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Amplitude Growth Functions of Auditory Nerve Responses to Electric Pulse Stimulation With Varied Interphase Gaps in Cochlear Implant Users With Ipsilateral Residual Hearing

Marina Imsiecke[1], Andreas Büchner[1,2], Thomas Lenarz[1,2], and Waldo Nogueira[1,2]

Abstract

Amplitude growth functions (AGFs) of electrically evoked compound action potentials (eCAPs) with varying interphase gaps (IPGs) were measured in cochlear implant users with ipsilateral residual hearing (electric-acoustic stimulation [EAS]). It was hypothesized that IPG effects on AGFs provide an objective measure to estimate neural health. This hypothesis was tested in EAS users, as residual low-frequency hearing might imply survival of hair cells and hence better neural health in apical compared to basal cochlear regions. A total of 16 MED-EL EAS subjects participated, as well as a control group of 16 deaf cochlear implant users. The IPG effect on the AGF characteristics of slope, threshold, dynamic range, and stimulus level at 50% maximum eCAP amplitude ($level_{50\%}$) was investigated. AGF threshold and $level_{50\%}$ were significantly affected by the IPG in both EAS and control group. The magnitude of AGF characteristics correlated with electrode impedance and electrode-modiolus distance (EMD) in both groups. In contrast, the change of the AGF characteristics with increasing IPG was independent of these electrode-specific measures. The IPG effect on the AGF $level_{50\%}$ in both groups, as well as on the threshold in EAS users, correlated with the duration of hearing loss, which is a predictor of neural health. In EAS users, a significantly different IPG effect on $level_{50\%}$ was found between apical and medial electrodes. This outcome is consistent with our hypothesis that the influence of IPG effects on AGF characteristics provides a sensitive measurement and may indicate better neural health in the apex compared to the medial cochlear region in EAS users.

Keywords

electric-acoustic stimulation, neural health, electrically evoked compound action potential, amplitude growth function

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Progressive auditory nerve degeneration is known to occur in patients suffering from severe hair cell loss, especially in areas where inner hair cells (IHCs) are destroyed (Johnsson, 1974; Zimmermann et al., 1995). Supporting cells, which are primarily lost after IHC loss, have been found to play a large role in neuronal degeneration (Sugawara et al., 2005). In cochlear implant (CI) users, the survival of the auditory nerve, that is, neural health, is particularly important, as electric stimulation largely depends on the excitability of the spiral ganglion cells (SGCs) for an accurate signal transmission. Consequently, neural health is assumed to be partially responsible for the variability in speech reception performance among CI users (Pfingst et al., 2015; Seyyedi

[1]Clinic for Otorhinolaryngology, Hannover Medical School, Hannover, Germany
[2]Cluster of Excellence "Hearing4All," Hannover, Germany

Corresponding author:
Waldo Nogueira, Deutsches HörZentrum Hannover, Karl-Wiechert-Allee 3, 30625 Hannover, Germany.
Email: nogueiravazquez.waldo@mh-hannover.de

et al., 2014). In recent years, CI implantation criteria have been expanded from completely deaf patients to patients suffering from high-frequency hearing loss that cannot be treated with a traditional hearing aid (von Ilberg et al., 1999). With further advances in more flexible designs and atraumatic insertion of the electrode array, the preservation of residual hearing has improved to the point where a very small (<15 dB hearing level [HL]) decrease in threshold in up to 50% of cases is observed, depending on electrode type (Gantz et al., 2009; Gstoettner et al., 2004; Skarzynski et al., 2007; Suhling et al., 2016). The electric hearing via the CI is then combined with a hearing aid component in the same ear, thus providing electric-acoustic stimulation (EAS) to the patient (Turner et al., 2010). Due to the survival of IHCs in the apical areas in these EAS users, better neural health might be assumed. To test this hypothesis and investigate whether responses of the auditory nerve can be used to assess neural health, a group of EAS users participated in an experiment of measuring electrically evoked responses.

Temporal bone studies with deceased human CI users have been inconclusive, with some showing a relation between SGC count and speech reception performance (Kamakura & Nadol, 2016), and others reporting no effect (Fayad & Linthicum, 2006; Xu et al., 2012). In addition, when investigating the temporal bones of bilaterally implanted adults postmortem, Seyyedi et al. (2014) found that the differences of SGC density between the two ears significantly predicted the difference in speech reception performance within each subject. This finding may reflect the possibility that interpatient speech reception performance variability also depends on nonperipheral factors such as cognition (Finke et al., 2016; Holden et al., 2013; O'Neill et al., 2019), potentially confounding the relation between SGC survival and speech reception outcomes. Overall, several studies have found a correlation between speech reception performance and indirect measures of neural health, such as duration and onset of hearing loss (Holden et al., 2013; Nadol et al., 2001). However, strong variability persists, which poses difficulties when seeking the optimal approach to CI fitting in the clinical routine. Consequently, an assessment of the state of the auditory nerve in CI users would be helpful to infer possible solutions, if speech reception performance stays below the expected outcome levels.

In animals, responses from the auditory nerve, such as the electrically evoked compound action potential (eCAP), and electrically evoked auditory brainstem responses (eABRs) were found to be related to neural survival following deafness induced by ototoxic drugs (Hall, 1990; Prado-Guitierrez et al., 2006; Shepherd & Javel, 1997). Several characteristics of the objective measures have been investigated. The threshold of detectable eCAP responses have been found to increase after deafening (Prado-Guitierrez et al., 2006; Stypulkowski & Van den Honert, 1984), while response amplitudes consistently decrease after treatment with ototoxic drugs (Agterberg et al., 2008; Hall, 1990; Shepherd & Javel, 1997). Factors such as the latency of the first negative peak of the eCAP have also been shown to be dependent on neural health, with shorter latencies in deafened animals (Ramekers et al., 2014).

Quantified histological measures of the auditory nerve have been shown to correlate significantly with suprathreshold eCAP response characteristics in a number of studies. Prado-Guitierrez et al. (2006) reported that the SGC survival correlated with changes in eCAP amplitude growth function (AGF) response caused by both longer interphase gaps (IPGs) and phase durations (PDs). Differences in SGC density may be correlated with the effects on the eCAP of changing PD and IPG for several reasons. One mechanism of the IPG effect might involve a change in cell membrane characteristics. The neuronal membrane acts as a leaky integrator and with progressive levels of demyelination the time required for sufficient charge integration increases. The probability of a neuron firing in response to the first phase of a biphasic stimulus (before charge is removed by the opposing phase) is increased when an IPG is placed between the two phases (Ramekers et al., 2014; van den Honert & Mortimer, 1979). Thus, the IPG effect provides a measure for temporal integration capabilities of the neurons in a target population. A further possible mechanism relates to the difference in neural density. Higher slopes of AGFs obtained from increasing stimulus intensities have been positively correlated to a higher number and density of surviving auditory neurons (Hall, 1990; Pfingst et al., 2015; Smith & Simmons, 1983). Ramekers et al. (2014) measured AGFs with varying IPGs and found that in guinea pigs several eCAP and AGF characteristics correlated significantly with SGC density. eCAP amplitude, AGF slope, and N_1 latency increased with IPG and also with spiral ganglion count, while the threshold and the stimulus intensity needed to reach 50% of the maximum eCAP amplitude, termed $level_{50\%}$, decreased. They also assessed the change in each characteristic with an IPG increase from 2.1 to 30 μs. The degree to which N_1 latency, AGF slope, and $level_{50\%}$ changed with increasing IPG correlated with the SGC packing density. Recently, Brochier et al. (2021b) showed that, based on a reanalysis of animal data and a theoretical model, the most appropriate method to estimate neural health consists of measuring the dB offset between the linear portions of eCAP AGFs for two stimuli differing only in IPG, which is similar to the $level_{50\%}$ characteristic.

