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Evaluating and comparing behavioural and electrophysiological estimates of neural health in cochlear implant users

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Abstract

Variations in neural health along the cochlea can degrade the spectral and temporal representation of sounds conveyed by cochlear implants (CIs) . We evaluated and compared several methods that have been proposed as estimates of neural health patterns, in order to explore the extent to which the different measures provide converging and consistent neural health estimates. All measures were obtained from the same 11 users of the Cochlear Corporation CI. The two behavioural measures were multipulse integration (MPI) and the polarity effect (PE), both measured on each of seven electrodes per subject. MPI was measured as the difference between thresholds at 80-pps and 1000-pps, and PE as the difference in thresholds between cathodic- and anodic-centred quadruphasic (QP) 80-pps pulse trains. It has been proposed that good neural health corresponds to a large MPI and to a large negative PE (lower thresholds for cathodic than anodic pulses). The electrophysiological measure was the effect of interphase gap (IPG) on the offset of the ECAP amplitude growth function (AGF), which has been correlated with spiral ganglion nerve density in guinea pigs. This “IPG offset” was obtained on the same subset of electrodes as for the behavioural measures. Despite high test-retest reliability, there were no significant correlations between the neural health estimates for either within-subject comparisons across the electrode array, or between-subjects comparisons of the means. A phenomenological model of a population of spiral ganglion neurons was then used to investigate physiological mechanisms that might underlie the different neural health estimates. The combined experimental and modelling results provide evidence that PE, MPI, and IPG offset reflect different characteristics of the electrode-neural interface.

Keywords: cochlear implants, neural health, neural survival, ECAP, psychophysics, inter-phase gap, polarity effect, multi-pulse integration, computational modelling

I. Introduction

Cochlear implants (CI) restore a sense of hearing to people with sensorineural hearing loss by stimulating the spiral ganglion neurons (SGN) of the auditory nerve. The ability of a cochlear implant (CI) to transmit speech information partly depends upon the condition of the stimulated neural population (Seyyedi *et al.*, 2014). Estimates of neural health patterns along the length of the cochlea may help to guide the optimization of sound processing strategies, by identifying electrodes in healthy neural regions that might benefit from focussed stimulation (Bierer, 2010), or electrodes in unhealthy neural regions that could be candidates for deactivation (Garadat *et al.*, 2013; Zhou, 2017; Goehring *et al.*, 2019). Several different methods to estimate neural health patterns along the cochlea have been proposed. This study explores the extent to which the different measures provide converging and consistent estimates of neural health. We consider a combination of both behavioural and electrophysiological measures of neural health.

The behavioural neural health estimates that were evaluated were multipulse integration (MPI) and the polarity effect (PE). MPI is measured as the slope of the function relating psychophysical detection thresholds to stimulation pulse rate. As pulse rate is increased, detection thresholds decrease, with the slope being steeper at pulse rates greater than 1000 pps in both animal studies (Kang *et al.*, 2010; Pfingst *et al.*, 2011; Zhou *et al.*, 2015) and studies in CI listeners (Shannon, 1985; 1989; McKay and McDermott, 1998; Kreft *et al.*, 2004; Zhou *et al.*, 2012; Zhou *et al.*, 2015). This characteristic rate-threshold function is consistent with a temporal integration mechanism (Shannon, 1989; McKay and McDermott, 1998; McKay *et al.*, 2003; Carlyon *et al.*, 2005), whereby the neural excitation elicited by consecutive pulses is summed in a sliding integration window. At sufficiently high pulse rates ($> \sim 1000$ pps), an additional facilitation mechanism lowers thresholds further through capacitive charging of the neural membrane by sub-threshold pulses (Middlebrooks,

2004; Boulet *et al.*, 2016). The magnitude of the MPI slope for pulse rates below 1000 pps has been positively correlated with SGN density in guinea pigs (Kang *et al.*, 2010; Pfingst *et al.*, 2011; Zhou *et al.*, 2015), and with between-ear differences in speech perception for bilateral CI users (Zhou and Pfingst, 2014). These results have led to the use of MPI as a behavioural estimate of neural health in humans (Hughes *et al.*, 2014; Zhou and Pfingst, 2014; 2016b; a; McKay and Smale, 2017; Zhou and Dong, 2017; Zhou *et al.*, 2018).

