Neural health in cochlear implant users with ipsilateral residual hearing

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Studies in cochlear implant (CI) users have shown a correlation between neural health and speech reception performance. Recently, electrically evoked compound action potentials (eCAP) with varying interphase gaps (IPG) have been used to estimate neural health. In the present study, we investigated eCAP characteristics in CI users with ipsilateral residual hearing (electric-acoustic stimulation, EAS). We hypothesized that neural health is better in apical areas in EAS users than in basal areas, due to increased hair cell survival. Amplitude growth functions (AGF) with varying IPGs of 2.1 and 10 μs were measured in 19 MED-EL Flex recipients with residual hearing. The eCAP characteristics slope, N_1 latency and stimulus level at 50% maximum eCAP amplitude were investigated for the effect of IPG across electrode positions and were correlated to speech perception outcomes and duration of hearing loss. CI users without residual hearing were used as a control group to compare the patterns of slope, latency and 50% maximum amplitude between both IPGs. IPG showed a significant effect on the eCAP characteristics. The change in stimulus level for the 50% maximum amplitude showed a significant difference between electrode 1 and 3 as well as 1 and 4 in EAS users, maybe indicating impaired neural health in the medial region and validating the measurement in EAS users.

INTRODUCTION

Progressive auditory nerve degeneration is known in patients suffering from severe hair cell loss, and survival of the auditory nerve (i.e. neural health), is partially assumed to be responsible for the variability in speech reception performance among cochlear implant (CI) users (Seyyedi *et al.*, 2014; Pfingst *et al.*, 2015). Several studies found a correlation between speech reception performance and indirect measures of neural health, such as duration of hearing loss (Holden *et al.*, 2013; Nadol *et al.*, 2001). However, a strong variability persists, and the state of the auditory nerve cannot be quantified in living humans. Studies in animals that employed objective measures such as the characteristics of the electrically evoked compound action potential (eCAP) have suggested that it can be used to determine the state of the auditory nerve (Prado-Guitierrez *et al.*, 2006). Recently, eCAP amplitude growth functions (AGF) with

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varying inter-pulse gaps (IPG) have been suggested by Ramekers *et al.* (2014) to analyze the refractory ability of the auditory nerve, which is impaired when the auditory nerve suffers from degeneration. They found that in guinea pigs several characteristics of eCAP and AGF recordings correlated significantly with quantified histological measures of the auditory nerve. For single pulses, the difference in N_1 latency, averaged across the three highest current levels, AGF slope and stimulus intensity needed to reach 50% of the maximum eCAP amplitude, also called current offset, all correlated highly to the spiral ganglion cell (SGC) packing density with varied IPG for normal hearing and deafened animals. The difference in latency decreased with higher density (i.e. better neural survival), and the difference in slope increased with better neural health.

An objective measure of neural health could help to understand and predict speech reception in CI users. The electric-acoustic stimulation (EAS) population, combined with available imaging data of the implant, offers the possibility to validate neural health measures under the assumption that this population has better neural health in the apex than in the base of the cochlea.

METHODS

19 EAS subjects participated in the measurement. A control group of 19 CI users without residual hearing (250 Hz $>$ 90 dB HL) was matched in age and duration of hearing loss to the EAS users. There was a mean difference of 2 years for age, whereas there was a difference of 12 years for duration of hearing loss.

AGFs were measured using the automatized, continuous eCAP measurement function of the MAESTRO (MED-EL, Innsbruck, Austria) fitting software called AutoART for two different IPGs of 2.1 and 10 μs. The amplitude of the single pulse electric stimulation in proprietary charge units (qu) was steadily increased until the subject indicated the loudest acceptable loudness level (LAPL) (Gärtner *et al.*, 2018), upon which the stimulation of the current electrode was stopped. The algorithm of the software then determined the threshold and slope of the AGF by fitting a sigmoid function. Additionally, the latency of the first negative peak was determined. The four most apical electrodes (numbers 1-4) and one basal electrode (9, or 8 if not possible) were measured in EAS users and all electrodes in CI users.

The eCAP characteristics slope, N_1 latency and 50% maximum amplitude were analyzed towards changes per IPG, and these changes were compared across the electrode array. 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 patterns across cochlear location. The eCAP characteristics were analyzed for correlation to indirect measures of neural health, such as duration of hearing loss and speech reception performance. The latter was either obtained by a matrix sentence test in 65 dB noise (Wagener *et al.*, 1999, OLSA) in the EAS users, or with a sentence test (Hochmair-Desoyer *et al.*, 1997, HSM) in quiet at 65 dB presentation level for CI users.