In humans, electrophysiological measurements have been performed to assess the state of the auditory nerve, as concluded from the animal studies, and

examine correlations to speech reception performance. The relationship between eCAP and AGF characteristics and speech reception outcomes has, in contrast to expectations from animal studies, not been found to be strong in humans. While the mere presence of an eCAP response was found to significantly predict speech reception performance in numerous studies (Buchman et al., 2011; Jeong & Kim, 2013; Teagle et al., 2010), specific eCAP characteristics show less predictive strength. Brochier et al. (2021a) used different stimulus changes to compare behavioral estimates to electrophysiological experiments with eCAP AGFs and concluded that these measures reflect different characteristics of the electrode-neuron interface, which complicates the comparison between different studies. Several studies that investigated the correlation between AGF slope and speech reception performance have reported mixed results, with only some significant correlations (van Eijl et al., 2017). Kim et al. (2010) reported a significant correlation between the slope of the AGF and speech tests results with the CNC word and a sentence test in noise in hybrid (i.e., EAS) CI recipients. This relationship persisted for one traditional electrode array but not for another electrode type that was tested and was only significant for the CNC word test. DeVries et al. (2016) found a significant positive correlation between the eCAP amplitude at moderately high stimulus levels and a combined vowel and consonant recognition score. Brown et al. (1990) reported moderate correlations between the slope of the AGF and speech reception performance by word and sentence recognition but did not report on the significance value. In contrast, Gantz et al. (1994) and Franck and Norton (2001) only found low or nonsignificant correlations, respectively, between AGF slopes and sentence recognition scores.

Schvartz-Leyzac and Pfingst (2016) argued that there are influences of electrode impedance caused by fibrous tissue or new bone growth on eCAP amplitude and AGF slope. However, the across-site differences in the effect of IPG changes on eCAP characteristics did not correlate with the across-site impedance differences. This potential dissociation between impedance and eCAP changes indicates that the analysis of IPG-related eCAP and AGF characteristics across different IPGs may provide a promising approach to investigate the status of neural health in humans. Moreover, the recent work by Brochier et al. (2021a) supports the use of measures based on the IPG effect on the dB offset of the linear portions of the eCAP AGFs. This approach could therefore help in the search for an objective measure of neural health in CI and EAS users, to possibly understand the variability in speech reception performance and predict outcomes directly after the implantation with a CI. To be applicable in the clinical routine, a reliable and objective estimation of neural health is required. Evidently, nonfunctional hair cells cause a decrease in spiral ganglion density (Johnsson, 1974; Sugawara et al., 2005; Zimmermann et al., 1995) so that a comparison between the results from the apex and the base of the cochlea in EAS users and furthermore the comparison between overall outcomes from EAS and CI users could show the feasibility of this neural health measurement paradigm. Motivated by observations in animal experiments, the current study investigates a measurement paradigm with varied IPGs, hypothesizing differences in the effects of varying IPG on AGF characteristics between and within EAS and CI subjects. In addition, known indirect measures of neural health, such as duration of hearing loss, are investigated for correlation to the IPG effects on AGF characteristics in EAS and CI users, to evaluate whether this measurement paradigm might be useful in the objective estimation of neural health.

Methods

Subjects

Sixteen EAS users, who had been implanted with MED-EL Flex 28, 24, 20, or the Hannover custom-made device Flex 16 (Timm et al., 2018) and retained residual hearing in the low frequencies, participated in the experiment. The hearing thresholds of EAS subjects at 250 Hz and at the apical electrodes are given in Table 1. An estimation of the hearing threshold at the electrodes' place frequencies was obtained based on the Stakhovskaya et al. (2007) frequency map and by linearly interpolating the HL in dB from the neighboring audiometric frequencies. A control group of 16 CI users without residual hearing (250 Hz > 90 dB HL) was recruited. Although the aim was to have the control group matched to the EAS group in terms of age and duration of hearing loss, there was a mean difference of 3 years in age and a mean difference of 14 years in duration of hearing loss. Duration of hearing loss was assessed by the date of diagnosis of high-frequency hearing loss or self-reported onset, if it deviated strongly. All subjects gave written informed consent to the experiments, as approved by the Hannover Medical School's institutional review board. Their demographic data are shown in Table 2.

Compound Action Potentials

AGFs were measured using the automatized, continuous eCAP measurement system of the MAESTRO (MED-EL GmbH, Innsbruck, Austria) fitting software called AutoART for two different IPGs of 2.1 and 10 µs. AutoART uses an alternating polarity artifact reduction paradigm. The four most apical electrodes (Numbers

Table 1. Hearing Level (HL) Data of Subjects With Measured HL in dB for 250 Hz and Interpolated HL in dB for the Locations of the Most Apical Four Electrodes.

	EAS users																
HL (dB)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	CI users
250 Hz	20	85	85	40	30	20	50	15	75	55	25	75	15	60	25	70	>90
@ El #1	91	AL	101	92	93	AL	102	100	AL	91	87	107	84	109	104	87	AL
@ El #2	97	AL	109	95	102	AL	105	100	AL	95	90	AL	88	AL	105	88	AL
@ El #3	100	AL	99	AL	AL	AL	105	100	AL	101	92	AL	90	AL	105	85	AL
@ El #4	100	AL	99	AL	AL	AL	105	100	AL	102	95	AL	90	AL	104	90	AL
α_{ins} (°)	316	348	532	342	450	237	347	254	346	220	220	397	242	192	324	351	577
f_p (kHz)	1	0.8	0.4	0.9	0.6	2.1	0.8	1.8	0.9	2.4	2.4	0.7	1.9	2.9	1	0.8	0.3

Note. Place frequency (f_p) of the electrodes was calculated based on the insertion angle (α_{ins}) with the frequency table proposed by Stakhovskaya et al. (2007), f_p and α_{ins} are indicated for the most apical electrode (El #1). Data are shown for individual EAS users (Column Numbers 1 to 16) and the average across CI users, which did not have residual hearing above 500 Hz. EAS = electric-acoustic stimulation; CI = cochlear implant; HL = hearing level; AL = audiometer limit.

Table 2. Subject Data of Matched Pairs of Electric-Acoustic Stimulation (EAS) Users and Control Group of CI Users Without Residual Hearing.

	EAS users					CI users			
#	Age	CI use	Dur HL	Electrode	HSM	Age	CI use	Dur HL	HSM
1	43	0.9	9	Flex 20	94	39	2.3	18	62
2	66	2.7	63	Flex 20	75	67	0.9	66	5
3	62	1.5	36	Flex 28	60	59	2.8	15	92
4	39	1.9	26	Flex 28 PI	86	42	2.9	29	16
5	82	3.8	10	Flex 24	63	82	2.3	4	38
6	48	1.4	16	Flex 16	94	49	1.8	47	43
7	49	2.9	35	Flex 20	52	42	2.9	29	46
8	52	1.6	20	Flex 16	90	54	4.4	14	77
9	61	1.7	21	Flex 24	63	60	3.3	48	0
10	68	2.7	12	Flex 16	85	67	3.3	58	8
11	62	2.6	9	Flex 16	87	57	3.5	10	44
12	54	2.5	50	Flex 28	79	49	2.8	46	30
13	46	1.7	11	Flex 24 PI	90	50	3.2	1	87
14	71	1.5	21	Flex 24 PI	21	67	3.1	64	5
15	46	1.5	10	Flex 28 PI	89	45	2.7	6	54
16	78	8.7	9	Flex 20	51	71	2.3	NA	64

Note. Pair number (#), age at testing, duration of implant use, and duration of hearing loss (Dur HL), all in years, as well as speech reception performance in % correct with the HSM sentence test (Hochmair-Desoyer et al., 1997) as well as electrode type for EAS users is given, PI indicates partial insertion (Lenarz et al., 2019). The electrode type of CI users was Flex 28. CI = cochlear implant; HL = hearing level; HSM = Hochmair-Schulz-Moser.

