are divided in 6 minor HL subjects (<50 dB HL at 1 kHz) and 7 major HL subjects (≥50 dB HL at 1 kHz). At the 12% frequency change the minor SNHL subjects showed generally smaller ACC amplitudes than the NH subjects, and the major SNHL subjects showed smaller amplitudes than the minor SNHL subjects.

3.2.4. Multiple regression analyses of ACC thresholds to hearing loss and psychophysical measures

In order to investigate whether ACC threshold correlated to FDT or SRT after correction for hearing loss, multiple regression analyses were conducted and results are presented in Table 2. No collinearity was found between factors with multiple regression for both FDT and SRT (Tolerance>0.6, VIF<1.3). Multiple regression analysis for FDT with ACC threshold and hearing loss as factors revealed that a significant contribution of ACC threshold was only found for 1 kHz (R^2=0.29, $p = 0.022$; Table 2). Multiple regression analysis for SRT with both ACC threshold and hearing loss as factors revealed no significant added value of ACC threshold. SRT was therefore predicted by hearing loss and not by ACC threshold. This implies that the correlations of ACC threshold with psychophysical measures were mostly explained by hearing loss.

4. Discussion

Despite the interest in the ACC as an objective measure to assess auditory functioning, most studies have only used these recordings in experimental laboratory settings. In the present study, we assessed its clinical value in normal hearing subjects and patients with sensorineural hearing loss. Our results demonstrate that objective ACC thresholds recorded to frequency changes have a moderate to strong correlation with psychophysical frequency discrimination thresholds. In addition, ACC thresholds increase with hearing loss and higher ACC thresholds are associated with poorer speech perception in noise. However, since speech perception and frequency discrimination could mostly be explained by hearing loss the clinical value is limited when current audiometry can be used to assess hearing loss.

4.1. ACC thresholds in normal-hearing subjects

ACC thresholds in the NH subjects at 0.5, 1 and 2 kHz varied between 0.3% and 3%, at 4 kHz NH ACC thresholds varied between 0.5% and 5% (Fig. 6). Several previous studies, all in normal-hearing subjects, assessed ACC thresholds. He et al. (2012) reported ACC thresholds, determined in 12 subjects of a similar age, in response to a frequency change with one base frequency of 0.5 kHz, and reported thresholds between 1% and 2%, which is in line with our findings at 0.5 kHz. Harris et al. (2008) used stimuli with two base frequencies of 0.5 and 3 kHz and found thresholds ranging between 0.8% and 1.8% in 10 young subjects (age 18–30) and between 1.2% and 3.4% in 10 older subjects with normal hearing (age 65–80). In our population no age effect was found on ACC thresholds. This might be explained by the relative small number of NH subjects or the different age distribution in our study compared to the study population of Harris et al.

A study by Brown et al. (2017) used a frequency change stimulus with a base frequency of 262 Hz and determined ACC thresholds by visual inspection, the reported ACC thresholds varied from 5 to 25 cents, which is comparable to 0.3%–1.5%. These ACC thresholds correspond with the percentages found in our study. In addition, they compared ACC thresholds between two groups: musicians and non-musicians, and concluded that the musician group showed smaller frequency discrimination thresholds. The