	EAS users				CI users		
ID	**Age**	**CI use**	**Dur HL**	**Electrode**	**Age**	**CI use**	**Dur HL**
c01	43	0.9	9	Flex 20	39	2.3	18
c02	66	2.7	63	Flex 20	67	0.9	66
c03	62	1.5	36	Flex 28	67	3.1	64
c04	39	1.9	26	Flex 28 PI	42	2.9	29
c05	82	3.8	10	Flex 24	82	2.3	4
c06	48	1.4	16	Flex 16	49	1.8	47
c07	49	2.9	35	Flex 20	50	1.5	27
c08	52	1.6	20	Flex 16	54	4.4	14
c09	61	1.7	21	Flex 24	60	3.3	48
c10	68	2.7	12	Flex 16	67	3.3	58
c11	62	2.6	9	Flex 16	63	1.7	12
c12	54	2.5	50	Flex 28	49	2.8	46
c13	46	1.7	11	Flex 24 PI	50	3.2	1
c14	71	1.5	21	Flex 24 PI	71	2.3	NA
c15	46	1.5	10	Flex 28 PI	45	2.7	6
c16	44	2.2	40	Flex 16	42	3.3	29
c17	56	2.0	10	Flex 24	59	2.8	15
c18	78	8.7	9	Flex 20	80	2.8	5
s03	64	1.2	44	Flex 24	61	1.9	58

Table 1: Subject data with subject ID, age at testing, duration of implant use, and duration of hearing loss (dur HL), all in years, for electric-acoustic stimulation (EAS) users and control group of CI users without residual hearing. Electrode type for EAS users is given, for CI users was Flex 28.

RESULTS

The AGFs for two electrodes (i.e. apical electrode contact number 1 and basal electrode number 9, or in one case 8) and for both IPGs are shown in Figure 1 for all subjects with residual hearing. A variability in dynamic range is visible, most AGFs stop between 20 to 30 qu, at which subjects indicated LAPL. Also, a high variability in the slope of the individual AGFs can be observed, with a very pronounced case of no elicited response in the basal electrode of subject ID c13. The eCAP response of some subjects did not exceed noise levels before LAPL was reached. Thus the estimation of the eCAP is missing in these subjects (IDs c03, c16, c17, s03) for different electrodes.

Differences in the AGFs, elicited by the different combinations of electrode position and IPG, become apparent, and these characteristics were further compared and analyzed. Based on the findings of Ramekers *et al.* (2014) and Schvarzt-Leyzac and Pfingst (2018), the characteristic slope (i.e. increase in eCAP amplitude per charge unit), stimulus intensity needed to reach 50% maximum amplitude and the latency of the N_1 component, which is not shown in the AGFs, were chosen to be further

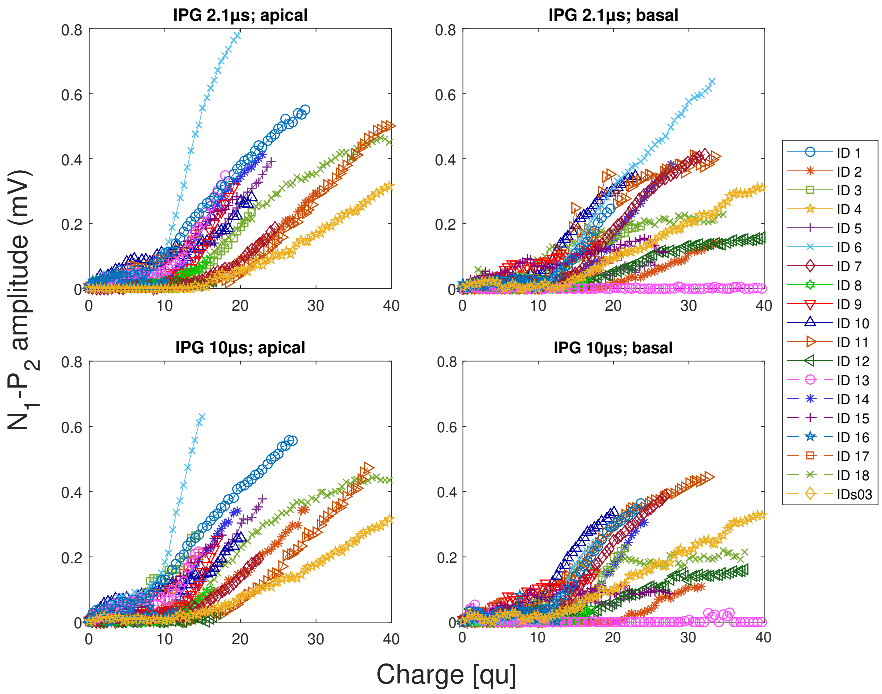

Fig. 1: eCAP amplitude growth functions in dependency of stimulus charge for individual EAS users for apical (left) and basal electrodes (right) and IPGs of 2.1 (top) and 10 μs (bottom).

analyzed.