1–4) and one basal electrode (Number 9) were stimulated in EAS users and all electrodes in CI users. Two neighboring electrodes in both apical and basal direction were used as recording electrodes, which allows for the selection of the best recording and the reduction of artifacts between specific stimulation-recording electrode pairs (Strahl et al., 2018).

The amplitude of the single pulse electric stimulation in charge units (nC) was steadily increased in a continuous paradigm (Gärtner et al., 2018). Upon reaching the loudest acceptable presentation level, which the subject indicated in real time, the stimulation of the current electrode was stopped. The PD of the single phase of the biphasic pulse stimulus was determined by the software, based on the individual impedance of the electrode to avoid out-of-compliance stimulation and a maximum charge level, set to 40 nC, based on clinical experience. The eCAP amplitude was defined as the difference in voltage between N_1 and P_2 peaks, obtained from a two-dimensional surface fitted to all eCAP responses of the AGF (Strahl et al., 2018). The input–output function was then fitted using a Boltzmann sigmoid

according to the following equation, with the eCAP amplitude V in microvolts (μV), the stimulus charge q in nC and the fitting parameters A–D:

$$V_{eCAP} = A + \frac{B}{1 + e^{-\frac{q-C}{D}}} \quad (1)$$

A denotes the noise level of the measurement and was not analyzed further. The remaining fitting parameters were used as output parameters to assess changes with IPGs and differences between stimulation sites, as they correspond to physiological properties, that is, B defines the maximum N_1-P_2 amplitude; C the stimulus level to achieve 50% (denoted $level_{50\%}$) of said maximum N_1-P_2 amplitude and $4D$ the dynamic range. In addition, the slope of the linear increase at C is defined as $B/4D$ and the threshold given by $C - 2D$, as shown in Figure 1. A further parameter, the N_1 peak latency, was considered, as it has been shown to be correlated to neural health in animals (Ramekers et al., 2014). However, in some cases, the N_1 peak was not observable as it occurred in the time interval after stimulus onset in which a signal blanking technique was applied to reduce the stimulus artefact and avoid saturation of the biosignal amplifier. For an IPG of 10μs, this results in a maximal delay of the measurement onset at 193 µs after stimulus onset. To avoid any bias due to the different measurement onsets between IPGs, the shortest allowed N_1 data point was set to 200 µs after stimulus onset. Consequently, the data point that was chosen was aligned for the two measurements with different IPGs, as otherwise a confounding IPG effect would be introduced into the AGF estimation.

However, this introduces a systematic error by underestimating the eCAP amplitude in cases where the actual N_1 peak lay within the blanking time, making the measure of absolute eCAP amplitude unreliable. Still, as the AGF is fitted with a sigmoid function, the only parameter that is affected by a reduced amplitude growth is the scaling factor B. The other characteristics that are obtained from Equation 1 are similarly affected for both IPGs and can still be investigated. They are threshold ($C - 2D$), normalized slope ($1/4D$), dynamic range ($4D$), and the inflection point (C), that is, $level_{50\%}$. Both normalized slope and dynamic range are investigated, as dynamic range was chosen to be investigated on a logarithmic scale (i.e., $4D_{dB}$), based on the arguments of McKay (2012), which are explained in the Results section with Figure 3.

The obtained data, containing the AGFs, was exported from the software and analyzed using custom-made software in MATLAB. As the distance between neural population and recording electrode has a scaling effect, which might influence the eCAP response, only directly neighboring recording electrodes are used for the analysis. The eCAP characteristics were analyzed in terms of the effects of changes in the IPG and these changes were compared across the electrode array.

As the type of the electrode and the resulting insertion depth differs strongly across subjects, the insertion angle of individual electrodes was obtained from medical

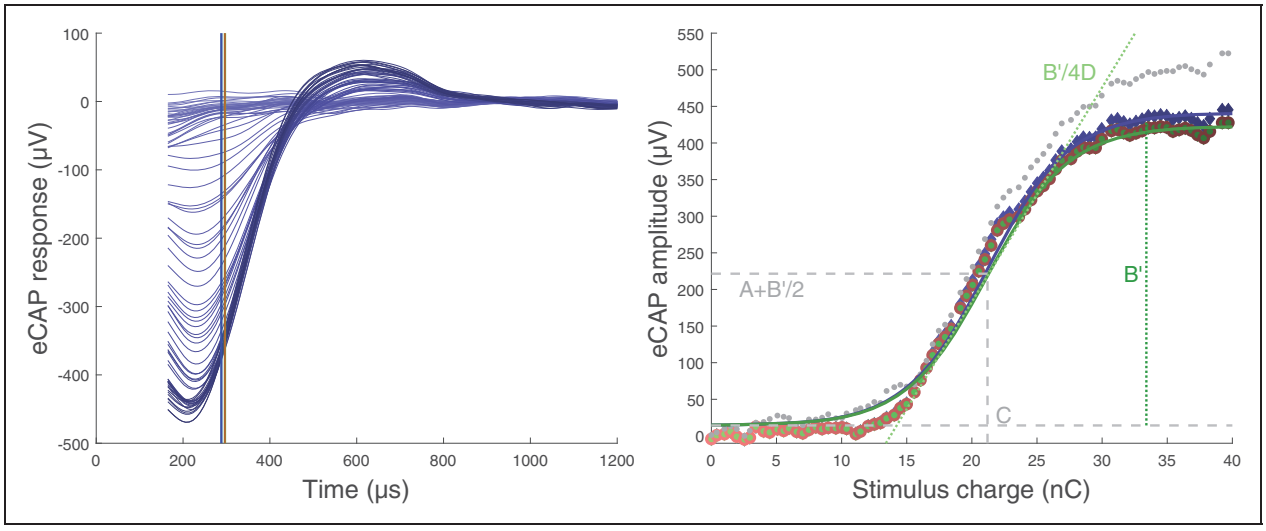

Figure 1. Left: Raw data of one exemplary measurement run (blue shades) with indication of theoretical N_1 loss through blanking (vertical lines). Right: Schematic illustration of the characteristics of the amplitude growth function (AGF) illustrating the blanking effect for the different IPGs (blue for 2.1 and green for 10 μs), and the correction of the IPG affected blanking for 2.1 μs (red circles). By introducing the shift, the IPGs can be compared again (green diamonds vs. red circles) but will result in a lower growth than in an unblanked case (gray eCAP amplitude). Sigmoidal fits of Equation 1 with the AGF slope ($B'/4D$), inflection point (C or $level_{50\%}$), and maximum amplitude (B') are indicated.

EAS = electric-acoustic stimulation; CI = cochlear implant; SNR = signal-to-noise ratio; HSM = Hochmair-Schulz-Moser.

imaging data (cone beam computer tomography) that is available for routine electrode position assessment in the clinic. The same imaging data were used to infer the distance between the electrodes and the modiolar wall (electrode-modiolus distance [EMD]), as illustrated in Figure 2. Consequently, eCAP characteristics can be analyzed across electrode insertion angle for all subjects. In a second step, the results of the two subject groups (with and without residual hearing) were compared to each other by identifying differences in the eCAP AGF characteristics across cochlear location. Our hypothesis was that EAS users retain better neural health in apical areas due to their residual hearing.

Statistical Analysis

A viable estimation of the AGF characteristics could only be obtained if a stable eCAP AGF response was measured. This was not possible for every electrode in all subjects, as the loudness percept sometimes exceeded loudest acceptable presentation level already at medium stimulation intensities and hence no significant sigmoid fit could be obtained. Approximately 70% of all measured AGFs (across electrodes, IPGs, and subjects) resulted in a reliable sigmoid fit. Consequently, data are missing for specific IPGs and electrodes so that an overall statistical analysis of the IPG and electrode effect, for example, by an analysis of variance, is not possible. Changes with IPG are assessed by paired two-sided Wilcoxon signed-rank tests, while differences between electrodes, insertion angles (apical vs. basal, using median split), and subject groups (EAS vs. CI) are evaluated by unpaired two-sided Mann–Whitney U-tests. A Bonferroni correction was applied to compensate for the four characteristics that were tested.