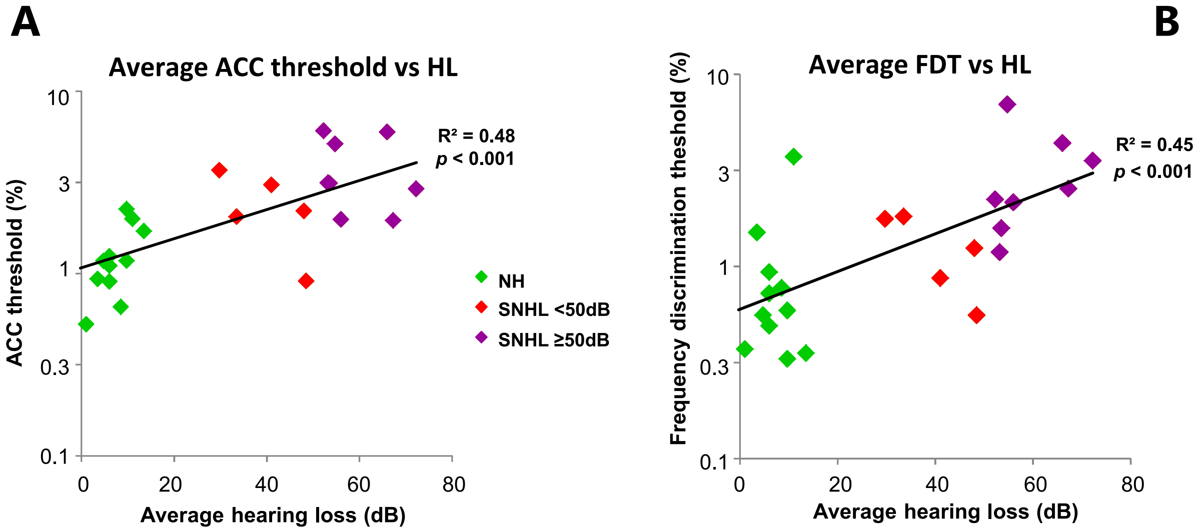

Fig. 5. **A** ACC threshold (averaged across 0.5, 1, 2 and 4 kHz) as function of PTA hearing loss for all subjects. Correlations per separate base frequency are presented in Table 1. **B** Frequency discrimination threshold (averaged across 0.5, 1, 2 and 4 kHz) as function of PTA hearing loss for all subjects. Correlations per separate base frequency are presented in Table 1.