PE is measured as the difference in psychophysical detection thresholds between asymmetric pulse shapes in which the portion where charge that is most concentrated in time is anodic *vs.* where it is cathodic (Carlyon *et al.*, 2013; Macherey *et al.*, 2017). Modelling studies show that cathodic pulse shapes preferentially stimulate the peripheral processes of an SGN fibre, while anodic pulse shapes preferentially stimulate the central axon (Rattay *et al.*, 2001; Joshi *et al.*, 2017; Resnick *et al.*, 2018). In general, SGN degeneration begins with the peripheral processes and progresses towards the central axon. Theoretically, a population of SGN fibres with peripheral degeneration and healthy central axons would have a higher cathodic-centred than anodic-centred threshold (high PE), whereas a population of SGN fibres with healthy peripheral processes and central axons would show a smaller threshold difference between pulse shapes (low or negative PE). At low levels, PE varies across the electrode array within subjects (Macherey *et al.*, 2017; Carlyon *et al.*, 2018; Goehring *et al.*, 2019; Jahn and Arenberg, 2019), suggesting that PE at threshold might be a localized indicator of peripheral neural health. Both Jahn and Arenberg (2019) and Mesnildrey *et al.* (in press) provide psychophysical evidence for PE as an estimate for neural health. Both studies found that PE was correlated with thresholds for symmetric pulses obtained with focussed stimulation, which have been shown to be estimates of combined properties of the electrode-neural interface (neural health, electrode position, and impedance). Importantly, this correlation was significant even when the effects of electrode-modiolar distance (“EMD”, an

estimate of the distance of the electrode from the auditory nerve) were removed. It should also be noted that the model proposed by Rattay *et al.* (2001) predicts that PE may also be affected by EMD, although we know of no evidence that it correlates with the PE independently of focussed thresholds.

We used features calculated from the electrically-evoked compound action potential (ECAP) as the electrophysiological estimates of neural health. While many absolute ECAP measures, such as maximum ECAP amplitude (Shepherd and Javel, 1997) and slope of the ECAP amplitude growth function (Ramekers *et al.*, 2014; Pfingst *et al.*, 2015) have been positively correlated with neural health in animals, these measures are prone to the influence of non-neural factors such as electrode position (Shepherd *et al.*, 1993) and impedance (Schvartz-Leyzac and Pfingst, 2016). Non-neural factors are especially relevant in humans, who have larger cochleas and longer durations of deafness compared to other animals, leading to wider electrode-to-electrode variance in electrode position and impedance. To remove the influence of non-neural factors, ratios can be calculated between absolute ECAP features that are measured with different stimulus parameters (e.g. interphase gap [IPG] or phase duration). These differential ECAP measures can potentially partial out the effects of non-neural factors, which are assumed to be the same across stimulus conditions. In separate guinea pig studies, Prado-Guitierrez *et al.* (2006) and Ramekers *et al.* (2014) measured the dB difference in current level required to elicit an equal normalized ECAP amplitude at different IPGs, and found that this “IPG offset” was correlated with SGN density. These results have led to measures such as the IPG offset (and similar differential ECAP measures) being commonly used to estimate local neural health along the array in humans (Kim *et al.*, 2010; Schvartz-Leyzac and Pfingst, 2016; McKay and Smale, 2017; Hughes *et al.*, 2018; Schvartz-Leyzac and Pfingst, 2018). We recently evaluated different ways of defining the

effect of IPG on neural responses, and concluded that the IPG offset provided a robust measure that was minimally affected by non-neural factors (Brochier *et al*, submitted).

In the present study, the electrophysiological measure of IPG offset and the behavioural measures of PE and MPI were evaluated and compared in a group of 11 CI users at seven different electrode locations spanning the array. Within-subject and between-subject correlations were evaluated to determine the extent to which the different neural health estimates provide converging information. It was hypothesized that if each of these measures reflects a similar characteristic of neural health, then significant within-subject and between-subject correlations would be found between all of the measures.