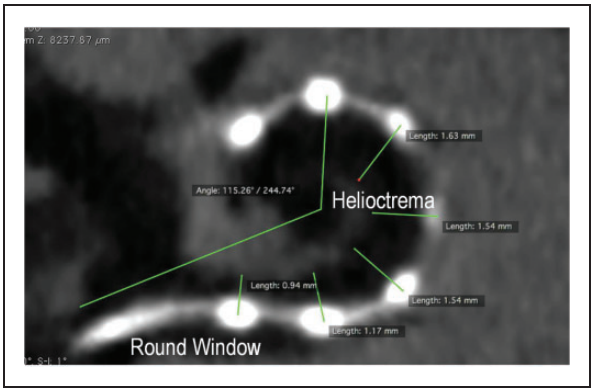

Figure 2. Screenshot From the Clinical Imaging Software (Osirix) for the Estimation of Electrode Insertion Angle (Exemplary Electrode 7) and Electrode Distance to Modiolar Wall (EMD, Electrodes 8 to 12) From the Medical Imaging Data Using a 3D Rendering of Cone Beam Computer Tomography of the Temporal Bone. The 3D data are only shown for one plane, thus not the complete electrode array is visible.

Indirect Measures

To investigate the feasibility of analyzing the IPG effect to obtain insights about neural health, indirect measures of neural health were investigated. Duration of hearing loss and the individual speech reception performance of the tested ear were assessed from data available from the routine clinical tests in the German Hearing Center at the Hannover Medical School. The Hochmair-Schulz-Moser (HSM) sentence test (Hochmair-Desoyer et al., 1997) was used, which contains everyday sentences, and % correct scores are obtained for 65 dB sound pressure level presentation level of the speech and a 10 dB signal-to-noise ratio to the continuous background noise.

Results

Underlying Analysis

AGFs were measured in all subjects for Electrodes 1, 2, 3, 4, and 9 for IPGs of 2.1 and 10 µs and analyzed for changes based on IPG, electrode location, and subject group (EAS or CI). In Figure 3, example measurements for both IPGs and Electrodes 1 (apical) to 9 (basal) are shown for one subject of each of the EAS (red circles) and CI (blue diamonds) groups. The AGFs are shown as a function of the stimulus charge in nC (left), as well as a function of the logarithm with reference to 1 nC (right). In psychoacoustic forward masking experiments, McKay (2012) argued that the change in stimulus should be investigated on a logarithmic scale, as it physically corresponds to the effective changes experienced by neural structures, irrespective of the absolute current change that is elicited at possible different distances between neurons and stimulus electrode. This is reflected in the right panels of Figure 3, which show similar slopes between the different AGFs across IPG, with the stimulus electrode number resulting in an offset between AGFs, but the different IPG values not resulting in a change in AGF slope. Changes due to increases in IPG, especially regarding the AGF slope, become more apparent on the linear scale, which has also been used in other experiments to successfully predict spiral ganglion survival in animals (Ramekers et al., 2014) and speech performance in human CI users (Schvartz-Leyzac & Pfingst, 2018). As the current subject group of EAS users was to be investigated for influences of a possible predictive force of eCAP AGF characteristics for neural health in apical and basal areas, the slope, that is, increase in eCAP amplitude over stimulus intensity, was determined on the basis of the AGF as a function of linear charge. Note that previously mentioned studies used absolute slope, whereas in the current study, the comparison between IPG needed the

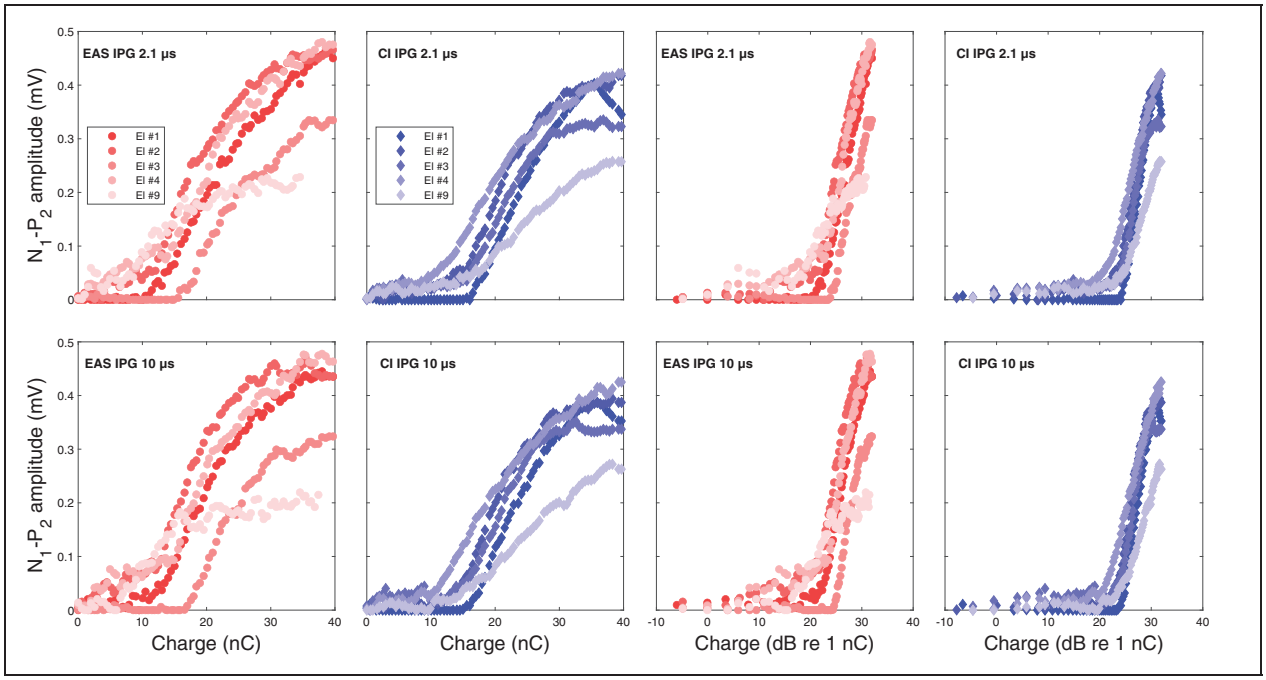

Figure 3. Exemplary eCAP amplitude growth functions, in dependency of stimulus charge (left) and dB of charge (right) for one individual EAS (red circles) and one CI (blue diamonds) user for the two IPGs of 2.1 (upper panels) and 10 μs (lower panels), with electrode number indicated by color, with apical electrodes in dark and basal electrodes in light shade.
IPG = interphase gap; EAS = electric-acoustic stimulation; CI = cochlear implant.

normalized slope due to the blanking of the N_1 peak in some cases. As normalized slope ($1/4D$) is investigated on the linear scale, while dynamic range ($4D_{dB}$) is analyzed on the logarithmic scale, both offer unique insights into the data and are useful in the comparison to results of previous studies.

eCAP AGF Characteristics

The following characteristics were to be compared and analyzed, based on the findings of Ramekers et al. (2014) and Schvartz-Leyzac and Pfingst (2018): The eCAP AGF threshold, dynamic range, normalized slope, and stimulus intensity needed to reach 50% maximum amplitude ($level_{50\%}$), also called current offset.

Figure 4 shows these properties as a function of individual insertion angles, which varied strongly across subjects. In CI users, threshold and $level_{50\%}$ were significantly different between apical to basal electrodes (median split with insertion angle) for 2.1 µs IPG (both $p < .001$), whereas for 10 µs IPG, the difference between apical and basal electrodes was significant for threshold, absolute slope, and $level_{50\%}$ (all $p < .01$). In EAS users, these measures also seemed to differ, but this difference did not reach statistical significance after Bonferroni correction ($0.0125 < p < .05$).