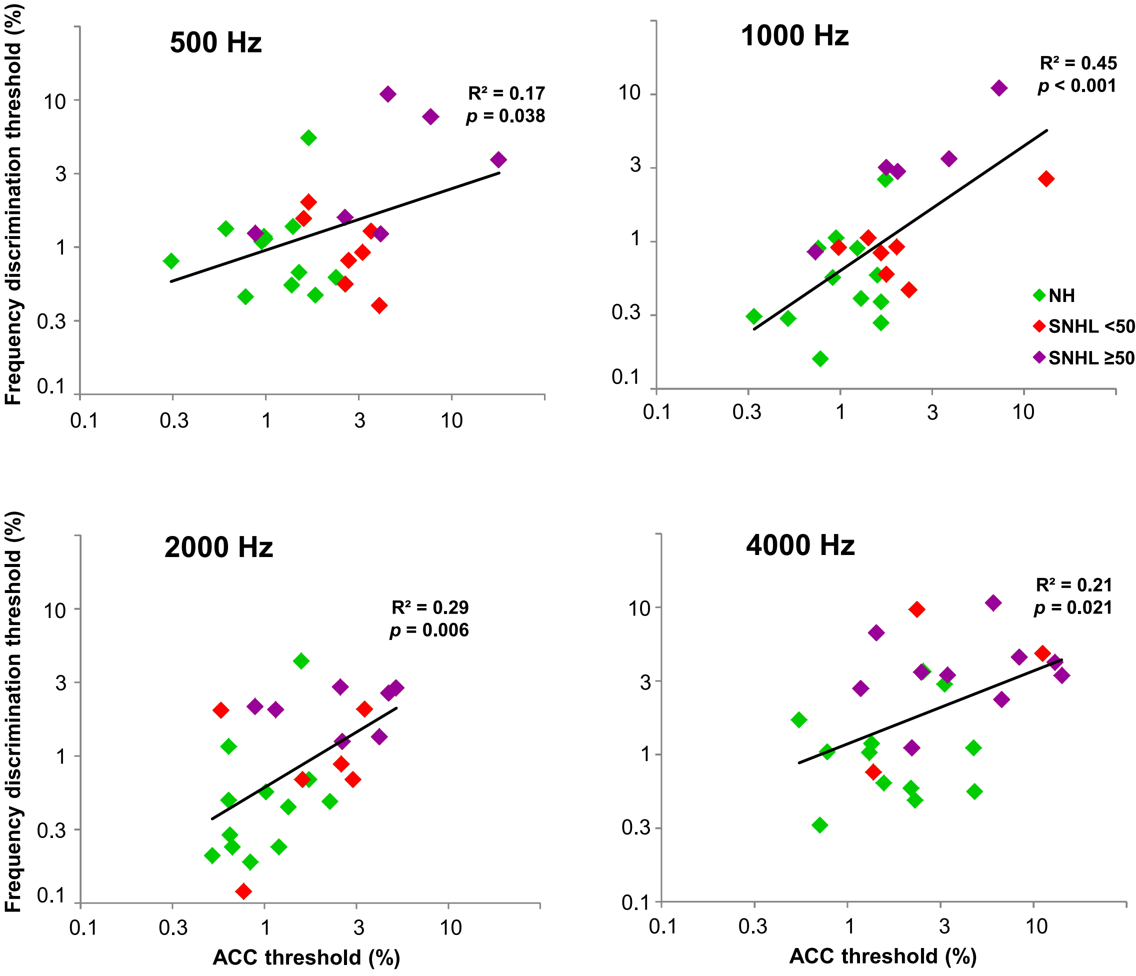

Fig. 6. Psychophysical frequency discrimination thresholds (FDTs) as a function of ACC threshold per base frequency.

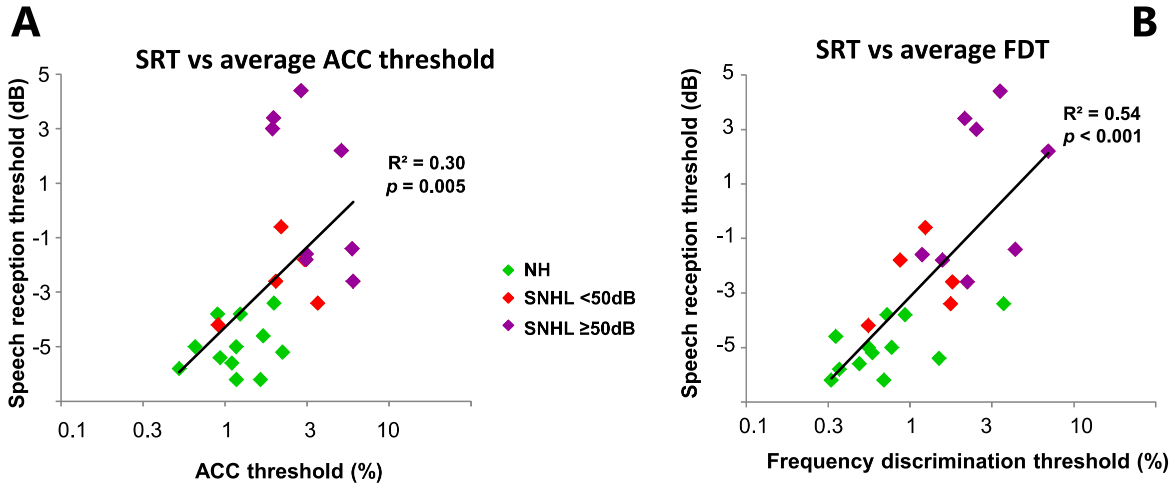

Fig. 7. **A** Speech reception threshold (SRT) as a function of ACC threshold (averaged across 0.5, 1, 2 and 4 kHz) for all subjects. SRTs as a function of ACC threshold per separate base frequency are presented in Table 1. **B** Speech reception threshold (SRT) as a function of discrimination thresholds (FDTs) (averaged across 0.5, 1, 2 and 4 kHz) for all subjects. FDTs as a function of ACC threshold per separate base frequency are presented in Table 1.

ACC thresholds in the musician group were found around 10 cent, comparable to 0.5%–0.7%, significantly lower than in the non-musician group around 20 cent, comparable to 1%–1.5%. In line with these results, Liang et al. (2016) showed that musicians displayed larger ACC amplitudes and lower psychophysical frequency discrimination thresholds compared to non-musicians. ACC thresholds were not determined in that study. Based on these two studies musical training appears to improve frequency discrimination ability, accompanied by generally larger ACC amplitudes and lower ACC thresholds. In contrast to these two studies (Liang et al., 2016; Brown et al., 2017), ACC thresholds in the current study had no relation to musical experience. The fact that this effect did not oc-

Table 2
Multiple regression analysis.