The changes of these three characteristics due to changes in IPG were obtained in EAS subjects and in a control group of CI recipients without residual hearing. For both groups, all three characteristics were significantly higher with 10 μs than with 2.1 μs IPG (paired t-test $p < 0.01$ for EAS, $p < 0.001$ for CI) across all measured electrodes. The differences in slope, latency and maximum amplitude were also significantly different for the two groups ($p < 0.001$). These differences were also assessed on a basis of the insertion angle of the electrode, which was measured, as comparing the electrode contact number is not feasible for EAS and CI users with very different electrode types and insertion depths. Figure 2 shows the changes in eCAP characteristics across the measured range of insertion angles for both groups EAS (red circles) and CI (blue diamonds) users. Insertion in EAS users was more shallow, so that values only reached up to 400°. The overall trend showed different patterns for the three different characteristics and the two groups across insertion angle. For the change in slope the values decreased towards larger insertion angles (i.e. towards apical locations in EAS users). In contrast, this measure was lower in CI users in basal regions, but increased towards apical locations, resulting in reverse patterns for EAS and CI users. For the change in latency (Fig. 2 middle), the results of EAS and CI users were similar, and almost constant across the insertion angle. For 50% amplitude,

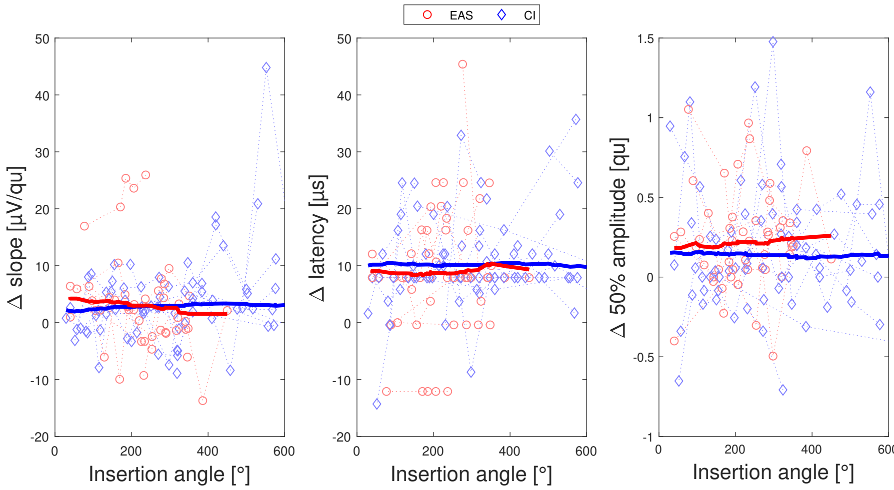

Fig. 2: Differences (Δ) in slope, N_1 latency and 50% maximum amplitude between the two measured IPGs for CI (blue diamonds) and EAS (red circles) users for individual insertion angles and the running average across insertion angle for both groups (lines).

results of CI users were constant across the electrode position, and values in EAS users increased. A statistical analysis between pooled apical and basal regions by median split did not show significant changes for any characteristic or between EAS and CI users, after correcting for the number of comparisons with a Bonferroni correction (significant $p < 0.05/3$). However, in EAS users, a significant difference ($p < 0.05$) between electrodes 1 and 3 as well as 1 and 4 was found for the change in stimulus intensity for 50% maximum amplitude. The data for the basal electrode was reduced due to missing eCAP responses, so that this might prevent a statistically significant difference. No difference was found in CI users, indicating a difference between apical and middle electrodes in EAS users. Additionally, there was a statistically significant difference between the most apical electrode of CI and EAS users.

