ECAP measures predict cochlear implant behavioural thresholds

Thesis

Submitted in partial fulfilment of Master of Biomedical Science

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DECLARATIONS

The author declares no conflict of interest in relation to this work.

This thesis is an original work of the author. Some aspects of these results have also been shown in:


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Aim: To estimate high rate stimulus behavioural threshold current levels of cochlear implant (CI) users by comparing peak amplitudes and associated latencies of electrically evoked compound action potentials (ECAPs) evoked by different stimulation pulse parameters.

Background: CIs create a perception of sound by electrically stimulating the cochlea. The current level for each electrode that corresponds to the minimum amount of stimulation required to create a perception of sound is presently determined through a lengthy and subjective clinical process. This process can be particularly challenging for infants and the long-term deaf. With adequate stimulation, peripheral auditory neurons generate an electrical response called an ECAP. The minimum amount of stimulation required to elicit ECAPs has been assumed to be able to predict behavioural thresholds. This has been found to be untrue, and ECAP-based behavioural thresholds produce sub-optimal speech perception outcomes. There is evidence that differences between ECAP- and behavioural thresholds are caused by differences between individuals’ peripheral auditory neuron survival. Separately, there is evidence that the extent of change in certain ECAP measures with change in stimulation conditions is also affected by peripheral neural survival. We suggest that these ECAP measures may therefore be directly used to estimate differences between ECAP- and behavioural thresholds.

Methods: Amplitude growth function series with four different stimulation parameters were created from ECAP thresholds to C-levels for 52 electrodes of 10 adult CI users. ECAPs were recorded intracochlearly through neural response telemetry. The current level difference required to equalise ECAP amplitude, and the change in ECAP peak latency, between stimulation conditions was determined for each electrode. Behavioural thresholds at stimulation rates of 40, 500, 1000 and 2000 pps were determined for each electrode using a 3-interval-forced-choice task. Pearson correlations were performed between equalising CL and low rate changes in behavioural thresholds, both per electrode and per subject mean. Stepwise multiple regression was used to directly estimate higher rate thresholds.

Results: ECAP measures significantly improved ECAP threshold based predictions of higher stimulation rate behavioural thresholds (1000 pps: $R^2 = 0.338$, n = 52).

Conclusions: This technique is superior to purely ECAP threshold-based fitting, improving predictions of behavioural thresholds. These methods will require validation, but show promise as a new clinical method to create better speech-perception outcomes for certain CI users.
ABBREVIATIONS

3IFC – Three-interval-forced-choice
ACE – Advanced combination encoder (processing strategy)
AGF – Amplitude growth function
CI – Cochlear implant
CL – Current level
C-Level – Maximum current level that creates a perception of comfortably loud sound
CIS – Continuous interleaved sampling (processing strategy)
ECAP – Electrically evoked compound action potential
ECAP threshold/ECAP T – Minimum current level required to create a measurable ECAP response
Hz – Cycles per second
IPG – Interphase gap
MPI – Masker-probe interval
NRT – Neural response telemetry
PD – Phase duration
pps – Pulses per second
R – Pearson’s R
R² – Coefficient of determination
SD – Standard deviation
SGN – Spiral ganglion neuron
SPEAK – Spectral peak (processing strategy)
T-Level – Minimum current level required to create a perception of sound
µV – Micro volts
µs – Micro seconds

Note: All correlations reported in this thesis are in the form of Pearson’s R unless otherwise stated.
Introduction

Disabling hearing loss affects 360 million people, or 5.3% of the world’s population (WHO 2015). Sensorineural hearing loss is a loss of function in the cranial nerve VIII, inner ear, or processing areas of the brain and has a variety of potential causes including inflammation, noise exposure, ototoxic drugs, and genetic disorder. Cochlear implants (CIs) are a treatment option for certain kinds of severe sensorineural hearing loss, particularly those where the hearing loss is caused by abnormalities in the hair cells of the organ of corti in the cochlea, without significant damage to higher pathways.

While sensorineural hearing loss can be acquired later in life, it is frequently identified in newborn infant hearing screening tests. In cases of bilateral hearing loss in infants, early intervention is crucial, as an absence of activation of the neurological auditory pathways during a sensitive period disrupts normal development of the auditory cortex and impairs sound perception. In such cases, it is common for severely or profoundly hearing impaired infants to be referred to cochlear implantation early in life, often within two years of birth.

The tonotopic organisation of the cochlea is leveraged by the different stimulation sites of a multi-electrode CI. Stimulation at each electrode causes activation of spiral ganglion neurons (SGNs) that would normally respond to a particular frequency band of acoustic sound. The action potentials generated by SGNs travel along the cranial nerve VIII, through the brainstem and to the auditory cortex.

Once implanted, a CI must be set up to generate a stimulation output appropriate to the individual. Each patient’s psychophysical perception of stimuli differs. Higher-current electrical stimulation causes more SGN firing, which is perceived by the CI user to be a louder noise, whereas a lesser stimulus is perceived to be quieter. Stimuli are programmed in current levels (CLs), which represent clinical units of current. The CL at each single electrode that corresponds to minimum threshold (T-level) and maximum comfortable (C-level) perceptions must be stored in the speech processor. With 22 electrodes in a modern CI and T- and C-levels needing to be programmed at each electrode, CI setup can be an arduous process that usually relies entirely upon subjective behavioural feedback as to which CLs correspond to the T- and C-levels. Such feedback is clearly challenging to acquire from infants and those who have been deaf for long periods.

Modern CIs have a reverse telemetry function, enabling them to record electrical signals from the cochlea. When stimulated with a sufficient CL, most electrodes of most CI implantees return an SGN-derived signal termed an electrically evoked compound action potential (ECAP). Efforts have previously been made to find a
strong correlation between the CLs of T- and C-levels, and the minimum CL required to elicit an ECAP (ECAP threshold), however this has so far shown insufficient predictive ability for use in a fully objective fitting program.

This thesis will explore past research in the area of objective CI programming, and will propose then carry out an approach whereby particular non-threshold ECAP features are used to estimate T-levels.

**Cochlear implants**

*The normal cochlea*

A normally-functioning ear (Figure 1) works by channelling sound through the pinna and ear canal. Longitudinal vibration of the air causes oscillation of the ear drum, which is connected to one of three small bones, collectively referred to as the ossicles. The ear drum-ossicle system converts sound into mechanical energy. The most proximal bone, the stapes, connects to a labile membrane around the oval window of the cochlea. The movement of the stapes converts sound to a wave in the perilymph of the cochlear vestibule. Hair cells within the cochlea are tonotopically arranged; higher frequency sound stimulates the basal cochlea and lower frequency sound stimulates the apical cochlea. The cochlea achieves this through manipulating structural properties to induce a travelling wave along the basilar membrane with peaks in amplitude at the frequencies found in the source sound. At the peaks of the travelling wave, sheering force exerted by the tectorial membrane causes the opening of ion channels on the tips of stereocilia protruding from inner hair cells in the organ of corti on the basilar membrane. The opened ion channels allow the flow of ions into inner hair cells, creating a receptor potential. The receptor potential of the inner hair cells causes a release of neurotransmitters into the space between the hair cell and nerve terminal, which triggers action potentials in the dendrite of the SGN.
Hearing loss can be broadly categorised into two nonexclusive categories. Conductive hearing loss, where hearing loss is caused by abnormality of the outer or middle ear, and sensorineural hearing loss (SNHL), which is caused by abnormality of the inner ear, cranial nerve VIII, or central auditory system. It is the latter for which CIs are most often considered a treatment option. Typical aetiologies of those who undergo cochlear implantation include noise induced hearing loss, meningitis, and hereditary progressive hearing loss. Aetiology has no great association with speech perception outcomes (Linthicum and Anderson 1991), with the sole known exception of meningitis complicated by postmeningitic hydrocephalus, which causes central neurologic insults that can lead to reduced performance at speech perception tasks (Francis et al. 2004). CIs are contraindicated by certain types of congenital malformation of the cochlea or auditory nerve (Belal Jr 1986).
Figure 2 A coronal diagram of an electrode array implanted within a cochlea. Note that the electrode is depicted as implanted through a cochleostomy, rather than through the round window. Reproduced from Zeng et al. (2004).

Sound processing

CIs function through the principle that a sensation of hearing can be elicited in an otherwise sensorineurally deaf ear through direct electrical stimulation of its auditory nerve afferents (Figure 2). In achieving this outcome, the CI contains both internal and external features. The external part is worn behind the ear and contains a microphone, speech processor, radio frequency coil, and battery. The speech processor functions to convert environmental sound into a series of electric impulses that determines which electrodes should be activated and at what intensities.

The specific implementation of this process is referred to as the sound processing strategy. Selection of sound processing strategy has a major effect on speech understanding (Wilson and Dorman 2008). Ideally, a sound processing strategy should encode sound into stimulation patterns that reproduce the original sound spectrum and allows the user to perceive clear sounds and have a high speech understanding.
Continuous interleaved sampling (CIS) filters the microphone input with a bank of bandpass filters. The envelope of each bandpassed channel is extracted using a rectifier, followed by a lowpass filter. Each calculated envelope is assigned to one electrode, for which pulse trains are current-modulated to produce an electronic representation of the envelope of acoustic sound. Higher frequency channels are assigned to basal electrodes, and vice versa, to mimic the order of frequency mapping in a normal cochlea. Pulse trains are interleaved over time, so electrodes are stimulated sequentially (Wilson et al. 1991). Non-simultaneous stimulation of CIS avoids anomalous loudness percept issues that can occur through coincident electrode stimulation (Wilson et al. 1993).

Most speech processing strategies derived from CIS are of the $n$-of-$m$ type, where the algorithm selects only a subset of electrodes to stimulate in a given cycle rather than potentially stimulating all electrodes (Wilson and Dorman 2008). $n$-of-$m$ strategies are intended to reduce the density of information presented to the cochlea by deleting low amplitude channels while maintaining higher amplitude channels. This is believed to unmask the more important, louder stimuli. Conventionally, $n$-of-$m$ type strategies sequentially stimulate six to ten electrodes per cycle. Strategies of this type include the spectral peak (SPEAK) (McDermott 1989; McKay et al. 1992) and more recent advanced combination encoder (ACE) (Vandali et al. 2000) strategies.

**CI stimulation**

The output of the speech processing strategy employed by the speech processor is communicated to the internal receiver-stimulator through a radio frequency transmitting coil. The electrode array is inserted into the scala tympani of the cochlea, most often through the round window or by cochleostomy (Figure 2). A modern electrode array contains up to 22 electrodes. The spatially segregated electrodes stimulate sections of the auditory nerve that, ideally, each correspond to a different frequency band. Cls are therefore able to return some hearing functionality, including both frequency and temporal discrimination, to otherwise severely hearing-impaired people.

Cochlear implantation requires an arduous post-operative programming procedure. Each patient’s psychophysical perception of stimuli differs. The SGNs, whether stimulated electrically or acoustically, produce a greater firing of auditory nerve fibre action potentials for greater levels of stimulation, and a subjective perception of louder sound. Hence, supra-threshold, higher CLs create a louder perception of sound, and lower CLs create a quieter perception of sound. CLs represent the amplitude of the biphasic current pulse in microamperes, where current in $\mu$A = $10^8(100^\text{CL}/255)$ for modern Cochlear Ltd. devices. CLs
range from 0 to 255. The two other major cochlear implant manufacturers, Advanced Bionics and Med-El, use similar logarithmic programming units.

CLs corresponding to T- and C-level loudness percepts must be stored for each electrode in the individual’s map, which is saved in the speech processor and forms the behavioural dynamic range for the sound processing strategy. CI setup usually relies entirely upon subjective behavioural feedback as to which CLs correspond to T- and C-levels. This process is more complicated for children and those unable to provide reliable behavioural feedback, such as infants and the long-term deaf. For such patients, non-verbal behavioural cues can be used.

After suffering severe SNHL, auditory neurons degenerate in a manner not readily predictable amongst patients. The rate and extent of auditory neuron degeneration (Figure 3) depends on factors including aetiology and duration of deafness (Felix and Hoffmann 1985; Nadol Jr et al. 1989; Nadol 1997) but cannot presently be accurately predicted or determined, other than histologically. Despite this, SGN survival is thought to have a strong influence on percepts induced by electrical stimulation, with higher behavioural thresholds and smaller dynamic ranges associated with poorer cochlear health (Pfingst et al. 1981; Kawano et al. 1998). It has also been demonstrated that peripheral neural survival affects measured neural responses to stimulation at the level of the cochlea (Prado-Guitierrez et al. 2006; Ramekers et al. 2014) and brainstem (Miller et al. 1995; Prado-Guitierrez et al. 2006).
In most CI patients, speech perception improves steadily after cochlear implantation (Waltzman et al. 1992; McKinley and Warren 2000; Oh et al. 2003). Sharma et al. (2002) measured central auditory system development through P100 latency, which is a measure of cortical activation that is known to change predictably over the course of auditory system maturation. Comparison of implanted human subjects with normal hearing controls found that children with the longest period of auditory deprivation before implantation developed abnormal cortical response latencies to speech, whereas implanted children with short periods of auditory deprivation, 3.5 years or less, developed age-appropriate P100 latencies within 6 months of implantation. Their findings implied a period of maximum auditory cortical plasticity that is significantly diminished in most children by the age of 7. A similar study with a greater focus on measuring practical outcomes was by Connor et al. (2006), who found that children who had received their implants by

**Figure 3** A cartoon of auditory neuron and hair cell survival illustrated A) in a normally-hearing cochlea, and B) in a deafened cochlea. From Dorman and Wilson (2004).
2.5 years of age had exhibited bursts of growth in expressive vocabulary and consonant production accuracy, but that this burst diminished in magnitude as age at implantation increased. This ‘burst’ effect was found to be synergistic with the steady longer term improvement witnessed in all children.