A. Frequency discrimination vs *Hearing loss and ACC threshold*

Freq (kHz)	R^2 tot	p tot	R^2 HL	p HL	R^2 ACC	p ACC
0.5	0.309	**0.017**	0.261	0.050	0.048	0.622
1	0.576	**0.00012**	0.289	**0.021**	0.287	**0.022**
2	0.443	**0.0016**	0.301	**0.021**	0.142	0.186
4	0.451	**0.0014**	0.374	**0.0053**	0.077	0.322

B. Speech reception threshold vs Hearing loss and ACC threshold

Freq (kHz)	R^2 tot	p tot	R^2 HL	p HL	R^2 ACC	p ACC
0.5	0.551	**0.00015**	0.421	**0.0046**	0.130	0.244
1	0.682	**0.000006**	0.672	**0.000020**	0.010	0.891
2	0.760	$\mathbf{1.6 \times 10^{-7}}$	0.812	$\mathbf{2.2 \times 10^{-7}}$	−0.052	0.322
4	0.740	$\mathbf{3.7 \times 10^{-7}}$	0.799	$\mathbf{1.6 \times 10^{-7}}$	−0.059	0.096

A significant p value is indicated in bold.

cur in our study population might be due to the relatively small variation in musical experience with only 6 subjects having musical experience at recreational level, since subjects were selected on their hearing performance rather than musical experience. This is in contrast to the above mentioned studies, where the musicians were recruited at conservatories and all subjects were considered ‘professional musicians’. Given our study population, we are unable to draw conclusions on the effect of musical training on ACCs or frequency discrimination. Although ACC thresholds found in our study are comparable to those described in the literature, ACC amplitudes are larger than previously reported values. We assume that loudness plays a limited role in the ACC. Yet, to reduce this potential limited effect we aimed at similar loudness by presenting the stimuli at maximum comfortable level in the SNHL subjects, and at 75 dB SPL in NH subjects. ACC amplitudes within our NH group show a considerable variance between these NH subjects at the largest frequency change of 12%, for example ranging from 8 to 15 µV at 1 kHz (Fig. 4). Although these amplitudes are comparable to findings in our previous study in 12 young NH subjects (Vonck et al., 2019) values described in the literature vary and responses, evoked with frequency change magnitudes comparable to 12%, presented at comparable levels (70–80 dB SPL) are generally smaller (Dimitrijevic et al., 2008; Harris et al., 2008; He et al., 2012). As described in our previous study, amplitudes are highly dependent on stimulus parameters (Vonck et al., 2019). ACC amplitude is not only influenced by frequency change magnitude. Other factors within the stimulus, like duration of the base frequency component within the stimulus or frequency change rate, play a part as well. Variability in amplitudes presented in the literature might be due to differences in stimuli and parameters or differences in recording equipment and settings. Interestingly, these larger ACC amplitudes in our study did not lead to lower ACC thresholds compared to other studies, despite the differences in frequency-change stimuli between studies. ACC threshold assessment therefore appears to be less dependent on stimulus parameters than ACC amplitude measurement. Thus, the current findings combined with our previous study and comparison to other literature show that for the ACC, amplitudes considerably vary between subjects and between studies (Dimitrijevic et al., 2008; Harris et al., 2008; He et al., 2012; Vonck et al., 2019). Developing ACC amplitude measurement into a clinical tool, with reference values for NH subjects, might therefore be challenging, whereas ACC threshold appears to be a more robust measurement and would therefore be more suitable for clinical application. Knowledge on whether the ACC threshold is affected by stimulus presentation level would further strengthen the value of this method as a clinical objective measurement. For the development of the ACC threshold into a clinical applicable procedure it is not feasible to loudness balance the stimuli 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. If, in any condition, the loudness cues distorted the responses it would most likely cause false positives so therefore discrimination abilities might be overestimated but when discrimination is not observed this would likely be a true result and intervention based on that would be valid.