II. Methods

A. Participants

11 postlingually deafened cochlear implant users completed the series of behavioural and electrophysiological experiments. Permission to conduct the studies was granted by the National Research Ethics committee for the East of England, and subjects provided their written consent to participate. All subjects used devices from Cochlear Limited (Sydney, Australia). Details about each subject's age, implant type, duration of deafness, and aetiology are provided in Table I below.

For most subjects, the electrodes tested were, from most basal to most apical, electrodes number 3, 6, 9, 12, 15, 18, and 20. Electrode 3 was disabled for S9 and S10, so electrode 4 was used instead. For each of the tested electrodes, multipulse integration, polarity effect, and ECAP AGFs were measured. Subjects 2, 5, and 6 had no measurable ECAPs. For subjects 2 and 5, PE and MPI data were gathered, and for subject 6, only PE data were gathered.

B. Materials

Stimuli for the behavioural measures were generated in MATLAB and delivered to a Cochlear CP910 speech processor using Nucleus Implant Communicator software version 4 (NIC4), provided by Cochlear Limited. Electrophysiological measures were obtained with neural response telemetry (NRT) in Cochlear Custom Sound EP software version 5.2, also provided by Cochlear Limited. All stimuli were verified using a test implant and a digital oscilloscope.

C. Multipulse Integration

MPI was measured as the difference in behavioural detection thresholds between 80- and 1000-pulse-per-second (pps) cathodic-leading symmetric biphasic pulse trains for a subset of electrodes across the electrode array. The stimuli were in monopolar (MP) mode with a duration of 0.4 seconds, a phase duration of 25 μ s, and an interphase gap of 8 μ s.

Before determining thresholds, subjects completed a loudness-scaling procedure for both the 80-pps and 1000-pps stimuli on each electrode. During the loudness-scaling procedure, the level of the stimulus started at 0 CL units, and was then incrementally raised in small current steps while the subject gave feedback using a loudness chart (from number 1 for 'just noticeable' to number 7 'loud but comfortable'). This loudness-scaling procedure was used to ensure that stimulation never exceeded the 'loud but comfortable' level reported by the subject.

Thresholds were determined using an adaptive one-up/one-down procedure with no feedback. The participant was instructed to respond when they heard a sound by pressing the spacebar on a computer keyboard. The level of the stimulus started at 90% of the 'comfortable' (number 6) level reported in the loudness-scaling procedure, and was incrementally lowered or raised, depending on the subject's response. If the subject responded to a stimulus within three seconds of a stimulus onset, the level was reduced by

one step and another stimulus was played. If the subject did not respond to a stimulus within three seconds of the stimulus onset, the level of the stimulus was raised by one step. The procedure was completed when 8 reversals were reached. The initial step size was 4 CL steps (approximately 0.63 dB), and was reduced to 2 CL steps (approximately 0.31 dB) after 2 reversals. The detection threshold for one run was calculated as the mean of the last 6 reversals.

Two runs of detection thresholds were obtained for each electrode and each pulse rate, and the overall detection threshold was calculated as the average of the two runs on each electrode. For each subject the order of testing the electrodes was randomized for the first run, and repeated in reverse order for the second run. To further minimise effects of testing order, the first run was obtained for both pulse rates before the second run was obtained, and the order of pulse rates for the second run was reversed. Half the subjects began the test with the 80 pps condition, and half began the test with the 1000 pps condition.

D. Polarity Effect

PE was measured as the difference in thresholds between cathodic-centered and anodic-centered quadraphasic (QP-C and QP-A, respectively) pulse trains, at a stimulation rate of 80 pps with a pulse duration of 42 μ s and an interphase gap of 8 μ s. A pulse duration of 42 μ s was used rather than 25 μ s to ensure audibility, and to remain consistent with other studies that have measured the polarity effect with QP pulses (Carlyon *et al.*, 2013; Macherey *et al.*, 2017).