Implantation at 12 to 24 months of age leads therefore to near-normal language development in most CI users (Svirsky et al. 2000). This is thought to be related to the concept of sensitive periods, whereby pre-lingually deaf children have not yet undergone the neuroplastic changes that ‘lock in’ language and auditory networks (Ramkalawan and Davis 1992; Nicholas and Geers 2007). It has therefore been proposed that early intervention is crucial (Svirsky et al. 2000; Connor et al. 2006). Together, this evidence informs the clinical importance of early implantation in deaf infants in order for maximum longer term speech perception benefit to be derived from the prosthesis.

**Neural responses to electrical stimulation**

Neurons comprise the main communicative and computational units of the peripheral and central nervous systems. Neurons are excitable, connecting to one another through synapses to form neural networks and transmissive structures. Through ion pumps and channels, neurons control soma ion concentrations. Manipulation of these ion channels allow neurons to generate action potentials; brief fluctuations in membrane potential propagated through the neuron. It is primarily through these action potentials that neurons transmit information.

By ‘artificially’ creating voltage changes by introducing electrical stimuli, voltage-gated channels can be triggered to open, and should the electrical stimulus be strong enough, an action potential will fire. This is the basis upon which CIs function to activate SGNs and send auditory information to an otherwise deaf person’s brain. These electrically evoked auditory action potentials can be measured by internal or external recording electrodes, and it is through these recordings that scientists have sought to gain some understanding of the function of the auditory system. With some exceptions (e.g. Van Wieringen et al. 2008), human auditory nerve potentials are evoked using symmetric biphasic rectangular charge-balanced current pulses (Hambrecht 1985; Merrill et al. 2005). Such stimuli evoke electrical activity that is determined by both the number of participating neurons and the degree of synchronisation in discharge over time (Goldstein and Kiang 1958).

We may be able to make inferences about psychophysical perception of cochlear stimulation by measuring peripheral neural responses to that same stimulation. We turn to the ECAP a measure of cochlear neural firing in response to stimulation. The ECAP is an electrical potential generated by the SGNs of the cochlea in response to certain types and magnitudes of stimulation. ECAPs can be recorded from an electrode positioned
in the middle ear near the cochlea (e.g. the promontory or round window niche), from an electrode positioned within the cochlea, by scalp electrodes, or in animal models, on the surgically exposed nerve trunk. The modern intracochlear system of ECAP measurement was developed commercially by Cochlear Ltd. in the Nucleus CI24M implant as neural response telemetry (NRT) (Brown *et al.* 1998). NRT is the measurement of an ECAP using one of the electrodes of the implanted device itself as a recording electrode. The ECAP, as measured intracochlearly through NRT, is analogous to the near-field version of the whole-nerve Wave I ABR response (Miller *et al.* 2008).

It is through NRT that we hope to find a clinically convenient, simple, and reliable tool to automate the CI fitting process.

**ECAPs**

**ECAP stimulation and response**

Like all commonly used CI stimuli, ECAPs are evoked by rectangular charge-balanced biphasic pulses with four key modifiable features: rate, interphase gap (IPG), phase duration (PD), and current (Figure 4). Rate is the frequency, measured in pulses per second (pps), at which pulses are presented to the cochlea. IPG is the length of time between each phase of the pulse (µs). PD is the length of time each phase is presented (µs) (Briaire and Frijns 2005). Current is determined by CL, which is, as previously described, a clinical unit of current.

![Figure 4](image.png)

*Figure 4* key modifiable features of CI stimuli. Current amplitude (µA, or CLs); Phase duration (µs); Interphase gap (µs); and rate of stimulation, as measured by the number of biphasic stimuli presented to the cochlea per second (pps).
The ECAP response is comprised of N1 and P1 peaks. Under conventional stimulation conditions, a negative N1 peak is generally recorded between 200 and 500 μs from probe pulse onset, followed by a smaller positive P1 peak occurring at 500 to 800 μs (Brown et al. 1998). The N1 to P1 amplitude can be up to 2 mV. Beyond a threshold CL and below a maximum CL, the amplitude grows as CL is increased (Figure 5). In the form of NRT, the primary advantage that ECAPs have over other evoked potentials, such as auditory brainstem responses or cortical potentials, is that they can be recorded quickly from CI users of all ages, and that doing so does not require application of scalp surface recording electrodes. Measurements are not dependent on attention, are not affected by muscle artefact nor are they affected by sleep or sedation (Abbas and Brown 2006).

![Figure 5 ECAPs recorded through the Nucleus CI24M at different probe current levels](image)

**Figure 5** ECAPs (left) recorded through the Nucleus CI24M at different probe current levels (right). As probe current level is increased, the characteristic ECAP shape emerges giving strong N1 and P1 peaks. The N1 latency decreases as current level is increased, in this case occurring outside of the recording window at higher CLs. Adapted from Abbas et al. (1999).

When measuring ECAPs using NRT, recordings are conventionally made through an intracochlear electrode offset two positions along the array from the stimulus electrode. NRT software interfaces with the CI, controlling the stimulus parameters of the stimulating electrode, as well as receiving data from the recording electrode. ECAPs can be successfully recorded at the majority of electrode positions in the majority of implantees (Abbas et al. 1999). A key downside of the use of ECAPs, however, is that recording so close to the
stimulating electrode, and so soon after stimulus onset, results in a large stimulus artefact (de Sauvage et al. 1983).

**Artefact isolation**

After evocation by a probe pulse, the ECAP response occurs during the period of that probe’s voltage decay. The ECAP N1 peak generally occurs between 200 and 500 μs after stimulus onset, whilst the decay of the artefact languishes for up to 1 ms. Artefact coinciding with the ECAP response can be orders of magnitude greater in voltage than the ECAP response itself. Processing must therefore separate the ECAP from the stimulus artefact.

![Figure 6](image)

*Figure 6* the four stimulus conditions used in the forward masking method of artefact isolation (left). Waveforms recorded from each condition (top right). The resultant waveform after recordings of all four conditions are subtracted, as described in text (bottom right). ‘Masker advance’ is the ‘masker probe interval’ also discussed in text. Reproduced from Brown et al. (2000).

The most common artefact isolation technique is the subtractive forward masking method developed by Brown et al. (1990), an adaption of the method first proposed by de Sauvage et al. (1983) (*Figure 6*). Under this technique, recordings are made from four conditions: 1) a probe-alone condition, with the presentation of a single biphasic current pulse, 2) a masker-plus-probe condition of two biphasic current pulses 3) a masker-alone condition of a single biphasic pulse coincident in time with the masker of the two-pulse sequence, and 4) a switch-on condition with no stimulus.
Under forward masking, the ECAP is extracted by subtraction of the recording made in the masker-plus-probe condition from the recording made in the probe-alone condition, and addition of the result to the recording made in the masker-alone condition. The switch-on condition is used to remove artefact produced by the implant regardless of the presence of masker/probe stimuli. The response to the masker-plus-probe condition contains both the voltage decay of masker and probe, and neural response to the masker, with the probe not eliciting an ECAP as it is presented within the refractory period of the SGNs following their response to the masker. SGN refractoriness is controlled by the masker-probe interval (MPI), the time between the masker and the probe in the masker plus probe condition. To ensure that most auditory nerve fibres are within the refractory period, the MPI must be short. Despite some limited evidence that at least some proportion of SGNs may be able to fire less than 400 μs after a masking stimulus, largely based on mathematical extrapolation of refractory periods in a cat model (Miller et al. 2001), MPIs used in human ECAP literature tend to range from 400 to 500 μs (Lai et al. 2002; Morsnowski et al. 2005).

Another crucial consideration in the forward masking paradigm is of masker CL, where the masker must fully saturate any SGNs that would otherwise be caused to fire by the probe. In earlier research (e.g. Lai et al. (2002); Hughes et al. (2000)) it was common for masker levels to be fixed independent of varying probe levels, based on the findings of Brown and Abbas (1990). This is in contrast with Westen et al. (2011), who found that very high current masker stimulation can decrease recorded ECAP amplitudes. The setting of masker CL at a varying level above the probe CL was proposed by Lai (1999), and it is now a common approach in Cochlear Ltd. products to use a masker level 10 CL above probe. It may also be a consideration in ECAP studies on conscious humans that as ECAPs tend to be measured in the upper end of a person’s behavioural dynamic range a fixed masker level may be construed by a participant as exhausting. Assumptions implicit in the forward masking paradigm may not be strictly true (Sainz et al. 2005; Alvarez et al. 2008), however careful selection of MPI and masker CL allow recovery of ECAPs that are generally accurate and comparable across electrodes and subjects.

The use of ECAPs in fitting cochlear implants
ECAPs were initially developed with the intention of clinical relevance. To this end, some of the earliest research on ECAPs looked at their use in predicting T- and C-levels. This technique involves finding ECAP threshold (the lowest CL able to elicit an ECAP response), then determining to what extent ECAP threshold is correlated with the T- or C-levels.
One of the earliest studies to attempt to correlate ECAPs with behavioural levels was Brown et al. (2000), who used NRT software to find correlations between ECAP thresholds and T- and C-levels in 44 adults. Behavioural thresholds were determined from participants' maps, as set by their audiologist at 250 pps more than 3 months after initial processor switch-on. The overall correlation with behavioural thresholds was moderate at around R = 0.55. Under similar experimental conditions, Di Nardo et al. (2003) found correlations of 0.62 and 0.72 respectively, again using map settings at 1 month post switch-on. Noticing that ECAP thresholds 'follow the slope' of behavioural levels across electrodes, Brown et al. (2000) proposed a procedure whereby the behavioural threshold on one electrode was conventionally determined, the ECAP threshold for that electrode determined, then the difference between the T- and C-levels and the ECAP threshold on that electrode was computed. This ECAP offset based mapping system then applied the respective offset values to ECAP thresholds across other electrodes. Though still relying upon at least two behavioural judgements, this system was reported to improve the prediction of map T- and C-levels to 0.83 and 0.77, respectively.

Hughes et al. (2000) used a similar methodology but with child, rather than adult, subjects. Correlations between ECAP thresholds and T- and C-levels were 0.70 and 0.72 respectively, without use of the ECAP threshold offset procedure. These higher correlations were speculated to be because the conservative techniques used by audiologists to determine children's behavioural levels mean a narrower dynamic range is found, where T-levels are suprathreshold and C-levels are below actual comfortable levels. Additionally using the ECAP-offset increased correlations between predicted and actual map T- and C-levels to 0.85 and 0.89 respectively. Franck and Norton (2001) found behavioural levels in adults at least 3 months post switch-on at stimulation rates of 80 pps and 250 pps using the 'modified ascending loudness judgements with knob' technique of Skinner et al. (1995). At a behavioural rate of 80 pps, correlations between ECAP threshold and T-level were around 0.76, while at the higher behavioural rate of 250 pps, correlations degraded to around 0.60.

In infants, who are unable to provide accurate verbal behavioural feedback, the method of Brown et al. (2000) has become the standard fitting practice amongst clinicians for setting of a preliminary map (Gordon et al. 2004). The necessity of even just two accurate behavioural responses gives the technique an innate potential to be inaccurate, in addition to the inaccuracy of ECAP profiles in predicting behavioural threshold profiles. Maps derived using this technique cause lower speech perception scores compared to traditional fitting methods (Seyle and Brown 2002; Wesarg et al. 2010). Perhaps even more concerning is that Brown (2003) found that setting T- and C-levels of all electrodes to the behavioural levels of a single anchor electrode gave a better approximation of actual behavioural levels than if the profile of ECAP thresholds had been used.
Similarly, Cafarelli-Dees et al. (2005) found a better approximation of actual T- and C-levels by using the group average of their cohort than by using ECAP threshold profiles. CI users have also been found to prefer an ECAP threshold profile based map that has been partially flattened (Botros and Psarros 2010). Together, this evidence indicates that use of ECAP threshold profiles in existing semi-automated fitting is at best suboptimal, and may not be a value-adding step in clinical practice.

It is important to note that the studies mentioned involve correlations between ECAP thresholds and either map behavioural levels, or behavioural levels determined by processes similar to those used clinically. These threshold-finding processes can cause random and systematic errors in determining behavioural levels. To reduce variability and create a consistent measurement technique, adaptive forced choice interval tasks allow a more accurately prediction of perceptual thresholds (Dixon and Mood 1948; Kingdom and Prins 2010). It is therefore advisable to use adaptive forced choice procedures to gain measures of T- and C-levels with a known level of precision and accuracy.

As tentatively explored by Gantz et al. (1994) and Franck and Norton (2001), there is a strong correlation between ECAP threshold and behavioural threshold when lower pulse rate stimuli are used, but this relationship degrades as stimulation rate increases. This was further explored by McKay et al. (2005), noting that whereas ECAP amplitude is related to the amount of neural activity elicited from a single pulse, the neural activity evoked by higher rate stimuli is a response to neural activity integrated over a number of stimulus pulses. It is not possible for ECAP thresholds alone to account for the effect of increased stimulation rate on behavioural threshold. Without achieving a consistently high correlation with minimal reliance upon human interpretation and behavioural feedback, ECAPs are not usable in fully objective CI fitting. As the high output rates of a modern speech processor foils the link between ECAP threshold and behavioural threshold, it is worth exploring the reasons why this is so.