4.2. ACC thresholds in hearing loss

As expected, we found that ACC thresholds increase with increasing hearing loss for all four frequencies between 0.5 and 4 kHz (Table 1, Fig. 5A). Literature on ACC thresholds in hearing loss is limited. One previous study recorded ACCs in five hearing-impaired children and compared these to five normal-hearing children, however, these authors did not observe ACC differences in hearing impairment (Martinez et al., 2013). A more recent study by Kang et al. (2018) used the ACC to determine cochlear dead regions in hearing-impaired adults. This study did not use frequency change stimuli, but recorded ACCs in response to a pure tone with varying intensity within a stimulus of threshold equalizing noise. These authors found higher ACC thresholds in hearing-impaired subjects with cochlear dead regions than in other hearing impaired subjects and normal hearing subjects. Furthermore, in the current study we did not conduct loudness balancing within the frequency change stimuli. Therefore we cannot exclude that some SNHL subject with sloping hearing loss perceived loudness changes when exposed to a frequency change stimulus. Studies on ACCs in response to sound level changes have shown that level changes of 2 or 3 dB evoke an ACC (Martin and Boothroyd, 2000; Harris et al., 2007). We estimate the change in sensation level for a 12% frequency change (the largest change applied), which is about 1/6 octave, is 1/6 of the threshold difference between the reference frequency and one octave higher as measured in pure tone audiometry. In 18 of 52 tested frequencies in 13 SNHL subjects the threshold differences were 15 dB or higher suggesting a sensation level change of 2.5 dB or higher. Loudness changes were smaller around the ACC threshold, therefore, overall the effect on the ACC threshold estimate can be assumed to be small.

4.3. ACC thresholds vs psychophysical frequency discrimination thresholds

In the current study the ACC thresholds had moderate to strong correlations to psychophysical FDTs for all four base frequencies, which confirm some earlier findings in literature. To date, only two preceding studies correlated ACC thresholds to FDTs (He et al., 2012; Brown et al., 2017). In line with our findings, these correlations were found to be significant by both He et al. (2012) (R^2=0.49, p<0.05) and Brown et al. (2017) (R^2=0.24, p = 0.027). Both used low frequency stimuli. He et al. (2012) used a base frequency of 500 Hz in young NH subjects. Brown et al. (2017) used a base frequency of 262 Hz in young normal hearing musicians and non-musicians, and determined ACC thresholds by visual inspection. A third study by Harris et al. (2008) correlated ACC thresholds to psychophysically assessed frequency modulation detection thresholds, in 8 older subjects. They found significant correlations, for ACC thresholds at a base frequency of 0.5 kHz to frequency modulation detection thresholds at 0.5 kHz (R = 0.85, p<0.05), and for ACC thresholds at a base frequency of 3 kHz to frequency modulation detection thresholds at 4 kHz (R = 0.76, p<0.05). In addition to these 3 studies, our results confirm the suggested correlation between ACC thresholds and frequency discrimination thresholds at different frequencies in NH and SNHL subjects. Furthermore, He et al. (2012) reported significantly higher ACC thresholds compared to psychophysical thresholds (t = 5.5, p<0.05). This is in line with our results with significant higher ACC thresholds at 0.5, 1 and 2 kHz. In other words, subjects were able to differentiate psychophysically between frequency changes that were smaller than the smallest frequency change that evoked an ACC response in that subject. Not only do ACC thresholds differ from FDTs by electrophysiological versus psychophysiological assessment, also the stimuli differ. ACCs are derived in response to a frequency increment within a continuous tone (within-stimulus frequency change), whereas FDTs are assessed by sequences of pure-tone pips separated by a silent interval with varying frequencies (across-stimulus frequency change). Psychophysical data on detection of frequency changes suggest similar thresholds as reported for frequency discrimination (around 0.5%, Liang et al., 2016).