Neither the absolute nor the normalized slope for the combined CI and EAS results correlated with the impedance ($p > .05$), in contrast to results by Schvartz-Leyzac and Pfingst (2018) who found a correlation with absolute slope. For the normalized slope, this was expected, as interelectrode differences are equalized. Threshold for the 10 µs IPG was significantly correlated with the impedance, but with low strength of correlation ($R^2 = .06$, $p = .004$) and was not significant for 2.1 µs ($R^2 = .04$, $p = .027$). The $level_{50\%}$ at the 2.1 µs and the 10 µs IPG was not statistically significantly correlated with electrode impedance after Bonferroni correction and obtained low R^2 ($R^2 < .04$, $.0125 < p < .05$). The EMD showed significant correlation with the threshold at 10 µs IPG ($R^2 = .07$, $p < .001$), with a similar trend for $level_{50\%}$ at 10 µs ($R^2 = .04$, $p = .020$), but not for either at 2.1 µs ($R^2 < .05$, $p > .03$). EMD and impedance did not correlate with dynamic range for either of the two groups or IPGs. All results are shown in Table 3.

IPG Effect

Some characteristics were significantly different with the 10 µs than with the 2.1 µs IPG (paired Wilcoxon test; $p < .0125$) across all measured locations. These characteristics were AGF threshold ($p < .001$ for EAS and CI users) and $level_{50\%}$ ($p < .001$ for EAS and $p = .012$ for CI users). As IPG had a significant effect on multiple eCAP AGF characteristics, the change in the measures was calculated by subtracting the values obtained with the

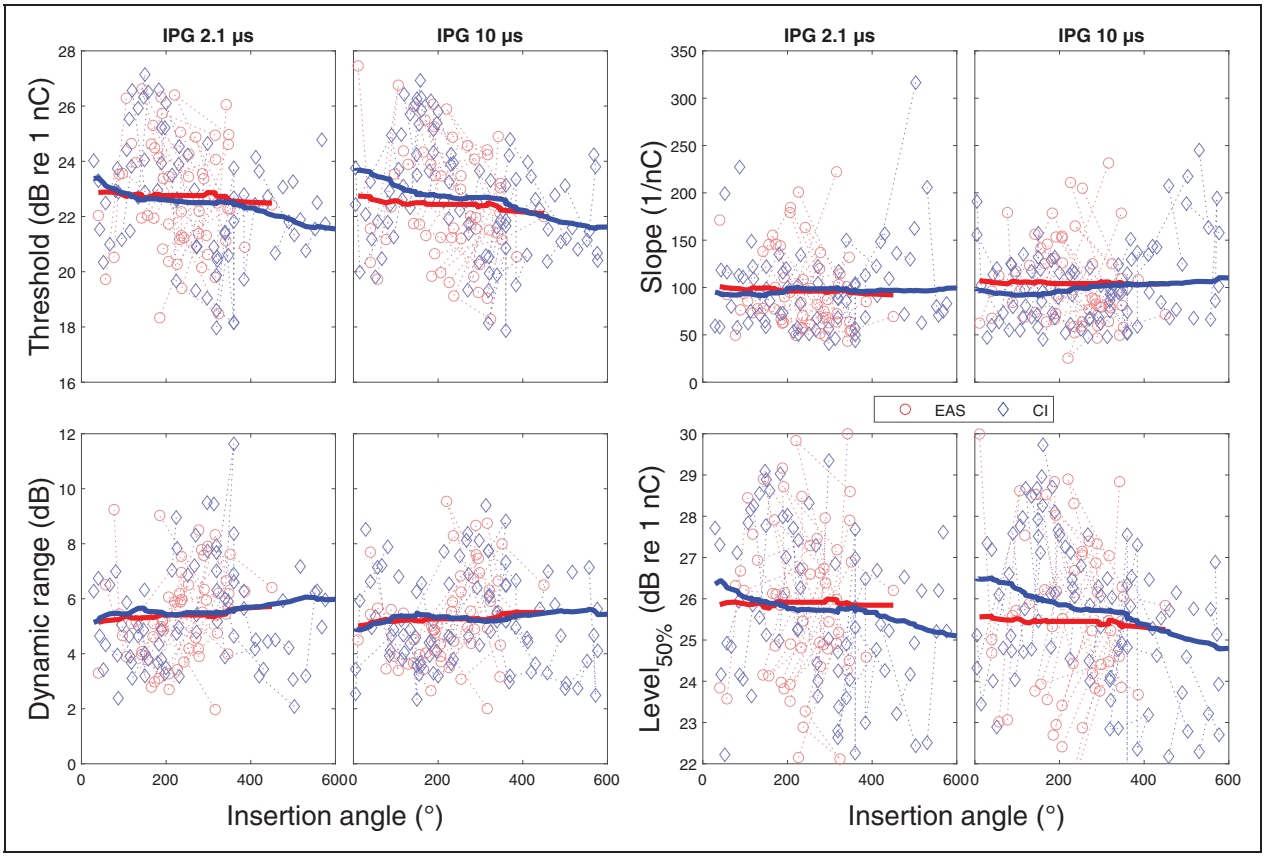

Figure 4. Influence of IPG on eCAP characteristics threshold, slope, dynamic range, and $level_{50\%}$ for EAS (red circles) and CI (blue diamonds) users for individual insertion angles and the running average for both groups (lines). eCAP AGF characteristics are shown for each IPG, either 2.1 (left) or 10 μs (right). Electrode factors impedance and electrode-modiolus distance (EMD) can be found in Figure 5 for comparison.
EAS = electric-acoustic stimulation; IPG = interphase gap; CI = cochlear implant.

Table 3. Statistics From Linear Correlation Analysis for all eCAP Characteristics per IPG and Electrode Contact Metrics Impedance and Electrode Modiolus Distance, for All Measured Electrodes of Pooled EAS and CI Subjects.

		Impedance		Electrode modiolus distance	
	IPG (µs)	R^2	p	R^2	p
Threshold	2.1	.04	.027	.04	.032
	10.0	.06	.004	.07	<.001
Absolute slope	2.1	.03	.060	.01	.360
	10.0	.02	.078	.01	.331
DR	2.1	.00	.489	.03	.041
	10.0	.02	.085	.04	.025
$Level_{50\%}$	2.1	.04	.016	.01	.198
	10.0	.04	.020	.04	0.020

Note. Note that slope reported in this table is the nonnormalized, absolute slope per IPG, to preserve interelectrode variations in eCAP amplitude.
IPG = interphase gap.

2.1 µs IPG from those obtained with the 10 µs IPG; this is indicated by a Δ.