The effect of rate on behavioural levels

ECAPs have so far eluded use in a fully objective CI fitting system as correlation strength between ECAP threshold and behavioural threshold degrades as the stimulation rate increases (McKay et al. 2005). Low rate stimulation requires higher CLs to elicit a perception than higher rate stimulation (Figure 7) (Skinner et al. 2000). High rate stimulation is thought to convey a more fluid perception of sound and create a more realistic representation of speech to the CI user. Whilst the benefit of very high rates is questionable (Fu and Shannon 2000; Vandali et al. 2000; Zhang et al. 2011; Bonnet et al. 2012), clearly any attempt at estimating T- and C-levels must be applicable to conventionally used speech processor output settings.
The effect of rate of stimulation on an individual’s behavioural thresholds can be expressed through a behavioural threshold versus rate graph (Figure 7a). Such graphs are characterised by a reduction in behavioural threshold as rate of stimulation is increased (Skinner et al. 2000; Firszt et al. 2002; McKay et al. 2013a; McKay et al. 2013b). Though on aggregate there are enormous differences between the behavioural threshold versus rate graphs of individual electrodes, most of this variation is found in the low rate (<500 pps) section of the graph, whereas the higher rate (>500 pps) section has been found to exhibit similar slopes between electrodes regardless of variability in the lower rate section (Figure 7b) (McKay et al. 2013a). Kang et al. (2010) similarly found in guinea pigs a large difference between the slopes of low rate sections of behavioural threshold vs rate graphs depending on whether they were assigned to an experimental group expected to have high or low SGN survival. The group with higher levels of neural survival had much steeper low rate behavioural threshold vs rate slopes, whereas the group with lower levels of SGN survival had flatter slopes. Pfingst et al. (2011) histologically confirmed an association \( R = -0.67 \) between the <1000 pps behavioural threshold versus rate slope and SGN density in guinea pigs. Other indications of cochlear health, including hair cell density and a subjective ranking of the presence of peripheral SGN processes, similarly exhibited strong correlation with this slope.
Figure 7 A) Behavioural threshold versus rate of stimulation across subjects and electrodes. Current is in dB re 1 μA. B) Behavioural thresholds replotted in dB re the 500 pps threshold. The slopes of the low rate (40 to 500 pps) section of the graph have a great deal of inter-sample variability, whereas slopes in the high rate (>500 pps) section are similar. Reproduced from McKay et al. (2013a).

The cochlear-health associated difference between guinea pigs in multi-pulse integration at low rates was posited by Pfingst et al. (2011) to be caused by any of several mechanisms. Where both inner and outer hair cells are intact, an increase in rate, and therefore current delivered per unit time, would increase basilar membrane displacement through outer hair cell motility, causing changes in inner hair cell receptor potentials and leading to SGN firing. This, however, was concluded to be unlikely due to presence of steep low rate behavioural threshold vs rate slopes in human subjects inferred to have an absence of hair cells.
(Zhou et al., 2011). A more convincing explanation may be that in healthy cochleae, the effect of pulse rate on a single neuron is multiplied by the greater number of surviving SGNs (Botros and Psarros, 2010).

As previously discussed, correlation between ECAP threshold and behavioural threshold is strong at low rates of stimulation, but this relation degrades as rate of stimulation increases due to the hitherto unpredictable effect of rate on behavioural threshold. This variability has been found to have an association with cochlear health. If some aspect of ECAPs were a correlate of neural survival, it may therefore also predict the change in behavioural threshold with an increase in rate. As will be explained in the next section, there are two candidate methods that we will consider. A major caveat to this logical leap is that the histological association studies we consider have only been performed in a guinea pig model. Guinea pigs have a much faster rate of post–deafening SGN degeneration than humans, losing approximately 50% of their SGNs within six weeks of deafening (Gillespie et al. 2004). In humans, this same degree of SGN loss takes years (Nadol Jr et al. 1989). Because of this, guinea pigs are commonly used as an accelerated model of the peripheral neural decay suffered by deafened humans.

Unexplored potential for correlation between ECAPs and behavioural levels

The Δlatency effect

Ramekers et al. (2014) used guinea pigs to measure ECAP N1 peak latency changes for six weeks post-deafening. Guinea pigs were found to have progressively shorter N1 peak latencies at greater periods of time deafened. This result implies that the extent of neural degradation in guinea pigs is at least somewhat correlated with ECAP N1 peak latency. Furthermore, Ramekers et al. (2014) found an even stronger correlation between period deafened and the extent of N1 peak latency change with change in IPG from 2.1 to 30 μs at a fixed PD (this measure can more succinctly be referred to as Δlatency). Correlations between Δlatency and histological assessments of SGN packing density and perikaryal area (two measures of neural degeneration) were between 0.6 and 0.8. The association between greater change in latency under conditions of changing IPG, and poorer SGN survival, was hypothesised to be due at least in part to a shift in neural phase preference in response to the biphasic stimuli. Higher correlations tended to be found at higher CLs and when using longer PDs.

In applying these results to humans, it should be considered that Ramekers et al. (2014) use of long PDs was facilitated by their use of a transcranial recording electrode and alternating polarity forward masking. Further, high stimulus CLs were allowed by the anaesthetised state of the guinea pigs under survey, allowing
capture of ECAPs across the entire ECAP dynamic range without regard to exceeding C-level. Nevertheless, this technique shows potential to be trialled as an in situ measure of inner ear neural degeneration in humans. As Δlatency is thought to correlate with neural survival, the underlying cause of this correlation is thought to be related to the underlying cause of the separate correlation between neural survival and the low rate slope of the behavioural threshold versus rate function. Hence Δlatency may be used to estimate this low rate slope.

The IPG and PD effects
The ‘IPG effect’ and related ‘PD effect’ are based on an observation in guinea pigs by Prado-Guitierrez et al. (2006) and Ramekers et al. (2014) that the change in charge required to equalise ECAP amplitudes under conditions of changing stimulus IPG or PD is greater within a healthy cochlea than an unhealthy cochlea. One explanation for the presence of the IPG effect is that the two phases of current are intended to balance each other out. When the total charge delivered by the first phase is close to a neuron’s spike threshold, spike initiation can occur a short time after the end of the phase. The increased IPG delays the beginning of the second phase of the current stimulus, so increases spike probability (van den Honert and Mortimer 1979). In a cochlea that has suffered neural degeneration, there is thought to be an increased leakiness of the cell membrane to ions due to demyelination decreasing the efficiency of post-phase spike initiation (Prado-Guitierrez et al. 2006). This however may also be affected by neuronal phase preference. The PD effect may in contrast be caused by the degenerative demyelination process, which first occurs proximal to the receptor cells, affecting SGN dendrites and soma while leaving central axons predominantly myelinated (Shepherd and Javel 1997). In a healthier cochlea, peripheral processes will have a greater contribution to the ECAP response, causing a better integration of charge over time.

Hence, again, these phenomena (the ‘IPG’ and ‘PD’ effects) that are known to correlate with neural survival may therefore also be predicted to be observed to correlate with the low rate slope of the behavioural threshold versus rate function.
Initial expectations when ECAPs were first developed commercially were of ECAPs having clinical relevance. Our own field of research was presaged by Brown et al. (1998) with the belief that “Future research will most certainly be aimed at evaluating how the EAP (ECAP) can be used to facilitate the process of fitting the speech processor of the device to an individual user.”

Currently, CI fitting is a tiring process that involves the making of up to 44 loudness judgements. In people unable to make accurate loudness judgements, a combination of ECAP threshold profiles and behavioural responses is used. This present fitting method is known to create maps that are fundamentally less accurate than they would be if ECAP thresholds were discarded and flat profiles were used instead. This fitting method has also been found to cause worse speech perception outcomes than conventional fitting. Despite these drawbacks, the Brown et al. (2000) method of using a single loudness judgement and ECAP threshold profiles has been implemented commercially in such software packages as NUCLEUS FITTING SOFTWARE produced by Cochlear Ltd. and distributed to clinical audiologists (Botros et al. 2013).

ECAP thresholds correlate well with lower rate behavioural thresholds, but that correlation degrades as rate increases. It is hypothesised that the slope of the lower rate section of a behavioural threshold versus rate graph for a particular electrode is dictated predominantly by neural survival in the tissues surrounding that electrode (Pfingst et al. 2011), however there is at this time no direct measure of neural survival in living CI users. Histological experiments in animals have found the aforementioned correlates of neural survival: the Δlatency, PD and IPG effects (Prado-Guitierrez et al. 2006; Ramekers et al. 2014). We aim to use these effects to predict the low rate slope of behavioural threshold vs rate graphs by correlating measures of these effects directly with the low rate behavioural threshold slope. Further, if these correlations are sufficiently strong, we aim to use these measures in conjunction with ECAP threshold to directly predict higher rate behavioural thresholds using totally objective measures.

Our core hypotheses are that:

1) The per-electrode change in CL required to equalise ECAP amplitude under conditions of changing PD or IPG is able to predict the per-electrode change in T-level as stimulation rate is increased from 40 to 500 pps.

2) The per-electrode change in ECAP N1 peak latency under conditions of changing PD or IPG is able to predict the per-electrode change in T-level as stimulation rate is increased from 40 to 500 pps.
METHODS

Subjects

Fifteen adult cochlear implant users participated in this experiment. All were users of the CI24RE, CI512, or CI422 implants manufactured by Cochlear Ltd., with users of other implant types excluded due to older and less sensitive NRT systems. Type of implant, number of electrodes for which a full dataset was acquired, duration of time since implantation, duration of severe deafness, and aetiology for is shown in Table 1.

Table 1 participants used in this study. Certain subjects, denoted by L (left) and R (right), had bilateral implants. Intracochlear electrodes are numbered 1 to 22, basal to apical. Mean age was 65.6 (range 44 to 81). NA: no electrodes of this participant were used in the analysis.

<table>
<thead>
<tr>
<th>Subject code</th>
<th>Age</th>
<th>Implant type</th>
<th>Electrodes used</th>
<th>Time since implant</th>
<th>Duration of severe deafness</th>
<th>Aetiology</th>
</tr>
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<tr>
<td>CI1</td>
<td>81</td>
<td>CI24RE</td>
<td>5, 8, 13, 17</td>
<td>3 yrs</td>
<td>20 yrs</td>
<td>Noise induced, head injury, progressive</td>
</tr>
<tr>
<td>CI2</td>
<td>70</td>
<td>CI24RE</td>
<td>4, 5, 6, 7, 8, 17</td>
<td>7 yrs</td>
<td>20 yrs</td>
<td>Unknown, progressive</td>
</tr>
<tr>
<td>CI3</td>
<td>74</td>
<td>CI24RE</td>
<td>3, 4, 7, 10, 13, 16, 19, 22</td>
<td>7 yrs</td>
<td>30 yrs</td>
<td>Possible autoimmune, progressive</td>
</tr>
<tr>
<td>CI4</td>
<td>77</td>
<td>CI24RE</td>
<td>22</td>
<td>2.5 yrs</td>
<td>10 yrs</td>
<td>Unknown, progressive</td>
</tr>
<tr>
<td>CI5L</td>
<td>46</td>
<td>CI24RE</td>
<td>NA</td>
<td>7 yrs</td>
<td>35 yrs (prelingual)</td>
<td>Genetic, progressive</td>
</tr>
<tr>
<td>CI5R</td>
<td></td>
<td>CI512</td>
<td>NA</td>
<td>4 yrs</td>
<td>35 yrs (prelingual)</td>
<td>Genetic, progressive</td>
</tr>
<tr>
<td>CI6</td>
<td>77</td>
<td>CI512</td>
<td>5, 7, 10, 13, 16, 19, 22</td>
<td>5 yrs</td>
<td>50 yrs</td>
<td>Unknown, possible noise induced, sudden,</td>
</tr>
<tr>
<td>CI7</td>
<td>70</td>
<td>CI512</td>
<td>NA</td>
<td>6 months</td>
<td>30 yrs</td>
<td>Genetic, progressive</td>
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<tr>
<td>CI8L</td>
<td>79</td>
<td>CI422</td>
<td>NA</td>
<td>3 months</td>
<td>35 yrs</td>
<td>Genetic, progressive</td>
</tr>
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<td></td>
<td>CI24RE</td>
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<td>35 yrs</td>
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</tr>
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<td>5 yrs</td>
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<td></td>
<td>CI512</td>
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<td>2 yrs</td>
<td>5 yrs</td>
<td>Unknown, possible inner ear infections, sudden,</td>
</tr>
<tr>
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<td>47</td>
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<td>NA</td>
<td>5 yrs</td>
<td>25 yrs</td>
<td>Genetic, progressive</td>
</tr>
<tr>
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<td>51 yrs</td>
<td>Unknown, sudden</td>
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<tr>
<td>CI12</td>
<td>72</td>
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<td>3 yrs</td>
<td>10 yrs</td>
<td>Genetic, noise induced, sudden</td>
<td></td>
</tr>
<tr>
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<td>CI24RE</td>
<td>13, 16, 19, 22</td>
<td>6 yrs</td>
<td>11 yrs</td>
<td>Noise induced, inner ear infections, progressive</td>
</tr>
<tr>
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<td>CI422</td>
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<td>1 yr</td>
<td>15 yrs</td>
<td>Unknown, possible genetic, progressive</td>
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<td>2 yrs</td>
<td>3 yrs</td>
<td>Unknown, possible genetic, progressive</td>
</tr>
<tr>
<td>CI15R</td>
<td></td>
<td>CI512</td>
<td>6, 5, 4, 2</td>
<td>4 yrs</td>
<td>9 yrs</td>
<td>Unknown, possible genetic, sudden</td>
</tr>
</tbody>
</table>
Subject numbers were estimated at an earlier stage through an *a priori* power analysis. This is available at http://bit.ly/1QYQlma

The number of independent samples required at an effect size of $R = 0.7$ was estimated to be approximately 13. Inferences of true effect size and significance are best made from analyses performed on real data. We avoid *post hoc* inferences of power (Levine and Ensom 2001).

Participants were invited to take part through contact details supplied by the Royal Victorian Eye and Ear Hospital, East Melbourne, Australia. All participants had consented to their contact details being shared with researchers. Participant maps were acquired from the Royal Victorian Eye and Ear Hospital prior to the start of data collection. Histories were collected verbally from the participant then rectified, where possible, against clinicians’ notes and map details. All procedures were undertaken in a sound treated booth at the Bionics Institute, East Melbourne, Australia. Data collection took two to six sessions per participant, each session of up to two hours length, and participants were offered reimbursement for travel costs. The present study was performed under approval of the Royal Victorian Eye and Ear Hospital’s Human Research Ethics Committee, protocol number 14/1180H. All research was undertaken in strict compliance with the National Statement on Ethical Conduct in Human Research (NHMRC 2007).