4.4. Responses to frequency changes in hearing loss

The effect of hearing loss on FDTs and ACC thresholds in our study fits with the extensive literature on deteriorated frequency discrimination in hearing impairment (e.g., Tyler et al., 1983; Oxenham, 2008; Halliday et al., 2019). Assuming that frequency discrimination is based on temporal fine structure information, cochlear place information or a combination thereof (Moore, 2008; Oxenham, 2008; Moore and Ernst, 2012), a reduction of either of the information streams explains a decline in frequency discrimination. Damage to the inner hair cells and/or synapses and their afferent neurons affects neural firing reliability and thus the temporal information (Henry and Heinz, 2012). Due to damage to and/or loss of outer hair cells frequency tuning within the cochlea is diminished (Liberman and Dodds, 1984) which affects the place information. In several of the subjects hearing losses were severe (thresholds > 60 dB HL) reflecting severe hair cell loss, which when around the tested frequency will surely explain deterioration of frequency discrimination. The wide variability in cochlear damage that can be expected among the hearing-impaired subjects explains the variability in frequency discrimination (Fig. 6) with some individuals with minor loss performing as well as the best normal-hearing subjects, and some individuals with major loss performing quite poorly.

This large distribution in frequency discrimination over our population of hearing-impaired and normal-hearing subjects will have strengthened the correlation between ACC threshold and FDT. Indeed, after correction for hearing loss by multiple regression we only found a significant correlation between ACC threshold and FDT at one out of 4 frequencies (1 kHz, Fig. 6). However, this weak correlation may be related to the stimulus differences between ACC and FDT with ACC thresholds derived in response to within-stimulus frequency changes whereas FDTs were derived with across-stimulus frequency changes, as mentioned the previous section. The statistical power using N = 25 for the entire population was sufficient to assess the correlations of FDT or SRT with the ACC thresholds. For assessment of the contribution of ACC threshold in addition to hearing loss to explain SRT a larger sample size would have been desirable.

4.5. Clinical implications

Although pure tone audiometry and speech perception tests are routinely used in the clinic, it is remarkable that frequency discrimination tests are hardly ever conducted to assess hearing impairment. Our results support the clinical value of frequency discrimination tests, since average frequency discrimination had a strong correlation to SRT (Fig. 7B; R = 0.74, p<0.001*)*. Even for separate base frequencies, correlations between FDTs and SRT were strong for all 4 frequencies (Table 1G, R = 0.59–0.66, p<0.01). Frequency discrimination is not only relevant for speech perception in noise, but also indispensable for the appreciation of music. Frequency discrimination ability may vary within the normal hearing population, e.g. based on musical training or age, and deteriorates with hearing loss. This leads to a large variation of frequency discrimination within the hearing impaired. Musical training has been shown to improve frequency discrimination and speech perception (Parbery-Clark et al., 2009; Mandikal Vasuki et al., 2016). Also, in CI users improved frequency discrimination may lead to improvement of perception of everyday sounds including speech (Prevoteau et al., 2018). Frequency discrimination tests might therefore be clinically relevant in order to assess music appreciation in the hearing impaired. The clinical value in CI users remains to be investigated.

An objective measurement that reflects frequency discrimination is valuable in case behavioral tests are unreliable. These behavioral tests, such as tone audiometry, frequency discrimination or speech perception tests, can be unreliable in certain hearing impaired subjects, for example in young children, in cases of cognitive impairment or a language barrier. Based on our findings the ACC has potential for application as an objective assessment of frequency discrimination and it is correlated to speech perception. Following multiple regression analyses, the moderate to strong correlations between ACC and FDT could mostly be explained by hearing loss measured by tone audiometry. This latter finding limits the clinical added value of application of the ACC threshold in all other hearing impaired subjects, for whom reliable behavioral testing is very well possible. Furthermore, our ACC threshold assessment procedure with a stimulus duration of approximately 3.3 s (Fig. 2A), combined with several steps of averaged recordings and the use of 4 base frequencies leads to a total procedure duration of approximately 2 h. For a clinical application shorter stimuli (around 1 s, e.g., He et al., 2012), and less base frequencies should be used, which will considerably shorten the test duration.

We conclude that ACC threshold assessment holds promise as a valuable objective clinical tool in hearing impairment, indicative of frequency discrimination ability and speech perception in noise. The current clinical application we suggest would be in case behavioral tests are unreliable.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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