The loudness-scaling and detection-threshold procedures were identical to those described in the previous section, except that the two pulse conditions tested at each electrode were 80-pps QP-C and QP-A, rather than 80-pps and 1000-pps symmetric biphasic pulse trains.

E. ECAP Amplitude Growth Functions

80-pps symmetric biphasic pulse trains were presented in monopolar mode with a PD of 25 μ s and IPGs of both 8 μ s and 40 μ s. The recording electrode was always two apical (+2) from the stimulating electrode. The ground electrode for the probe pulse was MP1, and for the masker electrode was MP2. The effective sampling rate was 20 kHz, and the length of the measurement window was 1600 μ s. The masking pulse was always presented on the same electrode and at the same current level as the probe pulse, with a masker-probe interval of 400 μ s. The forward masking technique was used to remove stimulation artefacts (Brown *et al.*, 1990).

Before measuring ECAP AGFs, the loudness-scaling procedure from the previous two sections was completed for each of the tested electrodes. Recording parameters were optimized by measuring a single ECAP at the ‘loud but comfortable’ level for electrodes 3, 12, and 20, with recording amplifier gains of 40, 50, and 60 dB, and recording delays of 73, 98, and 122 μ s. The settings that maximized ECAPs were chosen and used for all ECAP AGF measurements. The range over which ECAP AGFs was measured was from level number 2 (‘very soft’) to level number 7 (‘loud but comfortable’), in steps of 3 CL units. 50-100 sweeps were taken at each level for each electrode. N1-P1 peak amplitudes were calculated automatically using Custom Sound EP.

Calculating the IPG Effect on ECAP AGF Offset

ECAP amplitudes (in dB re 1 μ V) were plotted as a function of input current (in dB re 1 μ A) for the short IPG of 8 μ s and the long IPG of 40 μ s. The IPG effect on ECAP AGF offset was calculated as the average difference (in dB) between the overlapping linear portions of the ECAP AGFs (McKay and Smale, 2017). The initial output range over which the offset was calculated was set to the entire overlapping region of ECAP outputs, and was

then adjusted to only include the linear portions of amplitude growth by excluding portions of the AGF which were at floor level or saturation level. The method for calculating the IPG offset is shown in Figure 1. This method was similar to the measurement of the IPG effect on ECAP offset used by Prado-Guitierrez *et al.* (2006), who measured the offset in the regions of 20-80% of the normalized ECAP AGFs, and by Ramekers *et al.* (2014) , who measured the offset at 50% of the normalized ECAP AGFs. Both studies showed that their measure of IPG effect on ECAP offset correlated with SGN density. Because we were not able to obtain full sigmoidal ECAP AGFs without exceeding the ‘loud but comfortable’ level for the subjects in this study, the overlapping linear region was used as the closest approximation to the method used in the animal studies.

All between-electrode correlations reported here were calculated using an ANCOVA with one measure as the dependent variable, the other measure as the covariate, and the subject as a random factor (Bland and Altman, 1986). This is mathematically equivalent to subtracting, for each measure and electrode, the mean value for that measure obtained for that subject across all electrodes, and then performing a Pearson correlation. This latter method is used when plotting correlations, so that each axis shows a normalised value relative to the mean for each subject.

III. Results

Run 1 and Run 2 were highly correlated for both PE ($R(10) = 0.75$, $p < 0.001$) and MPI ($R(9) = 0.82$, $p < 0.001$), suggesting good test-retest reliability for the behavioural measures (Figure 2).

An analysis of covariance (ANCOVA) with subject as a random factor was used to evaluate the correlations between PE, MPI, and the IPG Effect. No significant correlations were found between any of the proposed neural health estimates. PE was not correlated with

MPI ($R(9) = 0.11$, $p = 0.385$), MPI was not correlated with the IPG Effect ($R(7) = -0.29$, $p = 0.058$), and PE was not correlated with the IPG Effect ($R(7) = 0.02$, $p = 0.887$). The absence of correlations shows that the within-subject pattern of one neural health estimate across the electrode array is not predictive of the within-subject pattern of another neural health estimate across the electrode array, at least in our subject population.