Figure 5 shows the changes in eCAP characteristics due to an IPG increase across the measured range of insertion angles for both the EAS (red circles) and CI (blue diamonds) users. Electrode impedance and EMD are also shown across insertion angle. The change in characteristics with increased IPGs was not significantly correlated with either impedance or EMD. There was an interesting effect of EMD in dependency of insertion

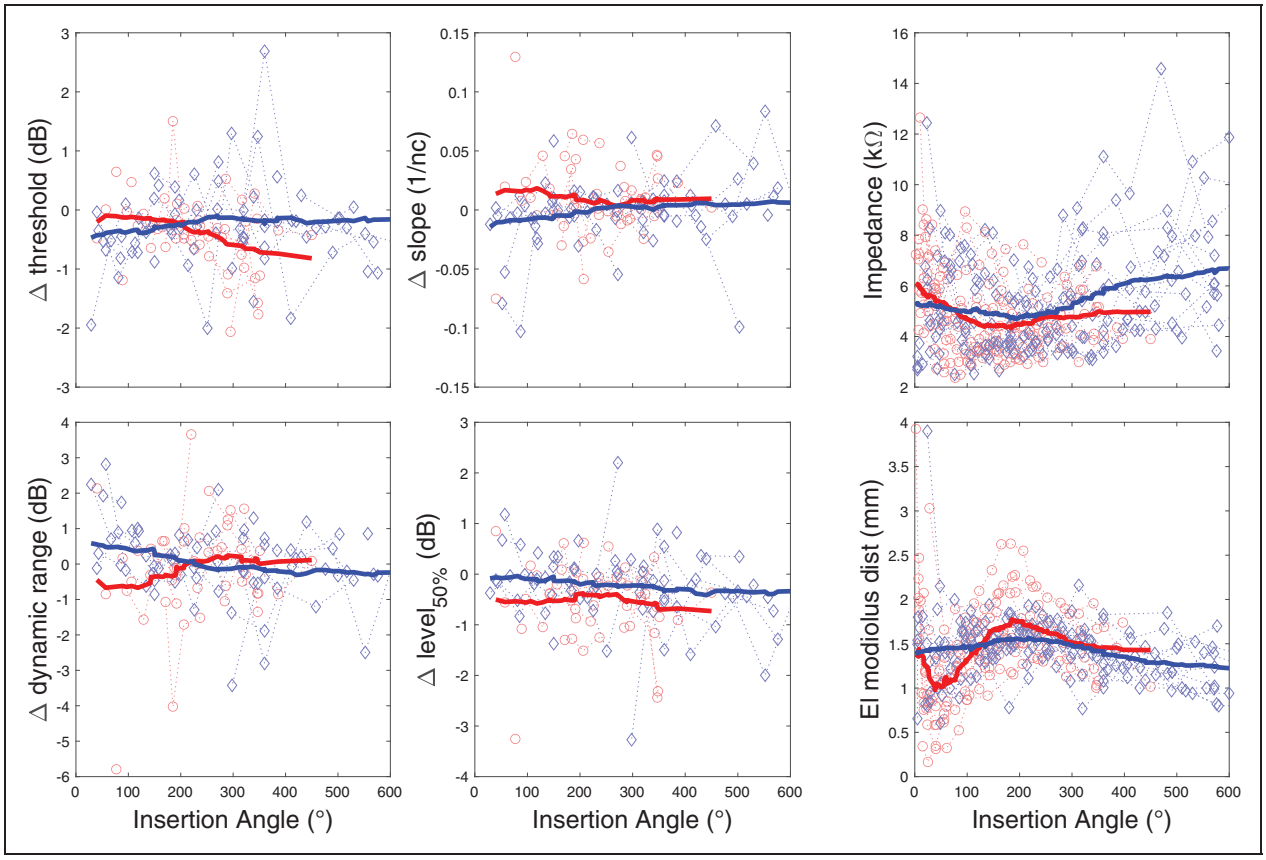

Figure 5. Change (Δ) with increased IPG of AGF characteristics threshold, slope, dynamic range, and $level_{50\%}$ as well as electrode characteristics impedance and electrode-modiolus distance for CI (blue diamonds) and EAS (red circles) users for individual insertion angles and the running average across insertion angle for both groups (lines).
eCAP = electrically evoked compound action potential.

angle for EAS subjects, with a sharp decrease and then increase in EMD in basal areas, with lower EMD at 0°–100° and higher EMD at 100°–200° insertion angle in EAS than in CI subjects. This may be due to the more shallow insertion of the electrode in EAS subjects, especially in cases with partial insertion, with the electrode not directly placed at the lateral wall. This more shallow insertion in EAS users can be seen in the highest insertion angles in the EMD and impedance plots, which only reached up to 500°. This electrode did not yield reliable AGF estimation so that it is not shown in the AGF characteristics, resulting in smaller maximum insertion angles (around 450°) for Δ characteristics.

The overall trend of AGF characteristics across insertion angles, indicated by the bold lines, showed different patterns for the different characteristics and the two groups. Different mean Δ threshold can be identified in apical areas (insertion angle $> 200°$) between EAS and CI users, while basal areas result in similar IPG effects of this characteristic. The opposite effect can be observed in Δ slope, Δ dynamic range, and Δ $level_{50\%}$, where EAS and CI subjects lie further apart for middle to more basal areas (insertion angle $< 300°$) and closer together in apical areas. However, variability between subjects and across insertion angles is quite high so that a statistical analysis revealed only a difference in Δ $level_{50\%}$ between EAS and CI subjects across all measured insertion angles ($p = .012$). A grouping by a median split across electrode insertion angle revealed some non-Bonferroni-corrected significant trends for the contrast between EAS and CI users, possibly indicating differences between apical and basal electrodes. For basal electrode contacts, the Δ slope and Δ dynamic range were significant at the comparison between EAS and CI subjects ($p = .034$ and $p = .037$ respectively), but not for apical contacts ($p = .139$ and $p = .174$).

The maximum insertion angle differs strongly between subjects, especially for the EAS users, with values ranging from 190° to 530° (see Table 1). As the most apical electrode is closest to residual hearing and is most likely to record responses from neural structures connected to surviving hair cells, it is of interest to analyze the electrode number as an effect of residual hearing. Compared across electrodes, significant contrasts of

the change of eCAP AGF characteristics were found in EAS users after Bonferroni correction: Δ $level_{50\%}$ was significantly different for Electrode 1 versus 3 ($p = .007$) and Electrode 1 versus 4 ($p = .009$). As the calculation of the change required a successful AGF estimation on the same stimulating and recording electrode for both IPGs, the number of available measurement combinations was strongly reduced in the IPG effect analysis. For example, only five data points for Electrode 9 remained for the EAS users so that this low number might prevent a significant result in the statistical analysis of Electrode 1 versus 9. Similarly, the comparison between Electrode 1 and 4 for Δ threshold was not statistically significant after Bonferroni correction ($p = .025$). In CI users, no significant differences of any change in AGF characteristic between these electrode pairs were observed ($p > .2$).

Indirect Measures of Neural Health

Duration of hearing loss and speech reception outcomes in each subject were correlated with the change due to IPG of the characteristics in the most apical electrode, as shown in Figure 6. The correlation coefficient R^2 and p values from linear regression analysis are given in each panel. Even though a general trend toward more negative changes between IPGs with longer duration of hearing loss can be observed for the AGF characteristics threshold and $level_{50\%}$, a significant correlation was only observed in EAS users for Δ threshold and Δ $level_{50\%}$. Δ $level_{50\%}$ reached high R^2 values in CI users, but no statistical significance ($R^2 = .52$, $p < .1$). For absolute characteristics for each IPG, there were no significant correlations observed ($R^2 < .1$, $p > .05$).

To increase the power of the statistical analysis, EAS and CI groups were combined to assess correlations with a linear regression. For the combined regression of EAS and CI users to predict duration of hearing loss and speech perception, the resulting R^2 and p values are given in Figure 6 alongside the results for the individual groups. For duration of hearing loss, the characteristic Δ $level_{50\%}$ of the eCAP AGF resulted in a significant linear regression ($R^2 = .38$, $p = .004$). Similarly, Δ threshold reached high $R^2 = .24$, but no significant correlation after Bonferroni correction ($p = .028$).