**Procedures**

To allow replication of these procedures, a copy of the procedures document referred to during experimental sessions is available at http://bit.ly/1jUFLBH
Electrophysiological measurements

Stimulus parameters

ECAP measurements were obtained for each subject via neural response telemetry through CUSTOM SOUND EP version 4.0 provided by Cochlear Ltd. Per-electrode impedance was checked prior to each session. Shorted electrodes were not used.

ECAP stimuli were cathodic-leading biphasic single pulses. Probe active electrode was set, by default, as intracochlear electrodes 1, 4, 7, 10, 13, 16, 19, or 22, with MP1 as probe indifferent electrode. Recording electrode was 2 electrodes offset from probe active electrode, and recording indifferent electrode was MP2. Electrodes MP1 and MP2 were extracochlear. The standard forward masking procedure of Brown *et al.* (1990) was used to remove artefact, with an MPI of 500 μs and masker pulse set 10 CL above probe pulse. Four PD/IPG probe parameter conditions were used: 1) PD 25 μs IPG 8 μs, 2) PD 40 μs IPG 8 μs, 3) PD 25 μs IPG 40 μs, 4) PD 40 μs IPG 40 μs. NRT recordings were averaged over 50 sweeps with minimum stimulus duration of 500 ms. NRT recordings were made at a 40 pps presentation rate. Amplifier delay was set, by default, to 122 μs, measured from stimulus offset, and amplifier gain was set by default to 60 dB (referenced to input).

Determining usable ECAP range

For each electrode, the CL range from ECAP threshold to maximum comfortable CL was determined for each of the above four PD/IPG conditions. Stimulation was performed through CUSTOM SOUND EP running on a Windows 7 laptop, connected to the volunteer’s receiver-stimulator through a Cochlear Ltd. programming pod and coil. The software’s ‘stimulate only’ function was used, manually increasing the CL while monitoring the participant’s indicated loudness rating. Stimulation for each electrode and condition began well below the expected behavioural threshold, and increased until the researcher identified an ECAP response (approximate ECAP threshold) using the voltage versus time plot recorded and generated by the software. The CL was further increased to a level that the participant identified as ‘very loud’ by pointing to a categorical loudness scale (*Figure 8*). In some cases, stimulation went out of compliance (where the charge required by the stimulus is greater than the implant is able to deliver, indicated by the NRT software) or showed evidence of amplifier saturation (where the NRT recording is contaminated by artefact) prior to achieving maximum comfortable level. Artefact contamination was in some cases reduced by decreasing amplifier gain to 50 dB, or increasing delay to 130 μs. These settings were kept constant for all NRT recordings made under the four PD/IPG conditions within any single electrode.
Figure 8 the loudness category scale used by participants to express their perception of loudness in response to stimuli presented through ImpRess and Custom Sound EP.

Probe active electrodes that did not have a detectable ECAP below the C level under at least one PD/IPG condition were replaced by an adjacent electrode. Where none of a participant’s electrodes had usable ECAPs, that participant was removed from the study (Table 1). In a very small number of cases, participants indicated mild pain, facial muscle twitching, or other uncomfortable sensations at high CLs for particular electrodes, in which case those CLs were not repeated.

Amplitude growth functions
Amplitude growth functions (AGFs; plots of stimulus level (CL) against ECAP N1 to P1 peak amplitude (μV)) were used to make comparisons between the four stimulus conditions for each electrode. AGFs were acquired by programming AGF stimuli series in Custom Sound EP as CSV files. AGF stimuli series were programmed as five or seven CLs equally spaced across the usable ECAP range (from approximate ECAP threshold CL to maximum comfortable CL) for each of the four pulse parameter conditions on each electrode, using settings identical to those detailed in the ’stimulus parameters’ section. While running AGF stimuli series through Custom Sound EP, participants were allowed to read quietly, and were closely monitored for any discomfort. Voltage versus time series data were exported for each NRT recording (Figure 9), with ECAP peaks and amplitudes determined automatically through Custom Sound EP’s AutoNRT-based peak picking software.
Behavioural measures

Behavioural measures were made using the same electrodes as for the electrophysiological measures using ImPResS software. Behavioural thresholds were determined at rates of 40, 500, 1000, and 2000 pps. The stimulation mode was MP1+2. IPG and PD were set to typical speech processor settings of 8 and 25 μs respectively. The stimulus duration was 500 ms.

ImPResS outputs signals of desired parameters via a coil that connects to the CI of the volunteer. ImPResS also interfaces with a response box through a serial connection, allowing the participant to respond to stimuli. Starting well below behavioural threshold for each electrode, CL was increased until the participant indicated a sound perception using Figure 8. This approximate behavioural threshold was used as the starting point for a more accurate threshold finding procedure using an adaptive three-interval-forced-choice (3IFC) task (Dixon and Mood 1948; Wetherill and Levitt 1965; Levitt 1971). This task involved three intervals, two of which were periods of silence, and one, randomly selected, containing a stimulus. A 2 down 1 up algorithm was used, where the participant must get two consecutive answers correct for the CL to decrease, while a single incorrect answer will cause the CL to increase. The CL in this procedure asympotes to the 70.7% correct point on the psychometric function. An initial step size of 5 CL over an initial two turns, followed by a step size of 2 CL over eight subsequent turns, was used. The CLs of the last six turns were averaged. The adaptive 3IFC task was repeated for each of the four rates of stimulation (40, 500, 1000, 2000 pps), for each electrode. Participants were given breaks as required to reduce incidence of mental exhaustion.

Analysis

Behavioural data

The hypotheses of this study are that low rate behavioural threshold changes are predicted by 1) the change in CL required to equalise ECAP amplitude when changing stimulus parameters, and 2) the change in ECAP N1 peak latency when changing stimulus parameters.

Three measures of the low rate behavioural differences were used: 1) The per-electrode change in low rate behavioural threshold, where the electrode’s 40 pps threshold was subtracted from the 500 and 1000 pps thresholds, respectively, to give 40 to 500 and 40 to 1000 pps behavioural threshold differences. 2) The subject-normalised change in low rate behavioural threshold. To calculate this, the per-subject average 40 to 500 and 40 to 1000 pps behavioural threshold changes were determined, then subtracted from the behavioural threshold change for each electrode of that subject. Each electrode is therefore plotted ± the subject’s mean. This removed the effects of inter-subject variability. 3) The subject-mean changes, where the
40 to 500 and 40 to 1000 pps behavioural threshold change was averaged across all electrodes of each participant. This removed the effects of intra-subject variability.

Separately, high rate (1000 to 2000 pps) behavioural threshold differences have been reported to be relatively consistent between individuals (McKay et al. 2013a). To independently test this assumption, the per-electrode mean and standard deviations of the low rate (40 to 500 and 40 to 1000 pps) behavioural threshold changes were compared with those of the high rate (1000 to 2000 pps) behavioural threshold changes.

**Average linear shift to equalise amplitude**

AGFs for each of the four PD/IPG stimulus conditions were plotted in SigmaPlot version 13.0 for each electrode. In calculating the change in CL required to equalise ECAP amplitude between IPG conditions, Ramekers et al. (2014) made comparisons at the 50% level of Boltzmann functions fitted to their AGFs, effectively at the midpoint of the ECAP dynamic range. Our use of conscious human subjects gives limited ability to record at high CLs, preventing a fully characterised AGF and therefore an inability to determine the 50% level. ECAP AGFs are characterised by relatively flat tails at the lowest and highest CLs within the ECAP dynamic range, but have linear sections in the middle of the dynamic range (Figure 10 A). As an alternative to the Ramekers et al. (2014) method, we pruned the non-linear data points and fit a linear regression using SigmaPlot (Figure 10 B). Fixed minimum and maximum ECAP amplitudes within the range of amplitudes of all four conditions in each electrode’s pruned plot were determined. These amplitudes were substituted into the linear model to interpolate what stimulus CLs would be required to evoke ECAPs of those amplitudes for each of the four PD/IPG stimulus conditions. Though Cochlear Ltd. software only accepts integer CLs, for the purposes of these comparisons, linear model interpolated CLs were left with three significant figures.
Figure 9 ECAP of CI12, E16 (electrode 16) recorded with stimulus parameters of PD 25 µs, IPG 8 µs at 231 CL. Original NRT recording (black circles) and spline interpolation (red line). Peak latency is calculated as the time at which the lowest voltage occurred between 200 and 500 µs along the spline interpolated line. ECAP amplitudes were calculated by Custom Sound EP based on the original NRT data points, rather than the spline interpolated data.

Figure 10 A) example of raw amplitude growth functions recovered from the four PD and IPG conditions for CI9, E19. Each point represents the N1 to P1 amplitude of an ECAP, such as that in Figure 9. B) The same amplitude growth function, trimmed of non-linear points, fitted with a linear model (red) per PD/IPG condition, and with a line (black) across equal minimum and maximum amplitudes within the range of the trimmed plots. The black line defines the amplitude that was substituted into the linear model for each amplitude growth function, in order to calculate the CL that evokes the ECAP amplitude of that condition.
CLs at both the minimum and maximum of the shared AGF range within each electrode (Figure 10 B) were subtracted for: the effect of changing both PD and IPG (PD, IPG: 25, 8 – 40, 40 μs); the effect of changing IPG at a PD of 25 μs (25, 8 – 25, 40 μs); the effect of changing IPG at a PD of 40 μs (40, 8 – 40, 40 μs); the effect of changing PD at an IPG of 8 μs (25, 8 – 40, 8 μs); and the effect of changing PD at an IPG of 40 μs (25, 40 – 40, 40 μs). For these five shifts, the subtraction of the maximum and minimum were averaged, creating the ‘average linear shift’. Note that in all cases subtractions were performed in an order that would produce a positive value, i.e., subtracting the less excitatory stimulus from the more excitatory stimulus.

Correlation with low rate behavioural threshold changes were performed for the effect of changing both PD and IPG, the effect of changing IPG at a PD of 25 μs, the effect of changing IPG at a PD of 40 μs, the effect of changing PD at an IPG of 8 μs, and the effect of changing PD at an IPG of 40 μs, however the results presented in the body text of the results section focus on the simultaneous change in PD and IPG. Supplementary material is given in the appendices.

Matching the three measures of behavioural threshold, three average linear shift measures were used: 1) The per-electrode change in CL required to equalise ECAP amplitude. 2) The subject-normalised change in CL required to equalise ECAP amplitude, where the average subject change in CL to equalise ECAP amplitude for each of the five PD/IPG changes was determined, then subtracted from the change in CL required to equalise ECAP amplitude for each of that subject’s electrodes. Each electrode’s shift is ± the subject’s mean shift. 3) The subject-mean change in CL required to equalise ECAP amplitude, where linear shift was averaged across each of the subject’s electrodes, and data were compared on a per-subject basis.

N1 peak latency
We hypothesise that the extent of N1 peak latency change caused by change in stimulus PD and IPG is correlated with neural survival. NRT, which measures N1 peak latency from probe onset, has a sampling resolution of 22 samples per ms. NRT recordings were smoothed through spline interpolation in MATLAB version R2015a (Figure 9), before the application of a custom peak picking script that found the time value corresponding to the minimum amplitude value between 200 and 500 μs. To prevent detection of N1 peak latency from random noise, a latency value was not given when the total amplitude range between 200 and 500 μs was less than 20 μV. All interpolated latency plots were manually inspected, and raw data latencies were substituted for interpolated latencies in a small number of cases where spline interpolation output was spurious.
Measures of average latency shift required comparison of latencies between the AGFs of the four PD/IPG stimulation conditions. Two methods were used.

Method 1
Using the pruned-linear AGF plot, the range of ECAP amplitudes common to all four stimulation conditions was identified. Within this common amplitude range, each stimulation condition's ECAP N1 peak latencies were averaged, giving a single mean latency value for each stimulation condition of each electrode.

Probe CL, as well as PD/IPG of the stimulus, affects ECAP N1 peak latency (see Figure 5). Minimum and maximum ECAP amplitudes within the range of the NRT recordings were not equal between conditions. To remove the confounding influence of probe CLs evoking ECAPs outside the mutual amplitude range of each condition, method 2 was developed to improve latency data for later participants.

Method 2
The improved latency method was used for CI3, CI11, CI12, CI13, and CI15.

The improved latency method removed the effect of probe CL by evoking ECAPs of equal amplitude for each of the four PD/IPG conditions for each electrode. For the amplitude growth functions of each electrode, the minimum, median, and maximum ECAP amplitudes within the range of the four PD/IPG conditions were determined. The CL required to evoke the minimum, median, and maximum amplitude for each condition was interpolated using each condition's respective AGF linear model. Rounded CLs corresponding to minimum, median, and maximum ECAP amplitudes were then programmed into an amplitude growth function series for each of the four conditions, using stimulation conditions identical to those set out in 'stimulation parameters'.

The latency amplitude growth functions generated for each of the four PD/IPG conditions per electrode produced ECAPs of approximately equal amplitude corresponding to minimum, median, and maximum amplitude (Figure 11). Each NRT was smoothed using spline interpolation in MATLAB as described above, then N1 peak latencies corresponding to the minimum, median, and maximum amplitudes the AGF of each PD/IPG condition were averaged to give mean latency per AGF.
Average shift in latency

Regardless of which method was used, the Δlatency effect was quantified as the change in ECAP N1 peak latency with change of both PD and IPG (PD, IPG: 25, 8 – 40, 40 μs); of change of IPG at a PD of 25 μs (25, 8 – 25, 40 μs); of change of IPG at a PD of 40 μs (40, 8 – 40, 40 μs); of change of PD at an IPG of 8 μs (25, 8 – 40, 8 μs); and the effect of changing PD at an IPG of 40 (25, 40 – 40, 40 μs).