Figure 3 shows the correlations between MPI and PE, MPI and IPG Effect, and PE and IPG Effect. In the upper panels, the mean value across electrodes for each subject was subtracted from the measurement at each electrode. The lower panels show the correlations between the mean values across electrodes for each subject. A Fisher R to z transform was used on the correlation coefficients for each individual to calculate the 95% confidence interval for the range of across-electrode correlations for each comparison of neural health estimates. The 95% confidence interval for the range of correlation coefficients for MPI and PE was 0.03 ± 0.4 ; for MPI and IPG Effect it was -0.27 ± 0.33 ; for PE and IPG Effect it was 0.04 ± 0.39 .

The between-subject correlations of the mean of each neural health estimate across the array were also calculated, and are plotted in the bottom row of Fig. 3. No significant correlations were found between any of the estimates of neural health. Mean MPI across the array was not correlated with mean PE ($R(9) = 0.35$, $p = 0.322$) or mean IPG effect ($R(7) = 0.12$, $p = 0.783$), and mean PE was not correlated with mean IPG effect ($R(7) = 0.068$, $p = 0.873$).

As noted in the Introduction, a number of previous studies have shown that the PE is positively correlated with the average threshold obtained with both polarities (Carlyon *et al.*, 2018; Jahn and Arenberg, 2019), or with thresholds obtained with symmetric pulses (Mesnildrey, 2017). Our results replicate both of those findings: PE was positively correlated

with the mean of QP-A and QP-C thresholds ($R = 0.59$, $p < 0.001$, Figure 4A), and with 80-pps thresholds obtained with biphasic pulses ($R = 0.40$, $p < 0.001$). MPI was correlated with the mean of 80 pps and 1000 pps biphasic thresholds ($R = 0.35$, $p < 0.001$, Figure 4B).

IV. Discussion

MPI, PE, and the IPG offset, all proposed measures of neural health, were evaluated and compared in 11 CI users. There were no significant correlations between the neural health estimates for either within-subject comparisons across the electrode array, or between-subjects comparisons of the means. This was true despite high test-retest reliability and highly significant correlations between the PE effect and the MPI with overall threshold measures (Fig. 4). The results therefore suggest that each of these neural health estimates reflect different characteristics of the electrode-neural interface. “Neural health” is a broad term, comprised of many potentially independent factors including SGN density, the distribution of firing thresholds, demyelination and degeneration of peripheral processes and/or the central axon, and temporal properties of the remaining SGNs. The section below implements a computational model to explore what factors may have contributed to the different neural health estimates.

A. Computational Modelling of the Neural Health Estimates

A phenomenological model of a spiral ganglion neuron (Joshi *et al.*, 2017) was used to investigate the physiological mechanisms that might underlie the different neural health estimates. The model from Joshi *et al.* (2017) was well-suited for this investigation for several reasons. It models each neuron using both a peripheral process and a central axon, each characterised by separate exponential integrate-and-fire point-processes, allowing us to simulate neural degeneration by disabling the peripheral processes of a population of neurons. The model also includes sub-threshold and supra-threshold feedback loops, which

account for temporal properties of neurons (Boulet *et al.*, 2016), allowing the investigation of various pulse shapes (e.g. different IPGs and QP pulses) and stimulation rates (e.g. 80 pps and 1000 pps). Additionally, the model is parametrized so that demyelination of the peripheral process or central axon can be modelled by increasing the membrane capacitance, and by reducing the membrane conductance (Resnick *et al.*, 2018). Finally, the use of this phenomenological model was preferable compared to other biophysical models (Rattay *et al.*, 2001; Briaire and Frijns, 2005; Smit *et al.*, 2010), because those biophysical models have been shown to inaccurately estimate the effect of pulse rate on detection thresholds (Bachmaier *et al.*, 2019). Because of the model's computational efficiency, we were able to generate populations of 500-1000 neurons with various means and standard deviations of firing thresholds. For each of the neural health estimates, we tested the effect of number of neurons, mean firing threshold, standard deviation of the firing thresholds, presence of the peripheral processes, and central axon demyelination. A more detailed description of the model, together with the MATLAB source code, is provided by Joshi *et al.* (2017).