Duration of hearing loss and speech reception outcomes in each subject were correlated to the change due to IPG of the three characteristics, in Figure 3 this is shown for the results of the most apical electrode, but results are similar for other electrodes or means across electrodes. Duration of hearing loss did not show significant correlation in either CI nor EAS users, and no consistent effect of duration of hearing loss is visible. As the available results were reduced due to missing data in many subjects, the statistical power is reduced.

For speech test outcomes, two different measurements were used, as the performance of the two groups is highly variable. EAS subjects reach ceiling performance in the HSM sentence test in quiet and also in noise at 10 dB SNR, while SRTs are not commonly tested in the clinical routine at the Hannover Medical School (MHH), so that OLSA results are not available in CI users. Each group was individually analyzed for correlations between IPG effects and speech performance, without significant results.

However, no significant effects could be observed in the current data. A multiple linear regression that took into account the effect of age and duration of hearing loss showed a significant correlation to speech reception performance in EAS group (R^2 = 0.49, p = 0.005), but not in CI users (R^2 = 0.28, p = 0.081). However, none of the eCAP characteristics predicted the speech reception performance or significantly improved the regression model with age and duration of hearing loss ($p > 0.05/3$), indicating that no information about neural health could be gained with these characteristics in the current subject group.

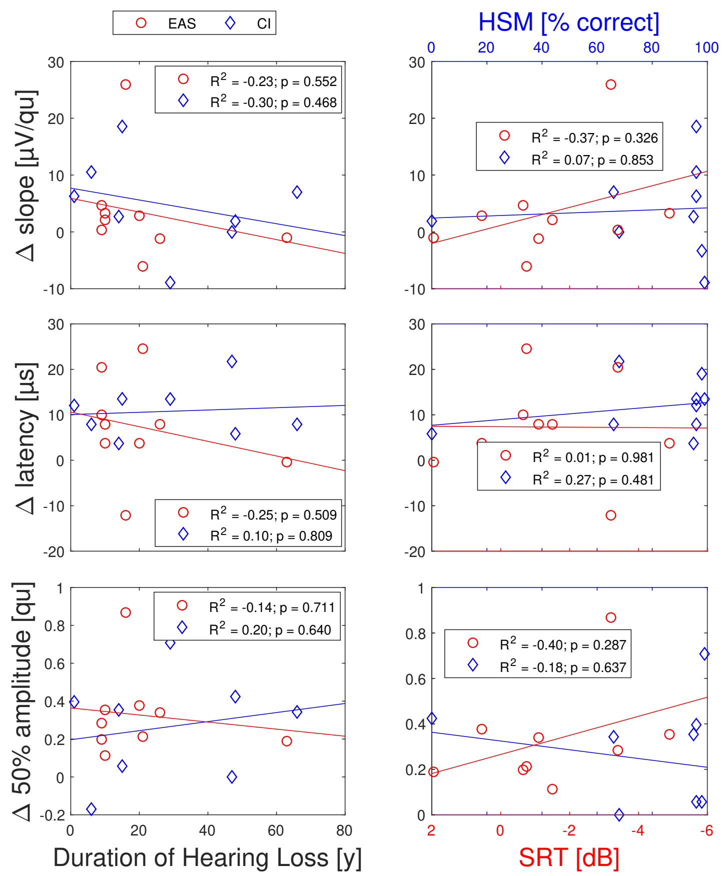

Fig. 3: Differences (Δ) in slope, N_1 latency and 50% maximum amplitude between the two measured IPGs for CI (blue diamonds) and EAS (red circles) users in dependency of duration of hearing loss (left) and speech reception performance (right, speech reception threshold (SRT) of OLSA for EAS and HSM in quiet for CI users).

DISCUSSION AND CONCLUSION

Neural health in EAS and CI users was assessed with eCAP recordings of different IPGs, assuming that the difference in eCAP characteristics caused by the IPG is an indication of the state of neural health (Ramekers et al., 2014). IPG had a significant effect on all characteristics. IPG elicited changes to N_1 latency, slope and maximum amplitud, whiche were compared across electrode location for each individual subject and between the two matched groups. The change in slope and 50% maximum amplitude showed reverse patterns across electrode position for EAS and CI groups, but no significant effects between pooled apical and basal areas. A difference in stimulation intensity for 50% maximum amplitude in apical electrodes of EAS users corresponds to findings of better neural health by Ramekers *et al.* (2014). Duration of deafness did not show a clear influence on eCAP characteristics, opposing the results in animals (Ramekers *et al.*, 2014). The change in slope seems to decrease with increasing duration of hearing loss for both EAS and CI users, but the lack of more data limits the statistical power. Speech reception performance also did not correlate to any of the characteristics. It is possible that large inter-subject variability due to differences in cognitive ability confounds the effect of peripheral neural health on speech performance outcomes, and thus, the results reported by Schvarzt-Leyzac and Pfingst (2018) could not be extended to the inter-subject level. The quite low number of successful AGF fits for some electrodes reduced the strength of the results, and furthermore, the influence of other factors on the indirect measures such as duration of hearing loss and speech perception seems to be higher than the effect of neural health. Thus, the effect of IPG could not be shown in this study.