As with behavioural data, normalisation was performed by finding the mean latency shift for each of the five linear shifts within each participant. Latency shifts for each electrode were then subtracted from the subject mean linear shift. Normalised latency shift per electrode was plotted ± subject mean.

Finally, the subject-mean latency shift was calculated for each of the five linear shifts, with data compared on a per-subject basis.
ECAP threshold

ECAP thresholds were extrapolated from the linear section of the AGF, where the linear model was solved for the CL where ECAP amplitude equals zero. This technique is similar to that used in earlier extrapolation-based automated NRT software, such as Charasse et al. (2004), but differs substantially from the AutoNRT method of Botros et al. (2007). An AGF extrapolation technique was used because a full AutoNRT dataset was not available for all electrodes. Behavioural thresholds were determined at a PD of 25 μs and IPG of 8 μs. It was therefore ECAP AGFs similarly evoked with PD 25 μs and IPG 8 μs stimuli from which ECAP threshold extrapolation was performed.

Correlations

Pearson correlations were performed in SIGMAPLOT between the 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural differences and each of the five linear shifts for each of 1) per-electrode amplitude data, 2) normalised amplitude data, 3) subject-mean amplitude data, 4) per-electrode N1 peak latency data, 5) normalised N1 peak latency data, and 6) subject-mean N1 peak latency data.

Pearson correlations were also performed between ECAP threshold and the 40, 500, 1000, and 2000 pps behavioural thresholds.

Stepwise regression

Stepwise regression was performed in MINITAB version 17, where the 40, 500, 1000, and 2000 pps behavioural thresholds were predicted with, in the initial step, ECAP threshold, and in the second step, the change in CL required to equalise ECAP amplitude when changing stimulus parameters from PD 40 IPG 40 μs to PD 25 IPG 8 μs.
RESULTS

ECAP presence

Most participants had ECAP thresholds below C for each of the four stimulation conditions on at least some of the sampled electrodes (Table 2). CI5, CI7, CI8, and CI15L had no ECAPs below C for any surveyed electrode. Electrodes were not randomly sampled; more electrodes tended to be sampled for subjects without detectable ECAPs. The following results are from subjects for whom ECAPs were measurable for each of the PD/IPG stimulation conditions.

Table 2 amount of electrodes with or without detectable ECAPs below C for any of the four PD/IPG stimulation conditions, per participant.

<table>
<thead>
<tr>
<th>Numbers of Electrodes</th>
<th>With ECAPs</th>
<th>Without ECAPs</th>
<th>Total tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI1</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>CI2</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>CI3</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>CI4</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>CI5L</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>CI5R</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>CI6</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>CI7</td>
<td>0</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>CI8L</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>CI8R</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>CI9L</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>CI9R</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>CI10</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>CI11</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>CI12</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>CI13</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>CI14</td>
<td>1</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>CI15L</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>CI15R</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>74 (48%)</td>
<td>79 (52%)</td>
<td>153</td>
</tr>
</tbody>
</table>

NRT traces under two PD/IPG conditions for one electrode of one participant are shown in Figure 12. ECAP amplitude increased with increasing CL of the stimulus. Amplitude growth functions under all four stimulus PD/IPG conditions for one electrode of one participant are shown in Figure 13.
Figure 12 NRT recordings of CI12, E16 at PD 25 μs IPG 8 μs (left), and PD 40 μs IPG 40 μs (right), annotated with CL of the stimulus. Black circles: raw data points, red lines: spline interpolation of the raw data. ECAP amplitudes of the two PD/IPG conditions are roughly similar, but are evoked by a much lower CL in the longer PD/IPG condition.

Figure 13 Amplitude growth functions for CI9, E13, for four different stimulus conditions. Linear models based on the linear sections of the amplitude growth functions are shown in red.
Behavioural threshold changes

Previous reports have showed that behavioural thresholds change with rate of stimulation. The unpredictability of this change leads to poor estimations of higher rate behavioural thresholds. Per-subject average thresholds for the ten included subjects are shown in Figure 14, with a wide spread in both mean absolute threshold and mean threshold change with increase in stimulation rate.

Figure 14 each participant’s average behavioural threshold at rates of stimulation of 40, 500, 1000, and 2000 pps. X-axis scale is logarithmic. Averages are calculated from all of each participant’s surveyed electrodes, as shown in Table 2.

We hypothesise the low rate (40 to 1000 pps) section of the behavioural threshold difference to be explainable by ECAP-based correlates of neural survival, and that the higher rate (>1000 pps) section is relatively constant amongst CI users. The 40 to 500 and 40 to 1000 pps behavioural threshold differences had standard deviations of 10.83 and 14.09 CL, respectively, while the high rate 1000 to 2000 pps behavioural threshold difference had a standard deviation of 7.76 (Table 3). A histogram of the distribution of high rate differences shows that, despite a smaller standard deviation, there is still a large spread, and that assumptions about high rate behavioural threshold change would be invalid for at least some electrodes of some users (Figure 15). Mean and standard deviations of behavioural threshold changes are given for each participant in Appendix 1, Table 12.
Table 3 mean and standard deviation for changes in CL between behavioural thresholds at different rates of stimulation.

<table>
<thead>
<tr>
<th>Rate</th>
<th>Mean (CL)</th>
<th>Standard Deviation (CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 500 pps</td>
<td>12.720</td>
<td>10.833</td>
</tr>
<tr>
<td>40 to 1000 pps</td>
<td>23.482</td>
<td>16.945</td>
</tr>
<tr>
<td>1000 to 2000 pps</td>
<td>14.093</td>
<td>7.763</td>
</tr>
</tbody>
</table>

Figure 15 histogram of the 1000 to 2000 pps behavioural threshold change for each electrode sampled, in 3 CL bins.

**ECAP threshold and behavioural threshold correlations**

ECAP thresholds are the traditional objective predictor of behavioural thresholds. ECAP threshold was well correlated with the 40 pps threshold, but this correlation degraded as rate of stimulation increased, with minimal predictive ability of the 2000 pps behavioural threshold (Table 4; Figure 16). A significance level of $P < 0.05$ is used throughout, without adjustment for multiple comparisons, following the philosophical arguments of Rothman (1990).

Table 4 correlation between the amplitude growth function linear ECAP threshold and 40, 500, 1000, and 2000 pps behavioural thresholds.

<table>
<thead>
<tr>
<th></th>
<th>40 pps threshold</th>
<th>500 pps threshold</th>
<th>1000 pps threshold</th>
<th>2000 pps threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R$</td>
<td>$P$</td>
<td>$R$</td>
<td>$P$</td>
</tr>
<tr>
<td>ECAP T</td>
<td>0.572</td>
<td>&lt;0.001</td>
<td>0.455</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
PD and IPG amplitude effects

One of the key hypotheses of this study is that the CL change required to equalise ECAP amplitude when ECAP stimulus PD or IPG is changed, is correlated with the change in behavioural threshold CL when rate of stimulation is increased from 40 to 500 or 1000 pps. Three approaches to these correlations were taken: 1) all subject correlation, of every electrode of every participant; 2) normalised correlations, where the subject mean is subtracted from the data of each electrode, removing inter-subject variability; and 3) subject mean correlations, where data of all electrodes of each subject are averaged and plotted against each other, removing intra-subject variability.

All subject correlations

The CL required to equalise ECAP amplitude when changing IPG and PD has a moderate correlation with the 40 to 500 and 40 to 1000 pps differences, but an insignificant correlation with the 1000 to 2000 pps difference (n = 52) (Table 5), which is consistent with our hypothesis. The relationship between the 40 to 500 pps behavioural threshold change and the simultaneous change in PD and IPG is shown in Figure 17, with graphs for separate PD and IPG changes shown in Appendix 1, Figure 25 and Figure 26.
Table 5 correlations between the CL change required to equalise ECAP amplitude when changing IPG and PD, and the 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences. The ‘all effect’ consists of changes from PD 25, IPG 8 to PD 40, IPG 40 μs.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>0.411</td>
<td>0.002</td>
<td>0.423</td>
</tr>
<tr>
<td>IPG effect at PD 25 μs</td>
<td>0.399</td>
<td>0.003</td>
<td>0.439</td>
</tr>
<tr>
<td>IPG effect at PD 40 μs</td>
<td>0.322</td>
<td>0.02</td>
<td>0.304</td>
</tr>
<tr>
<td>PD effect at IPG 8 μs</td>
<td>0.436</td>
<td>0.001</td>
<td>0.469</td>
</tr>
<tr>
<td>PD effect at IPG 40 μs</td>
<td>0.352</td>
<td>0.011</td>
<td>0.315</td>
</tr>
</tbody>
</table>

The cause of the correlations between changing both low rate threshold changes and IPG, and low rate threshold changes and PD, may have separate neurophysiological underpinnings, however, as proxies for neural health, both effects are correlated with each other. As it is changing both PD and IPG (from PD 25, IPG 8 to PD 40, IPG 40 μs) that causes the biggest equalising CL change, and hence may potentially reduce the effects of random error, from here onwards it is only this combined ‘all effect’ that will be presented in the body text. More detailed correlations are provided in Appendix 1, but show patterns generally consistent with that of the ‘all effect’.
Figure 17 change in CL required to equalise ECAP amplitude when changing stimulus (from PD 25, IPG 8 μs to PD 40, IPG 40 μs) against the 40 to 500 pps behavioural threshold difference.

Normalised correlations
Normalised changes in CL required to equalise ECAP amplitude between PD and IPG conditions, and normalised lower rate behavioural threshold changes showed no significant correlation \((n = 51)\) (Table 6; Figure 18). CI4 was excluded from the normalised analysis due to an insufficient number of electrodes.

Correlations for each IPG and PD condition are given in Appendix 1, Table 13.

Table 6 correlations between the normalised CL change required to equalise ECAP amplitude when changing both IPG and PD, and the normalised 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(R)</td>
<td>(P)</td>
<td>(R)</td>
</tr>
<tr>
<td>All effect</td>
<td>-0.036</td>
<td>0.804</td>
<td>-0.048</td>
</tr>
</tbody>
</table>
Subject mean changes in CL required to equalise ECAP amplitude between PD and IPG conditions, and lower rate behavioural threshold changes, were highly correlated (n = 10) (Table 7; Figure 19). Though these correlations were not significant, this may be attributable to the small sample size rather than a lack of real effect. The correlation with the 1000 to 2000 pps behavioural threshold change was far weaker than those of the lower rate changes. Correlations for each IPG and PD condition are given in Appendix 1, Table 14.

Table 7 correlations between the per subject mean CL change required to equalise ECAP amplitude when changing both IPG and PD, and the per subject mean 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>p</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>0.589</td>
<td>0.073</td>
<td>0.533</td>
</tr>
</tbody>
</table>
Latency effects

The second ECAP-based measure that this study hypothesised would correlate with low rate changes in behavioural threshold is the change in ECAP N1 peak latency caused by change in PD and IPG of the stimulus. As with the IPG/PD effects, three approaches to this correlation were taken: 1) all subject correlation, of every electrode of every participant; 2) normalised correlations, where the subject mean is subtracted from the data for each electrode, removing inter-subject variability; and 3) subject mean correlations, where all electrodes of each subject are averaged and plotted against each other, removing intra-subject variability.

All subject correlations

Correlations between each electrode’s N1 peak latency change and behavioural difference were not significant \( (n = 52) \) (Table 8; Figure 20). This is did not support our hypothesis. Correlations for each IPG and PD condition are given in Appendix 1, Table 15. Correlations were also performed for changes in latency at the highest CLs of the amplitude growth functions within the range of all four conditions, which are similarly insignificant (Appendix 1, Table 16).
Table 8 correlations between the change in ECAP N1 peak amplitude when changing both IPG and PD, and the 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 - 500 pps change</th>
<th>40 - 1000 pps change</th>
<th>1000 - 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>-0.038</td>
<td>0.788</td>
<td>-0.149</td>
</tr>
</tbody>
</table>

Figure 20 change in ECAP N1 peak amplitude when changing stimulus (from PD 25, IPG 8 μs to PD 40, IPG 40 μs) against the 40 to 500 pps behavioural threshold difference.

The distribution of ECAP N1 peak latency changes is shown in Figure 21. The increase in IPG or PD caused an increase in the N1 peak latency for every sample. A one-way ANOVA found a significant difference between group means ($P = 0.001$) (Appendix 2, Table 20). A post-hoc Tukey’s HSD test was performed to find significantly different means, which is shown graphically in Figure 21. Confidence intervals of the means are presented in Appendix 2, Table 22.
Figure 21 median boxplots of N1 peak latency changes with an increase in PD or IPG (N = 52 per condition). Error bars show the 10th and 90th percentiles. Group means that do not share a letter (A, B, C) are significantly different.

Normalised correlations
Intra-subject latency and behavioural threshold normalisation (n = 51) showed no significant correlation (Table 9). CI4 was excluded from the normalisation analysis due to an insufficient number of electrodes. Correlations for each IPG and PD condition are given in Appendix 1, Table 17.

Table 9 correlations between the normalised change in ECAP N1 peak amplitude when changing both IPG and PD, and the 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>0.06</td>
<td>0.677</td>
<td>-0.074</td>
</tr>
</tbody>
</table>
Figure 22 normalised change in ECAP N1 peak amplitude when changing stimulus (from PD 25, IPG 8 μs to PD 40, IPG 40 μs) against the normalised 40 to 500 pps behavioural threshold difference.

Subject mean correlations

The relationship between subject mean latency and mean behavioural threshold is not significant (n = 10) (Table 10). Correlations for each IPG and PD condition are given in Appendix 1, Table 18.