IPG Offset

The IPG offset was unaffected by the number of neurons, or by the mean and standard deviation of the firing thresholds of the neural population. It was very subtly affected by removing the peripheral processes. The greatest reduction in IPG effect occurred by disabling the peripheral system and modelling demyelination of the central axon by increasing the membrane capacitance and reducing the membrane conductance.

In Figure 5, the number of spikes generated by a population of 1000 neurons is shown as a function of input current level. The stimuli were identical to those used for the IPG offset measure in the behavioural portion of the experiment (duration of 0.4 seconds, 80 pps stimulation rate, 25 μ s phase duration, IPGs of 8 and 40 μ s). The IPG offset is largest for the

healthy neural population (blue lines), and is only slightly reduced by removing the peripheral processes removed (orange lines). When peripheral processes are removed and central axon demyelination is applied, the IPG offset decreases, as shown by the yellow and purple lines. For the yellow lines, central axon demyelination was modelled by doubling the membrane capacitance and halving the membrane conductance, and for the purple lines, membrane capacitance was quadrupled and conductance was quartered.

This modelling result suggests that IPG offset might be a measure of central axon demyelination. The main support in the literature for the use of IPG offset as an estimate for neural health are the studies by Prado-Guitierrez *et al.* (2006) and Ramekers *et al.* (2014), which both showed correlations between SGN density and IPG offset. It is likely that SGN density, as estimated in these studies, co-varies with central axon demyelination. SGN density was estimated by counting the nuclei of SGN fibres, which lie in the soma between the peripheral processes and the central axon. As mentioned in the introduction, SGN degeneration generally begins at the periphery, moves to the soma, and then the central axon begins to demyelinate. Therefore, the amount of central axon demyelination is probably related to the number of degenerated soma. Interestingly, the model suggests that the IPG offset is not directly affected by the number of remaining nerves, but rather by the change in the properties of those remaining nerves.

Polarity Effect

Like the IPG offset, PE was unaffected by the number of neurons, or by the mean and standard deviation of the firing thresholds of the neural population. PE could however be modelled by disabling the peripheral processes. Figure 6 shows the number of spikes generated by a modelled population of 1000 SGN fibres as a function of input current, throughout the 0.4-second duration of cathodic-centered (dotted lines) and anodic-centered

(solid lines) QP stimuli (stimulation rate 80 pps, phase duration 42 μ s, IPG 8 μ s). It was assumed that the detection threshold was reached when a certain number of spikes were generated. For this example, the threshold number of spikes was set at 10000, but any choice of number would lead to a qualitatively similar result. For the neural population with healthy peripheral processes, the threshold for cathodic-centered pulses was slightly lower than the threshold for anodic-centered pulses. For the population without peripheral processes, the threshold for anodic-centered pulses was approximately 2 dB lower than the threshold for cathodic-centered pulses. When (additionally) the central axon was demyelinated, PE was unaffected.

This result suggests that PE may be a measure of the survival of the peripheral processes, consistent with other modelling studies (Rattay *et al.*, 2001; Resnick *et al.*, 2018). The modelling implies that unlike IPG offset, PE is *not* further affected by central axon demyelination, which could help to explain why IPG offset and PE were not found to be correlated.

Multipulse Integration

MPI was affected by the standard deviation of the firing thresholds of the population of neurons, with larger MPIs associated with larger standard deviations. Figure 7 shows the number of spikes as a function of input current level for pulse trains with stimulation rates of 80 pps (dotted lines) and 1000 pps (solid lines). The blue curves were measured for a population of 1000 SGNs with a 3 dB standard deviation of firing thresholds, and the orange curves were measured with a population of 1000 SGNs with a 0.5 dB standard deviation of firing thresholds. Similar to the modelling of PE, the detection threshold was assumed to occur at 10000 neural spikes, though the results would be qualitatively similar for any number of spikes. The difference between thresholds for 80 pps and 1000 pps pulse trains

was approximately 4 dB for the population with a large standard deviation of firing thresholds, and 3 dB for the population with a small standard deviation.