The hypothesis of better neural health in EAS subjects was confirmed in 50% maximum amplitude in the most apical electrode. IPG effects are limited to a difference between the apical and medial electrodes in EAS users. Possibly larger differences in IPG would have been more sensitive, regarding the high variability across subjects. A study with bilateral EAS/CI subjects is also feasible to investigate the effect of residual hearing. Significant differences in the change in 50% maximum amplitude were found in EAS users between the most apical electrode to middle electrodes, but not within CI users or in comparison to basal electrodes. It seems that 50% maximum amplitude is the most sensitive measure in humans with multicausal hearing loss and should be further investigated in higher numbers of subjects and viable electrodes.

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REFERENCES

Gärtner, L., Lenarz, T., and Büchner, A. (**2018**). “Fine-grain recordings of the electrically evoked compound action potential amplitude growth function in cochlear implant recipients,” Biomed. Eng., **17**(1), 140, doi: 10.1186/s12938-018-0588-z.

Hochmair-Desoyer, I., Schulz, E., Moser, L., and Schmidt, M. (**1997**). “The HSM sentence test as a tool for evaluating the speech understanding in noise of cochlear implant users,” Am. J. Otol., **18**(6), 83.

Holden, L., Finley, C., Firszt, J., Holden, T., Brenner, C., Potts, L., Gotter, B., Vanderhoof, S., Mispagel, K., Heydebrand, G. et al. (**2013**). “ Factors affecting open-set word recognition in adults with cochlear implants,” Ear Hear., **34**(3), 342, doi: 10.1097/AUD.0b013e3182741aa7.

Nadol, J., Burgess, B., Gantz, B., Coker, N., Ketten, D., Kos, I., Roland, J., Shiao, J., Eddington, D., Montandon, P. et al. (**2001**). “ Histopathology of cochlear implants in humans,” Ann. Otol. Rhinol. Laryng., **110**(9), 883–891.

Pfingst, B.E., Zhou, N., Colesa, D.J., Watts, M.M., Strahl, S.B., Garadat, S.N., Schvartz-Leyzac, K.C., Budenz, C.L., Raphael, Y. and Zwolan, T.A. (**2015**). “ Importance of cochlear health for implant function,” Hear. Res., **322**, 77-88, doi: 10.1016/j.heares.2014.09.009.

Prado-Guitierrez, P., Fewster, L.M., Heasman, J.M., McKay, C.M., and Shepherd, R.K. (**2006**). “Effect of interphase gap and pulse duration on electrically evoked potentials is correlated with auditory nerve survival,” Hear. Res., **215**, 47-55, doi: 10.1016/j.heares.2006.03.006.

Ramekers, D., Versnel, H., Strahl, S.B., Smeets, E.M., Klis, S.F.L., and Grolman, W. (**2014**). “Auditory-nerve responses to varied inter-phase gap and phase duration of the electric pulse stimulus as predictors for neuronal degeneration,” J. Assoc. Res. Oto., **15**(2), 187-202, doi: 10.1007/s10162-013-0440-x.

Schvartz-Leyzac, K.C., and Pfingst, B.E. (**2018**). “Assessing the Relationship Between the Electrically Evoked Compound Action Potential and Speech Recognition Abilities in Bilateral Cochlear Implant Recipients,” Ear Hearing, **39**(2), 344-358, doi: 10.1097/AUD.0000000000000490.

Seyyedi, M., Viana, L.M. and Nadol, J.B. (**2014**). “ Within-subject comparison of word recognition and spiral ganglion cell count in bilateral cochlear implant recipients,” Otol. Neurotol., **35**(8), 1446, doi: 10.1097/MAO.0000000000000443.

Wagener, K., Kühnel, V., and Kollmeier, B. (**1999**). “Development and evaluation of a German sentence test I: Design of the Oldenburg sentence test,” Zeitschrift Für Audiologie, **38**, 4-15.