Table 10 correlations between the per subject mean change in ECAP N1 peak amplitude when changing both IPG and PD, and the per subject mean 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>0.209</td>
<td>0.562</td>
<td>0.143</td>
</tr>
</tbody>
</table>
Stepwise regression to estimate 1000 pps thresholds

There was robust correlation between ECAP threshold and 40 pps behavioural threshold, and separately the CL change required to equalise ECAP amplitude between changing PD and IPG conditions and the 40 to 1000 pps behavioural threshold difference. There is no correlation between these two predictors (Appendix 2, Table 19). Stepwise regression was performed, predicting the 40, 500, 1000, and 2000 pps behavioural thresholds using ECAP threshold and the PD/IPG effect as predictors (Table 11). Adding the effect of changing PD and IPG as a term to the model always improved the prediction above ECAP threshold alone.
The multiple regression equation (Eq. 1) describes the predictive relationship between the variables for the 1000 pps behavioural threshold, where $T$ is the ECAP threshold and $A$ is the PD and IPG effect.

$$1000 \text{ pps} = 67.7 + 0.924 \times T - 3.122 \times A$$  \hspace{1cm} (Eq. 1)

Mallows’ Cp is low, suggesting that overfitting has not occurred. The $R^2$ value of the model is greatly improved by the addition of the PD and IPG effect term, and both steps are significant. The standard error of the regression ($S$) is high. Predicted versus actual fits are shown in Figure 24, demonstrating the low precision of the stepwise model.

Multiple regression equations are also given for the 40, 500, and 2000 pps thresholds (Appendix 2, Eq. 2, 3, 4).
High rate threshold change variability

In previous literature (Kang et al. 2010; Pfingst et al. 2011; McKay et al. 2013a), low rate (<1000 pps) behavioural threshold changes have been found to be highly variable and driven by neural survival, whereas higher rate (>1000 pps) behavioural threshold changes have been found to be consistent amongst subjects. Much of this previous work, with the exception of McKay et al. (2013a), has been performed in animal models. Our data does find that higher rate behavioural threshold changes have slightly smaller variability than lower rate changes (1000 to 2000 pps SD = 7.76 CL; 40 to 500 pps SD = 10.83 CL) (Table 3). However, a histogram of high rate behavioural differences of all electrodes shows a wide distribution (Figure 15). If, for example, an electrode’s 1000 pps behavioural threshold is known and the 2000 pps is to be estimated, these data predict a 14 CL threshold change on average. For some electrodes, this would over- or under-estimate the true threshold change by about 14 CL. If the higher rate threshold change was estimated in a population where the 1000 pps threshold itself was estimated, the compounding error might produce very inaccurate threshold predictions.

The consistent changes between individuals at high, but not low, pulse rates is hypothesised by Middlebrooks (2004) to be caused by the small amount of time between stimulus pulses being insufficient for neurons to recover from depolarisation. After a neuron depolarises to fire an action potential, active and passive processes work with the insulating effect of the myelin sheath to repolarise the cell to its resting membrane potential. At high pulse rates, the timing of the pulses is thought to prevent significant influence of these active and passive repolarisation processes to occur. Neural health factors such as degree of myelination, therefore, are unable to affect multi-pulse integration at high rates of stimulation (Middlebrooks 2004), so similar high rate behavioural threshold changes are seen regardless of neural health factors. Our results strongly suggest that this explanation is not universally applicable.

Our results showed a large degree of both inter- and intra-subject variability in high rate behavioural threshold change variability (Appendix 1, Table 12). Intra-subject variability suggests that changes along the electrode array do influence high rate behavioural threshold differences; however it is not known what these changes may be. One possibility is that in a profoundly degenerated cochlea, all neurons that can be recruited by the electrode at this current have been recruited and are all firing action potentials at the highest rate they are capable of, meaning that there is no further increase in neural activity, and hence no further decrease in threshold, after rate increases beyond a certain point. Supporting this, Shepherd and Javel (1997)
found that neurons in cats with poorer cochlear health had a lower maximum firing rate. Another possibility is that the increase in rate caused a reduction in skin depth of the alternating current (sensu Hayt 1981).

**PD and IPG amplitude effects**

The all-electrode IPG and PD amplitude effects correlated moderately well with the 40 to 500 pps (R = 0.411) and 40 to 1000 pps (R = 0.423) behavioural threshold differences, but had no significant correlation with the 1000 to 2000 pps behavioural threshold difference. This is consistent with our hypothesis that the change in CL required to elicit ECAPs of equal amplitude while changing PD and IPG is correlated with behavioural threshold changes in the 40 to 1000 pps region, but not within the 1000 to 2000 pps region. This also supports the implicit hypothesis that each of these factors are themselves correlated with, and dependent on, cochlear neural survival. These correlations suggest that the IPG and PD effects are usable in making better estimates of higher rate behavioural thresholds.

The all-electrode correlation, however, conflates inter- and intra-subject variation. To remove the influence of inter-subject variation, the normalisation procedure following Bierer et al. (2015) was used. Inter-subject variation could, for example, be driven by differences in cochlear physiology or aetiology that affect charge integration, or other baseline differences that can cause offsets to measures along the entire electrode array. Normalisation relies on the assumption that there is a large degree of intra-subject variation. The pattern of pathology along the length of the cochlea in a deaf CI-implanted ear is not uniform (Hinojosa and Marion 1983) and there is some evidence that this has functional relevance (Khan et al. 2005).

We found no significant correlations for normalised PD/IPG effect data (Table 6). The most likely reason for this is that the assumption of there being a large extent of intra-subject variation is invalid for this group of participants. If all electrodes within one participant, for example, represent very poor neural health, whilst all electrodes of another participant represent very good neural health, the normalisation procedure of subtracting each electrode from the subject mean will cause the data for different electrodes to have very similar values. Another contributing factor may have been that for many participants only a small number of electrodes were sampled. In such cases, even if there is substantial variation along the electrode array, the sample may not reflect the full range of variation.

The direct comparison of subject means, in contrast, removes intra-subject variability and considers only inter-subject variability. This increased correlation strength (Table 14) when compared with the all-electrode correlations. Despite an increase in correlation strength, the P-values were not significant, with the exceptions of the IPG effect at PD 40 μs and the PD effect at IPG 8 μs, with the 40 to 500 pps behavioural
threshold change. Because of the large number of correlations made, it cannot be inferred from Table 14 that correlations for these two conditions in particular represent a real effect. However, it is remarkable that correlations and \( P \)-values are comparatively higher for the 40 to 500 pps correlation than for the 40 to 1000 pps correlation, and that these are both much higher than those for the 1000 to 2000 pps correlation, which is a trend consistent with the hypothesis. The process of comparing per-subject means reduced sample size, as the 52 sampled electrodes were averaged across the respective ten participants. This low sample size may be the cause of the high \( P \)-values.

If the subject mean correlations do represent a real effect that is stronger than the per-electrode correlation, it must also be considered whether such a correlation has increased clinical utility over predictions made per electrode. That is, whether predicting the subject’s mean low rate behavioural threshold change to a high degree of accuracy is more useful than predicting the subject’s per electrode low rate behavioural threshold change to moderate accuracy. If this system were used, it is possible that predicted behavioural threshold changes for a CI user with large variation in neural survival along their array would be very inaccurate for some electrodes.

A similar study to our ‘all-electrode’ IPG correlations was performed by McKay et al. (2005), which failed to find a significant correlation between the change in CL required to equalise ECAP amplitude between NRT stimulation conditions of IPG 8 and 45 μs and the difference between ECAP threshold and the 900 pps behavioural threshold. Our findings contrast with these earlier findings, which may be explained by key differences in methodology. The former study 1) used 26 electrodes of 8 participants, a size of limited statistical power and perhaps not representative of a wide range of cochlear health, whereas in our study, the high variability of 40 to 1000 pps behavioural threshold changes suggests that participants and electrodes can be inferred to have a large spread in neural survival; 2) used the CL offset between ECAP threshold and the 900 pps behavioural threshold, whereas our study directly measured 40 pps to 500 and 1000 pps behavioural threshold differences; 3) used subjective measures of NRT threshold (researcher inspection of the NRT waveform) and behavioural threshold (clinic-equivalent methods, rather than an adaptive procedure averaged over turnpoints); 4) found CL change required to equalise ECAP amplitude near ECAP threshold, where a smaller proportion of neural units fire, rather than at ECAP amplitudes nearer the middle of the ECAP dynamic range.

Considering the all-electrode correlations, there were higher correlations for the 40 to 500 pps behavioural threshold change with the change in IPG at a PD of 25 μs (\( R = 0.399 \)) than at PD of 40 μs (\( R = 0.322 \)) (Table 5).
Similarly, with change in PD, there were higher correlations for the change in PD at IPG 8 μs (R = 0.469) than at IPG 40 μs (R = 0.352). A similar pattern of higher correlations where the static parameters were smaller was seen for the 40 to 1000 pps correlations. One explanation for this is that where the static parameter was smaller, the change in the variable parameter was a larger proportion of the total stimulus. There is indeed an interaction effect; the magnitude, but not standard deviation, of the change in CL required to equalise ECAP amplitude with change in PD or IPG is larger when the static parameter was smaller (Figure 25, Figure 26).

The only comparable procedure presented in the literature (Figure 7 I, J, Ramekers et al. 2014) found similar results for effect size and spread but reported no increase in correlation strength (a similar correlation was performed by Prado-Guitierrez et al. (2006) but at PDs >100 μs and without presenting detailed data that would allow comparison of results gathered at the longer and shorter PD). More likely, in this case, is that the higher correlations at lower fixed parameters are driven by the extreme value apparent in Figure 25 C) and Figure 26 C). There were therefore no convincing differences between correlations performed between the different PD and IPG conditions, even though the four conditions may 1) relate to slightly different aspects of neural health, and 2) operate at different ratios of the total stimulus, where the equalising CL is of a greater average magnitude with a smaller fixed parameter. It is possible that differences between these conditions would be quantifiable in a study with greater statistical power.

\textbf{ΔLatency effects}

Correlations between behavioural threshold changes and the Δlatency effect were not significant under any of the conditions. Our hypothesis is therefore not supported. If lower rate behavioural threshold changes are dictated by neural survival, as shown by Pfingst et al. (2011) and implied by the significant correlations found for the PD and IPG effect in our data, then this suggests that, in our study, ECAP N1 peak latency changes with change in PD and IPG are not themselves affected by neural survival. This finding contrasts with Ramekers et al. (2014), who histologically found an association between the extent of change in ECAP N1 peak latency with change in stimulus IPG and PD, and neural survival. There are several possible reasons for these conflicting results. First, Ramekers et al. (2014) used a guinea pig model. Guinea pig and human cochleae differ physiologically (Figure 3, Fernández 1952), so phenomena may not always be generalizable.

Second, Ramekers et al. (2014) averaged latency measurements of ECAPs evoked by stimuli at the three highest amounts of charge, which were near-saturation and explained the upper limit of the ECAP dynamic range. The equivalent CLs in humans would generally produce an extremely loud perception of sound and could not be used in a conscious human participant. Our alternative to the Ramekers et al. (2014) latency procedure was to find the average N1 peak latency of the linear section of the amplitude growth function.
within the amplitude range of the functions common to all four stimulation conditions. It may be that latency changes with change in IPG and PD at higher CLs, where a larger proportion of neurons are recruited, does correlate with cochlear health, whereas at lower CLs this correlation is reduced. Indeed, \( \Delta \) latency effect correlations were found by Ramekers \( \textit{et al.} \) (2014) to become insignificant as stimulus charge was reduced. To partially counter this, we also performed correlations for N1 peak latency changes at the highest CL within the common amplitude range of the amplitude growth functions of the four conditions for each electrode (Table 16). As with the data averaged over the CL range, none were significant, though even the highest CLs used to collect these data did not approach the region of the ECAP dynamic range used by Ramekers \( \textit{et al.} \) (2014). Subtraction of change in latency with change in PD/IPG at the lowest common amplitude, from change in latency with change in PD/IPG at the highest common amplitude, revealed differences of around 5 \( \mu \text{s} \) (Table 21). This implies that the absolute latency change with change in PD or IPG is the same regardless of where in the range of our measured AGFs the latency change is calculated from.

Third, Ramekers \( \textit{et al.} \) (2014) used an external recording electrode, whereas the present study accepted the limitations of the cochlear implant’s internal hardware. NRT recordings had a sampling rate of approximately 22 samples per ms (Figure 9). This sampling rate may be inadequate to capture ECAP N1 peak changes at the temporal resolution required, so spline interpolation was applied to NRT recordings prior to latency processing. The random error in over and under predicting actual N1 peaks may have partially obfuscated any real \( \Delta \) latency effect. Similar to the PD and IPG effects, Ramekers \( \textit{et al.} \) (2014) found a greater effect size with wider range when changing IPG, where PD was set to 20 \( \mu \text{s} \) (80 \( \mu \text{s} \) range), than when PD was set to 50 \( \mu \text{s} \) (40 \( \mu \text{s} \) range). However this is not reflected in our data (Figure 21), despite such range differences being of an order that the 48 \( \mu \text{s} \) NRT sampling period should be capable of detecting.

Fourth, Ramekers \( \textit{et al.} \) (2014) explains the \( \Delta \) latency effect as likely being due to neural degeneration causing a shift in excitatory preference from cathodic-first to cathodic-second stimuli, where for the latter an increase in IPG will cause a proportional delay in the N1 peak due to ECAP N1 peak latency being measured from stimulus onset. The present study used all cathodic-first stimuli. In contrast, Ramekers \( \textit{et al.} \) (2014) used an alternating-polarity artefact isolation technique where both cathodic-first and anodic-first stimuli were used to isolate the ECAP response.