The idea that MPI is related to the standard deviation of firing threshold is supported by recent literature investigating MPI in human CI listeners. MPI has been shown to be related to spatial selectivity, with higher MPI in monopolar mode compared to bipolar mode (Zhou *et al.*, 2018), and higher MPI on electrodes with wider spatial spread of excitation compared to a narrow spread of excitation (Zhou and Pfingst, 2016b). Additionally, in our behavioural results, MPI was positively correlated with the mean detection threshold for 80-pps and 1000-pps biphasic pulse trains, suggesting that higher current levels (higher current spread) leads to higher MPI. If the spread of excitation at a particular electrode were relatively wide compared to other electrodes, then the distribution of membrane voltages at nearby SGN fibres would also be wider, leading to a larger standard deviation of firing thresholds. One contributing factor to the spread of excitation is the electrode-modiolus distance. In guinea pigs, the electrode-modiolus-distance remains relatively constant across the electrode array, and variation in MPI between groups of animals deafened for different amounts of time is largely influenced by the health of the SGN fibres. In humans, EMD varies considerably along the length of the cochlea (Long *et al.*, 2014), and the number of recruited nerve fibres (and the standard deviation of their firing thresholds) would depend not only on the health of the nearby SGN fibres, but also on the spread of excitation. A better estimate of neural survival using MPI might be measured using focussed thresholds (bipolar or tripolar mode) (Zhou *et al.*, 2018).

MPI was also affected by the number of neurons and by the removal of the peripheral processes. However, the direction of these effects was unexpected, with higher MPI for lower number of neurons and for the population without peripheral processes. When populations of 500 and 1000 neurons were tested (with equal standard deviations), the smaller population of

500 neurons had a larger MPI than the larger population of 1000 neurons (3.8 dB versus 2.9 dB). When the peripheral processes were removed, MPI increased for both the 500- and 1000- neuron populations (to 5 dB and 4.6 dB, respectively). Figure 8 shows MPI as a function of the standard deviation of firing thresholds for populations of 1000 neurons and 500 neurons.

Limitations of the modelling

It should be emphasized that the model was used as an exploratory method to better understand factors that contributed to the different neural health estimates. The model was based on data from feline SGNs (Miller *et al.*, 1999; Shepherd and Javel, 1999; Miller *et al.*, 2001), so the exact values of the results may differ from studies in human CI listeners. Additionally, the parameters used to model peripheral degeneration and central axon demyelination were coarse approximations of the real biophysical processes. Nevertheless, the model does help to explain how the different neural health estimates could vary independently of one another.

Future considerations for neural health estimates

The personal customization of CI speech processing based on individual neural characteristics is important for optimizing outcomes in CI users. As with other precision medicine, the benefits of a treatment rely upon the accuracy of the diagnostics. Neural health estimates have become increasingly popular, but a consensus has not been reached on the best estimates to use. This study has shown that different neural health estimates are not necessarily interchangeable, as they measure different properties of the electrode-neural interface. In some sense, this distinctiveness could be advantageous, because each of the measurements provides unique information about neural health. For example, in each of our tested subjects, IPG offset and PE could be used in combination to estimate the degree of

peripheral and central SGN degeneration along the length of the array. However, due to resource limitations in a clinical setting, it would be more desirable to have a single objective measure that could quickly scan the array and determine the quality of the electrode-neural interface.

Important new information may come from past and future attempts to use neural health estimates to optimize speech processing strategies. While some studies have shown improved speech-in-noise perception by deactivating electrodes with poor modulation detection (Garadat *et al.*, 2013) or high low-rate thresholds (Zhou, 2017), a similar strategy that deactivated electrodes with a large PE did not provide any benefit (Goehring *et al.*, 2019). To our knowledge, there has not been an electrode deactivation strategy that has used the IPG offset. Focussed stimulation strategies (Arenberg *et al.*, 2018; de Jong *et al.*, 2019) might also benefit by selecting which electrodes to focus and which electrodes to disable based on some neural health estimate.