For the speech reception performance, no characteristic resulted in a significant correlation in either CI or EAS subjects, but Δ threshold showed a trend toward higher R^2 values of .24 for CI users, but this did not reach statistical significance ($p = .22$). Even though no statistical significance was observed, of the tested characteristics, Δ threshold and $level_{50\%}$ seem to be the most interesting to relate changes in eCAP to indirect measures of neural health. It should be noted that the individual factors of age and low-frequency pure tone

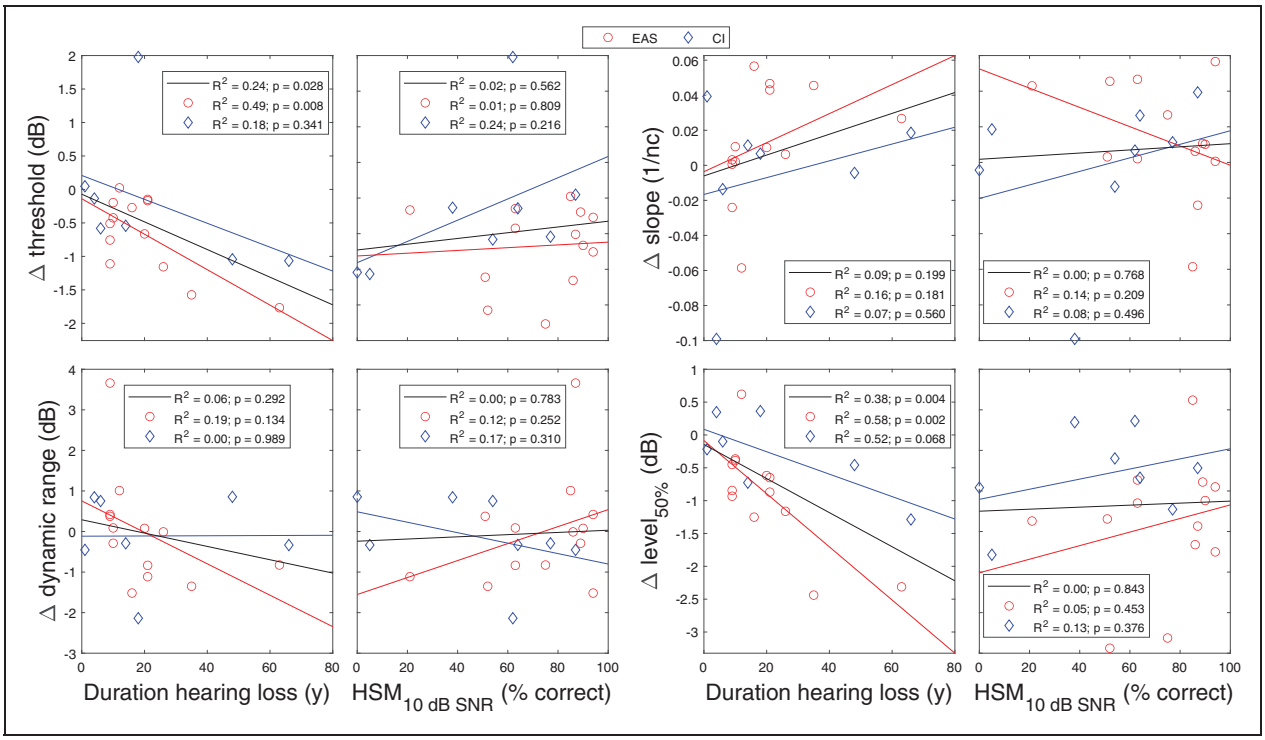

Figure 6. Change (Δ) in threshold, slope, dynamic range, and $level_{50\%}$ in apical electrodes with increased IPG for CI (blue diamonds) and EAS (red circles) users in dependency of duration of hearing loss (left) and speech reception performance (right), with correlation and significance values for each group and combined (black).

audiometry (PTA), with deaf CI subjects set to a PTA of 120 dB, were investigated for possible correlations with the indirect measures of neural health. While neither showed a correlation with the duration of hearing loss, the low-frequency PTA was highly significantly related to the speech perception performance ($R^2 = .37$, $p < .001$), with higher PTA, that is, worse residual hearing, resulting in poorer speech perception scores. In the EAS group, the HSM test often reaches ceiling results, as they tend to outperform traditional CI users, possibly limiting the potential statistical significance in the individual eCAP characteristics. When the linear regression model including the low-frequency PTA, which resulted in a significant prediction of the speech perception, is augmented with the different AGF characteristic changes across IPG, the significance level falls below the Bonferroni corrected p value (not shown in Figure 6). Seemingly, the eCAP AGF characteristics investigated in this study provide no additional information for the estimation of speech perception in this subject sample.

Discussion

Comparison of eCAP Measures Across Electrode Location

Neural health in EAS and CI users was assessed with eCAP recordings using different IPGs, assuming that the changes in AGF characteristics caused by the change in IPG are an indication of the state of neural health (Prado-Guitierrez et al., 2006). The change in IPG had a significant effect across all measured electrodes on the eCAP AGF characteristics, namely the threshold and the stimulus intensity at which 50% of the maximum amplitude was reached ($level_{50\%}$). In contrast to findings reported by Schvartz-Leyzac and Pfingst (2016), the slope of the AGF as a function of linear charge increase did not significantly differ with increased IPG for either EAS or CI users. This might be due to the blanking effects caused by the recording delay, which necessitated the normalization of the slope to compare the two IPGs. For the absolute slope, IPG did have a significant effect ($p < .001$), when only considering AGFs for which blanking of the N1 curve did not occur. This then corresponded to findings by Schvartz-Leyzac and Pfingst (2016). However, this exclusion criterion caused the loss of 40% of the data, making the normalization of the slope more feasible for further analysis of the IPG effect.

The AGF characteristic of threshold, using the IPGs of 2.1 and 10 µs, showed a significant correlation with the electrode and subject-specific factors, namely electrode impedance and EMD, in agreement with other studies in humans (DeVries et al., 2016). The same trend was seen in $level_{50\%}$ but was not significant after correction. As argued by Schvartz-Leyzac and Pfingst (2016), these values of AGFs are found to be influenced by external factors such as differences in electrode impedance, caused by different tissue characteristics, as well as the distance to the modiolus, where the action potentials are generated. This makes a comparison of the absolute eCAP AGF characteristics measured with fixed IPG difficult to interpret across different subjects with highly varying impedances and EMDs. In contrast, changes (Δ) in AGF characteristics as an effect of increasing IPG did not correlate significantly with either the impedance or the EMD. These results suggest that using the effect that a varying IPG has on the eCAP AGF characteristics is a suitable measure to assess neural health, independently of electrode contact characteristics.

Δ $level_{50\%}$ seemed to depend on the insertion angle and showed a difference between EAS and CI users in the basal electrodes, with a stronger reduction in EAS users. An offset was found between EAS and CI users across all electrodes and was significant. In principle, this result seemed to be contradictory to the original hypothesis, namely that EAS users retain better neural health at the apex in comparison to CI users. However, there are at least two potential reasons that may support the hypothesis: (a) The AGFs generally reach saturation levels by stimulating an extended range of SGC populations; thus, the value of $level_{50\%}$ could represent global neural health and not only a specific location. (b) Results in basal areas are more strongly influenced by EAS users with shallower electrode insertions, who also retain a better overall residual hearing. Consequently, the reduction in Δ $level_{50\%}$ in EAS users corresponds well to findings of better neural health in animals by Ramekers et al. (2014). No significant differences between EAS and CI users were obtained for other AGF characteristics across insertion angle. Prado-Guitierrez et al. (2006) observed higher threshold and slope changes with better neural health. In the current study, these findings could not be observed in EAS or CI subjects when comparing apical and basal areas or the subject groups.

In EAS users, insertion angle across all electrodes alone might not be a good representation of the electrodes location with respect to the residual hearing and the assumed higher density of SCGs in the area of residual hearing. For this reason, the results were analyzed based on electrode number, as apical electrodes are located closer to the residual hearing. In the EAS subject group, significant differences between Electrodes 1 and 3 as well as Electrodes 1 and 4 were found, with a stronger decrease of the Δ $level_{50\%}$ value and reduced Δ threshold values. Comparisons between other electrodes did not show significant eCAP AGF changes with IPG increase. As a larger change toward more negative Δ $level_{50\%}$ correlated to higher spiral ganglion density in guinea pigs (Ramekers et al., 2014), this finding might

indicate that a change in value of Δ $level_{50\%}$ corresponds to a difference in neural health between apical and medial electrodes. This would have been expected to be stronger in relation to even more basal electrodes (i.e., Number 9), but the low number of successfully characterized AGFs prevents a meaningful assessment of the contrast Electrode 1 versus 9. However, in CI users, no significant differences between electrodes were found. This may support, the hypotheses that first, there is an effect toward better neural health in the most apical electrode in EAS users and second, that the estimation of neural health by eCAP measurements with varying IPG is possible in humans.