In the present study, for both PD-fixed conditions where the IPG was changed from 8 to 40 \( \mu \text{s} \), the average increase in N1 peak latency was approximately 37 \( \mu \text{s} \) (Appendix 2, Table 22). In both IPG-fixed conditions where the PD was changed from 25 to 40 \( \mu \text{s} \), the average increase in N1 peak latency was approximately 31 \( \mu \text{s} \).
Ramekers et al. (2014) recorded change in N1 peak latency with change in IPG from 2.1 to 30 μs at PDs of both 20 and 50 μs. The range of the latency changes was much wider for the fixed PD 20 μs samples than for the fixed PD 50 μs samples (Figure 7 K, L, Ramekers et al. 2014). As previously mentioned, this effect is not mirrored in our own data, with no significant difference in mean and no appreciable difference in range between the 25 and 40 μs PD-fixed samples (Figure 21). This lack of a difference between N1 peak latency changes for the change in IPG at fixed PDs of 20 and 40 μs is a significant point of difference between the two studies. Furthermore, Ramekers et al. (2014) found that when increasing IPG from 2.1 to 30 μs (PD fixed at 20 μs) guinea pigs with high SGN packing densities had N1 peak latency changes of between -40 and 0 μs, whilst animals with lower SGN packing densities had latency changes of between 0 and +35 μs, illustrating a supposed shift from the cathodic to anodic phase being excitatory. Data from electrodes in the present study showed changes in N1 peak latency consistently greater than 0 μs. This difference between the two studies may imply a lack of effect related to differing neurophysiological responses to changed stimulation parameters. Alternatively, the use of both cathodic-first and anodic-first stimuli, through alternating polarity artefact isolation, may have contributed to these results. Indeed, Ramekers et al. (2014) puts forth the possibility that a 20 μs PD cathodic-leading phase separated from the balancing anodic-second phase by a 2.1 μs IPG is insufficient to allow spiking of NH cathodic-excitable neurons, and so negative change in N1 peak latency for NH neurons is a function of the IPG increase causing NH neurons to shift from spiking predominantly in response to the cathodic phase of anodic-leading pulses, to instead spike predominantly in response to the cathodic phase of the cathodic-leading pulses. This explanation would only apply under an alternating polarity system, so may explain why negative changes in N1 peak latency were not detected under our forward masking artefact isolation.

In a heterogeneous population of cat neurons, Shepherd and Javel (1999) found that each neuron had a preference for either excitatory anodic, or cathodic, stimulation. When stimulating a single neuron with a pulse in which the second phase is excitatory, the N1 peak latency change is approximately equal to IPG change. Conversely, if it is the first phase that is excitatory, then an increase in IPG would not increase N1 peak latency. In the present study, for a change in IPG from 8 to 40 μs (at PD 40 μs), 90% of the data fall between 22 and 47 μs (Figure 21). An ECAP can loosely be interpreted to be a conflation of both the total number of neurons firing in response to the stimulus, and the probability of each neuron firing in response to that stimulus along a time axis. Therefore, one interpretation of the positive and narrow range of ECAP N1 peak latency changes with change in IPG at PD 40 μs, is that for most, or all, neurons excited by a particular electrode, is that it was the second (anodic) phase of the stimulus that was excitatory. Supporting this is the
findings of Macherey et al. (2008) and Macherey et al. (2006), who found strong evidence that, in contrast with most animal models, human SGNs tend to find the anodic phase excitatory. If it were the first (cathodic) phase that had been excitatory for the majority of neurons for some electrodes, the increase in IPG would not have caused a lengthening of N1 peak latency for those electrodes.

A weaker correlation was also found by Ramekers et al. (2014) between degree of neural survival and absolute ECAP N1 peak latency, where, for example, with both PD and IPG both fixed at 30 μs, guinea pigs inferred to have a high degree of neural survival had an average ECAP N1 peak latency of about 390 μs, whereas guinea pigs inferred to have a lower degree of neural survival had an average ECAP N1 peak latency of about 305 μs. This was not a direct hypothesis of the present study, however we did not find any significant correlation between absolute N1 ECAP threshold and low rate behavioural threshold change per electrode (data not shown).

**Stepwise regression model**

Stepwise regression showed that adding the IPG and PD effect as a term significantly increased the predictive power of the ECAP threshold in estimating the 1000 pps behavioural threshold. There is a significant and moderate correlation between the two predictors and the actual 1000 pps threshold. This model is superior to a purely ECAP threshold-based objective fitting model. Clinically, ECAP threshold profile based fitting combined with at least one behavioural measure is used to create initial maps for infants (Brown et al. 2000), which is a procedure known to be sub-optimal (Smoorenburg et al. 2002; Gordon et al. 2004).

The standard error of the estimate for the stepwise regression model predicting the 1000 pps threshold is high (S = 23.487 CL), which suggests that predicted thresholds are, on average, quite far from actual thresholds (Figure 24). Despite this, the S value is smaller than that for the ECAP-alone estimate of the 1000 pps threshold (26.236). It should also be considered that in the present study, ECAP thresholds were extrapolated from the amplitude growth function. One of the key problems with the extrapolated AGF method (van Dijk et al. 2003; Charasse et al. 2004; Litvak and Emadi 2005) is that the extrapolated threshold is dependent on which part of the ECAP AGF curve is sampled. In most clinical applications today, visual ECAP detection systems are used, where ECAP linearity is not a confounding influence (Botros et al. 2007). Because of a lack of an entire AutoNRT dataset, we used an AGF extrapolation technique, however with the benefit that AGF linearity was established and largely similar between the four PD and IPG conditions. This consistently overestimated true ECAP thresholds, and would have suffered random error due to differences in ECAP AGF lower CL tails. Indeed, our correlations between ECAP threshold and behavioural thresholds (Table
are much lower than those reported in the literature (Brown et al. 2000; Franck and Norton 2001). Whilst the model’s S value is high, it is only slightly higher than that of the ECAP threshold correlation.

Limitations and improvements

In the present study, the IPG and PD effects were combined in creating the stepwise regression model. The two effects are highly correlated with each other as both are being used as electrophysiological correlates of neural health. However, increasing IPG does not increase total charge delivery to the cochlea; it merely gives a longer period after the first phase in which neurons are able to fire before the balancing second phase (van den Honert and Mortimer 1979; Shepherd and Javel 1999). The IPG effect may, for example, be driven by a healthy cochlea having a higher density of neurons near spike threshold. In contrast, an explanation for the PD effect is partial demyelination of an unhealthy cochlea causing poorer charge integration when PD is increased. These two explanations are clearly strongly related to cochlear health, but ultimately have different drivers. Whereas Prado-Guitierrez et al. (2006) performed correlations between change in CL required to equalise ECAP amplitude with change in IPG, with SGN packing density, Ramekers et al. (2014) added perikaryal area as a measure of neural health. The two measures were found to be strongly related to each other, but with substantial variation, particularly in subjects with significantly degraded cochleae. The mechanisms behind these two measures of cochlea health appear to be somewhat different (Richardson et al. 2005; Agterberg et al. 2009; van Loon et al. 2013). Importantly, these two measures have different impacts on the electrical properties of the system, where SGN soma size is correlated with membrane capacitance (Loeb et al. 1983; Limón et al. 2005), and packing density can influence current flow. Despite correlation between the PD and IPG effects, it may therefore be useful to use variables as separate terms in a multiple regression model for predicting high behavioural rate thresholds. One route through which this could be achieved is through the fitting of a partial least squares regression (Wold 1985), which is highly tolerant of co-linearity amongst predictors.

In proposing a clinically useful model of objective ECAP and stapedius reflex-based CI fitting, Gordon et al. (2004) separated the basal (1 to 15) and apical (16 to 22) electrodes and used different ‘clinical correction factor’ offsets of ECAP threshold to estimate behavioural threshold. In effect, he created a different ECAP threshold based model for predicting apical and basal behavioural thresholds. Regions of the cochlea may be correlated between individuals, for example due to consistently different neurophysiology of the apical and basal regions, or because the neurons activated by basal electrodes code for a perception of higher pitch sound, and that it is these neurons that tend to degrade first in many cases of deafness. It has also been reported that CI users generally prefer to set the loudness on basal electrodes at relatively lower CLs (Kwon
and van den Honert 2006), possibly because higher pitched percepts generated at the basal end of the cochlea can be less comfortable at equal loudness than lower pitched percepts produced at the apical cochlea, though this issue may only be present at higher CLs. If cochlear regions are correlated between subjects, it may be beneficial to create separate multiple regression models for particular electrode regions.

Data gathered from multiple electrodes across an array can be assumed to be correlated, proportional to distance offset along the array. Statistical analyses performed on all-electrode data make the potentially invalid assumption that each sample is independent. At its worst, it could be seen that each truly independent sample (each subject) is being weighted by the number of observations made on that subject (the amount of electrodes sampled from that subject), causing misleading correlation outputs. This may be somewhat corrected by normalisation and subject-mean procedures described in the methods and results sections. One way to avoid this problem could be to create a stricter electrode sampling protocol, whereby only electrodes that are offset by a certain amount of places from one another may be included in an analysis. In the present study, use of directly adjacent electrodes was avoided where possible, but due to the limits of practicality were used in several participants (Table 1).

This study leveraged the ability of modern CIs to intracochlearly record electrical potentials in response to stimulation from an adjacent electrode of the same array. NRT has a sampling rate of approximately 22 samples per ms. This sampling resolution is set to a hardware limitation in the analogue to digital converter within the implanted CI. Double resolution mode, as discussed by Abbas et al. (1999) and used with the CI22M series implants, increases the effective sampling rate by presenting the same stimulus twice, but recording the response at time points offset by half the period of the sampling rate by manipulating the amplifier delay. This feature was explored, but not ultimately used, by the present study because of a consistent apparent shift in the voltage of one of the two interleaved responses (Appendix 2, Figure 27). A similar jagged effect of interleaved sampling has been reported when amplifier delay is set to less than about 99 µs (delay is measured from probe offset), speculated to be caused by amplifier artefact saturation of the earlier, but not later, recording of the response (Abbas et al. 1999). This is likely to have been the cause of the jaggedness in most of our higher resolution recordings, despite that our amplifier delay was set to a slightly higher 122 µs. It is therefore suggested that high resolution sampling, which has hitherto not often been used in the cochlear implant literature (with some exceptions, e.g. Lai et al. (2002) and Cafarelli-Dees et al. (2005) on the CI24M platform), is further explored, coupled with a longer amplifier delay setting than that used in the present study. This may not be suitable for certain electrodes and stimulus parameters as greater delay can cut off the N1 peak. We did, however, observe that the jagged effect decreases as a ratio of total ECAP
As CL increases, suggesting that jaggedness is not proportional to neural response (data not shown). This suggests that problems with high resolution recording amplifier saturation can also be avoided simply by recording at a CL higher in the ECAP dynamic range. Low NRT sampling rates in existing hardware are ultimately a significant hindrance to acquiring accurate ECAP N1 peak latencies and, to a lesser degree, ECAP N1 to P1 amplitudes. Another solution to recording ECAPs at higher sampling resolution is, as in Ramekers et al. (2014), the use of external recording electrodes. External recording systems, however, are far less practical than intracochlear NRT in a clinical context.

The data ultimately used in this study were recorded from older, post-lingually deafened adults, whereas it is pre-lingually deaf infants for whom this system perhaps holds the greatest benefits (Manrique et al. 2004). Though ECAPs benefit for being peripheral responses to stimulation and so do not undergo much of the neural plasticity-derived changes that occur at higher levels of neural processing both due specifically to noise exposure, and also to normal cortical maturation, ECAP measures and behavioural thresholds do exhibit changes in infants before stabilising at approximately 12 months post switch-on (Hughes et al. 2001; Gordon et al. 2006). Some of these changes are likely driven by changes in the interface between cochlear tissue and the implanted electrode, evidence of which is given by bone and tissue growth in the implanted cochlea, as well as chemical and textural changes on the electrode surface (Brummer and Turner 1977; Ni et al. 1992; Clark et al. 1995; Peeters et al. 1997; Li et al. 1999). This presents the dual problem of 1) changing behavioural thresholds over time, and 2) uncertain influence of the differing electrical and neural properties of the newly-implanted cochlea on the ECAP measures made in the present study. An obvious solution might be to replicate the present study in adults for whom the device is newly activated, matching the newly implanted cochlea of a pre-lingual deaf infant. Such a solution, however, is far from ideal as the cochlea of a post-lingually deaf adult is quite different to the cochlea of a pre-lingual deaf infant. Impedance and threshold changes in infants stabilise after 12 months, but impedance in adults stabilise after approximately three months, which is suggested to be related to different degrees of bone and tissue growth in the infant and adult cochleae (Hughes et al. 2001; Mosca et al. 2014). Further, a typical post-lingually deaf adult differs in aetiology and cochlear pathology. Together, this evidence points to it being a necessary step that, prior to informing clinical practice for newly implanted adults and children, it would be necessary to replicate the methodology in populations that more closely match the two respective groups.

Our study did not attempt to make predictions of C-levels as these data were outside the scope of the hypotheses. As previously discussed, a major point of difference between our and many preceding studies is our use of a 3IFC threshold-finding task, rather than map thresholds, to determine accurate behavioural
thresholds that minimise systematic and random error. Similarly for C-levels, many ECAP-based objective fitting studies (e.g. Holstad et al. (2009)) have used map-based C-levels. The C-level corollary of the 3IFC task for T-levels is a loudness-balancing task in the upper end of a CI user’s behavioural dynamic range following a methodology analogous to that of McKay and Henshall (2003). Use of PD and IPG effect-based ECAP measures to predict C-levels is an opportunity for further study. Alternatively, similar to the existing ECAP threshold profile-based fitting used clinically in infants, fully objective fitting could be achieved with T-level predictions offset by a conservative prediction of the patient’s dynamic range, effectively creating a T-level offset, rather than ECAP threshold-offset, clinical fitting method.