V. Conclusion

The combined experimental and modelling results provide evidence that PE, MPI, and IPG offset reflect different characteristics of the electrode-neural interface. Despite high test-retest reliability, no correlations were found between the different neural health estimates, for either within-subject comparisons across the electrode array, or for between-subject comparison of the means. Modelling results suggest that PE may be related to peripheral neural health, IPG offset may be related to central axon demyelination, and MPI may be related to the standard deviation of firing thresholds (which in turn may be affected by spread of excitation).

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TABLE 1. Information about the participants in the study.

	Age	Implant type	Duration of profound hearing loss before implantation	Duration of implant use	Aetiology
S1	69	CI24RE	48	14	Hereditary
S2	65	CI24RE	13	4	Ear infection, ototoxic antibiotic
S3	66	CI422	18	4	Exposure to loud sounds
S4	57	CI522	17	4	Maternal rubella and ear infection
S5	67	CI522	1.5	3.5	Unknown
S6	78	CI522	5	3.5	Otosclerosis, noise exposure
S7	66	CI512	20	2	Exposure to loud sounds
S8	75	CI24RE	10	15	Scarlet fever, viral infections, and Meniere's Disease
S9	43	CI522	14	2.5	Hereditary
S10	30	Hybrid	14	12	Perinatal deafness due to ototoxic antibiotic
S11	57	CI522	3	2	Hereditary

Figure Captions

Figure 1. Amplitude growth functions (AGFs) for subject 11, electrode 18, obtained at the 8- and 40 μ s IPG (blue and orange lines). The arrows illustrate the “IPG offset” between the two functions, which is defined as the mean difference between overlapping linear portions of the two ECAP AGFs (on a log input-log output scale).

Figure 2. Test re-test reliability was tested by measuring the correlation between the first and second run of the PE measurement (left panel) and MPI measurement (right panel). The Pearson correlation coefficients and p-values were calculated from an ANCOVA with subject as a random factor. Each axis shows the value of for each subject and electrode relative to the mean value across electrodes for that run number.

Figure 3. The figures show the correlation analyses between the different neural health metrics. The upper panels show within-subject correlations across the electrode array, and the lower panels show the between-subject correlations of the means across the electrode array. For the between-electrode correlations, each axis shows the value of for each subject and electrode relative to the mean value across electrodes for that measure. None of the neural health metrics were significantly correlated, either for within-subject or between-subject comparisons.

Figure 4. PE was positively correlated with the mean QP threshold and MPI was positively correlated with the mean biphasic threshold.

Figure 5. Modelling results for the IPG offset. The number of spikes generated by a population of 1000 neurons is shown as a function of input current level. The stimulus was identical to the electrophysiological experiment, with a duration of 0.4 seconds, a stimulation

rate of 80 pps, and an IPG of either 8 us (dotted lines) or 40 us (solid lines). The different colours represent different amounts of SGN degeneration.

Figure 6. Modelling results for the polarity effect. The number of spikes generated by a population of 1000 neurons is shown as a function of input current level. The stimulus was identical to the behavioural PE experiment, with a duration of 0.4 seconds, a stimulation rate of 80 pps, and cathodic-centered (dotted line) or anodic-centered (solid line) quadraphasic pulses. The different colours represent different amounts of SGN degeneration.

Figure 7. Modelling results for multipulse integration. The number of spikes generated by a population of 1000 neurons is shown as a function of input current level. The stimulus was identical to the behavioural experiment, with a duration of 0.4 seconds and a stimulation rate of 80 pps (dotted line) or 1000 pps (solid line). The different colours represent different standard deviations of firing thresholds for the modelled neural populations, with orange corresponding to a small standard deviation of 0.5 dB, and blue corresponding to a large standard deviation of 3 dB.

Figure 8. Multipulse integration as a function of the standard deviation of firing thresholds, for populations of 1000 neurons (orange line) and 500 neurons (blue line).

Figure 1

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Figure 2

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Figure 6

Figure 7

Figure 8

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