In animals, the absolute value of maximum eCAP amplitude has been shown to correlate significantly to SGC packing density (Hall, 1990). However, the absolute value has been assumed to be influenced by factors such as electrode position and location, as well as possible changes of the cochlea such as fibrosis or ossification (Schvartz-Leyzac & Pfingst, 2016). Hence, assessing the change in eCAP amplitude for increasing IPG values is assumed to be feasible but did not result in a significant correlation to duration of hearing loss (Schvartz-Leyzac & Pfingst, 2016) or spiral ganglion count (Ramekers et al., 2014). Several aspects might also result in a poorer outcome in studies with human subjects, for example, the long history of hearing loss and different etiologies, which result in differences between subjects regarding hair cell and neural survival. Furthermore, the stimulation intensity necessary to reach the saturation of neural response is oftentimes perceived as too loud by humans. In this study, we often found insufficient stimulation levels to be the case, impeding a reliable fitting of a sigmoid function. Another confounding effect in this study is the blanking of the N_1 component, which might result in a stronger increase in eCAP amplitude with increased IPG for subjects with greater neural loss (Ramekers et al., 2014). An underestimation of the IPG effect in case of good neural survival might be the consequence with the current measurement setup. This limits the applicability of eCAP AGF characteristics, and especially eCAP amplitude, as a predictor of neural health in the clinical practice.

Comparison to Indirect Measures of Neural Health

An indirect measure of neural health was used to compare with the IPG effect on eCAP AGF characteristics. Objective estimations of neural health are generally based on neural cell counts, which have been used in animal or temporal bone studies of deceased CI users (Hall, 1990; Seyyedi et al., 2014). As the auditory nerve is known to degenerate with time after onset of hearing loss (Nadol, 1997), the duration of hearing loss prior to implantation is assumed to reflect the status of neural health. In contrast, duration of deafness was not assessed, as some subjects retain residual hearing (EAS group). For absolute eCAP AGF characteristics, Schvartz-Leyzac and Pfingst (2016) found a correlation between duration of hearing loss and the AGF slope at 7 µs IPG, which was not the case in the present study for either IPG 2.1 or 10 µs.

Duration of hearing loss did not show a clear influence on the change of eCAP characteristics with increased IPG, in contrast to the results in animals (Prado-Guitierrez et al., 2006; Ramekers et al., 2014). The change of normalized slope did not show a correlation to either duration of hearing loss or speech perception. Similarly, Schvartz-Leyzac and Pfingst (2016) did not find a correlation of duration of hearing loss with the change of linear slope using a higher IPG increase (30 – 7 µs IPG). In this study, Δ threshold seemed to decline with increasing duration of hearing loss for combined EAS and CI users, in correspondence to findings in animals (Ramekers et al., 2014), but the lack of more data limits the statistical power. This relation was significant for EAS users only. A significant correlation of duration of hearing loss with Δ $level_{50\%}$ was found, with high correlation values, and less reduction of threshold in subjects with shorter duration of hearing loss, which is in good agreement with observations in animals (Ramekers et al., 2014) as well as the output of the theoretical model and reanalysis of animal data by Brochier et al. (2021a).

In accordance with the model-based conclusions of Brochier et al. (2021a), this study indicates the eCAP AGF characteristic Δ $level_{50\%}$ might have the highest predictive power and should be assessed in further studies in humans. It should be noted that the highest correlation were found for the apical electrodes, indicating toward an effect of neural health in apical areas, with lower duration of hearing loss probably corresponding to better neural health (Sugawara et al., 2005).

Speech reception performance did not correlate with any of the eCAP characteristics, but this relation has also not been clear in other studies as well (van Eijl et al., 2017). Kim et al. (2010) reported a significant correlation of the AGF slope for single IPGs with the speech recognition in EAS as well as CI users, but not for the change of AGF slope due to an IPG increase. Correspondingly, DeVries et al. (2016) found an effect of the absolute eCAP amplitude at comfortably loud stimulus levels on the vowel and consonant recognition score. In this study, data were only shown for the changes of the eCAP characteristics with increased IPG; the values with neither 2.1 µs nor 10 µs IPG resulted in a significant prediction of speech reception performance. It is possible that large intersubject variability due to differences in cognitive ability confounds the effect of peripheral neural health on speech performance outcomes in this study. Especially the complexity of the speech reception measure used in this study might

be the reason for a missing relation, as other studies used simpler speech stimuli such as vowels and consonants (DeVries et al., 2016; Schvartz-Leyzac & Pfingst, 2018). In a study using bilateral CI users, Schvartz-Leyzac and Pfingst (2018) successfully predicted the magnitude of difference of speech perception performance across ears with the magnitude of the IPG effect change in eCAP linear slope. This finding could not be extended to the intersubject level in the present work.

Clinical Applicability

Differences between apical and medial electrodes in the IPG effect on eCAP AGF $level_{50\%}$ were found in EAS users, which might indicate that the measurement of the characteristic hint at neural survival and could be used in the clinical routine to estimate the local state of cochlear health. The eCAP characteristics for the two used IPGs were found to correlate to factors of the electrode contact such as the impedance and the EMD and are thus less useful, as they depend strongly on inter- and intrasubject variations. Possibly a larger increase in IPG would have been more sensitive in assessing the changes in eCAP AGF characteristics, regarding the high variability across subjects. Adapting the measurement protocol would not pose a problem for the clinical applicability and might result in stronger results. However, a larger IPG will result in even louder auditory percept (Carlyon et al., 2005; McKay & Henshall, 2003), possibly resulting in a decrease in the number of measurements that reach the saturation stimulus charge, at with which the AGF can successfully be fitted.

A future study with bilateral EAS subjects is feasible to investigate the effect of residual hearing on neural health and the correlation of the latter to speech perception at an intrasubject level. In this study, high variability due to different etiologies and progresses of hearing loss might have been the confounding factor that prevented further insights about neural health. It seems that mainly Δ $level_{50\%}$ is the most sensitive eCAP characteristic in humans with multicausal hearing loss, a result which is in agreement with the model and reanalysis of data by Brochier et al. (2021a). In previous studies, it has been shown that speech perception may be enhanced after the deactivation of specific electrodes that suffer from poor neural health in the vicinity (Bierer & Litvak, 2016; Zhou & Pfingst, 2014). If further insights are gained on the relation between eCAP AGF characteristics and neural health in EAS users, an analysis on the basis of single electrodes might be possible to identify so called *dead regions* in an implanted cochlea. Consequently, eCAP AGF measures would provide an easy and accessible feature to objectively infer neural health in both EAS and CI users and assist with the programming of speech processors by clinical audiologists.

Conclusion

In the present study, the applicability of eCAP AGF measures for the estimation of neural health in EAS and CI subjects was tested by comparing these measures using two values of IPG. The obtained changes in eCAP characteristics were found to be independent of interelectrode and intersubject factors such as impedance and EMD. The differences between apical and medial electrodes in the IPG effect on the level necessary to reach half-maximum eCAP amplitude ($level_{50\%}$) seem to confirm the hypothesis of better neural health in EAS subjects. Global neural health seems to be better in EAS users, as represented by larger changes in $level_{50\%}$ in EAS users than in CI users, comparable to findings in guinea pigs. The changes in threshold and $level_{50\%}$ with IPG changes were found to correlate with duration of hearing loss, validating this measure to be sensitive to changes in neural health.

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ORCID iD

Marina Imsiecke https://orcid.org/0000-0002-0868-6778

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