A major concern for the clinical translation of the procedure described in this study is that not all CI users have detectable ECAPs at probe currents below C, and that it is necessarily difficult to acquire C levels from the target infant population. One solution may be to repeat this study’s procedures at ECAP amplitudes much lower in the full ECAP dynamic range. If these methods were successful at lower ECAP amplitudes, this reduces the likelihood that the CL is in excess of a patient’s C-level. Another potential solution is to make ECAP recordings intraoperatively so C-levels do not need to be considered. As previously discussed, T, C, and at least some ECAP measures change after implantation before stabilising 12 months post-switch on for infants (Hughes et al. 2001). It is possible that intraoperative ECAP-based behavioural threshold predictions would not suit an infant in the longer term, though could be an adequate initial map. ECAPs can however be favourably contrasted with cortical evoked potentials, a key competing method of objective fitting, which shows significant variability in morphology in response to cortical maturation over the first 14 years of a child’s life (Pasman et al. 1999), and is greatly affected by age of implantation, duration of deafness, and duration of CI use (Beynon et al. 2002; Sharma et al. 2002; Alvarenga et al. 2013). Similarly, with particular regard to fitting CIs in children, ECAPs compare favourably against evoked cortical potentials as behavioural threshold prediction with the latter has so far required multiple recording electrodes, long recording sessions, and computationally intensive signal processing (Visram et al. 2015), and cannot be performed intraoperatively.
ECAPs were initially recorded with the hope that they would one day be able to be used to estimate CI behavioural levels, and hence bring objectivity to the mapping process. With the immediate failure of ECAP thresholds to adequately predict higher rate behavioural thresholds, research into objective fitting has used alternative ECAP features (McKay et al. 2005; Morsnowski et al. 2005; McKay et al. 2013a), cortical potentials (Visram et al. 2015), and the stapedius reflex (Gordon et al. 2004; Crawford et al. 2009; Cinar et al. 2011) in objective fitting regimes. These have so far failed to be adopted into fully objective CI programming systems due to inaccuracy, unreliability, or difficulty in clinical implementation. In contrast with many previous objective fitting methods, ECAP measures used in our study are near-identical to measures routinely made through CI fitting software in audiologists’ clinics.

Though we find no evidence to support the hypothesis that extent of change in N1 peak latency with change in PD or IPG is correlated with low rate behavioural threshold differences, there is strong support for the hypothesis that the change in CL required to equalise ECAP amplitude when PD or IPG is changed, is correlated with low rate behavioural threshold differences. Furthermore, adding the PD/IPG effect as a predictive term to a regression between ECAP threshold and behavioural threshold significantly increased the strength of the regression, and improved model predictions of higher rate behavioural thresholds. With future verification of these findings, the techniques proposed in this thesis may significantly improve objective mapping processes in CI clinics.


Rothman, KJ (1990) No adjustments are needed for multiple comparisons. Epidemiology 1, 43-46.


## Behavioural threshold changes

Table 12 mean and standard deviation of behavioural threshold changes for each participant. A full dataset was collected for only one electrode of CI4.

<table>
<thead>
<tr>
<th></th>
<th>40 to 500 pps</th>
<th>40 to 1000 pps</th>
<th>1000 to 2000 pps</th>
<th>40 to 500 pps</th>
<th>40 to 1000 pps</th>
<th>1000 to 2000 pps</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI1</td>
<td>32.825</td>
<td>51.74</td>
<td>21.3425</td>
<td>2.583621</td>
<td>3.060229</td>
<td>2.88152</td>
</tr>
<tr>
<td>CI2</td>
<td>18.165</td>
<td>35.115</td>
<td>18.55</td>
<td>4.881827</td>
<td>5.319642</td>
<td>4.471881</td>
</tr>
<tr>
<td>CI3</td>
<td>17.56163</td>
<td>31.53875</td>
<td>15.725</td>
<td>10.14319</td>
<td>11.29776</td>
<td>8.870898</td>
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<tr>
<td>CI4</td>
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<td>1.333</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CI6</td>
<td>5.785743</td>
<td>10.46829</td>
<td>11.03171</td>
<td>4.892297</td>
<td>7.112762</td>
<td>7.89327</td>
</tr>
<tr>
<td>CI9</td>
<td>20.8668</td>
<td>38.4668</td>
<td>18.6664</td>
<td>8.558663</td>
<td>9.118139</td>
<td>5.385505</td>
</tr>
<tr>
<td>CI11</td>
<td>2.666929</td>
<td>3.286</td>
<td>5.095143</td>
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<td>3.105595</td>
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<td>CI12</td>
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<td>8.102942</td>
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PD and IPG amplitude effects

All subject correlations

Figure 25 correlation between 40 to 500 pps behavioural threshold change and the CL change to equalise ECAP amplitude with a change in stimulus condition of A) IPG 8 to 40 μs at PD 25 μs; B) IPG 8 to 40 μs at PD 40 μs; C) PD 25 to 40 μs at IPG 8 μs; D) PD 25 to 40 μs at IPG 8 μs.
Figure 26 correlation between 40 to 1000 pps behavioural threshold change and the CL change to equalise ECAP amplitude with a change in stimulus condition of A) IPG 8 to 40 μs at PD 25 μs; B) IPG 8 to 40 μs at PD 40 μs; C) PD 25 to 40 μs at IPG 8 μs; D) PD 25 to 40 μs at IPG 8 μs.

Table of per-electrode correlations for each stimulus condition is provided in the results section.

Normalised correlations
Table 13 correlations between the normalised CL change required to equalise ECAP amplitude when changing IPG and PD, and the normalised 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.
### Subject mean correlations

Table 14 correlations between the mean per subject CL change required to equalise ECAP amplitude when changing IPG and PD, and the mean per subject 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
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<th>1000 – 2000 pps change</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>0.589</td>
<td>0.073</td>
<td>0.553</td>
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<tr>
<td>IPG effect at PD 25 μs</td>
<td>0.478</td>
<td>0.162</td>
<td>0.443</td>
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<tr>
<td>IPG effect at PD 40 μs</td>
<td>0.633</td>
<td>0.049</td>
<td>0.579</td>
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<tr>
<td>PD effect at IPG 8 μs</td>
<td>0.635</td>
<td>0.049</td>
<td>0.568</td>
</tr>
<tr>
<td>PD effect at IPG 40 μs</td>
<td>0.473</td>
<td>0.168</td>
<td>0.419</td>
</tr>
</tbody>
</table>

### ΔLatency effect

All subject correlations

Table 15 correlations between the change in amplitude growth function average ECAP N1 peak amplitude when changing IPG and PD, and the 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>-0.038</td>
<td>0.788</td>
<td>-0.149</td>
</tr>
<tr>
<td>IPG effect at PD 25 μs</td>
<td>-0.015</td>
<td>0.919</td>
<td>-0.118</td>
</tr>
<tr>
<td>IPG effect at PD 40 μs</td>
<td>0.025</td>
<td>0.859</td>
<td>-0.041</td>
</tr>
<tr>
<td>PD effect at IPG 8 μs</td>
<td>-0.083</td>
<td>0.561</td>
<td>-0.172</td>
</tr>
<tr>
<td>PD effect at IPG 40 μs</td>
<td>-0.042</td>
<td>0.766</td>
<td>-0.011</td>
</tr>
</tbody>
</table>

Table 16 correlations between the change in amplitude growth function maximum ECAP N1 peak amplitude when changing IPG and PD, and the 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
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</thead>
<tbody>
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<td></td>
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<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>0.076</td>
<td>0.593</td>
<td>0.128</td>
</tr>
<tr>
<td>IPG effect at PD 25 μs</td>
<td>-0.085</td>
<td>0.547</td>
<td>-0.032</td>
</tr>
<tr>
<td>IPG effect at PD 40 μs</td>
<td>0.084</td>
<td>0.556</td>
<td>0.067</td>
</tr>
<tr>
<td>PD effect at IPG 8 μs</td>
<td>0.005</td>
<td>0.974</td>
<td>0.093</td>
</tr>
<tr>
<td>PD effect at IPG 40 μs</td>
<td>0.199</td>
<td>0.157</td>
<td>0.215</td>
</tr>
</tbody>
</table>

### Normalised correlations

Table 17 normalised correlations between the change in amplitude growth function average ECAP N1 peak amplitude when changing IPG and PD, and the 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>0.06</td>
<td>0.677</td>
<td>-0.074</td>
</tr>
<tr>
<td>IPG effect at PD 25 μs</td>
<td>0.091</td>
<td>0.526</td>
<td>0.03</td>
</tr>
<tr>
<td>IPG effect at PD 40 μs</td>
<td>-0.031</td>
<td>0.828</td>
<td>-0.146</td>
</tr>
<tr>
<td>PD effect at IPG 8 μs</td>
<td>0.112</td>
<td>0.434</td>
<td>0.046</td>
</tr>
<tr>
<td>PD effect at IPG 40 μs</td>
<td>-0.009</td>
<td>0.949</td>
<td>-0.124</td>
</tr>
</tbody>
</table>
Subject mean correlations

Table 18 per subject mean correlations between the change in amplitude growth function average ECAP N1 peak amplitude when changing IPG and PD, and the 40 to 500, 40 to 1000, and 1000 to 2000 pps behavioural threshold differences.

<table>
<thead>
<tr>
<th></th>
<th>40 – 500 pps change</th>
<th>40 – 1000 pps change</th>
<th>1000 – 2000 pps change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>All effect</td>
<td>0.209</td>
<td>0.562</td>
<td>0.143</td>
</tr>
<tr>
<td>IPG effect at PD 25 μs</td>
<td>0.118</td>
<td>0.745</td>
<td>-0.012</td>
</tr>
<tr>
<td>IPG effect at PD 40 μs</td>
<td>0.364</td>
<td>0.302</td>
<td>0.375</td>
</tr>
<tr>
<td>PD effect at IPG 8 μs</td>
<td>-0.321</td>
<td>0.366</td>
<td>-0.43</td>
</tr>
<tr>
<td>PD effect at IPG 40 μs</td>
<td>0.22</td>
<td>0.541</td>
<td>0.232</td>
</tr>
</tbody>
</table>
Table 19: The effect (the change in CL required to equalise ECAP amplitude when changing the stimulus from PD 25, IPG 8 μs, to PD 40, IPG 40 μs) correlated with ECAP threshold shows no significant association.

<table>
<thead>
<tr>
<th>All effect and ECAP threshold</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.054</td>
<td>0.705</td>
</tr>
</tbody>
</table>

Table 20: One-way ANOVA showing a statistically significant difference in group means for Figure 21.

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>Adj SS</th>
<th>Adj MS</th>
<th>F-Value</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>3</td>
<td>1756</td>
<td>585.4</td>
<td>5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Error</td>
<td>204</td>
<td>22113</td>
<td>108.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>207</td>
<td>23869</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 21: Change in latency at low CLs subtracted from change in latency at high CLs within the common range of AGFs recorded for the four PD/IPG conditions. Mean values are small, suggesting little difference between the change in latency with change in PD/IPG regardless of whether that change was calculated at a low, or high, ECAP amplitude. Large standard deviations may be a product of the extensive random error introduced by the spline interpolation, as discussed in the body text.

<table>
<thead>
<tr>
<th>change in</th>
<th>Mean (µs)</th>
<th>SD (µs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD and IPG</td>
<td>8.874</td>
<td>24.781</td>
</tr>
<tr>
<td>IPG at PD 25 µs</td>
<td>5.124</td>
<td>19.082</td>
</tr>
<tr>
<td>IPG at PD 40 µs</td>
<td>3.169</td>
<td>21.510</td>
</tr>
<tr>
<td>PD at IPG 8 µs</td>
<td>5.705</td>
<td>18.557</td>
</tr>
<tr>
<td>PD at IPG 40 µs</td>
<td>3.75</td>
<td>17.629</td>
</tr>
</tbody>
</table>

Table 22: Means, standard deviations, and 95% confidence intervals for change in latency under the four PD/IPG conditions in Figure 21. Group means that do not share a letter are significantly different. Conf. Int. stands for confidence interval.

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>Mean (µs)</th>
<th>SD (µs)</th>
<th>95% Conf. Int.</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in IPG at PD 40 µs</td>
<td>52</td>
<td>36.35</td>
<td>11.06</td>
<td>(33.51, 39.20)</td>
<td>A, B</td>
</tr>
<tr>
<td>Change in IPG at PD 25 µs</td>
<td>52</td>
<td>37.93</td>
<td>10.45</td>
<td>(35.08, 40.77)</td>
<td>A</td>
</tr>
<tr>
<td>Change in PD at IPG 8 µs</td>
<td>52</td>
<td>32.33</td>
<td>10.27</td>
<td>(29.49, 35.18)</td>
<td>B, C</td>
</tr>
<tr>
<td>Change in PD at IPG 40 µs</td>
<td>52</td>
<td>30.76</td>
<td>9.83</td>
<td>(27.91, 33.60)</td>
<td>C</td>
</tr>
</tbody>
</table>
Multiple regression equations 2 to 4 describe how the variables predict the 40 pps, 500 pps, and 2000 pps behavioural thresholds. $T$ is the ECAP threshold and $A$ is the PD and IPG effect.

\[
\begin{align*}
40 \text{ pps} &= 32.5 + 0.916T - 1.263A \\
500 \text{ pps} &= 55.7 + 0.924T - 3.122A \\
2000 \text{ pps} &= 67.7 + 0.924T - 3.122A
\end{align*}
\]

Figure 27 NRT recordings made on CI13, electrode 19, under identical stimulation settings at A) 'high resolution' 2x mode, and B) normal 1x resolution. In this example, the N1 peak of the 2x NRT is indistinct, and one of the two interleaved samples shows evidence of amplifier saturation. Conversely, the N1 peak of the 1x resolution NRT shows clearer N1 and P1 peaks, allowing what is inferred to be a more accurate recording of both the N1 to P1 amplitude, and the N1 peak latency despite a lower sampling rate.
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Author/s:
SMALE, NICHOLAS

Title:
ECAP measures predict cochlear implant behavioural thresholds

Date:
2015

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